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DETECTION OF SYNTHETIC CANNABINOIDS IN URINE: MODERN ANALYTICAL METHODS AND LABORATORY PRACTICES

Urmantayev A.T.

Institute of Forensic Examination in the Turkestan Region Republican State Budgetary Enterprise Center of forensic examination of the Ministry of Justice of the Republic of Kazakhstan, Turkestan, Kazakhstan

The article presents a comprehensive review of modern approaches to the detection of synthetic cannabinoids and their metabolites in urine, taking into account both the pharmacochemical characteristics of these compounds and the analytical methods used for their identification in forensic chemical and clinical toxicology. The key differences between natural cannabinoids and their synthetic analogues are summarized, including features of chemical structure, mechanisms of interaction with cannabinoid receptors, as well as the nature of cognitive, behavioral, and physiological effects. Special attention is paid to modern immunochromatographic test systems used at the stage of primary toxicological screening for synthetic cannabimimetic metabolites in urine. Their analytical sensitivity, specificity, and diagnostic limitations are analyzed, which are largely due to the rapid expansion of new psychoactive substances and the structural variability of synthetic cannabinoids. Modern confirmatory analytical methods-gas chromatography–mass spectrometry (GC-MS) and liquid chromatography–tandem mass spectrometry (LC-MS/MS)-are discussed in detail. Key stages of biological sample preparation are described, along with analytical challenges associated with the identification of low-concentration and thermolabile compounds. A critical evaluation of analytical strategies aimed at improving the accuracy, reproducibility, and diagnostic significance of laboratory results is provided, taking into account the continuous emergence of new structurally modified synthetic cannabinoids.

Keywords: *synthetic cannabinoids, immunochromatography, chromatography–mass spectrometry, urine, metabolites, new psychoactive substances, quantitative analysis, toxicological screening.*

1.Introduction

Cannabis is the most affordable drug in the world [1, 2]. According to the UN Office on Drugs and Crime (UNODC), about 4% of the adult population of the world has used cannabis at

Correspondence address: Urmantayev Aidarali Tursinaliyevich, Institute of Forensic Examination in the Turkestan Region Republican State Budgetary Enterprise "Center of forensic examination of the Ministry of Justice of the Republic of Kazakhstan", Kyzylorda highway, building 14D, Turkestan, Republic of Kazakhstan. 161200, e-mail: aidar_ali@bk.ru, turkestan-cse@mail.ru

least once in their life. The therapeutic use of cannabis and its derivatives is rapidly expanding and has been considered for the treatment of various health conditions, such as; multiple sclerosis, muscle cramps, nausea during chemotherapy, to improve appetite in AIDS patients, as well as against chronic pain and muscle cramps, and in certain forms of cancer t [3, 4]. The primary psychoactive component of cannabis is Δ-9-tetra-hydro-cannabinol (THC), which interacts with the CB1 and CB2 receptors; this interaction causes the main psychotropic effects [5, 6]. New psychoactive substances (NPS) that contain synthetic cannabinoids (SC) have recently been used for recreational purposes [7, 8]. The psychotropic effects of SC may be similar to those experienced with cannabis, but they are more unpredictable and severe than those related to cannabis [7, 9, 10]. Reported side effects associated with the use of SC are; impaired coordination, paranoia, severe anxiety, convulsions, vomiting, confusion, heart rhythm disturbances, and nausea [1, 2, 7].

Since 2004, manufacturers of illicit drugs began to produce herbal mixtures under various brands, for example, “Spices” and “K2” [11]. They started entering the European market in 2006 [12]. Chemical additives are sprayed on any dried plant material and consumed to achieve psychoactive effects. To circumvent regulatory barriers, These products, have been soldin many countries as incense, or as products suitable for aromatherapy not for human consumption [13]. In most cases these preparations come without a declaration of ingredients, and even when a c a list of ingredients is provided, the content of the SC is not indicated [14]. SC were first registered in Germany for recreational use in December 2008, and forensic experts discovered several synthetic cannabinoids (SC) in such herbal mixtures [15]. They were identified in smoking blends sold as herbs sprayed or mixed with one or more synthetic compounds under different names (e.g. Spice, Yucatan, Cold, K2 or Black Mamba). They could be easily purchased for several years online, at petrol stations, or in “head stores” [16]. In 2008, the media in Germany claimed that these products were a “legitimate” alternative to marijuana, but could not be detected using common drug tests [17]. The most frequently detected compounds in the first generation of Spice products were CP-47,497 and the JWH series [18], named after John William Huffman, a professor at Clemson University. He first synthesized them in the laboratory during the 1990s when studying human endocannabinoid receptors and he was evaluating their potential use as therapeutic [19]. Since then, the types of Spice and new SC have been constantly increasing. SC can cause severe toxicity and, as such, the development of analytical methods for the detection of these compounds in various biological matrices is very important for clinical and forensic purposes. However, for the detection of SCs and metabolites in biological samples, the use of conventional drug screening tests, is difficult because SCs is structurally different from delta-9 tetrahydrocannabinol (THC), [20, 21]. The development of analytical methods for synthetic cannabinoids in biological samples is a problem not only for forensic examination in Kazakhstan, but throughout the world for several reasons; the lack of available reference materials, low concentrations of synthetic cannabinoids in the body and the similarity of

structures of various metabolites, which may complicate the work of forensic experts. This article evaluates the progress made to date towards the analysis of synthetic cannabinoids and their metabolites in urine samples. The most promising methods that could be implemented in Kazakhstan are also considered.

2.Pharmacochemical properties of synthetic cannabinoids

Synthetic cannabinoids are called synthetic substances that are able to interact with one of the famous cannabinoid receptors - CB1 or CB2, which are present in human cells. They cause psychotropic effects similar to the action of delta-9-tetrahydrocannabinol (hereinafter - Δ9-THC) - cannabis alkaloid [22, 23]

The CB1 receptors are located mainly in the brain and spinal cord and are responsible for the characteristic physiological and psychotropic effects of cannabis. This explains the variety of effects produced by marijuana. Its main psychoactive effect is due to the influence of Δ9- THC on the cerebral cortex. Memory impairment in marijuana users occurs due to the effect of Δ9-THC on the hippocampus. The effect on the motor functions develops as a result of the impact of Δ9-THC on the motor centers [24].

The CB2 receptors are mostly located in the spleen and on cells of the immune system; this explains their immunomodulatory effect. Binding of synthetic cannabinoids to cannabinoid receptors can cause (partial) agonistic, inverse agonistic or antagonistic effect. For drug treatment practices are of interest exhibiting high affinity and full agonistic activity to CB1 receptors (Table 1) [24].

Table 1.

Differences between pharmacological and toxic effects of natural and synthetic cannabinoid

Natural cannabinoids (NC)	**Synthetic cannabinoids (SC)**
Partial agonists of cannabinoid receptors CB1 and CB2	Complete agonists for cannabinoid receptors CB1 and CB2
Cannabinoid tetrad (hypothermia, analgesia, catalepsy, motor suppression activity) is least pronouncedin the following order: JWH-018> JWH-073> Δ9-THC [24].	Cannabinoid tetrad most expressed in the following order: JWH-018> JWH-073> Δ9-THC.
Metabolic products are inactive	Metabolic products are substantially active, in some cases they can act as inverse CB1 agonists.

Sympathomimetic activity moderate	Sympathomimetic activity is 2-3 times higher than natural cannabinoids
Ability to cause hallucinations - with overdose (hallucinatory-delusional syndrome as a manifestation of overdose)	Ability to cause hallucinations - 5 times higher than that of Δ9-THC (hallucinatory-delusional syndrome as a manifestation of acute intoxication)
Antiemetic effect	Nausea, vomiting
Anxiolytic) effect	Anxiety

3. Analytical methods for synthetic cannabinoid detection

The SCs cannot be detected by the conventional screening methods used for Δ9-THC. Cannabinoids are not detected with standard immunochromatographic tests employed for narcotic substances [25, 26, 27, 28]. A state of intoxication can be caused by ultra-low doses of a substance therefore, detectability is directly related to the sensitivity of the method used. Specialized gas chromatographic and mass spectrometric methods have been developed for the identification of both intact SCs and their products rapid metabolism in the human body.

There are a number of difficulties associated with the identification of the composition of synthetic cannabinoids. These include but are not limited to: lack of samples for comparison, constant composition change in response to the introduction of prohibitive measures, and the extensive use by the manufacturer of masking agents of natural origin such as tocopherol (vitamin E), eugenol or fatty acids [29]. Smoking mixtures are expected to contain at least 15 different herbal ingredients. Different combinations of this ingredients give a wide range of different product that can cause different effects. There is no doubt that understanding the clinical pharmacology aspects of these of psychoactive substances is key in assessing the toxicity and the effects produced by these substances [30, 31, 32, 34]. Significant progress in determining the chemical composition of smoking mixtures have been made through the use of gas chromatography methods coupled to mass spectrometry detection (GC-MS) [22, 34].

One of the emerging problems with the recognition of synthetic cannabinoids in biological matrices is the constant development of new synthetic cannabinoids, because new drugs cannot be detected using existing analytical methods [35].

Non-target screening provides a more suitable approach for analyzing known or unknown SCs. Much work has been done to develop fast, high-resolution MS screening methods that can be updated more quickly with the help of new drugs with untargeted detection of all ions to fit the constantly changing menu of detectable drugs. For non-targeted screening of synthetic cannabimimetics in urine, a method has been proposed, based on the fact that during the exchange substances are formed metabolites, having in their based on the same basic structure as the original substance. Knowing the mass of the latter, as well as the main possible metabolic pathways can be considered a set of molecular and pseudomolecular ions of metabolites and,

based on the initial, basic structure of the analyte, we can assume some common ions-products and calculate their exact mass. In order to reduce the number of probable candidates, the accuracy of the determined masses can be used: for stretched molecules, the permissible difference in masses is 10 ppm, and for product ions, no more than 20 ppm. A prerequisite for this screening option is the presence of common ions [36, 37, 38].

Urine is one of the most common matrices used in drug testing because of the sample volume, high drug concentrations, and longer drug detection interval compared to blood and oral fluid. New SCs can be identified in blood and oral fluid if the testing laboratory has access to structural information and makes use of an untargeted analytical approach. However, the ability to detect these potent drugs is limited, so it is important to identify metabolites of the urinary marker as targets. In forensic and clinical cases of SC, urine samples are hydrolyzed with b-glucuronidase to increase sensitivity to the total concentration of SC, and the characteristic metabolites of phase I are selected as metabolites of urinary metabolites to confirm SC intake. Most ICs are released as glucuronides or sulfates after metabolism of phase II. In addition, phase II glucuronides and sulfates are not as stable as phase metabolites and can be spontaneously converted into the corresponding glycones [36].

3.1 Sample preparation.

In the study, sample preparation was carried out as follows. The deconjugation of phase II metabolites was performed by acidic and enzymatic methods. With acid deconjugation to 2.5 ml of urine 0.25 ml of hydrochloric acid (conc.) was added and heated for 60 minutes at temperature is 90–95°C. The mixture was extracted with chloroform (3 ml), centrifuged and the separated organic phase was evaporated to dryness in a stream of nitrogen at a temperature not higher than 45°C. With enzymatic deconjugation to 2.5 ml 50 µl of β-glucuronidase and 1 ml of phosphate buffer (0.8 M, pH 5.5) were added to urine. The mixture was incubated at 37°C for 24 hours. The subsequent steps were the same, as with acid deconjugation. The dry residue was dissolved in 100 µl of phase A (for LC-MS / MS) or (for GC-MS) was derivatized by trimethylsilylation or methylation.

Trimethylsilyl (TMS) derivatives were obtained in 50 µl of a mixture of ethyl acetate and BSTFA (1:1 by volume) at 50°C for 30 min. For methylation (Me) residue dissolved in a mixture of dry dimethyl sulfoxide (100 µl) and hydroxide tetramethylammonium (5 µl) with continuous stirring for 2 min, after which 20 µl methyl iodide was added and mixed again for 10 minutes. Then an aqueous solution of ammonia (0.1 M, 2 ml) was added and extracted with ethyl acetate (3ml) The separated organic phase was washed with 2 ml of ammonia solution of the same concentration and evaporated to dryness. The residue was dissolved in 50 µl of ethyl acetate and injected into the chromatograph.

3.2 GC-MS.

For the detection and identification of metabolites the same study used 6890 gas chromatographs coupled to 5975VL single-quadrupole mass spectrometers (Agilent Technologies, Santa Clara, USA). Separation was performed using columns: weakly polar HP-5ms (30 m × 0.25 mm × 0.25 μm) and mid-polar DB-5ms (15 m × 0.25 mm × 0.25 μm) operating in three gradient modes. All three programs had the same initial stages: 50 ° C (0.5 min), 99°C / min (100°C, 1 min) and differed in the next two (Table 2).

Table 2.

The final stages of the temperature program of two columns for three modes

Mode No.	Column			
	HP-5ms		DB-17ms	
	Rise, °C / min	Plateau, ° C	Rise, °C / min	Plateau, ° C
1	15	280	9	280
2	35	300	20	300
3	60	320	40	320

The injector and interface temperatures were 270°C and 290°C, respectively. Samples (0.2 μl) were injected without being split (splitless), carrier gas helium (1ml / min). Mass spectra were recorded by electron impact ionization (70 eV), the ion source and quadrupole temperatures were 230 °C and 150°C, respectively.

3.3 LC-MS / MS.

Liquid chromatography-mass-spectrometric measurements performed using a 1200 microflow chromatograph with a Zorbax column Eclipse XDB-C18 (2.1 × 150 mm, 3.5μm, 40°C) associated with a 6460 tandem (three-quadrupole) mass spectrometer (Agilent Technologies). Divisions carried out in a gradient mode with mobile phases A (ammonium formate, pH 5, 20mM) and B (acetonitrile) according to the following program: 40 vol.% of phase B (1 min); linear gradient to 90 vol.% of phase B (15 min) with preservation of the composition for 4 min The flow rate is 0.25ml/min, the volume of the injected sample is 5μl. Mass spectra recorded in the mode of positive electrospray ionization; drying gas nitrogen, 300 ° C (7 l/min). The voltage on the capillary tip and the fragmenter was 3500, 500 and 80V, respectively; collision energy 20V.

3.4 Discussion

In fig. 1 shows the structural formulas considered cannabimimetics and their metabolites. The main directions of metabolism JWH-018 and JWH-073 are considered in [39-44] (Fig. 1). In most cases monohydroxylated forms (M6) are characterized by the highest content, whose hydroxyl

groups are located on (ω-1) -th carbon atoms side N-alkyl chains. To detect these forms most convenient the method of derivatization is trimethylsilylation [39, 41, 45].

Dealkylated hydroxylated metabolites (M1-M4) were initially detected in urinary samples in significant concentrations for the case of JWH-018 [39, 45]. In their structures, hydroxyl groups can be in different positions of the indole and naphthalene residues.

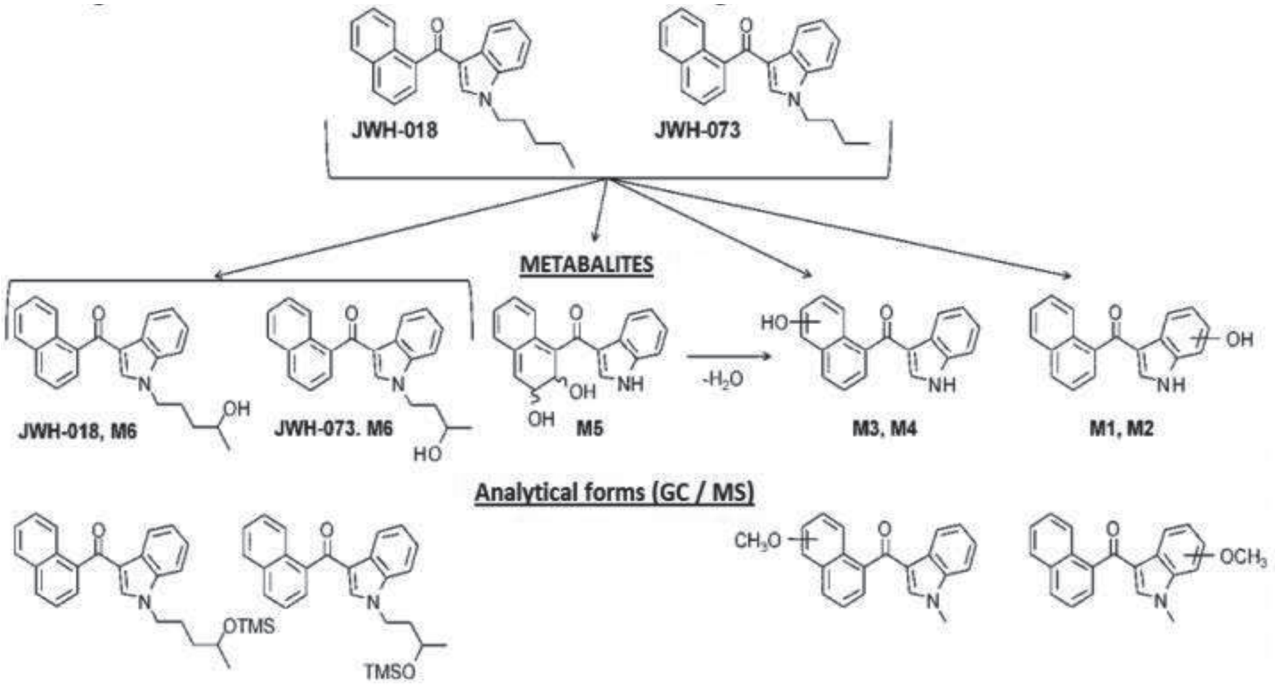

Fig. 1. Major metabolites JWH-018 and JWH-073 and their analytical forms (GC-MS)

According obtained with the method reported in 3.1, 3.2 and 3,3, the metabolite dihydrodiol M5 can only be detected after enzymatic deconjugation of urine samples using glucuronidase (apparently, as a result of epoxidation and subsequent hydrolysis naphthalene residue [46]. In addition, acid hydrolysis of M5 leads to dehydration, and, as a result, to the formation of M3 and M4. Since it is currently unknown if compounds M3 and M4 are products of enzymatic hydrolysis of M5 in vivo, or they remove water as a result of spontaneous non-enzymatic processes, then these compounds can be considered as metabolites and forms artifacts, or their mixture. For simplicity, the M3 and M4 connections following presentation will be referred to as metabolites [45].

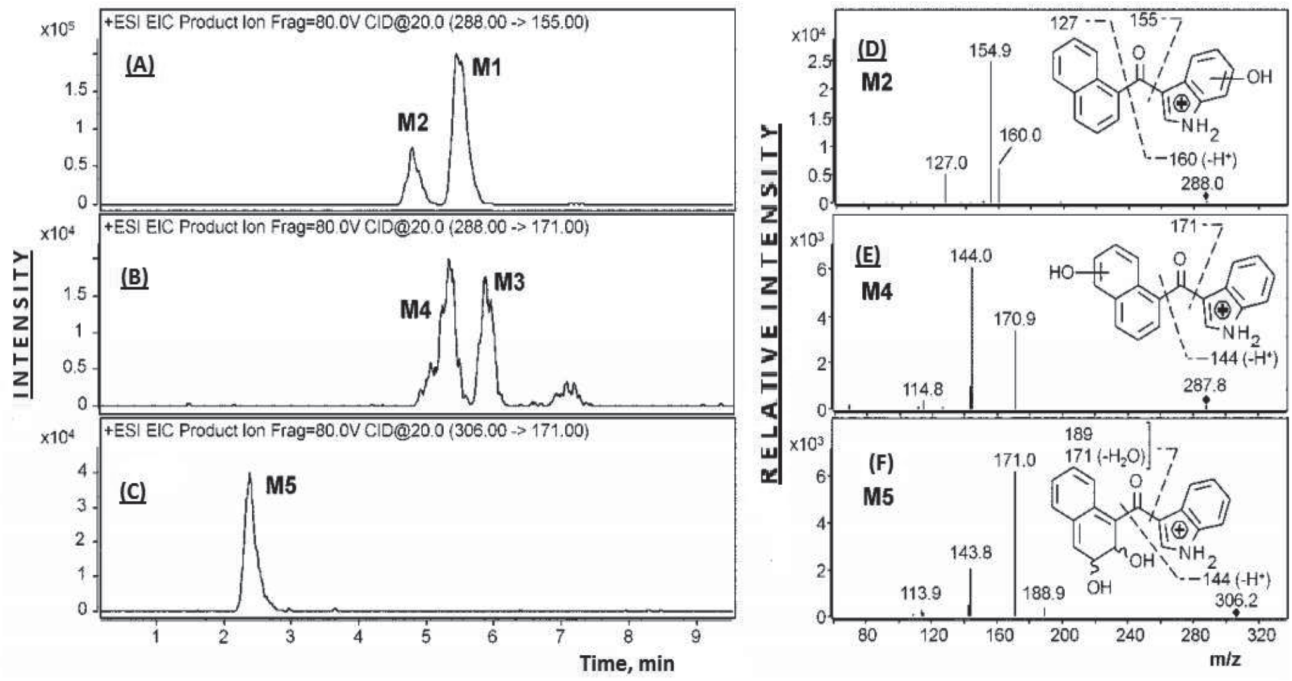

Fig. 2. Ion chromatograms (LC-MS/MS) of dealkylated extracts metabolites JWH-073 (A-C), enzymatic deconjugation. Mass spectra main products and fragments of protonated dealkylated structural Metabolites (D-F)

Fragmentation of protonated metabolites M1-M5 results in the cleavage of the bond between the carbonyl group and the aromatic residues, as well as (for M5) in the dehydration of the dihydrodiol derivative. As shown in fig. 2A-C the amount observed for the M3 and M4 metabolites is slightly less than M1, M2 andM5.

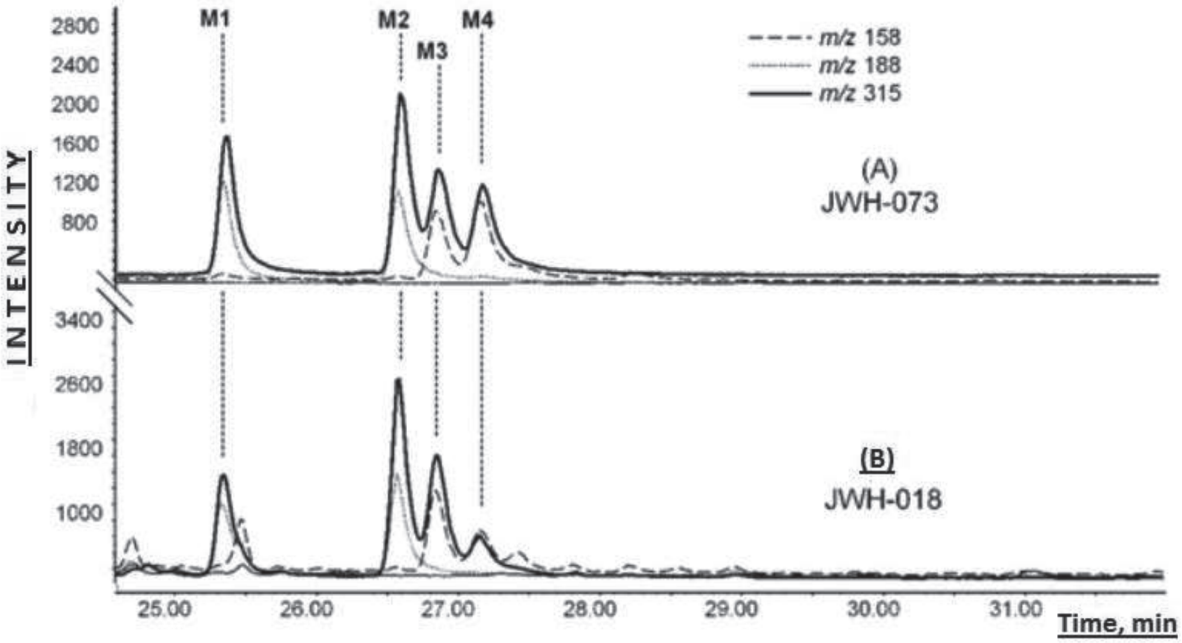

Fig. 3. Ion chromatograms of extracts (SIM mode, GC-MS) methylated metabolites M1-M4 in urinary specimens positive for JWH073 (A) and JWH-018 (B). Acid Deconjugation, HP-5ms column

The reliability of detection of metabolites is determined, in particular, by their concentration in the urine samples (which is strictly correlated to the time of sampling after smoking), as well as by the dose and the smoker's physiological characteristics (Fig 3).

Conclusions

Synthetic cannabinoids are the fastest growing and the most popular among new psychoactive substances not only in Kazakhstan, but throughout the world. Forensic toxicology laboratories involved in the analysis of synthetic cannabinoids and their metabolites are under increasing pressure to develop reliable detection methods. The everchanging structure of synthetic cannabinoids, and the availability of new species on the market, create great difficulties for forensic experts to identify these drugs in in biological matrices. Several methods have been investigated in this article for the analysis of synthetic as cannabinoids The GC-MS and LC-MS / MS methods showed the identification of four dealkylated monohydroxylated urinary metabolites JWH-018 and JWH-073 with their chromato-mass-spectrometric characteristics. A cost-effective method for determining the use of synthetic cannabinoids using the example of JWH-018 and JWH073 without the possibility of their differentiation is proposed. The method is based on the detection of dealkylated metabolites in the urine of smokers by GC-MS method after sample preparation, including acid deconjugation and synthesis of methyl derivatives. In this method, compared with the method for determining trimethylsilyl derivatives, there is some decrease in sensitivity, however, its advantage is that there is no need to use silylating derivatizing agents that cause the modification of stationary phases to detect a number of synthetic cannabimimetics and their metabolites in biological objects.

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ВЫЯВЛЕНИЕ СИНТЕТИЧЕСКИХ КАННАБИНОИДОВ В МОЧЕ: СОВРЕМЕННЫЕ МЕТОДЫ, АНАЛИТИЧЕСКИЕ ПОДХОДЫ И ЛУЧШИЕ ЛАБОРАТОРНЫЕ ПРАКТИКИ

Урмантаев А.Т.

В статье представлен комплексный обзор современных подходов к выявлению синтетических каннабиноидов и их метаболитов в моче, учитывающий как

фармакохимические особенности данных соединений, так и аналитические методы их обнаружения в судебно-химической и клинической токсикологии. Обобщены ключевые различия между природными каннабиноидами и их синтетическими аналогами, включая как особенности химической структуры, механизмы взаимодействия с каннабиноидными рецепторами, так и характер когнитивных, поведенческих и физиологических эффектов. Особое внимание уделено современным иммунохроматографическим тест-системам, применяемым на этапе первичного токсикологического скрининга синтетических каннабимиметических метаболитов в моче. Проведён анализ их аналитической чувствительности, специфичности и диагностических ограничений, обусловленных быстрым обновлением спектра новых психоактивных веществ и структурной вариабельностью синтетических каннабиноидов. Подробно рассмотрены современные методы подтверждающего анализа - газовая хроматография–масс-спектрометрия (GC-MS) и жидкостная хроматография-тандемная масс-спектрометрия (LC-MS/MS). Освещены ключевые этапы пробоподготовки биологических образцов, а также аналитические трудности, связанные с идентификацией низкоконцентрированных и термолабильных соединений. Проведена критическая оценка аналитических стратегий, направленных на повышение точности, воспроизводимости и диагностической значимости результатов лабораторных исследований, с учётом постоянного появления новых структурно модифицированных синтетических каннабиноидов.

Ключевые слова: *синтетические каннабиноиды, иммунохроматография, хромато-масс-спектрометрия, моча, метаболиты, новые психоактивные вещества, количественный анализ, токсикологический скрининг.*

ՍԻՆԹԵՏԻԿ ԿԱՆՆԱԲԻՆՈԻԴՆԵՐԻ ՀԱՅՏՆԱԲԵՐՈՒՄԸ ՄԵԶՈՒՄ. ԺԱՄԱՆԱԿԱԿԻՑ ՎԵՐԼՈՒԾԱԿԱՆ ՄԵԹՈԴՆԵՐ ԵՎ ԼԱԲՈՐԱՏՈՐ ԼԱՎԱԳՈՒՅՆ ՓՈՐՁԱԳԻՏԱԿԱՆ ՊՐԱԿՏԻԿԱՆԵՐ

Ուրմանչեև Ա. Տ.

Հոդվածում ներկայացված է մեզում սինթետիկ կաննաբինոիդների և դրանց մետաբոլիտների հայտնաբերման ժամանակակից մոտեցումների համալիր ակնարկը՝ հաշվի առնելով ինչպես տվյալ միացությունների ֆարմակոքիմիական առանձնահատկությունները, այնպես էլ դրանց հայտնաբերման վերլուծական մեթոդները դատա-քիմիական և կլինիկական տոքսիկոլոգիայի շրջանակներում: Ամփոփվել են բնական կաննաբինոիդների և դրանց սինթետիկ անալոգների միջև առկա հիմնական տարբերությունները՝ ներառյալ քիմիական կառուցվածքի առանձնահատկությունները, կաննաբինոիդային ռեցեպտորների հետ փոխազդեցության մեխանիզմները, ինչպես նաև ճանաչողական, վարքաբանական և ֆիզիոլոգիական ազդեցությունների բնույթը:

Հատուկ ուշադրություն է դարձված ժամանակակից իմունոխրոմատոգրաֆիկ թեստային համակարգերին, որոնք կիրառվում են մեզում սինթետիկ կաննաբիմիմետիկ մետաբոլիտների

առաջնային տոքսիկոլոգիական սկրինինգի փուլում: Կատարվել է դրանց վերլուծական զգայունության, առանձնահատկության և ախտորոշիչ սահմանափակումների գնահատում՝ պայմանավորված նոր հոգեակտիվ նյութերի սպեկտրի արագ ընդլայնմամբ և սինթետիկ կաննաբինոիդների կառուցվածքային բարձր փոփոխականությամբ:

Մանրամասն քննարկվել են ժամանակակից հասպատող վերլուծական մեթոդները՝ գազային քրոմատոգրաֆ-մասս-սպեկտրոմետրիա (GC-MS) և հեղուկ քրոմատոգրաֆ-տանդեմ մասս-սպեկտրոմետրիա (LC-MS/MS): Լուսաբանվել են կենսաբանական նմուշների նախապատրաստման հիմնական փուլերը, ինչպես նաև այն վերլուծական դժվարությունները, որոնք կապված են ցածր կոնցենտրացիա ունեցող և ջերմազգայուն միացությունների նույնականացման հետ:

Քննադատորեն են գնահատվում այն վերլուծական ռազմավարությունները, որոնք ուղղված են լաբորատոր հետազոտությունների արդյունքների ճշգրտության, վերարտադրելիության և ախտորոշիչ նշանակության բարձրացմանը հաշվի՝ առնելով նոր կառուցվածքային մոդիֆիկացված սինթետիկ կաննաբինոիդների մշտական ի հայտ գալը:

Բանալի բառեր. *սինթետիկ կաննաբինոիդներ, իմունոխրոմատոգրաֆիա, քրոմատոմասս-սպեկտրոմետրիա, մեզ, մետաբոլիտներ, նոր հոգեակտիվ նյութեր, քանակական վերլուծություն, տոքսիկոլոգիական սկրինինգ:*

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