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Single-dose Acute Toxicity of 4-F-MDMB-BUTINACA Designer Cannabis Drug: LD50 and Histological Changes in Mice

Elkhatim H. Abdelgadir ElAmin[1], Renad H. F. Albloi[2], Abdulsallam Bakdash[3], Sachil Kumar[4]

[1,3,4]Assistant Professor, [2]Master Student, Department of Forensic Sciences, College of Criminal Justice, Naif Arab University for Security Sciences, Riyadh-Kingdom of Saudi Arabia.

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Abstract

The purpose of this research was to evaluate the single-dose toxicity of 4-F-MDMB-BUTINACA in Swiss albino mice using histopathological analysis of liver and kidney specimens.

The experimental protocol included oral treatment of mice with different doses (5, 50, 300, 2000 mg/kg body weight of 4-F-MDMB-BUTINACA) for 24 hours. At the end of the treatment, blood samples had been drawn, and renal and hepatic tissues have been excised from the experimental mice groups for histological examinations.

The results revealed that dose-dependent treatment with 4-F-MDMB-BUTINACA causes mild tremor clinical signs with low doses and photophobia (sensitivity to light) and even cessation of breathing as a potential cause of death with high doses in treated mice.

The LD_{50} value of 4-F-MDMB-BUTINACA was 32.60 mg/kg, which is considered as a chemical compound of low toxicity. Histological studies confirmed that liver and kidney toxicities have been manifested in the findings of congestion, necrosis, inflammation, and bleeding within the liver and to lesser extent in the kidneys.

Keywords: Forensic Toxicology; 4-F-MDMB-BUTINACA; Synthetic Cannabinoid; LD_{50}; Histopathol**ogy;** Mice.

Introduction

The vast majority of new psychoactive substances are synthetic cannabinoids (SCs).[1] SCs were published for the first time in Europe in the early 2000s. Between 2010 and 2011, the popularity of SCs in the USA has increased, and rates of poison control systems in the 2 years have accelerated by 240%.[2] A number of studies are increasing that associate SCs with acute behavioral and physiological effects. Numerous in vitro studies have also demonstrated high cytotoxicity in various cell types for some of SCs.[3-7]

Acute systemic toxicity is an assessment of adverse effects that occur on a known route (oral, dermal or inhalation) within 24h following exposure to a single or multiple dose of a test substance.[8] The test material is consumed and dispersed into different parts of the body until a systemic adverse effect is

Corresponding Author: Sachil Kumar, Assistant Professor, Department of Forensic Sciences, College of Criminal Justice, Naif Arab University for Security Sciences, Riyadh-Kingdom of Saudi Arabia.

Mobile: +966-570124971

Email: skumar@nauss.edu.sa

achieved after administration.[9] The regulatory body requires an acute toxicity test study to mark and classify human substances.[10-12]

J. W. Trevan developed the LD_{50} (median lethal dose) test in 1927 to measure the dose of a test drug that causes 50% mortality in a given species of animals. It is used to calculate the possible dangers of chemicals to humans.[13]

The acute toxic potential of substances must be assessed in order to ascertain the adverse effects that can occur as a result of unintended or intentional short-term exposure.[14] Based on the outcome of the acute toxicity test, the toxicity of the test drug can be determined. LD50 substances below 5 mg/kg are considered highly toxic whereas LD50 substances above 15,000 mg/kg are considered to be relatively inoffensive (Table 1).[15]

4F-MDMB-BUTINACA also known4F-MDMB-BINACA (Methyl 2-[[1-(4-fluorobutyl) indazole-3-carbonyl]amino]-3,3- dimethyl-butanoate) was first reported to the EMCDDA in November 2018. In 2019, the Institute of Forensic Medicine in Erlangen (Germany) analyzed three unlabeled, seized herbal blends and detected 4F-MDMB-BINACA as the active ingredient.

In spite of growing concern about the increased rates of 4F-MDMB-BUTINACA usage and its effects, there is a lack of information on how to cope with these problems. Consequently, the purpose of this study was to investigate the single-dose toxicity, and histopathological changes caused by4F-MDMB-BUTINACAin Swiss albino mice.

Materials and Methods

Drug Preparation and Animals

4F-MDMB-BUTINACA was purchased from Cerilliant (Round Rock, TX, USA). The drug was first dissolved in dimethyl sulfoxide (DMSO) (final concentration was 2%) and then taken to its final volume with corn oil. As a vehicle control, DMSO and corn oil were also used.

A total of 30 swiss albino male mice, aged 6 weeks and weighing approximately 20±25 g, were obtained from the Experimental Animal Care Center, King Saud University. The animals were maintained in climate-controlled rooms (23±2°C, relative humidity of 55±5%)with diurnal lighting (12:12-hour light: dark photoperiod) with free access to water and commercial pelleted diet (Saudi Grains Organization, Riyadh, KSA). Before starting the experiment, the mice were acclimatized to the laboratory atmosphere for 1week.

LD50 and Acute Toxicity Symptoms

The single-dose study was conducted in accordance with OECD 423 guidelines for testing of chemicals.[16] A total of 30 mice were divided into five groups, one of which was used as a control. Each group consisted of 3 males and 3 females.

In order to assess acute toxicity, five groups of mice were orally gavaged with 4-F-MDMB-BUTINACA at dosages of 5, 50, 300, and 2000 mg/kg body weight (bw) in a final volume of 0.25 mL. A control group received only vehicle control.

The mice were individually observed for their general behavior at 1, 2, 3, 5, and 24 h after treatment. The number of deaths within this period was recorded, and LD_{50} (the dose that kills 50% of animals) was determined according to the probit method (method of least squares) using the (Software Stat Plus) (Ver. 2015 Build 5.9.8.5 ©2015).

Necropsy was performed on all animals, and renal as well as hepatic tissues was preserved in 10% buffered formalin for histopathological analysis.

Histopathological Procedures

In an automated tissue processor (Tissue–tek VIP-5, from SAKURA), formalin-preserved hepatic and renal tissue samples from 4-F-MDMB-BUTINACA-dosed rats and the control group were processed. The tissues were then processed into paraffin wax blocks using standard procedures. Paraffin sections (4–5 µm) were stained with hematoxylin and eosin, the conventional staining technique.Stained sections were examined for histopathological changes.

Statistical analysis

The significance of variations between means was compared at every time point the use of Duncan's multiple range test (DMRT) after ANOVA for one-way classified data.[17]

Results

Acute toxicity symptoms and LD50

The administration of 4-F-MDMB-BUTINACA in low and high preload doses brought about

severe clinical symptoms, including tachycardia, convulsions, and difficulty in breathing. Further, an increase in locomotor activity of mice was also observed. Severe constriction and stiffness were observed for all muscles of the body. Similarly, narrowing of the eyes and prominent blood vessels in the ears were observed. There were deaths after dosage ranging from 1 to 24 h; however, the animals which survived exhibited normal behavior, similar to the animals in the control group. The toxicity was observed to be a dose-dependent phenomenon. The LD_{50} value was calculated to be 32.60 mg/kg bw (Table 1, Figure 1).

Table 1: Number of deaths by sex and dose for oral 4-F-MDMB-BUTINACA.

Gender	Dose mg/kg/ BD	Total	No. dead	Log of Dose	Mortality	Corrected Mort.	Probits
Male	2.5	3	0	0.398	0.00	8.33	3.625
	5	3	0	0.699	0.00	8.33	3.625
	50	3	1	1.699	33.33	33.33	4.33
	300	3	3	2.477	100.00	91.67	6.445
	2000	3	3	3.301	100.00	91.67	6.445
Female	2.5	3	0	0.398	0.00	8.33	3.625
	5	3	0	0.699	0.00	8.33	3.625
	50	3	2	1.699	66.67	66.67	5.44
	300	3	3	2.477	100.00	91.67	6.445
	2000	3	3	3.301	100.00	91.67	6.445
Combination	2.5	6	0	0.398	0	4.17	3.25
	5	6	0	0.699	0.00	4.17	3.625
	50	6	3	1.699	50.00	50.00	5
	300	6	6	2.477	100.00	95.83	6.445
	2000	6	6	3.301	100.00	95.83	6.445
Control M+F	0	6	0	0	0.00	0	0

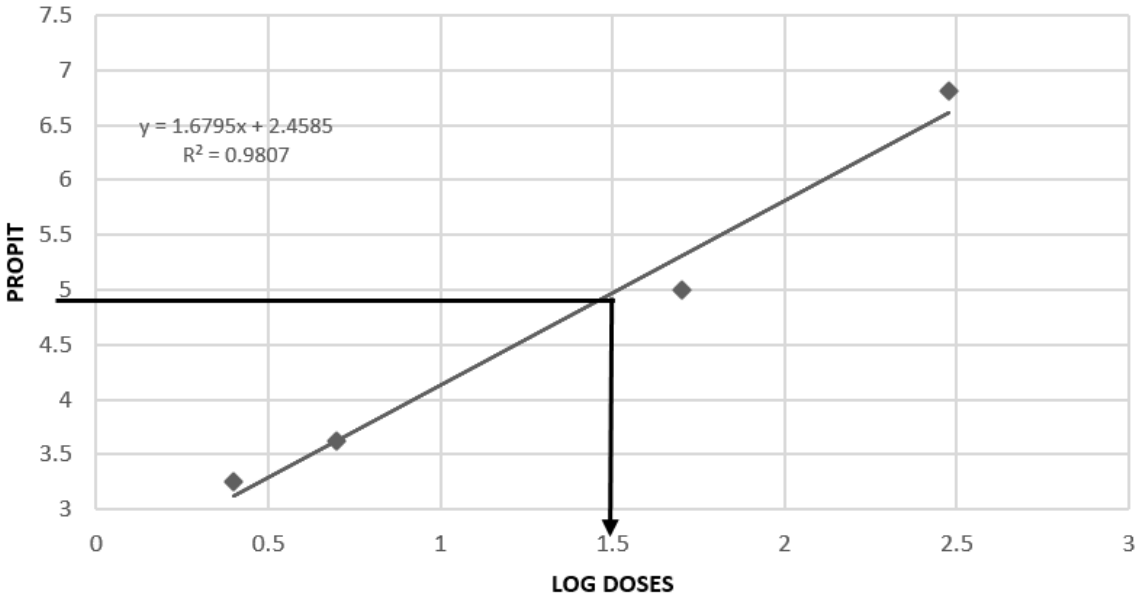

Figure 1: Curve graph for applying propite analysis to male and female mortality outcomes.

Figure 2: Photomicrograph of Liver(H&E-400X).

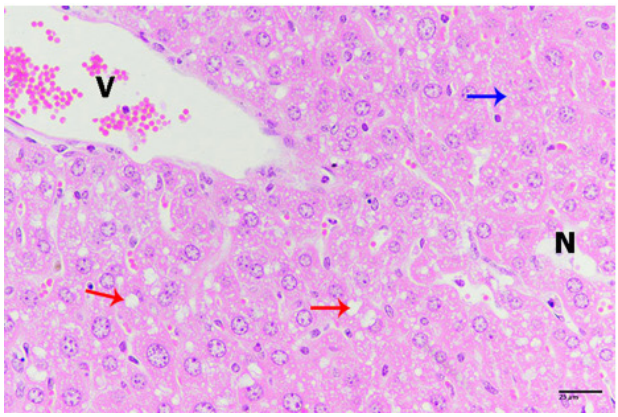

Figure 2a: Male mice liver treated with (5mg/kg) of 4-F-MDMB-BUTINACA.

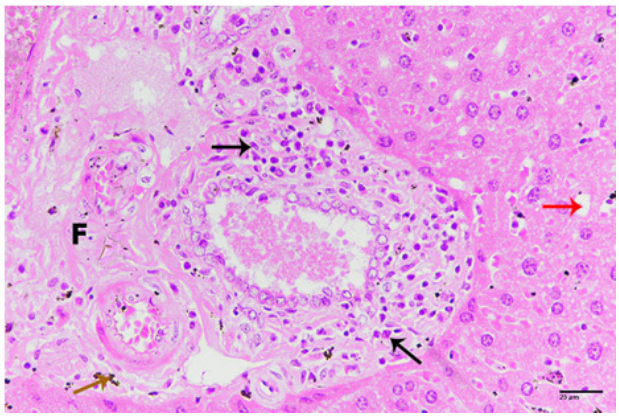

Figure 2b: Male mice liver treated with (50mg/kg) of 4-F-MDMB-BUTINACA.

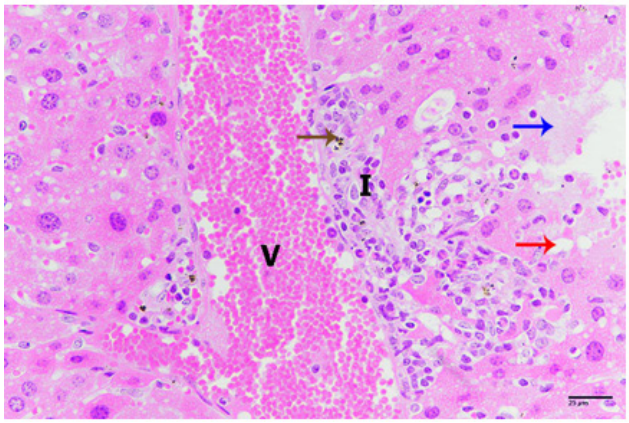

Figure 2c: Female mice liver treated with (300mg/kg) of 4-F-MDMB-BUTINACA.

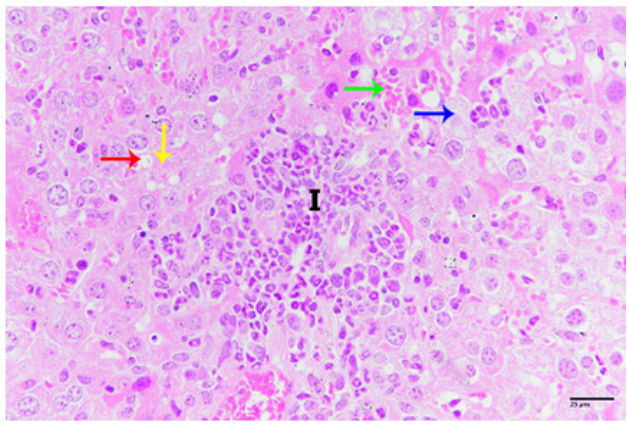

Figure 2d: Female mice liver treated with (2000 mg/kg) of 4-F-MDMB-BUTINACA.

Figure 3: Photomicrograph of Renal(H&E-400X).

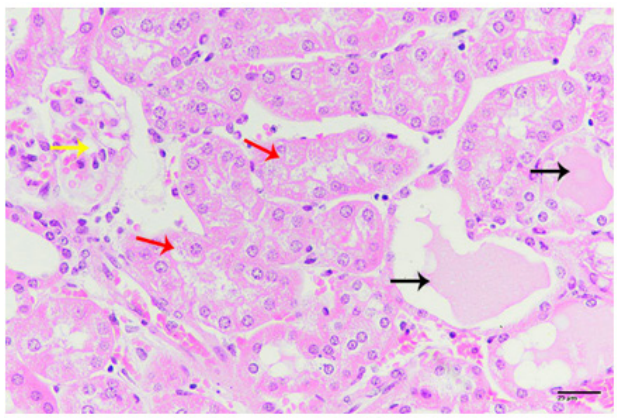

Figure 3a: Male mice kidney treated with (5mg/kg) of 4-F-MDMB-BUTINACA.

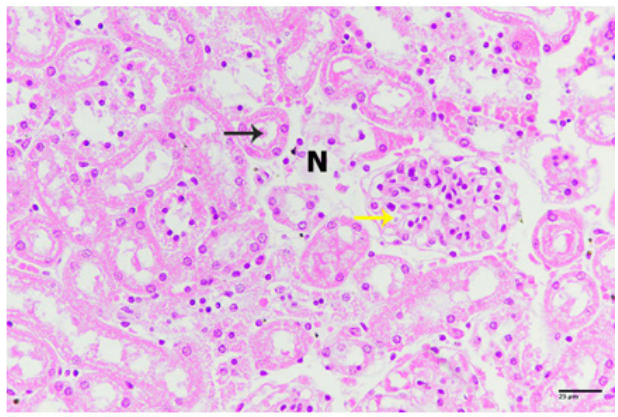

Figure 3b: Female mice kidney treated with (50mg/kg) of 4-F-MDMB-BUTINACA.

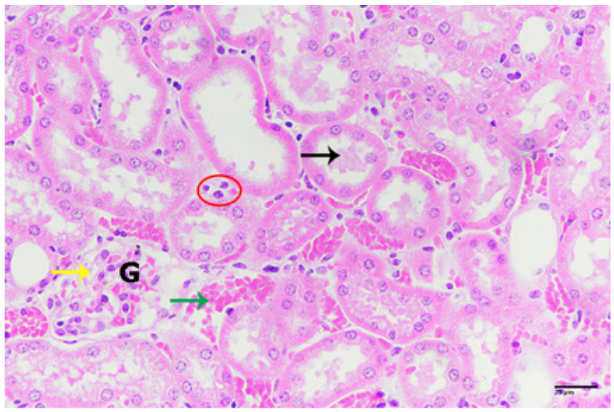

Figure 3c: Female mice kidney treated with (300mg/kg) of 4-F-MDMB-BUTINACA.

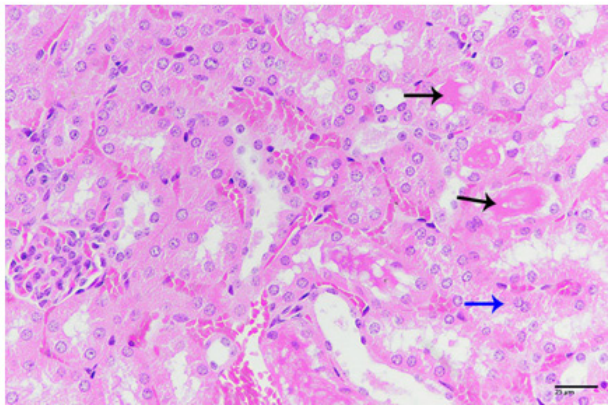

Figure 3d: Male mice kidney treated with (2000mg/kg) of 4-F-MDMB-BUTINACA.

Figure 4: Photomicrograph of Heart(H&E-400X).

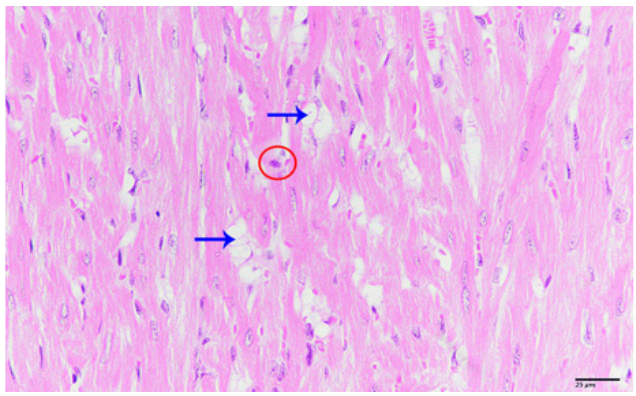

Figure 4a: Female mice treated with (5mg/kg) of 4-F-MDMB-BUTINACA.

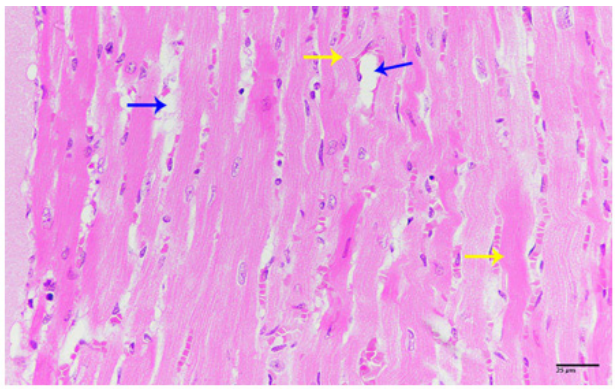

Figure 4b: Male mice cardiac muscles treated with (50mg/kg) of 4-F-MDMB-BUTINACA.

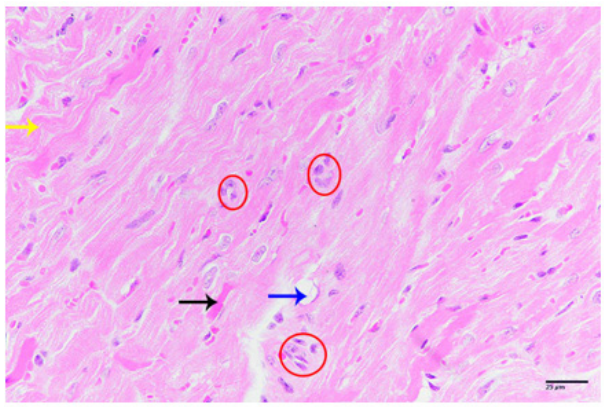

Figure 4c: Female mice treated with (300mg/kg) of 4-F-MDMB-BUTINACA.

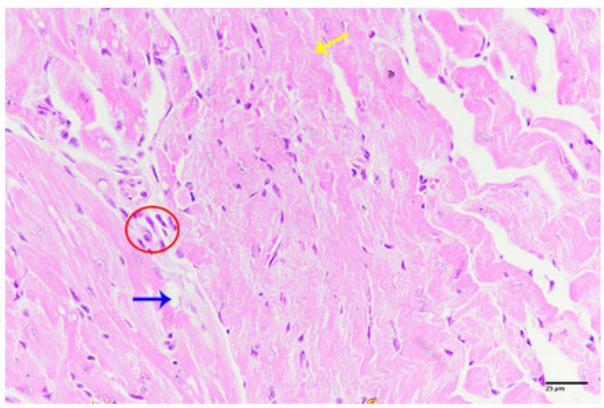

Figure 4d: Female mice treated with (2000mg/kg) of 4-F-MDMB-BUTINACA.

Histological studies

Liver histology after 24 h of treatment. Both male and female mice were treated with low and high doses of 4-F-MDMB-BUTINACA. Control liver section from mice treated with a vehicle showed normal hepatic structure marked by central vein surrounded with anastomose network of hepatocytes with central abundant nuclei. Sometimes, hepatocytes looked binucleated due to its regeneration, besides

hepatocytes were separated from each other by blood sinusoid that contained Kupffer cells. Liver of both male and female mice were treated with (5mg/kg) of 4-F-MDMB-BUTINACA.revealed more pathological signs as congested veins with erythrocytes, more cytoplasmic degeneration and steatosis, besides too presence of hemosiderin granules, dilated vein with thickened wall, hepatocytes suffered from cytoplasmic degeneration, steatosis and necrosis (Fig. 2a). Liver of both male and female mice were treated with (50 mg/kg) of 4-F-MDMB-BUTINACA posted a great incidence of inflammation and macrophages, wide dilatation of vein filled with edema, hepatocytes showed steatosis and heavy incidence of hemosiderin granules, in addition, wide fibro-granulomatous reaction surrounded the bile duct consisted of inflammatory cells mixed with layers of fibrosis, hepatocytes showed steatosis and depositions of hemosiderin (Fig. 2b). Liver of both male and female mice were treated with (300 mg/kg) of 4-F-MDMB-BUTINACA displayed widely dilated and congested vein with erythrocytes surrounded by inflammation, hepatocytes showed steatosis and hyaline degeneration besides to precipitation of hemosiderin granules, displayed cytoplasmic degeneration, micro and macro-steatosis (Fig. 2c). Liver of both male and female mice were treated with (2000mg/kg) of 4-F-MDMB-BUTINACA exhibited aggregation of leukocytic infiltration besides to hemorrhage, hepatocytes displayed cytoplasmic degeneration and steatosis, others showed hyaline degeneration and some hepatocytes exhibited karyolysis which indicator for apoptosis, congested vein and steatosis besides to hemosiderin granules (Fig. 2d).

Kidney histology after 24 h of treatment. Both male and female mice were treated with low and high doses of 4-F-MDMB-BUTINACA.Control kidney section from mice treated with a vehicle Control renal tissue posted normal structure with abundant glomeruli in the Bowman's capsule, besides too presence of tubules sections as proximal convoluted tubules, distal convoluted tubules rather than collecting tubules. kidney of both male and female mice were treated with (5 mg/kg) of 4-F-MDMB-BUTINACA revealed atrophied and distorted glomeruli and tubular casts, some changed as atrophied glomeruli with foam cells, tubular cells showed marked degeneration and filled with edema (Fig. 3a) . kidney of both male and female mice were treated with (50 mg/kg) of 4-F-MDMB-BUTINACA exhibited wide necrotic areas filled with scattered inflammatory cells, glomeruli showed degeneration and foam cells, tubules showed severe degeneration and tubular casts, atrophied glomeruli with foam cells, in addition to hemosiderin presence (Fig. 3b). kidney of both male and female mice were treated with (300 mg/kg) of 4-F-MDMB-BUTINACA displayed distorted glomeruli filled with foam cells, tubules showed degeneration and casts, additionally, hemorrhage and leukocytic inflammatory exudate were seen (Fig. 3c) kidney of both male and female mice were treated with (2000mg/kg) of 4-F-MDMB-BUTINACA showed severe tubular degeneration and Casts filled degenerated tubules (Fig. 3d).

Heart histology after 24 h of treatment. Both male and female mice were treated with low and high doses of 4-F-MDMB-BUTINACA. Control cardiac section from mice treated with a vehicle showed normal cardiac muscles fibers characterized by disc central nuclei stained blue rather than striations and intercalated discs. Cardiac muscles of both male and female mice were treated with (5 mg/kg) of 4-F-MDMB-BUTINACA displayed many degenerated foci some aggregations of inflammatory cells, faint myocardial fibers associated with inflammatory cells depositions (Fig. 4a). Cardiac muscles of both male and female mice were treated with (50 mg/kg) of 4-F-MDMB-BUTINACA exhibited widely necrotic areas filled with erythrocytes and inflammatory cells and degenerated foci besides to wavy myocardial fibers due to contraction (Fig. 4b). Cardiac muscles of both male and female mice were treated with (300 mg/kg) of 4-F-MDMB-BUTINACA posted marked pathological changes as focal degeneration in the myocardial fibers, other fibers showed wavy appearance, scattered aggregations of inflammatory cells and small infarctions (Fig. 4c). Cardiac muscles of both male and female mice were treated with (2000 mg/kg) of 4-F-MDMB-BUTINACA cardiac muscles of female mice showed more degeneration and necrosis in addition to increase of inflammation and wavy myocardia fibers due to more contraction (Fig. 4d).

4-F-MDMB-BUTINACA -treated mice showed degeneration in liver and kidney tissues to varying degrees. Histological changes in liver included small aggregation of inflammatory cells besides to some cytoplasmic degeneration with karyolysis, vein congested with hemorrhage and edema and steatosis degeneration. Renal tissue showed degeneration of

the cell tubules and appearance of foam cells that looked empty in the glomerulus, tubular degeneration increased besides too presence of tubular casts and glomeruli suffered from atrophy accompanied by increasing the Bowman's space. Cardiac muscle fibers showed vacuolar degeneration of myocardial fibers and aggregations of inflammatory cells.

Discussion

Designer drugs have recently become a sensation and in order to circumvent drugs laws, these compounds are synthesized with subtle changes in their chemical structures compared to conventional psychotropic substances.[18] Since4-F-MDMB-BUTINACA has a varied legal status in different countries,[19] determining its toxicity and multiple effects in laboratory animals is critical for forensic investigation.

There were many toxic symptoms exhibited by the treated mice that began shortly after administration, indicating that the drug was rapidly absorbed and distributed. 4-F-MDMB-BUTINACA has low toxicity on the Hodge and Sterner toxicity scale of 24-h acute toxicity.[20] The LD_{50} of 4-F-MDMB-BUTINACA was 32.60 mg/kg bw. This is a low value in comparison to natural cannabis drugs, particularly the active ingredient in the tetrahydrocannabinol (THC) cannabis, which has LD_{50} values of 42 and 482 mg/kg bw when administrated intravenously and orally, respectively. However, it was found that 4-F-MDMB-BUTINACA toxic symptoms were similar to THC cannabis in occurrence, the most important of which is decreased locomotor activities with low doses and stimulated movements and jumping with high doses (Beaulieu 2005). In contrast, 4-F-MDMB-BUTINACA symptoms appear faster and within a shorter time. In comparison to other designer cannabis drugs such as CP-47497, CP-55940, UR-144, JWH-133, JWH-149, JWH 073, and NM-2201(the orally LD_{50} values in mice were 5000, 5600, 5600,5000, 5600, 5600, and 2460 mg/kg/BW, respectively), THJ-2201 is considered more toxic.[21]

Presently,4-F-MDMB-BUTINACApharmacological statistics are unavailable, but they should possess affinity to cannabinoid receptors similar to AM-2201.[22-23] There are several individuals who reported their experience on drug-user forums after the oral administration of 4-F-MDMB-BUTINACA. Most of the users used oil, milk, alcohol, and butter to consume the drug orally. They claim that outcomes began to appear after 50 min, peaking after ~3 h and subsiding after 4–5 h. The user also claimed that effects were extremely similar to dextromethorphan and multiple bongs. Signs mentioned by most of them covered slamming the head several times into the wall or on the floor, depressed breathing, increased heart rate, and violent shaking.[24] Unfavorable reactions along with kidney pains, muscle spasms, and paranoia have been also stated on drug-user forums.[22]

This is the first study to explore the cytotoxic effects of 4-F-MDMB-BUTINACA on liver and kidney tissues. This study indicates that 4-F-MDMB-BUTINACA has high toxicity, its toxic effects on liver tissue were close to the effect of cocaine, which is classified as highly toxic and causes liver damage and inflammation.[25] The inflammation, necrosis, and congestion seen in kidneys of 4-F-MDMB-BUTINACA -treated mice were similar to the changes found by Dargan et al. (2014), who studied the effects of methoxetamine (analogue of ketamine) in renal toxicity in mice.[26]

Conclusion

4-F-MDMB-BUTINACA is of high acute toxicity but had rapid effects after administration. Toxic effects began with mild tremors at low doses and progressed to photophobia and even cessation of breathing with high doses. In hepatic tissue, small aggregation of inflammatory cells besides to some cytoplasmic degeneration with karyolysis, vein congested with hemorrhage and edema and steatosis degeneration. Renal tissue showed degeneration of the cell tubules and appearance of foam cells that looked empty in the glomerulus, tubular degeneration increased besides too presence of tubular casts and glomeruli suffered from atrophy accompanied by increasing the Bowman's space. Cardiac muscle fibers showed vacuolar degeneration of myocardial fibers and aggregations of inflammatory cells.

Ethics Clearance

Ethical approval for this study was obtained from Naif Arab University for Security ScienceEthics Committee (**Nauss-Rec-21-06**).

Source of Funding: Nill

Conflict of Interest: Nill

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