

# Synthetic Marijuana: A Recent Turmoil in Substance Abuse

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## ÖZET:

Sentetik esrar: Madde bağımlılığında yeni bir zehir

Esrar tüm dünyada olduğu gibi, Türkiye’de de en yaygın kullanılan yasadışı psikoaktif maddelerden biridir. Polis raporları, çok sayıda tutuklamalar ve rekor miktarda ele geçirilen esrar miktarı, esrar üretim ve tüketiminin yükselişte olduğuna dair ipuçları vermektedir. Bitkisel esrarın yanısıra, son zamanlarda “sentetik esrar” olarak da adlandırılan yeni ve potansiyel olarak daha tehlikeli bir grup kimyasal maddeler de sokaklarda belirmeye başlamıştır. İlk bakışta bir doğal/bitkisel karışım gibi görünen bu maddeler, az para ile yeni deneyimler arayanları, özellikle de genç bireyleri bağımlılık tuzagına çekmektedir. Kan veya idrar örneklerinde bu maddelerin tespit edilmesindeki zorluklar esrardan dolayı kanun ile başı dertte olan bazı kullanıcılar için cazip bir seçimdir. Yapısal olarak farklı olan sentetik esrar bileşikleri, esrarın birincil psikoaktif bileşeni olan  $\Delta 9$  tetrahidrokanabinol (THC) gibi, beyinde aynı kannabinoid reseptörlerine bağlanır ve benzer farmakolojik özellikler oluşturur. Bununla birlikte, sentetik esrar, bitkisel THC’den daha güçlü ve zaman zaman ölümcül yanıtla neden olmaktadır. Toplum sağlığı ve güvenliğine doğrudan ve dolaylı tehditleri nedeniyle bu sentetik maddelerin tanınması, kontrolü ve kullanıcıların tedavisi için acil yasal ve idari yaptırımlar, eğitim ve diğer düzenlemeler gerekmektedir.

**Anahtar sözcükler:** esrar, sentetik kannabinoidler, uyuşturucu istismar, sahte ot, Bonzai, Spice, Jamaika K2

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## ABSTRACT:

Synthetic marijuana: a recent turmoil in substance abuse

As in the rest of the world, marijuana has been one of the most commonly abused psychoactive illicit substances in Turkey. Recent police reports of record amount of marijuana seized and numerous arrests are evidence that the production and consumption of marijuana is on the rise. Lately, a newer and potentially more problematic group of chemicals, so called *synthetic marijuana*, became available on the streets. Its appearance as an herbal mixture fools the interested crowd that it is a natural, and therefore presumed to be safe, substance that can be used to have a “good time” or seek new experiences. Its cheaper price attracts younger individuals who cannot afford marijuana. Difficulties in detecting it in blood or urine samples make it more attractive to most marijuana users who already have trouble with the legal system. While structurally different, synthetic marijuana compounds bind to the same cannabinoid receptors in the brain and peripheral organs and convey similar pharmacological properties as  $\Delta 9$ -Tetrahydrocannabinol (THC), the primary psychoactive constituent of marijuana. However, synthetic marijuana is more potent than naturally-occurring THC, causing serious, and at times lethal, outcomes. Due to the imminent hazards to public safety, urgent regulations including criminal, civil and administrative penalties, sanctions and regulatory controls of substances should be imposed on the manufacture, distribution, possession and importation of these synthetic cannabinoids.

**Keywords:** marijuana, synthetic cannabinoids, drug abuse, fake weed, Bonzai, Spice, Jamaika K2

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## INTRODUCTION

Marijuana is a commonly abused substance which is often consumed for its psychoactive and physiological effects. Lately, a synthetic derivate of herbal marijuana has become popular among individuals who have drug dependence problems. Before the medical and legal authorities became aware of the risks of these novel groups of chemicals, they started taking their toll on some people, e.g. a 20-year-old healthy male soldier in Istanbul, who immediately died after using a substance called *Bonzai* and an 18-year-old healthy male who was found dead at a construction site in Bursa with packages of *Bonzai* and a 'bucket' (a device, which is used to smoke *Bonzai*) beside of his body<sup>1,2</sup>. Hospital emergency services report that the vast majority of users are children and young adults<sup>3</sup>. In July 2014, Bagcilar Training and Research Hospital admitted more than 20 of these *Bonzai* users and 2 of them lost their lives<sup>4</sup>. In contrast to regular marijuana users, *Bonzai*-influenced people exhibit strange and agitated behaviors and are damage their surroundings, and become a burden and threat to the police force, emergency medical teams and other people who try to help them<sup>3</sup>. These compounds are readily available on the Internet, still legal in many countries, marketed as natural safe substances, and undetectable by conventional drug screening tests. They are very popular and are particularly appealing to young people, as young as 10-11 years old, who are seeking different experiences. There is some public awareness about the danger of these novel narcotic substances; however, almost nothing is known in terms of pharmacology, toxicology, safety, and treatment even among the medical authorities.

### Marijuana and Synthetic Marijuana (SM)

Marijuana is a preparation of the cannabis plant which is often consumed for its psychoactive and physiological effects, which can include heightened mood or euphoria and relaxation. The

United Nations Office on Drugs and Crime (UNODC) considers it the most-used illicit drug in the world and has estimated that there are between 119 million and 224 million cannabis users worldwide, ranging from 2.6 to 5 per cent of the adult population<sup>5</sup>. The principal psychoactive component of marijuana is delta-9-tetrahydrocannabinol (THC), which produces similar effects to naturally synthesized endocannabinoids in the human body, by activating the same cannabinoid receptors (CB1 and CB2)<sup>6,7</sup>.

Synthetic marijuana (SM) products are laboratory-made chemicals (designer drugs) which are functionally similar to THC<sup>8,9</sup>. Although structurally different, SM binds to the same cannabinoid receptors (CB) in brain and peripheral organs<sup>10</sup>. Most people use these as "marijuana alternatives" in an attempt to avoid the laws that make marijuana illegal. SM products are also known as "Spice drugs", "fake weed" or "legal highs". The liquid containing the chemical is sprayed on herbal potpourris which are sold as natural highs under brand names. When smoked, SM produces similar effects to those of natural marijuana, such as heightened mood or euphoria and relaxation soon after the consumption. Since 2008, SM has started to appear in herbal smoking mixtures sold on websites, at some gas stations and in "head shops" under the brand names *Spice Gold*, *Yucatan Fire*, *Bonzai*, *Jamaika*, *Jamaican Gold Supreme*, *Aroma*, *Blaze*, *Blueberry Haze*, *Dank*, *Demon Passion Smoke*, *Genie*, *Hawaiian Hybrid*, *K2*, *Magma*, *Ninja*, *Nitro*, *Ono Budz*, *Panama Red Ball*, *Puff*, *Sativah Herbal Smoke*, *Skunk*, *Spice*, *Ultra Chronic*, *Voodoo Spice* and others. More than 140 different SM products have been identified to date<sup>8</sup>.

### The Origin of Novel SM Substances and Their Marketing

SM products do not contain any tobacco or marijuana. They are usually a mixture of dried leaves from traditional herbal plants, which are marketed as being "100% organic herbs,"

insinuating that they are all natural and completely safe. Some of the SC products sold commercially claim to contain herbs traditionally used for medicinal purposes. However, most of the herbal ingredients listed by the manufacturers could not be found in these products, and most of these products may contain nothing but dried grass or weeds. They are present in the market in various colors such as green, brown, blonde and red. They are sold in small foil packs or plastic zip bags. These products are often labelled “Not for human consumption” and marketed as “herbal incense”; however, none of the users follows the instructions on the package, that is to “burn this potpourri in a well-aired environment as herbal incense” as recommended on the package. The majority of the users blend the mixture with tobacco before smoking it. Some users prefer smoking the potpourri directly through a pipe. Some brands market their products as “herbal smoking blends for legal high” to create a fake image that they are legal alternatives to regular marijuana. Another form of synthetic cannabinoid (SC) is called *Bonzai*, which is a white powdery substance or a liquid that is sold as a fertilizer for bonsai trees and other plants. Since this fertilizer contains SC, users spray these on herbs and smoke it.

### The Manufacture of SM Substances

Animals and humans naturally synthesize endocannabinoids in the body as part of the endocannabinoid system which is believed to play a crucial role in bioregulation of inflammation, pain, memory, mood, brain reward systems, drug addiction, and metabolic processes, such as lipolysis, glucose metabolism, and energy balance. THC, the principal psychoactive component of herbal marijuana, and at least 84 other cannabinoids in the cannabis plant exert similar effects to endocannabinoids by activating the same cannabinoid receptors (CB1 and CB2) in the brain and in other parts of the body<sup>6</sup>.

The SC products produced in laboratories and sprayed on herbs for abuse were originally

designed to help scientists study the cannabinoid system in the human brain. HU-210 is a synthetic cannabinoid that was first synthesized in 1988 by a group led by Professor Mechoulam at the Hebrew University (“HU” stands for Hebrew University)<sup>11</sup>. HU-210 is more potent than natural THC from the cannabis plant and has an extended duration of action. HU-210 has been implicated in preventing the inflammation caused by amyloid beta proteins involved in Alzheimer’s disease, in addition to preventing cognitive impairment and loss of neuronal markers by preventing microglial activation that elicits the inflammation<sup>12</sup>. HU-210 is also a potent analgesic. This compound was first discovered in Spice Gold incense products seized at the US border in 2009 by U.S. Customs and Border Protection<sup>13</sup>. In 2010, the U.S. Drug Enforcement Administration used emergency powers to ban many synthetic cannabinoids due to concerns of a surge in emergency-room visits and calls to poison-control centers<sup>14</sup>. Adverse health effects associated with its use include seizures, hallucinations, paranoid behavior, agitation, anxiety, nausea, vomiting, racing heartbeat, and elevated blood pressure. International attention focused on K2, after the suicide of an American teenager from Iowa, who shot himself in the head with a hunting rifle in 2010<sup>15</sup>. He reportedly had smoked K2 with friends approximately one hour before his death. In 2012, President Obama signed the Synthetic Drug Abuse Prevention Act of 2012 into law which banned synthetic compounds commonly found in SC, placing them under Schedule I of the Controlled Substances Act<sup>16</sup>.

Other compounds which appear to be highly popular are the ones known as CP-47,497 and JWH-018. JWH-018 is an analgesic chemical that acts as a full agonist with an affinity for the CB1 receptor five times greater than that of THC. It was synthesized by Dr. Huffman, an organic chemist at Clemson University who was studying analogues and metabolites of THC<sup>17</sup>. JWH-018 may cause intense anxiety, agitation, and, in rare cases (generally with non-regular JWH users), has been assumed to be the cause of seizures and

convulsions by inhibiting GABA neurotransmission more effectively than THC.

In Turkey, JWH-018 was initially given the street name “Bonzai” and swiftly spread across Turkey in a number of forms. The Turkish Monitoring Centre for Drugs and Drug Addiction (TUBİM) reports that the majority (89.7%) of SM-related offences have taken place in Istanbul and in the Marmara Region, which is the known entrance point of those substances from Europe to Turkey<sup>18</sup>.

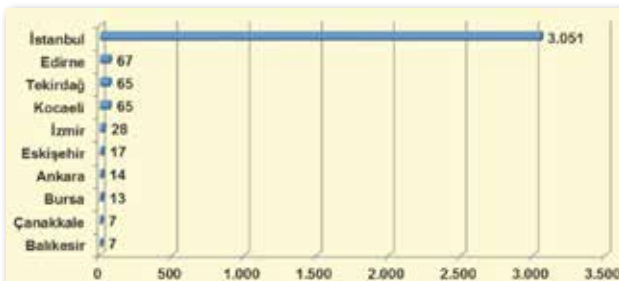


Figure 1: Top10 Locations of Synthetic Cannabinoid-Related Offences and the Number of Synthetic Cannabinoids Related Offences in 2012

### The Human Effects of THC vs SM Substances and Signs of Overdose

Herbal marijuana users usually experience a heightened mood or euphoria and relaxation soon after consumption (inhalation is faster than ingestion, as expected). In laboratory settings, the most common short-term physical effects are<sup>6,19</sup>:

- increased heart rate,
- lowered blood pressure
- muscle relaxation
- decreased intraocular pressure,
- reddening of the eyes

At higher doses, altered body image, auditory and/or visual hallucinations, and dissociative states have been reported. However, all those self-reported experiences are highly subjective and their intensity may differ between individuals.

Users of SM compounds usually report similar, but more intense, symptoms than those that occur with herbal marijuana. In point of fact, because there is no clinical study available in the current medical literature, the reports are all anecdotal, or

from the internet drug blogs of individuals sharing their experiences with these compounds. In those blogs, there is no consensus among users since there are many different blends and mixture of substances. Some users report that smoking SM products will produce a high similar to smoking marijuana, but it doesn't last as long. Some others felt a relaxed feeling, rather than the “head high” that herbal marijuana produces. None of the herbal smoking blends reviewed got great marks for taste, and they were found to be more “harsh” than herbal marijuana since they “make your throat burn and your lungs ache” long after you smoke them.

SM abusers who have been taken to emergency rooms report severe, life-threatening symptoms that include<sup>10,19</sup>:

- Severe agitation and anxiety
- Fast, racing heartbeat and higher blood pressure
- Nausea and vomiting
- Muscle spasms, seizures, and tremors
- Intense confusion, hallucinations and psychotic episodes
- Suicidal and other harmful thoughts and/or actions.

A group of users have described an instant panic attack in which they suddenly fall into an intense fear that they are going to die from a heart attack or stroke at any moment. The experience at first begins with a slight tingling which varies depending on the SM varieties in the potpourri, covers all the body, gets out of control with the accelerated heartbeat, and reaches a point where there is no hope to continue with life. Users describe this experience as if they came to the brink of death or a “*death trip*”.

Psychotic symptoms are also common after use and can precipitate psychosis in vulnerable individuals. A survey regarding the use and effects of SM in 15 patients with serious mental illness in a New Zealand forensic and rehabilitative service revealed that 69% of users experienced or exhibited symptoms consistent with psychotic relapse after smoking JWH-018<sup>20</sup>.

Dr. Huffman, PhD, the chemist who

synthesized a SM compound for research purposes, once said that he couldn't imagine why anyone would try it recreationally because of its deadly toxicity. Nevertheless, the number of users is rapidly rising, and so are overdoses. The 2012 Drug Abuse Warning Network (DAWN) Report from the U.S. Substance Abuse and Mental Health Services Administration (SAMHSA) states that toxicity due to synthetic marijuana resulted in 11,400 cases of emergency room visits in 2010<sup>21</sup>. The state of New Hampshire has declared a state of emergency due to the increase in the number of emergency room visits for overdose from the synthetic drug<sup>22</sup>. Medical Centers admit individuals due to dangerously high blood pressure and pulse rate after smoking SM products. The American Association of Poison Control Centers (AAPCC)<sup>23</sup> responded to about 3,200 calls related to synthetic marijuana and bath salts. In 2011, that number jumped to more than 13,000 calls. Sixty percent of the cases involved patients 25 and younger.

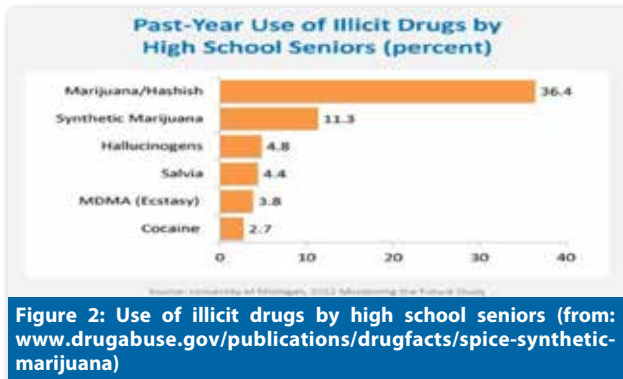


Figure 2: Use of illicit drugs by high school seniors (from: [www.drugabuse.gov/publications/drugfacts/spice-synthetic-marijuana](http://www.drugabuse.gov/publications/drugfacts/spice-synthetic-marijuana))

According to the National Institute on Drug Abuse<sup>24</sup> SM products are popular among young people; of the illicit drugs most used by high-school seniors, they are second only to herbal marijuana. In a recent survey of 1080 individuals between 18-25 years old, 9% reported SC use in the last month, a level higher than the reported use of opioids, cocaine, or hallucinogens<sup>25</sup>. SC use was significantly associated with male gender, not being enrolled in school, and with use of cigarettes, binge alcohol drinking, daily and weekly marijuana use, and other drugs of abuse.

Easy access and the misperception that SM products are "natural" and therefore harmless have likely contributed to their popularity. Another selling point is that the chemicals used in potpourris are not easily detected in standard drug tests. A recent study has reported that 20,017 randomly collected urine samples of US military personnel yielded 290 confirmed positive specimens (prevalence 1.4%), from 11 parent synthetic cannabinoids<sup>26</sup>. Compared to marijuana, SM exposures were more likely to be used through inhalation, to involve adults, to be used at a residence, and to result in serious outcomes<sup>27</sup>.

### SM Compounds are More Toxic Than Herbal THC

The endocannabinoid system is the target of naturally occurring endocannabinoids and herbal THC, as well as SM compounds which bind to the same cannabinoid receptors in the brain and peripheral organs and possess similar pharmacological properties. The current literature demonstrates that CB1 receptors are abundant in the brain; specifically in the mesocorticolimbic system, the spinal cord, and the peripheral neurons. CB1 receptors are particularly concentrated on gamma-aminobutyric acid (GABA) – releasing neurons (inhibitory neurons). Hence, activation of CB1 leads to retrograde suppression of neurotransmitter release. CB2 receptors are located peripherally, with a high density on immune-modulating cells and activated microglial<sup>6,7</sup>.

Although SM compounds exert their effects via the same cannabis receptors the individual experiences and clinical observations are totally different, as discussed earlier. While herbal marijuana users usually appear euphoric, interactive, mellow, and funny, individuals who use SC compounds present in a totally different clinical picture. They are angry, irritable, sweaty and agitated, similar to those under the influence of cocaine or amphetamines. One explanation would be that these compounds are structurally

different. While they stimulate CB receptors their affinity for the receptors and their potencies are much higher compared to endogenous or herbal cannabinoids. According to an article from the Huffman group, these new compounds bind to the CB1 receptor with a higher potency than naturally-occurring THC<sup>17</sup>. Unlike THC, which binds with almost equal affinity to CB1 and CB2 receptors, the new compounds exhibit more preference for CB1 receptors, which may produce more potent effects. Additionally, when consumed, herbal marijuana releases around 70 other cannabinoid chemicals, which may influence or balance the net effect of THC. For example, cannabidiol (CBD), another cannabinoid in herbal marijuana known for its anxiolytic and antipsychotic properties, could offset some of the anxiogenic and stimulant effects of THC<sup>28,29</sup>; its possible use has been discussed in length in our previous article<sup>30</sup>. The direct effect of a CB1 agonist without the other chemicals present would be expected to create more potent effects.

In addition to the severity of these toxic effects, some researchers report longer-lasting residual symptoms with SM compounds. Rominger et al. showed substantial short-term alterations of dopamine D2/3 receptors in a heavy user patient before and after acute detoxification from SM<sup>31</sup>. Some researchers describe a dependence syndrome for SMs corresponding to the ICD-10 and DSM-IV criteria since the clinical symptoms and physical withdrawal syndrome closely resemble that seen in cannabis dependence<sup>32</sup>. The extended effect of these compounds may be due to the fact that deactivation of SM may create other active metabolites which follow the effect of the mother compound, causing long term damage to the brain and other organs. The synthetic metabolites seem to retain full activity relative to the parent compound and bind to the receptor just as well as the drug itself<sup>26</sup>. Furthermore, there may be a delay in the metabolism and excretion of the SM compounds and their metabolites since SM compounds can cause renal damage in previously healthy men. It has been reported that

several SM users developed acute tubular necrosis confirmed by renal biopsies<sup>33</sup> and that their renal functions improved eventually with supportive treatment.

Several other health implications of these designer drugs have also been reported in case reports. Acute MI was diagnosed in young individuals within days after the use of K2. Since the incidence of ST-elevation MI is low among teenagers, an association with the drug use was suspected<sup>34</sup>. Acute cerebral infarctions were also reported in 2 young, previously healthy individuals with use of "spice"<sup>35</sup>. The imaging of both patients suggested an embolic etiology, which is consistent with reports of serious adverse cardiac events with "spice" use, including rhythm abnormalities and myocardial infarctions. A case report presents a case of idiopathic thrombocytopenia secondary to K2 usage which was attributed to the effects of SM on CB receptors on immune cells and thrombocytes<sup>36</sup>. All authors concluded that public education and awareness need to be heightened about the possible health implications of SMs.

### **Detection of SC Compounds in Biological Fluids**

In regular immunoassay drug tests, SM compounds do not cause a positive drug test for marijuana or other illegal drugs<sup>37</sup>, preventing their use in large scale drug screening programs. Being undetectable by conventional drug screening tests makes these chemicals more attractive to some individuals who are interested in "legal highs". Recently, it has been reported that JWH-018 can be detected in urine samples using "spice" screening immunoassays focused on both the parent drug and its omega-hydroxy and carboxy metabolites<sup>38</sup>. A novel liquid chromatography-tandem mass spectrometric (LC-MS/MS) method for simultaneously quantifying 20 synthetic cannabinoids and 21 metabolites in urine has been under development<sup>39</sup>. There is also a K2 / Spice Single Test Strip<sup>40</sup> available in the market; however, its reliability is unknown.

## Treatment of SM Intoxication and Abuse

Published case reports in general have demonstrated varying degrees of catatonia, an elevated heart rate, agitation, anxiety, dizziness, headaches, excessive sweating, slowed speech, and confusion. It has been observed that patients recovered to normal function in three to four hours, unless there was a major cardiac or other life-threatening condition<sup>10</sup>. Panic, anxiety, and catatonia may require treatment with benzodiazepines, where agitation and psychosis respond to antipsychotics and further observation. Intravenous fluids, oxygen and supportive care would help individuals to recover faster. Several metabolic abnormalities such as hyperglycemia, elevated creatinine, and elevated white blood cell count were also reported which may require further assessment to assure medical stability. Withdrawal phenomena and dependence syndrome after the consumption of “spice gold” was also reported<sup>32</sup>; however, there is no specific addiction or detoxification treatment available or necessary for the SM compounds.

## CONCLUSION

The demand for a “legal high” has been great in recent history which has set the stage for the synthetic drug market to take off. SM compounds have the ability to induce strong marijuana-like psychoactive effects, and they are readily available on the Internet marketed as natural, safe substances. SM products are particularly appealing to young and drug-naïve individuals seeking new experiences. Being undetectable by routine drug screening tests makes these drugs very popular among people who wish to avoid legal or social consequences. Medical and legal teams have difficulty keeping up with the production speed and variety of these compounds

### Synthetic Marijuana Pearls

- Synthetic marijuana does not contain marijuana, and is not a marijuana alternative
- SM is functionally, but not structurally related to THC,
- A lab-made chemical is dissolved in a liquid then sprayed on plant potpourri, labelled “Not for human consumption”
- The mixture is then smoked in cigarettes or inhaled from a device called a “kova”
- Consumption causes severe mental, behavioral and medical problems which could be lethal
- SM is not detectable in routine drug screening
- SM is very popular among young people who are seeking different experiences
- Almost nothing is known in terms of pharmacology, toxicology, safety, and treatment

and almost nothing is known in terms of pharmacology, toxicology, and safety. By the time one compound is made illegal, dozens of other iterations of the synthetic compound are already formulated and poised for release into the market. However, a recent survey showed that there was a significant decrease in SC use after the federal ban in the U.S. in July, 2012<sup>41</sup>, which supports the importance of legal regulations. A decrease in the illicit market is expected as a result of listing of a new psychoactive substance in the controlled substance list<sup>42</sup>.

While legal regulations should implement strict regulations, a public health message should be delivered to those individuals that SMs are not safe alternatives to marijuana and they can be lethal. According to the narcotics division of police there were 16 SM-related incidents reported in 2011 which resulted 116 arrests. This number climbed to 94 incidents and 206 arrests in the first half of 2014<sup>3</sup>. This rise indicates that the use of these compounds is spreading in our country, and they are posing a major risk to public safety which warrants immediate actions in the legal, social, medical and educational fields in limiting the supply and preventing the demand for these substances.

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