Synthetic Cathinones and Synthetic Cannabinoids

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Novel psychoactive substances (NPS) are compounds of natural and synthetic origin, similar to traditional drugs of abuse. NPS are involved in a contemporary trend whose origin lies in a thinner balance between legitimate therapeutic drug research and legislative control. The contemporary NPS trend resulted from the replacement of MDMA by synthetic cathinones in ‘ecstasy’ during the 2000s. The most common NPS are synthetic cannabinoids and synthetic cathinones. Interestingly, during the last 50 years, these two classes of NPS have been the object of scientific research for a set of health conditions.

NPS synthetic cathinones synthetic cannabinoids

1. Therapeutic Potential of Synthetic Cathinones and Synthetic Cannabinoids

1.1 Synthetic Cathinones: Therapeutic Potential

Synthetic cathinones-related effects bank on two primary mechanisms: monoamine uptake blockade resulting from transporter inhibition and increased monoamine release. In addition, the effects can be derived from the two mechanisms combined [1]. Regardless of the molecular mechanism involved, all synthetic cathinones increase extracellular monoamine concentrations in the brain, enhancing cell-to-cell monoamine signalling, and are potent inhibitors of NA transporter (NET) [2]. However, they differ in their inhibition profiles on DA transporter (DAT) and 5-HT transporter (SERT) and in their ability to release monoamines, which possibly explains clinical differences reported in their effects and toxicities [1][3][4][5]. Cathinone highly inhibits DAT but is a less potent SERT inhibitor [3]. MDPV is one of the first recreational synthetic cathinones and acts as a potent, selective monoamine uptake blocker, with high affinity for DAT and NET and weak for SERT, but has less impact on monoamine release than cocaine [4]. Still, comparing the uptake blocking capacity of both, MDPV is 10 and 50 times more potent as an uptake blocker than DAT and NET, respectively [1]. On the other hand, mephedrone and methylone act as nonselective monoamine uptake inhibitors [4] like cocaine and increase serotonin release like MDMA [5].

The observation of synthetic cathinones’ effects on CNS led to the study of their pharmacology and, eventually, their medical application to treat depression, chronic fatigue and obesity [6][7]. Otherwise, synthetic cathinones have also been used by undiagnosed attention-deficit/hyperactivity disorder (ADHD) adolescents, who self-medicate with synthetic cathinones [8].

1.2. Depression

Depression is a common illness that affects an estimated 3.8% of the world population (approximately 280 million people) [9]. Depression was ranked by the World Health Organization (WHO) as the single most significant contributor to global disability [10]. Common symptoms are sadness, irritability, emptiness or loss of interest in activities [11]. Depression is often attributed to a defective serotonergic function, but an ineffective compensatory response to abnormally high serotonergic function can also be responsible [12]. Especially when recurrent and with moderate or severe intensity, depression may become a serious health condition and, at its worst, may lead to suicide [10][13].

Synthetic cathinones, namely methcathinone and bupropion, might be used in the treatment of depression. Methcathinone was used as an antidepressant in the 1930s and 1940s, and bupropion is still prescribed for the treatment of depression and smoking cessation by the FDA [6][14].

1.3. Chronic Fatigue

Lethargy and chronic fatigue are complex multisystemic diseases characterized by severe fatigue, cognitive dysfunction, sleep difficulties and autonomic dysfunction [15]. In the 1970s, the synthetic cathinone pyrovalerone started to be used to treat lethargy and chronic fatigue [7]. This medicine is still an approved medication by the FDA. However, it is a Schedule V controlled substance and is rarely prescribed [2].

1.4. Obesity

Obesity is a worldwide issue that has nearly tripled since 1975. In 2016, more than 1.9 billion adults were overweight, and 39 million children under the age of 5 were overweight or obese in 2020 [16]. Obesity is a complex, multifactorial preventable disease primarily associated with excess adiposity, or body fatness [17]. This condition considerably increases the risk of chronic disease morbidity, disabilities, depression, type 2 diabetes, cardiovascular disease, certain types of oncologic pathologies and mortality [18]. If the secular trends continue, by 2030, an estimated 38% of the world's adult population will be overweight and another 20% will be obese [19].

In the past, two synthetic cathinones were used as appetite suppressants, namely amphepramone and metamphepramone (N,N-dimethylcathinone or dimethylpropion) [20][21][22]. Currently, only amphepramone is still in use.

1.5. Attention-Deficit/Hyperactivity Disorder

ADHD is among the most common neurobehavioral disorders in children. The clinical significance of the signs and symptoms of the disorder has been recognized for over two centuries [23]. It carries a high rate of comorbid psychiatric difficulties, such as oppositional defiant disorder (ODD), conduct disorder, mood and anxiety disorders, and also the consumption of substances of abuse. The societal costs of untreated ADHD are significant, including academic and occupational underachievement, delinquency, motor vehicle safety, difficulties with personal

relationships and excessive talking with impaired listening comprehension [23]. Scientists have not yet identified the specific causes of ADHD. Still, there is evidence that genetics contribute to the disorder, but factors such as being born prematurely, brain injury or the mother smoking, using alcohol or having extreme stress during pregnancy can also be involved [24]. The main features of the ADHD diagnosis are (1) the presence of inappropriate levels of hyperactive–impulsive and/or inattentive symptoms for at least 6 months; (2) symptoms occurring in different settings, and that cause impairments in living; (3) some of the symptoms first occurring in early to mid-childhood years of the person and (4) that no other disorder better explains the symptoms [24]. The clinical presentation of ADHD can be described as primarily inattentive, primarily hyperactive–impulsive, or combined, depending on the nature of the symptoms. Studies indicate that distraction is more powerfully associated with academic underachievement, low self-esteem, negative occupational outcomes and lower overall adaptive functioning [23]. Data reporting to 2016 described that, of the children with current ADHD, almost two-thirds were taking medication and around half of them had received behavioural treatment for ADHD in the past year [25].

Phenethylamines are a class of stimulants prescribed in patients with ADHD, namely methylphenidate. Methylphenidate and other ADHD pharmacotherapies influence the nucleus acumbens of adolescents with ADHD in the same way as cocaine. Hence, cocaine dependence in adolescents with ADHD might answer to therapeutic interventions that substitute cocaine with psychostimulants, such as MDPV [8]. Synthetic cathinones are substances with chemical structures related to phenethylamines, promoting similar effects. Nowadays, the use or potential use of cathinones to treat this disease is still a matter of debate, being hindered by the harmful secondary effects to users. However, undiagnosed ADHD adolescents often use bath salts to self-medicate, aiming to contain ADHD symptoms [26]. MDPV comes close to the effect of methylphenidate at low doses, and its self-administration can induce psychoactive effects that help alleviate ADHD symptoms, so adolescents might continue to experience enhanced concentration and overall performance [5]. It is important to note that bath salts can be found worldwide at a low cost in internet shops.

There is still a lack of knowledge around synthetic cathinones' therapeutic potential, with a great deal of room left for new studies to develop.

2. Synthetic Cannabinoids: Therapeutic Potential

2.1. Inflammatory Pathologies

Inflammation is an immune system's response to harmful stimuli, such as pathogens, toxic compounds and damaged cells, among others, crucial for initiating the healing process [27]. However, when the molecular and cellular events underlying acute inflammation become uncontrolled, the process may become chronic, developing chronic inflammatory diseases. Such is the case of arthritis and colitis. Several studies have shown that cannabinoids downregulate cytokine and chemokine production, suppressing inflammatory responses. Thus, synthetic cannabinoids are being investigated as novel therapeutics approaches to such conditions [28][29][30][31].

Arthritis

Rheumatoid arthritis is an inflammatory disease characterized by persistent synovitis, painful systemic inflammation and autoantibodies, which lead to joint damage and disability [32][33]. This condition results from an overactive immune system that leads to excessive and unregulated inflammation [33][34]. As a result of this event, the tissue invasion by immune cells and their effectors, such as pro-inflammatory cytokines, is prolonged, damaging the affected areas and provoking the typical symptoms of inflammation, namely pain, rubor, warmth and swelling [34]. The pathophysiology of arthritis is related to a series of catabolic events that lead to degradation and consequent loss of articular cartilage and resorption of subchondral bone [35][36]. The pathway that leads to these events seems to involve a complex network of signalling agents, including high levels of pro-inflammatory cytokines (e.g., IL-1, IFN-γ, TNFα, IL-17) and lower levels of the anti-inflammatory factor interleukin IL-10 [37][38][39][40]. Additionally, inflammatory arthritis is associated with increased production of nitric oxide (NO) due to activation of the nitric oxide synthase (iNOS) pathway [41]. Several cell types present within the joint, including chondrocytes, can be induced by pro-inflammatory cytokines to produce NO [40]. NO production in the early stages of arthritis may cause apoptosis in chondrocytes, contributing to cartilage degradation [42][43]. Additionally, there is evidence that NO synthesis reduces proteoglycan and type II collagen synthesis, both components of the cartilage extracellular matrix [42][44].

Considering that the endocannabinoid system plays an essential role in several processes, including inflammation and immune system modulation [45], which are implicated in inflammatory arthritis pathogenesis, synthetic cannabinoids are an object of medical research as a potential treatment for this condition. In 2005, Mbvundula et al. demonstrated that R-(+)-WIN-55,212, a nonselective cannabinoid receptor agonist, reduced NO production in chondrocytes, suggesting that some cannabinoids may prevent cartilage resorption through inhibiting cytokine-induced NO production by chondrocytes and by inhibiting proteoglycan degradation [46]. A similar effect was observed with the CB agonist CP-55,940 [29], which was also proven to stimulate osteoclast formation in vitro [30]. Moreover, Gui and collaborators have shown a reduction in osteoclast formation in osteoblast-bone marrow in the presence of the synthetic cannabinoid HU-308. The mechanism seems to involve the decrease in the levels of IL-6 and TNFα through the CB2 receptor [31]. Although targeting the cannabinoid system seems to be a promising therapeutic approach, cannabis-based drugs interact with receptors other than CB receptors, having unexpected outcomes in clinical studies compared to preclinical trials.

Colitis

Ulcerative colitis is a chronic, idiopathic inflammatory bowel disease characterized by relapsing and remitting mucosal inflammation [47]. This inflammation starts in the rectum, extends to the colon's proximal segments and results in diffuse friability and superficial erosions on the colonic wall and consequent bleeding [48]. The most common symptoms are blood in the stool and diarrhoea. In severe disease, the symptoms referred to can be accompanied by incontinence, increased frequency of bowel movements, abdominal discomfort, fever and others [48][49]. Both genetic and environmental factors have an essential role in ulcerative colitis development. Family history of inflammatory bowel disease has been reported as a relevant risk factor in this disease [50][51]. Moreover, factors such as drug use, changes in the gut microbiota composition and impaired mucosal immunity seem relevant in ulcerative colitis aetiology [48][52][53].

The pathophysiology of ulcerative colitis is complex since it involves impairment in the epithelial barrier, immune response, leukocyte recruitment and microflora of the colon [48][54][55]. Despite the complexity of the disease, here, just the influence of abnormal immune response and leukocyte recruitment in ulcerative colitis development is addressed. In physiological conditions, the single-layered intestinal epithelium behaves like a physical and immunological barrier that prevents direct contact between luminal microbiota and intestinal mucosa [56]. However, if the intestinal epithelium is injured, an immune response is initiated, leading to neutrophil recruitment. These neutrophils recognize, phagocytise and kill pathogenic agents and promote the production of cytokines and other pro-inflammatory factors that also regulate inflammation and immune system response [56][57][58][59][60]. Neutrophil accumulation in intestinal tissue can promote significant tissue damage when not properly eliminated [56].

In 2014, Fichna et al. demonstrated that AM-841, a preferential CB1 receptor agonist, reduces inflammation in the colon of mice with induced colitis, attenuates colitis and inhibits ulceration [28]. This effect is due to a decrease in immunocytes infiltration of the colonic tissue, improving the mucosal and muscle architecture and inhibiting its ulceration. More specifically, AM-841 inhibits fMLP-stimulated neutrophil migration, an essential feature of the anti-inflammatory action of this synthetic cannabinoid [28]. Indeed, fMLP is a chemical compound that attracts neutrophils [61]. It is worth mentioning that the AM-841 anti-inflammatory effects occur when this synthetic cannabinoid is administered prior to colitis induction, revealing its protective properties [28].

To understand AM-841 action on the cannabinoid receptors, Fichna and collaborators used mice with cannabinoid receptors CB1 and CB2 and without one or both receptors [28]. This experiment revealed that AM-841 did not attenuate colitis in mice in the absence of one or both cannabinoid receptors. As such, despite its preference for the CB1 receptor, the data suggest that just AM-841 action on both cannabinoid receptors alleviates colitis in mice [28].

Concluding, AM-841 displayed protective and therapeutic effects on colitis in mice through its anti-inflammatory action, mediated through the CB1 and CB2 receptors [28].

2.2. Neurodegenerative Pathologies

Neurodegenerative diseases are progressive, incapacitating conditions involving the function loss of nerve cells in the brain or peripheral nervous system, affecting millions worldwide. The hallmark of these pathologies is the accumulation of misfolded and aggregated proteins associated with neuroinflammation, infection, mitochondrial dysfunction and excitotoxicity. Phytocannabinoids and synthetic cannabinoids appear to be neuroprotective either by binding to the CB1 or CB2 receptors [62] and are used worldwide by patients with neurodegenerative diseases. Therefore, cannabinoid receptor agonists are a research field for therapeutic purposes. Notwithstanding, most of these substances were not approved by medicine regulatory agencies. Thereby, the potential therapeutic of synthetic cannabinoids is explored, focusing on Parkinson's disease (PD), Alzheimer's disease (AD) and neurocognitive disorders associated with HIV-1 [63][64][65][66][67].

Parkinson's' Disease

PD is a chronic, progressive neurodegenerative disease characterized by the loss of dopaminergic neurons in the substancia nigra pars compacta, a midbrain dopaminergic nucleus [68][69]. This pathology is the second most common neurodegenerative disorder worldwide, and its prevalence has been rising in the last three decades [70]. Its onset occurs mainly in later life, giving rise to resting generalized tremors, bradykinesia and rigidity [69][71]. Besides these symptoms, loss of smell, sleep dysfunction, mood disorders, constipation, excessive salivation and postural instability in the latter phase of the disease can be described [68][72]. The aetiology of Parkinson's disease is driven by a complex interplay between genetic and environmental factors [73][74].

PD is an α-synucleinopathy since it involves the abnormal accumulation of α-synuclein protein in the neuronal tissue [71]. This abnormal accumulation culminates in the generation of Lewy bodies, which leads to neuronal death in dopaminergic and non-dopaminergic brain areas. The loss of dopaminergic neurons leads to motor and non-motor symptoms that characterize PD [72][75]. Besides α-synuclein aggregation, other key molecular events have been associated with PD, such as mitochondrial dysfunction and oxidative stress, which lead to radical oxygen species (ROS) generation [76][77]. During the pathogenesis of PD, ROS generation damages the substancia nigra through lipid peroxidation, protein oxidation and DNA oxidation [76][78]. According to the available research, this event seems to be induced mainly by changes in the brain iron content, mitochondrial dysfunction and monoamine oxidase activation, an enzyme responsible for dopamine metabolization [77][79][80]. There is also evidence that oxidative stress can induce α-synuclein conformational changes and increase its aggregation [81][82].

In 2008, Del Rio and Velez-Pardo demonstrated that CP-55,940, a non-selective cannabinoid receptor agonist, and JWH-015, a preferential CB2 receptor agonist, protect and rescue lymphocytes against paraquat exposition [64]. Paraquat is a Parkinson's disease chemical inducer, and, in lymphocytes, induces mitochondrial damage and apoptosis through an oxidative stress mechanism involving ROS generation, namely superoxide anion radical (O_2^-), hydroxyl radical (OH) and hydrogen peroxide (H_2O_2) [83]. The authors showed that the abovementioned synthetic cannabinoids inhibit ROS formation, contributing to maintaining mitochondrial membrane potential and cell nucleus morphology [64]. According to this study, CP-55,940 and JWH-015 are protective due to potential anti-oxidative action. Subsequently, Velez-Pardo observed that CP-55,940 and JWH-015 attenuate paraquat-induced mitochondrial damage in the brain cortex of mice by scavenging O_2^- and H_2O_2 and avoiding Ca^{2+}-induced mitochondrial swelling, contributing to the maintenance of mitochondrial membrane potential [66]. The authors also revealed that JWH-015 has more effective and potent anti-oxidative effects when compared to CP-55,940. It is relevant to mention that CP-55,940 and JWH-015 exert an inhibiting effect against O_2^- and do not cause any changes in mitochondrial membrane potential in mitochondria not exposed to paraquat [66].

Alzheimer's Disease

AD is a neurodegenerative disease characterized by the deposition of β-amyloid peptide (Aβ) plaques and neurofibrillary tangles (NFT) of the protein tau [84][85]. AD is the most common type of dementia, a clinical syndrome that involves a progressive decline in two or more cognitive domains, including memory, language, executive and visuospatial function, personality and behaviour [86]. This disease is more commonly associated with elders, and its initial and most prevalent presenting symptom is episodic short-term memory loss with relative sparing of long-term

memory [84][87]. This event is followed by impairment in problem-solving, judgment, executive functioning, lack of motivation, and disorganization, culminating in multitasking and abstract thinking difficulties [88]. Genetic and lifestyle factors, such as smoking and a series of pathologies and conditions, such as cerebrovascular diseases, diabetes, hypercholesterolemia and depression, seem to be involved in AD aetiology [88][89][90][91].

As previously mentioned, the abnormal presence of extracellular plaques of insoluble Aβ and flame-shaped NFT of the microtubule-binding protein tau in neuronal cytoplasm, especially in brain regions involved in memory processes, are the two main mechanisms in AD [85]. According to amyloid cascade theory, the cerebral accumulation of Aβ, particularly Aβ42 form, is the main event causing AD [92][93][94]. Considering that Aβ42 is generated through cleavage of the amyloid precursor protein (APP), reports indicate APP metabolism dysfunction with a subsequent increase in Aβ levels as a possible mechanism that promotes AD [94][95][96]. Additionally, it was already observed that abnormal Aβ plaques induce the phosphorylation of tau protein, which spreads via microtubule transport to neighbouring neurons, contributing to their death [97][98]. The molecular mechanisms are not fully understood yet. Still, the studies suggest that Aβ induces a series of processes that lead to abnormalities in tau protein folding, phosphorylation, degradation and localization, leading to neuronal and synaptic atrophy and death resulting from excessive stimulation of neurotransmitter receptors in neuronal membranes, collapse in calcium homeostasis, inflammation and depletion of energy and neuronal factors [86][88][97].

In 2009, Tolón et al. showed that JWH-015 induced the removal of Aβ-amyloid peptide from human frozen tissue section belonging to Alzheimer's disease patients through the human macrophage cell line THP-1 [65]. It is worth mentioning that, without exposure to JWH-015, THP-1 macrophages cannot remove pathological deposits of Aβ-amyloid peptide.

Tolón and collaborators also showed that the JWH-015 effect is mediated by the CB2 receptor since adding SR144528, a CB2 receptor antagonist, cancels its effects in situ [65]. However, in vitro, the reversal of JWH-015 effects was not observed with the CB2 antagonist, which indicates a possible environment-dependent macrophage response. Through its action on CB2 receptors, JWH-015 exerts a stimulatory effect on the phagocytosis of Aβ-amyloid peptide by THP-1 macrophages, promoting its removal [65].

Concluding, the activation of the CB2 receptor by JWH-015 triggers the in situ phagocytosis of β-amyloid peptide by THP-1 macrophages, inducing its removal [65].

Neurocognitive Disorders Associated with HIV-I

Human immunodeficiency virus (HIV) is the causing agent of acquired immunodeficiency syndrome (AIDS), a chronic, potentially life-threatening condition caused by the human immunodeficiency virus [99]. This virus targets the immune system by destroying and impairing the function of immune cells, weakening the immunologic defences against a series of infections and pathologies [100]. Nowadays, anti-retroviral therapy (ART) is the available therapeutic option for AIDS. This therapy uses a set of medicines that target the enzymes reverse transcriptase, protease and integrase, among other vulnerable points in the HIV replication cycle [101]. Despite the

considerable success of ART, HIV-I associated neurocognitive disorders, such as asymptomatic neurocognitive impairment, mild neurocognitive disorder and dementia, are still prevalent conditions without therapeutic options [102][103][104].

In 2013, Hu et al. demonstrated that WIN-55,212 attenuates neuronal damage and apoptosis caused by the HIV-1 gp120 protein in a human mesencephalic neuronal and glial culture model [105]. This protein induces neuronal damage and apoptosis, specifically in dopaminergic neurons, by decreasing DA uptake through the reduction in DAT function, causing morphological changes, inducing oxidative stress and reducing its viability, judging by a decrease in the number of dopaminergic neurons and a loss of dendrites [105]. The nigrostriatal dopaminergic area is a critical brain region for the neuronal dysfunction observed in HIV-1-associated neurocognitive disorders [106]. Interestingly, it has been shown that WIN-55,212 inhibits gp120-induced O_2^- production, reducing oxidative stress. This effect was observed in the human mesencephalic culture exposed to gp120 alone and with purified human microglial cells that potentiate the neurotoxic effects of gp120 [105]. Hu and collaborators evaluated the capacity of WIN-55,212 to inhibit the migration of highly purified human microglia towards the supernatants generated from gp120-exposed human mesencephalic cultures. The authors found that the synthetic cannabinoid mentioned inhibits the migration of microglial cells, inhibiting the release of chemokines CCL2, CX3CL1, CXCL10 and cytokine IL-1β [67][105]. Finally, the CB2 receptor is the main one responsible for the effects of WIN-55,212 since its neuroprotection decreases more significantly in the presence of the CB2 antagonist SR144528 compared to the CB1 antagonist SR141716A [105].

2.3. Oncologic Pathologies

Since phytocannabinoids' anti-tumour properties discovery, several synthetic cannabinoids have been synthesized and subjected to research and trials as potential anticancer agents [107][108][109][110]. By interacting with cannabinoid receptors, synthetic cannabinoids can modulate crucial cellular signalling mechanisms and pathways for tumour development, including cell proliferation and survival [111]. As such, the antitumorigenic capacity of these compounds relies on the inhibition of tumour cell migration and proliferation, induction of apoptotic processes, reduction of tumour cell viability and blocking of angiogenesis and tumour invasion/metastasis [112][113]. The activation of these antitumorigenic processes by synthetic cannabinoids has been observed in several oncological studies, including multiple myeloma, osteosarcoma, glioblastoma multiforme and triple negative breast cancer [114][115][116][117].

Multiple Myeloma

Multiple myeloma is a clonal plasma cell proliferative blood disorder in which monoclonal plasma cells proliferate in bone marrow, leading to an overabundance of monoclonal paraprotein, destruction of bone and displacement of other hematopoietic cell lines [118][119]. Some common signs and symptoms include anaemia, bone pain or lytic lesions on X-ray, kidney injury and hypercalcemia, among others [120][121]. Despite its aetiology not being fully defined, the research on this topic indicates that environmental, lifestyle factors and genetic abnormalities in oncogenes, such as CMYC, NRAS and KRAS, are potentially critical for plasma cell proliferation [122][123].

In 2017, Barbado et al. demonstrated that WIN-55,212 reduces cell viability and induces selective apoptosis in multiple myeloma cell lines and spinal cord primary plasma cells of multiple myeloma patients while sparing normal cells from healthy donors, particularly hematopoietic stem cells [114]. This synthetic cannabinoid also suppresses tumour growth in mice [114].

These authors have shown that WIN-55,212 effects are mediated by apoptotic mechanisms, primarily through the activation of the initiator caspase caspase-2. Reinforcing this observation, in the presence of pan-caspase inhibitor Z-VAD-FMK, WIN55,212 pro-apoptotic effects are partially inhibited, showing that these effects are, at least in part, caspase-dependent [114].

To understand the process responsible for apoptosis induction, the authors evaluated the involvement of de novo synthesis of ceramides in the WIN-55,212-induced apoptosis. It was already demonstrated that ceramide is a potent suppressor that potentiates and drives the process of apoptosis [124]. It was observed that WIN-55,212 promotes the synthesis of ceramide through the upregulation of SPT, an essential enzyme in regulating ceramide synthesis [114][124]. The authors also demonstrated that WIN-55,212 also excerpts its effects through CB2 receptor activation since the CB2 receptor antagonists PGN-8, PGN-37 and PGN-70 blocked its action [114].

Osteosarcoma

Osteosarcoma is a malignant bone tumour characterized by osteoid production by malignant mesenchymal cells [125]. Its high degree of malignancy, strong invasiveness, rapid disease progression and extremely high mortality rate are associated with this pathology [126]. Osteosarcoma is the third most common cancer in adolescents [127]. Patients typically complain about localised and persistent pain usually noticed after an injury. Despite the patients being heavily treated for pain, the pain felt is never fully resolved [126][128]. Physical examination also allows observing warmth, skin vascularity or pulsations over the lesioned area [128]. Such as in multiple myeloma, osteosarcoma aetiology remains a poorly understood issue. However, available research indicates an important interplay of genetic and environmental factors, such as the exposition to certain types of radiation and chemicals, in osteosarcoma aetiology [125][129].

In 2019, Notaro et al. demonstrated that WIN-55,212 prevents cell migration and reduces extracellular levels of matrix metalloproteinases (MMP) 2 and 9 and drastically decreases intracellular levels of MMP9 in human osteosarcoma cell line MG63 [116]. MMP regulates many physiological and pathological processes, including normal tissue remodelling, angiogenesis, DNA replication, neurodegeneration and cancer [130]. This synthetic cannabinoid also prevents the release of secreted protein acidic and rich in cysteine (SPARC), inhibiting its secretion into the extracellular medium and promoting the upregulation of miR-29b1, a microRNA that inhibits cell proliferation and migration when overexpressed [116]. SPARC is involved in the regulation of cell adhesion and migration processes and tissue remodelling [131]. Notaro and collaborators also showed that the WIN-55,212-2 effects on cell migration are SPARC-independent and miR-28b1-dependent since, when SPARC expression is silenced in MG63 cells, by RNA interference, WIN55,212 continues to reduce cell migration [116]. Conversely, a reduction in cell migration is observed in cells transfected with miR-29b1 and treated with WIN-55,212 but not in

cells not transfected with this microRNA. These results demonstrate the importance of WIN-55,212-induced miR-29b1 upregulation to its anti-migratory effects [116].

Glioblastoma Multiforme

Glioblastoma multiforme is a primary malignant CNS tumour that arises from astrocytes [132][133]. Astrocytes are a sub-type of glial cells located in the CNS that provide physical and metabolic support to neuronal cells, including neuronal communication, nutrient supply and waste removal [134]. This oncologic pathology is the most prevalent, aggressive and invasive CNS tumour in adults [133][135]. Patients with glioblastoma multiforme can exhibit several symptoms, such as headaches, seizures, memory loss and functional impairment [136]. The aetiology of glioblastoma multiforme is poorly understood, the exposure to high dose ionizing radiation being the only aetiologic possibility confirmed [137]. Nevertheless, genetic and environmental factors in glioblastoma multiforme aetiology are an object of research [132].

In 2012, Gurley et al. found that KM-233, a non-selective CB1 and CB2 receptor agonist, causes a time-dependent change in the phosphorylation profiles of MEK, ERK1/2, Akt, BAD, STAT3 and p70S6K in the glioblastoma multiforme human cell line u87MG [115]. This synthetic cannabinoid also promotes a redistribution of the golgi–endoplasmic reticulum structures and an almost complete mitochondrial depolarization by a rapid increase in cleaved caspase 3 levels and significant cytoskeletal contractions, which are indicators of apoptosis [115]. The alterations in mitochondrial membrane polarization lead to mitochondrial integrity loss and the formation of autophagic compartments and vacuoles. The formation of these structures is an indicator of autophagy, evidencing the initiation of a mitochondrial-mediated autophagy process [115]. Additionally, KM-233 promotes an 80% reduction in tumour size by decreasing its growth rate without showing acute toxicity in the mice organs [115]. KM-233 effects are inhibited in the presence of SR141716A, a CB1 receptor antagonist, suggesting CB1 receptor involvement in the process. Concluding, KM-233 may be a potential treatment for glioblastoma multiforme cases through its pro-apoptotic and anti-proliferative properties [115].

Triple Negative Breast Cancer

Triple-negative breast cancer is a sub-type of breast cancer defined by the lack of expression of the three principal biomarkers associated with breast cancer: oestrogen receptor-α, progesterone receptor and human epidermal growth factor receptor 2 (HER2) [138]. These characteristics lead to a poorer prognosis and a reduced response to therapeutics, making this sub-type of breast cancer more aggressive and fatal [139]. Breast cancers represent the most common cancers diagnosed in women [140]. From this, about 10 to 15% correspond to triple-negative breast cancer [141]. The typical symptoms are similar to those observed in other forms of breast cancer, including partial or complete breast swelling, breast or nipple pain, nipple retraction and swollen lymph nodes [142]. Genetic factors, such as mutations in BRCA1 and BRCA2 genes, are key for triple-negative breast cancer aetiology [143][144]. These gene products act as cell growth suppressors, playing a protective role against tumorigenesis [145]. The evidence shows that mutations in these genes promote an increased risk of developing breast cancer [146].

In 2018, Greish et al. demonstrated that SMA-WIN, a nanomicellar formulation of WIN55,212, reduces tumour growth by promoting necrotic areas in the tumours in mice with triple-negative breast cancer 4T1 [117]. In addition, this formulation reduces the psychoactive effects of WIN-55,212 free form. The lower psychoactive effect is due to a significantly lower concentration of micelles in the brain when compared to the WIN-55,212 free form concentration, suggesting that blood–brain barrier permeability to the nanomicellar structure is reduced [117]. The studies indicate that the formulation has reduced blood–brain permeability and a propensity to accumulate in the tumour site [117].

3. Synthetic Cathinones: Adverse Effects

Synthetic cathinones produce distinct pharmacological effects, with psycho-stimulation and hallucinations. Taking the effects of mephedrone, for example, they are simultaneously psychostimulant (i.e., like amphetamine) and hallucinogenic (like MDMA). Therefore, synthetic cathinones and amphetamines share pharmacological properties, and, based on the extensive similarities in the effects of these drug classes, it might be predicted that these cathinones would cause neurotoxicity to DA and 5-HT nerve endings identical to methamphetamine METH and MDMA [1][147]. Moreover, overdose can occur after continuous daily consumption and can lead to psychological illness with paranoid or delusional mania symptoms. Finally, withdrawal syndrome was reported after suspension and was characterized by insomnia, lack of concentration, craving, nightmares and slight trembling [148]. In addition to the neuropsychiatric symptoms, consumers often present with sympathomimetic toxicity. Consistently, several cathinones have been associated with the development of serotonin syndrome, eventually leading to fatalities [149].

The symptoms described by clinicians include hyperthermia, agitated delirium, tachypnoea, coagulopathy, rhabdomyolysis and cardiac and other organs arrest or failure. In several cases, other psychoactive drugs have been detected in deceased patients [150]. Fatal cases related to the consumption of synthetic cathinones have been reported. However, many of these cases are associated with exposition to synthetic cathinones concomitantly with other drugs of abuse [6][150][151].

4. Synthetic Cannabinoids: Adverse Effects

The adverse effects promoted by synthetic cannabinoids are observed mostly at the neurological and psychiatric levels and in the cardiovascular and gastrointestinal systems [152][153]. In acute intoxication, the adverse effects include tachycardia, agitation, drowsiness, confusion, nausea and vomiting and hallucinations [153][154]. In most of the clinical cases recorded, the listed effects are not life-threatening and cease six to eight hours after consumption [155]. Before severe intoxication with these substances, the main manifestations identified are chest pain, myocardial infarction, acute kidney damage, seizures, acute psychosis, panic, hallucinations and paranoia, which may culminate in death attributed directly and indirectly to this set of synthetic cannabinoids [152][156][157][158]. The cases of death attributed directly to these compounds result from dysrhythmia, seizures and multiple organ failure, while deaths attributed indirectly to these cannabinoid receptor agonists come from hypothermia, development of trauma and self-mutilation [153][158][159].

In addition to the systems previously mentioned, the clinical manifestations triggered by synthetic cannabinoids are also identified at the neuromuscular, neurobiological and metabolic levels, respiratory and renal systems, eyes and mouth [152]. At the neuromuscular level, myoclonus may occur, a manifestation characterized by involuntary, brief and sudden muscle contractions and increased creatine kinase (CPK) enzyme levels, resulting from the destruction of muscle tissue [63][152]. At the metabolic level, it may verify hyperglycaemia) and hyponatremia [158]. Dyspnea and tachypnea can be identified in the respiratory system, and, in the renal system, urine production-related and renal failure-related dysfunctions may occur [160][161]. In the ocular system, mydriasis and weak reaction of the pupils to light exposure may occur, and the consumer may also experience a sense of dry mouth (xerostomia) [63][157]. In addition to the manifestations associated with the nervous system, after consuming synthetic cannabinoids, the consumer may exhibit headaches, irritability, sensitivity to light, cognitive difficulties and anxiety and, at the cardiovascular level, hypertension, palpitations, dysrhythmia and chest pain [155][157][158][162].

The use of these substances, through one or repeated exposures, may trigger an acute psychotic reaction in healthy subjects and lead to effects that mimic symptoms characteristic of a clinical diagnosis of schizophrenia, such as changes in perception, depersonalization, development of a dissociative state, auditory and visual hallucinations, disorganized behaviour and discourse and suicidal ideation [163][164]. These symptoms may manifest more intensely in individuals with an established diagnosis of psychotic pathology [163]

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