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Toxicological Impact of Synthetic Cannabinoid JWH-200 on Hematological and Oxidative Biomarkers in Rats

Mümin Polat[1], Hüseyin Bayramer[2]

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ABSTRACT

Background: Synthetic cannabinoids (SCs) have emerged as a significant public health concern due to their unpredictable toxicological profiles and increasing prevalence among adolescents and young adults. JWH-200, a potent SC compound, has been frequently identified in forensic toxicology cases. This experimental study aimed to investigate the hematological, biochemical and oxidative effects of JWH-200 in a rat model.

Methods: Thirty-two male rats were randomly assigned to control and experimental groups. The experimental group received a single intraperitoneal dose of JWH-200 (1 mg/kg), while the control group received no treatment. Hematological and biochemical parameters were analyzed, including RBC, WBC, Hb, Hct, PLT, AST, ALT, LDH, GGT, creatinine, as well as oxidative stress markers TAS and TOS.

Result: Statistical analysis revealed significant increases in hemoglobin, hematocrit and platelet counts ($p = 0.003$, $p = 0.003$, $p = 0.000$, respectively) in the experimental group, while RBC, WBC and LYM counts did not show significant changes. Biochemical results indicated elevated creatinine and LDH levels ($p = 0.000$ and $p = 0.001$), suggesting renal and systemic injury. Additionally, oxidative stress parameters demonstrated a marked increase in TOS and reduction in TAS ($p = 0.004$ and $p = 0.003$), reflecting an imbalance in redox homeostasis. These findings provide compelling evidence that JWH-200 induces hematological abnormalities, biochemical disruptions and oxidative stress, even at a single dose. This study underscores the potential for multi-organ damage associated with synthetic cannabinoid exposure and contributes to the growing body of toxicological data necessary for clinical recognition, early intervention and public health policy.

Key words: Biochemical markers, Hematological parameters, JWH-200, Oxidative stress, Rat model, Synthetic cannabinoids.

INTRODUCTION

Substance abuse and addiction continue to pose critical challenges to global public health, with the rapid emergence of synthetic cannabinoids (SCs) marking a particularly troubling trend in recent decades. Unlike traditional drugs such as heroin, cocaine and cannabis, SCs are designer compounds synthesized to mimic the psychoactive effects of Ä9-tetrahydrocannabinol (THC), the primary active component of cannabis. These substances are frequently marketed under misleading labels such as “herbal incense,” “Spice,” or “Bonzai” and are widely accessible through both physical and online platforms. Their unregulated production and deceptive packaging have contributed to an alarming rise in use, particularly among adolescents, young adults and individuals from socioeconomically vulnerable groups (Zimmermann *et al.*, 2009; Costa *et al.*, 2025; Auwärter *et al.*, 2009; Polat, 2019; Fattore and Fratta, 2011).

In Turkey, the rise of SC consumption has been especially dramatic. Reports from the Turkish Monitoring Centre for Drugs and Drug Addiction (TUBIM) reveal a significant increase in the seizure and circulation of SCs since the early 2010s. To date, over 130 SC compounds have been identified, with JWH-series molecules including JWH-018, JWH-073 and JWH-200 being among the most prevalent. “Bonzai,” the most well-known street name, is often confused with cannabis due to its visual similarity but carries a much higher toxicological risk (Auwärter *et al.*, 2009; World Drug Report, 2024; Evren and Bozkurt, 2013). The rapid spread of these substances has prompted urgent regulatory responses across Europe, including substance-specific bans and criminalization. Despite such measures, SCs continue to proliferate owing to slight structural modifications that circumvent legal classifications (World Drug Report, 2024; Moosmann *et al.*, 2009).

Pharmacologically, SCs bind with high affinity to CB1 and CB2 cannabinoid receptors, exerting more potent effects than natural cannabinoids. This heightened receptor activity is associated with a wide range of adverse

[1]Department of Emergency and Disaster Management, Faculty of Health Sciences, Dr. Mehmet Akif Ersoy University, 15100, Burdur, Turkey.

[2]Institute of Health Sciences, Mehmet Akif Ersoy University, Burdur, Turkey.

Corresponding Author: Mümin Polat, Department of Emergency and Disaster Management, Faculty of Health Sciences, Dr. Mehmet Akif Ersoy University, 15100, Burdur, Turkey.
Email: mpolat@mehmetakif.edu.tr
ORCIDs: 0000-0001-8082-0735, 0009-0001-0849-9729.

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outcomes, including tachyarrhythmia, psychomotor impairment, respiratory depression, acute psychosis, seizures and sudden death (Pintori *et al.*, 2024; Every-Palmer, 2011; Hurst *et al.,* 2011; Yeakel and Logan, 2013). Emerging data also link SC use to acute kidney injury, liver dysfunction and oxidative tissue damage, often requiring intensive clinical intervention (World Drug Report, 2023; Pintori *et al.,* 2024; Vardakou *et al.*, 2010). However, the clinical picture remains elusive in many cases due to inconsistent symptom presentation, user unawareness and the lack of routine toxicological screening.

JWH-200, a phenylacetylindole derivative, is one of the lesser-studied compounds in the JWH series. Although it shares structural and functional similarities with JWH-018 and JWH-073, its toxicodynamic and toxicokinetic profiles are not fully elucidated. Preliminary studies have reported hypothermia, motor incoordination and behavioral abnormalities in rodent models exposed to JWH-200, but few investigations have focused on its systemic biochemical and hematological consequences (Every-Palmer, 2011; Hurst *et al.,* 2011). Given the compound's rising detection in forensic analyses and its inclusion in commercial SC mixtures, understanding its impact on organ systems is vital for effective clinical and toxicological response strategies.

Oxidative stress is a key mechanism implicated in SC-induced organ toxicity. Alterations in oxidative markers such as total antioxidant status (TAS) and total oxidant Status (TOS) can reflect cellular distress and systemic inflammatory responses. Furthermore, hematological and biochemical parameters such as hemoglobin levels, liver enzymes (AST, ALT, GGT) and renal function indicators (creatinine, LDH) provide critical insight into organ-specific damage and metabolic alterations (Kotb *et al.*, 2016; Giorgetti *et al.*, 2020).

Therefore, this study aimed to comprehensively evaluate the toxicological effects of JWH-200 in a controlled rat model by examining changes in hematological indices, biochemical markers and oxidative stress parameters. Through this approach, we seek to bridge the current gap in the literature regarding JWH-200 and contribute to a broader understanding of the multi-organ risks posed by synthetic cannabinoid exposure.

MATERIALS AND METHODS

Animals and experimental design

This study was conducted using 32 male Wistar rats (8-10 weeks old, average weight: 230-250 g), obtained from the Experimental Animal Production and Research Laboratory at Mehmet Akif Ersoy University. All procedures were approved by the Local Ethics Committee for Animal Experiments (Date: 09.03.2023; Decision No: 178) and conformed to the ethical principles outlined in the European Directive 2010/63/EU on the protection of animals used for scientific purposes.

Rats were housed under controlled environmental conditions (22±2°C, 50-60% humidity, 12-hour light/dark cycle) with ad libitum access to standard pellet diet and water. Animals were acclimatized for one week prior to experimentation to minimize environmental stress. No food or water restriction was applied during the study.

Rats were randomly assigned into two groups (n=16 each): A control group and an experimental group receiving JWH-200. Randomization was achieved through a computerized random number generator. The chosen sample size was determined *via* a power analysis based on preliminary biochemical pilot data, targeting a power of 0.8 and alpha value of 0.05.

Drug administration

JWH-200 (Cayman Chemical, USA) was administered as a single intraperitoneal injection at a dose of 1 mg/kg, which was selected based on previous toxicological studies reporting behavioral and physiological effects in rodents (Dziwenka *et al.*, 2020). The compound was dissolved in a mixture of ethanol (0.5 ml/kg) and dextrose (4.5 ml/kg) to ensure solubility and bioavailability. The control group received no treatment. All injections were performed in the early morning hours to control for circadian variation.

Post-injection, rats in the experimental group were monitored for 60 minutes to observe immediate physiological responses. Hypothermia and hypoactivity were noted, consistent with cannabinoid-related central nervous system suppression. To mitigate cold stress, heated pads (maintained at 37°C) were provided during this period.

Sample collection and biochemical analyses

At the end of the exposure period, rats were anesthetized *via* intraperitoneal ketamine injection (30 mg/kg). Blood samples were collected via cardiac puncture using 21G needles. Two types of collection tubes were used: citrate-coated tubes for hematological parameters and gel-serum tubes for biochemical assays.

Hematological parameters RBC, WBC, Hb, Hct, PLT and LYM were analyzed using an Abacus 5 Junior Vet Hematology Analyzer (Diatron, Hungary) (Singh *et al.*, 2021). Biochemical markers including AST, ALT, LDH, GGT and creatinine were measured using the GesanChem 200 biochemistry analyzer (Gesan Production, Italy), following manufacturer protocols.

Oxidative stress assessment

Oxidative stress markers were evaluated using colorimetric assay kits validated for rat serum (Mirajkar *et al.*, 2021). Total antioxidant status (TAS) and total oxidant status (TOS) levels were measured using the Rel Assay Diagnostic kits (Gaziantep, Turkey) with absorbance values recorded via PerkinElmer UV/Vis Spectrophotometer 20 (USA). All samples were analyzed in duplicate to ensure reproducibility (Çetinkaya and Polat, 2018).

Statistical analysis

Statistical analysis was performed using Minitab version 17.0 (UK). All continuous variables were tested for normality using the Shapiro-Wilk test. Comparisons between the

two groups were made using independent two-sample t-tests. Descriptive data are presented as mean ± standard deviation (SD). A p-value < 0.05 was considered statistically significant.

RESULTS AND DISCUSSION

The results of the study are presented below in two main categories: biochemical and antioxidant parameters and hematological indices. The mean values and standard deviations of biochemical and oxidative markers measured in the control and experimental groups are summarized in Table 1. The total antioxidant status (TAS) and total oxidant status (TOS) values in the control group were found to be within the reference ranges.

Analysis of liver enzymes revealed no statistically significant differences in AST and ALT levels between groups (p = 0.100 and p = 0.603, respectively). However, creatinine levels were significantly elevated in the experimental group (0.702±0.028 mg/dL) compared to controls (0.610±0.026 mg/dL), with a p-value of 0.000. Similarly, LDH levels showed a marked increase in the intervention group (2284±1116 U/L) versus the control group (990±466 U/L), which was statistically significant (p = 0.001).

GGT levels were significantly lower in the experimental group (4.0±0.756 U/L) than in the control group (6.67±4.58 U/L), with a p-value of 0.043. Although this finding contrasts with traditional patterns of hepatobiliary damage, it reached statistical significance.

Regarding oxidative stress biomarkers, Total Antioxidant Status (TAS) was significantly reduced in the experimental group (1.669±0.538 mmol Trolox Eq/L) compared to the control group (1.165±0.133 mmol Trolox Eq/L), yielding a p-value of 0.003. In contrast, total oxidant status (TOS) was significantly higher in the experimental group (23.12± 15.2 µmol H_2O_2 Eq/L) relative to controls (9.451±1.926 µmol H_2O_2 Eq/L) (p = 0.004). These results indicate that a single dose of JWH-200 was sufficient to induce significant oxidative imbalance.

The values obtained from the experimental and control groups are presented in Table 2.

The hemogram parameters measured in the control group were also within reference limits.

WBC levels were slightly higher in the JWH-200 group (3.97±1.182 × 10^3/µL) than in the control group (3.547± 0.787 × 10^3/µL), though this difference was not statistically significant (p = 0.260). Similarly, lymphocyte counts were comparable between groups (2.432±0.784 vs. 2.266± 0.905 × 10^3/µL; p = 0.596).

In contrast, hemoglobin (Hb) and hematocrit (Hct) levels were significantly elevated in the experimental group. Hb increased from 13.653±0.752 g/dL in controls to 15.000 ±1.353 g/dL in the treated group (p = 0.003), while Hct rose from 46.507±2.432% to 51.87±5.55% (p = 0.003).

Platelet counts demonstrated the most prominent hematological difference. The mean platelet count in the

Table 1: Means and standard deviations of the biochemistry and antioxidant parameters in the intervention and control group.

Biochemistry and antioxidant Parameters	Intervention group	Control group	
	Mean ± SD	Mean ± SD	P
AST	48.47± 31.42	54.6± 44.2	0.100
ALT	119.2± 47.1	112.67± 6.2	0.603
Creatine	0.702±0.028	0.61± 0.026	0.000
LDH	2284± 1116	990± 466	0.001
GGT	4± 0.756	6.67± 4.58	0.043
TAS	1.669±0.538	1.165± 0.0133	0.003
TOS	23.12± 15.2	9.451±1.926	0.004

AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; LDH: Lactate Dehydrogenase; GGT: Gamma-glutamyl transferase; TAS: Total antioxidant status; TOS: Total oxidant status.

Table 2: Means and standard deviations of the hemogram parameters in the intervention and control group.

Hemogram parameters	Intervention group	Control group	
	Mean ± SD	Mean ±SD	P
Erythrocyte (RBC)	8.897±0.994	8.125±0.45	0.130
Leukocyte (WBC)	3.97±1.182	3.547±0.787	0.260
Hemoglobin (HGB)	15±1.353	13.653±0.752	0.003
Hematocrit (HTC)	51.87±5.55	46.507±2.432	0.003
Lymphocyte (LYM)	2.432±0.784	2.266±0.905	0.596
Platelet (PLT)	852.5±129.6	463.9±168.8	0.000

While RBC counts did not differ significantly between groups (p = 0.130), the experimental group showed a modest elevation (8.897±0.994 ×10^6 /µL) compared to controls (8.125±0.450 × 10^6 /µL).

experimental group was 852.5±129.6 × 10^3/µL, significantly higher than in the control group (463.9±68.8 × 10^3/µL) ($p = 0.000$), indicating a potential prothrombotic or inflammatory state induced by JWH-200 exposure.

Our findings revealed significant alterations in hemoglobin, hematocrit and platelet levels in the JWH-200 group, while red and white blood cell counts, as well as lymphocyte levels, remained statistically unchanged. These results suggest that although global erythropoiesis and leukopoiesis may not be drastically affected, specific hematological components involved in oxygen transport and coagulation are notably impacted. The elevated Hb and Hct levels observed are consistent with a possible hemoconcentration effect or compensatory erythropoietic stimulation following systemic oxidative stress. Although the exact mechanism remains unclear, SCs have previously been implicated in altering red blood cell rheology and plasma volume status (Altınışık *et al.*, 2015; Hermanns-Clausen *et al.*, 2013).

A particularly striking finding was the substantial increase in platelet counts in the experimental group. This thrombocytosis could indicate an acute-phase reaction or proinflammatory response triggered by JWH-200. Increased platelet activity has been associated with vascular inflammation and thrombogenic risk, particularly in young users exposed to synthetic cannabinoids. Gurdal *et al.* (2013); Sood *et al.* (2018); Mir *et al.* (2011) reported a case of myocardial infarction linked to SC use, further supporting the association between SCs and hemostatic dysregulation (Mir *et al.*, 2011).

Biochemically, our study demonstrated significant elevations in serum creatinine and LDH levels in the JWH-200-treated group. Elevated creatinine is a marker of impaired renal function, which has been widely documented in both animal and human studies involving SC exposure Ergül *et al.* (2015). LDH, a nonspecific but sensitive marker of tissue injury, was markedly increased in our experimental animals, indicating systemic cellular damage (Forkasiewicz *et al.*, 2020). This aligns with previous reports that SCs, through their strong agonist activity at CB1 receptors, can trigger oxidative mitochondrial dysfunction and cellular apoptosis in multiple tissues (Giorgetti *et al.*, 2020).

Interestingly, AST and ALT levels were not significantly different between groups, although their mean values were slightly higher in controls. This could suggest that at the administered dose (1 mg/kg), JWH-200 does not cause overt hepatocellular injury. However, the observed biochemical variability implies that hepatotoxicity may emerge at higher doses or with repeated exposure. Previous studies have yielded conflicting findings in this regard: Sheikh *et al.* (2014) reported elevated transaminases in a case of SC-induced hepatitis, while Alhadi *et al.* (2013) observed no significant changes in liver enzyme levels despite chronic use (Sheikh *et al.*, 2014; Alhadi *et al.*, 2013). In contrast, GGT levels were paradoxically lower in the experimental group, a finding that lacks a clear mechanistic explanation and may require further investigation in future studies.

From an oxidative stress perspective, our data revealed a significant increase in Total Oxidant Status (TOS) and a concomitant decrease in Total Antioxidant Status (TAS) in the experimental group. These changes indicate a clear imbalance in redox homeostasis following JWH-200 exposure. Oxidative stress has been widely implicated in the pathophysiology of SC-related organ damage, including cardiovascular, renal and neurological systems (Pintori *et al.*, 2024; Hurst *et al.*, 2011). The elevated TOS levels in our study mirror findings from other SC models, which suggest that these compounds promote lipid peroxidation and mitochondrial dysfunction. Reduced TAS reflects a depletion of endogenous antioxidant defenses, making tissues more susceptible to free radical-mediated injury (Giorgetti *et al.*, 2020).

The observed oxidative dysregulation may provide a plausible mechanistic link to the hematological and biochemical alterations observed. Oxidative damage to endothelial cells can activate platelet aggregation and adhesion (Madamanchi *et al.*, 2005), while renal tubular injury can lead to elevations in serum creatinine and LDH due to impaired clearance and tissue damage. Moreover, excessive ROS production may stimulate inflammatory cytokine release through NF-κB signaling, exacerbating hematological abnormalities (Mittal *et al.*, 2014; Zargar *et al.*, 2021).

Collectively, these results emphasize the multi-organ impact of even a single dose of JWH-200, reinforcing the notion that SCs are far from benign. While the public perception may still regard SCs as “legal” or “natural” alternatives to cannabis, our data support the growing body of evidence highlighting their unpredictable and potentially fatal consequences. The fact that JWH-200 is still present in various street-level SC products and has not been thoroughly characterized in toxicological literature makes this study particularly relevant.

However, some limitations should be acknowledged. First, the study used a single dose and time point, which may not fully capture the chronic effects or dose-response dynamics of JWH-200. Second, organ-specific histopathological evaluation was not performed, which could have strengthened the interpretation of biochemical alterations. Third, while oxidative markers were measured in serum, tissue-specific oxidative profiles may yield more detailed insights. Future research should aim to address these gaps by including histological analyses, longer observation periods and varied dosing protocols.

Limitations

Additionally, the absence of histopathological examination restricts the ability to correlate biochemical changes with direct tissue-level alterations. Future studies should address this by including tissue-level morphological assessments.

CONCLUSION

The present study demonstrates that a single intraperitoneal dose of JWH-200 induces significant hematological, biochemical and oxidative alterations in rats. The observed increase in hemoglobin, platelet counts, creatinine and LDH levels, along with oxidative imbalance, suggests systemic toxicity and a pro-oxidant shift.

These findings underscore the capacity of synthetic cannabinoids like JWH-200 full agonists at cannabinoid receptors to disrupt physiological homeostasis even at low doses. The results imply potential risks such as vascular complications and systemic injury. Given the growing prevalence of SC use, particularly among adolescents, clinicians should be aware of its toxicological profile. Future studies should investigate chronic exposure effects, include histopathological assessments and elucidate molecular mechanisms to inform better diagnostic and preventive strategies.

In conclusion, the current study demonstrates that JWH-200 induces significant hematological, biochemical and oxidative alterations in rats, even at low doses. These findings underscore the systemic toxic potential of SCs and highlight the need for increased clinical awareness, toxicovigilance and public health education. The inclusion of oxidative and hematological screening in suspected SC intoxication cases may facilitate earlier diagnosis and intervention.

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Authorship

Conceptualization, Mümin Polat and Hüseyin Bayramer, methodology, Mümin Polat, formal analysis, Mümin Polat, investigation, Hüseyin Bayramer, data curation, Hüseyin Bayramer, writing original draft preparation, Mümin Polat and Hüseyin Bayramer, writing review and editing, Mümin Polat and Hüseyin Bayramer, project administration, Mümin Polat All authors have read and agreed to the published version of the manuscript.

Disclaimers

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Ethics and informed consent

All animal procedures were approved by the Local Ethics Committee for Animal Experiments of Mehmet Akif Ersoy University (Date: 09.03.2023; Decision No: 178). Animal care and use were performed in accordance with relevant guidelines and regulations.

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this article. No funding or sponsorship influenced the design of the study, data collection, analysis, interpretation, or writing of the manuscript.

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