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Editorial

Dear Readers,

We present to you the first issue of our journal for 2024. In this issue, we have published 1 original article, 1 review and 2 case reports that we think you will read with pleasure and interest. We hope that your scientific support will continue to increase in 2024. We would like to thank everyone who contributed to our journal for their support and contributions.

We would like to inform you that we will accept the articles on environmental emergencies starting next issues.

Best Regards.

Eurasian Journal of Toxicology Editorial Board

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Epidemiological Attern of Extracorporeal Methods in Acute Poisoning: A-Five-Year Study

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Abstract

Background: The use of hemodialysis is a prevalent extracorporeal technique for managing the poisoning of certain patients.

Objectives: In this study, we examined the frequency of extracorporeal methods and the prognosis of using these methods in various poisonings.

Methods: This retrospective study was conducted at Loghman Hakim hospital in Tehran between 2016 and 2020. The study investigated all patients who were hospitalized and underwent hemodialysis at the poisoning center. The study analyzed demographic data, clinical information, and certain laboratory findings from a sample size of 980 cases. The data obtained from the study were analyzed using SPSS 22.

Results: 793 (80.9%) males and 187 (19.1%) females were investigated. The mean age of the subjects was 36.5±14 years. Methanol consumption was the highest cause of poisoning (858 cases, 87.6%). Hemodialysis was the most widely used extracorporeal method (971 cases, 99.1%). The median number of hemodialysis was 1 times and the maximum was 18. The mortality rate was 13.3%. Metabolic acidosis was observed in 823 cases (84%). Acute kidney injury (AKI) was present in 536 cases (54.7%).

Conclusions: Although there have been some published studies and conferences on extracorporeal methods for treating poisonings, the lack of cases treated with these methods has resulted in weak evidence. To address this issue and provide more widely applicable data, studies like this can help to improve the treatment of poisoned patients.

Keywords: Extracorporeal, hemodialysis, methanol, poisoning

Introduction

Poisoning is usually caused by swallowing poisons but can be caused by injections, inhalations, or exposure to body surfaces (skin, eyes, and mucous membranes). The general approach to the poisoned patient is divided into five stages; 1) stabilizing the patient's condition; 2) laboratory tests; 3) gastrointestinal, skin, or eye decontamination; 4) prescribing an antidote and 5) enhancing the removal of toxins from the body. Among the methods to enhance the removal of toxins from the body, the use of extracorporeal treatments (ECTR) such as hemodialysis and hemoperfusion play a significant function in saving the patient's life[1, 2].

Hemodialysis is the best treatment for water-soluble drugs, especially low molecular weight drugs, which have a low volume of distribution and low protein binding that can be rapidly distributed through the filter membrane. Some examples of these drugs are salicylates, ethanol, methanol and lithium[3,4]. In hemoperfusion, blood passes through a cartridge containing activated charcoal. Compared to hemodialysis, hemoperfusion is more effective in clearing the blood from most protein-bound drugs because the charcoal in the cartridge competes with the plasma proteins to bind to the drug, absorb the drug, and remove it from the bloodstream[1, 5].

Abel et al. reported the initial application of extracorporeal techniques in 1913, wherein they eliminated salicylates from a dog's body[6, 7]. Kyle et al. were first successfully using hemodialysis to treat barbiturates poisoning[6,8]. The initial extensive examination of employing hemodialysis in cases of sudden poisoning was presented by George Schreiner in 1958[6, 9]. Physicians and researchers have since conducted several studies on these methods, which have led to the identification of drugs and toxins that can be removed through these methods[10-13].

Despite the existence of studies and conferences on extracorporeal therapies, the lack of poisonings treated with these methods has resulted in weak evidence for their effectiveness. Considering that Loghman Hakim Hospital is one of the most reference places for the treatment of poisoned people, in this study we examined the frequency

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of extracorporeal methods and the prognosis of using these methods in various poisonings.

Methods

This study was performed as a retrospective study. By referring to the dialysis ward of Loghman Hakim Hospital in Tehran, all cases of poisoning from 2016-2020 were investigated and the desired variables were extracted. The sampling method was census (All relevant files were reviewed). From 68181 patients admitted to the poisoning wards, 980 underwent hemodialysis and hemoperfusion that were our sample size and 67201 patients were excluded.

The studied variables included age, sex, type of poisoning, history of underlying disease, medication use and habits, number of times the extracorporeal method was used, type of extracorporeal method, patient's outcome (death, healing, sequela or discharge by personal consent), laboratory tests result and vital signs.

This study has been approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences under the code IR.SBMU.RETECH.REC.1400.444.

The data obtained from the study were analyzed by IBM SPSS STATISTICS 22 (IBM Corp, Armonk, New York, USA). Initially, the statistical population's normal distribution was established through the Kolmogorov-Smirnov test. Subsequently, the central and descriptive indices were computed and articulated. All samples were subjected to a significance level of $P<0.05$.

Results

From 68181 patients admitted to the poisoning wards, 980 underwent hemodialysis and hemoperfusion that covered 1.4% of the cases. 793 (80.9%) males and 187 (19.1%) females were investigated. Some demographic information is shown in Table 1. The mean age of the subjects was 36.5±14 years. The age distribution was significantly different ($p<0.001$). 604 cases (61.6%) were in the age range of 21-40 years. 117 cases (11.9%) had intentional poisoning. As shown in Figure 1, the highest cause of poisoning was due to methanol consumption (858 cases, 87.6%). 830 cases (84.7%) had no previous history of the disease. Two cases had a history of kidney disease. 903

Table 1: Demographic information of the studied patients.

Variables	Frequency (%)
Gender (Male)	793 (80.9%)
Under 20 years old	100 (10.2%)
21-40 years	604 (61.6%)
41-60 years	211 (21.5%)
61-80 years	60 (6.1%)
Above 81 years	5 (0.5%)
Co-ingestion	62 (6.3%)
Smoking	46 (4.7%)
Alcohol consumption	627 (64%)
Opium abuse	75 (7.7%)
Stimulants abuse	13 (1.3%)
History of pervious disease	150 (15.3%)
History of taking medication	77 (7.9%)
Hemoperfusion	9 (0/9%)
Intubation	203 (20.7%)
ICU admission	187 (19.1%)
Antidote therapy	904 (92.2%)
Duration of hospitalization (day). median (min-max)	2 (1-116)
Death	130 (13.3%)

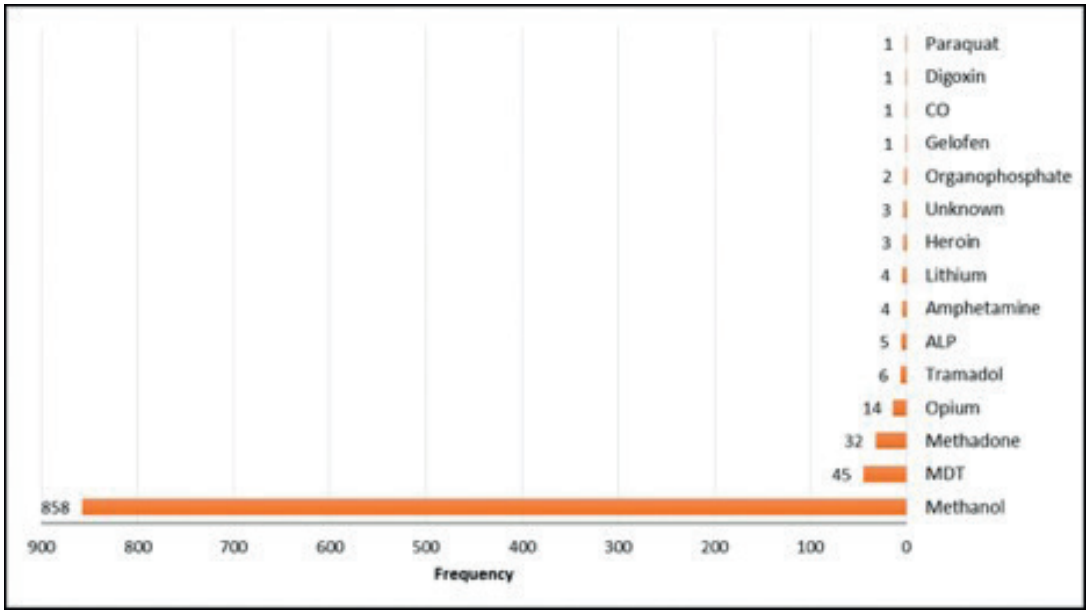

Figure 1: Cause of intoxication in the studied patients. MDT= Multiple Drug Toxicity.

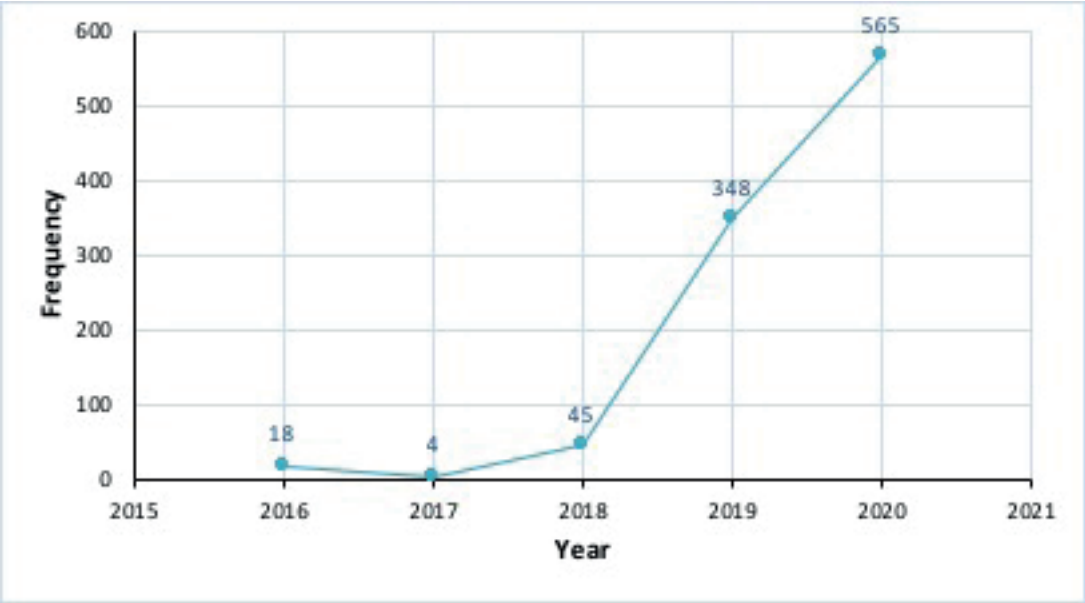

Figure 2: Frequency of extracorporeal methods during 2016-2020 years.

cases (92.1%) had no history of taking drugs and 627 (64%) cases had a history of alcohol consumption.

Hemodialysis was the most widely used extracorporeal method (971 cases, 99.1%). The median number of hemodialysis was 1 and the maximum was 18 times. Hemoperfusion was performed for 5 cases of methanol, 3 cases of multidrug and 1 case of methadone poisoning. As shown in Figure 2, there is a significant ($p<0.05$) increase in hemodialysis and hemoperfusion cases during 2019 and 2020. 36.25% and 59.8% of methanol poisoning cases were in 2019 and 2020, respectively.

The most used antidotes were ethanol and folic acid, which were 38.1% (373 cases) and 32.8% (321 cases), respectively. The median duration of hospitalization was 2 days. 792 cases (80.8%) recovered. In 15 cases (1.5%), injury caused by poisoning remained and the mortality rate was 13.3% (130 cases). 2 out of 9 individuals who underwent hemoperfusion did not survive, while the remaining 7 individuals successfully recovered. The mortality rate for the hemodialysis method was 13.18%, while the hemoperfusion method had a mortality rate of 22.22%.

Clinical and laboratory tests results are shown in Table 2. Metabolic acidosis was observed in 823 cases (84%). Acute kidney injury (AKI) was present in 536 cases (54.7%). Hypernatremia, hyperkalemia, increased BUN (Blood Urea Nitrogen) and hyperglycemia were observed in 3.3% (32 cases), 14% (137), 16.8% (165) and 24.1% (236) of patients, respectively. 84.3% of acute kidney injury (452) and 63.1% of deaths (82) were among patients with methanol poisoning.

Discussion

There are four categories of extracorporeal therapies based on their mechanism: hemodialysis and peritoneal dialysis fall under diffusion, hemofiltration is categorized under convection, hemoperfusion falls under adsorption, and therapeutic plasma exchange is classified under centrifugation[14, 15]. Hemodialysis offers several benefits compared to other extracorporeal treatments. It effectively and quickly removes toxins from the blood and dialysate due to its high flow rates. Additionally, it can simultaneously address other medical conditions like uremia, acid-base imbalances, and electrolyte abnormalities. Furthermore, hemodialysis is the most accessible, cost-effective, and time-efficient method available[14].

Table 2: Laboratory and clinical tests results.

	Frequency (%)
$13 \leq GCS < 15$	659 (67.2%)
$8 \leq GCS < 13$	62 (6.3%)
Coma (GCS < 8)	108 (11%)
Bradypnea	46 (4.7%)
Temperature (Mean±SD)	36.9±0.56
Bradycardia	14 (1.4%)
Tachycardia	145 (14.8%)
Hypotension	38 (3.9%)
Hypertension	293 (29.9%)
Metabolic Acidosis	823 (84%)
Acute Kidney Injury (AKI)	536 (54.7%)
Serum HCo3 (Mean±SD)	14.4±23.8
BUN (meq/l) (Mean±SD)	36.7±27.2
Creatinine (meq/l) (Mean±SD)	1.7±4.1
Blood Glucose (mg/dl) (Mean±SD)	132.5±66.6
Blood PH (Mean±SD)	7.2±0.4
Sodium (meq/l) (Mean±SD)	137.8±10.8
Potassium (meq/l) (Mean±SD)	4.7±3.4

In this study, the most used method was hemodialysis. The most common cause of hemodialysis was methanol poisoning (858 cases, 87.6%). 793 males and 187 females were investigated. 61.6% of cases were in the age range of 21-40 years. The total mortality rate was 13.3%. The mortality rate of hemodialysis method was 13.18% and hemoperfusion method was 22.22%.

A study has been conducted in Urmia in the same period of time in the poisoning center of Taleghani Hospital. This research involved the evaluation of 200 patients. The overall mortality rate was 31.5%. The main causes of poisoning among patients treated with hemodialysis were toxic alcohol (methanol, ethylene glycol) 43% and paraquat 29%. The most common signs and symptoms among patients were loss of consciousness 41% and gastrointestinal discomforts such as nausea, vomiting, and epigastric pain 34%[16]. In our study, methanol was the primary cause of poisoning, while paraquat was observed in only 1 case. The shift in the pattern of poisoning in 2 cities has resulted in a death rate of 13.18% among our hemodialysis patients, which is much lower than that reported in the aforementioned study.

According to methanol is the most common cause of poisoning, it can be assumed that these cases have increased due to the prevalence of coronavirus. Other studies confirm that methanol poisoning increased during the COVID-19 pandemic[17-21].

Methanol poisoning can happen through various means, such as ingestion, inhalation or skin contact. The symptoms of methanol poisoning can include digestive issues, suppression of the central nervous system, metabolic acidosis, and vision problems including blurred vision and even blindness[22, 23]. Data that was gathered by Hassanian Moghadam and colleagues in 2019 on individuals suffering from methanol poisoning across the globe revealed that the use of hemodialysis and antidotes could be a safe and effective treatment for patients affected by poisoning[24]. In our study, the most common toxin treated with hemodialysis was methanol. Also, most of the antidotes were related to the treatment of methanol poisoning.

A study has been done in Urmia on patients undergoing hemodialysis. In that study, 200 patients (158 males, 42 females) were studied. The reported mortality rates were 31.5%, with 79% of the deaths being male and 21% being female. The main reasons for poisoning in patients were toxic alcohols such as methanol and ethylene glycol, accounting for 43%, and paraquat, accounting for 29%[16]. Our research also found that methanol, a toxic alcohol, had the highest number of cases requiring hemodialysis, while paraquat was only associated with 1% of the substances.

Vivek et al. conducted a study on methyl alcohol poisoning and hemodialysis. They reported that 91 males with mean age 40 ± 8.5 years underwent hemodialysis, and 13 patients required a second session. Before hemodialysis, the mean pH was 7.11 ± 0.04 (range 6.70– 7.33) and mean bicarbonate levels were 8.5 ± 4.9 mmol/L (range 2–18). Three patients died due to methanol intoxication 25. In our study, 147 people (17.13%) of people poisoned with methanol needed hemodialysis more than once. 85 people (9.56%) of people poisoned with methanol died, which is higher than the above study (nearly 9 times).

A study on extracorporeal treatments for child and adolescent poisoning was conducted in California in 2013. 90 patients were examined. Hemodialysis was the main method of using extracorporeal treatments[26]. Our study also showed that hemodialysis is the main extracorporeal method for the treatment of poisoned people.

A study was conducted on the methanol outbreak in Rafsanjan in 2013. A total of 694 subjects were observed. Resistant metabolic acidosis was the primary reason for hemodialysis in 175 patients, out of which eight patients passed away. The serum methanol levels were only accessible for the deceased cases and not for the rest[27]. Our research also revealed that 84.2% of the patients (825 individuals) exhibited acidosis, indicating that one of the primary purposes of hemodialysis and hemoperfusion was to address acidosis.

In the case of opioid poisoning, extracorporeal treatment is not the best treatment. Typically, antidote and supportive treatments are enough to address the issue. Nevertheless, individuals who have reached end-stage kidney disease (ESKD) may experience an accumulation of specific opioids and their byproducts. To prevent toxicity in such cases, hemodialysis could be the solution. One of the primary active byproducts of morphine, morphine 6-glucuronide, may lead to lasting effects in ESKD patients, but it can be removed through dialysis6. Patients with renal impairment may experience accumulation of hydromorphone-3-glucuronide, which can be removed through hemodialysis[28]. In our study, after methanol, methadone (32 cases, 3.2%) and opium (14 cases, 1.4%) were the most hemodialysis toxins.

A man, aged 34, who had suicidal thoughts and took methadone, was studied. The patient's condition showed metabolic acidosis, acute renal failure, and rhabdomyolysis, which indicated the need for hemodialysis. After 11 days of hemodialysis, his metabolic disorders resolved but his hearing loss remained[29]. In our study, there were 32 cases (3.2%) with methadone poisoning. 81.25% of these cases had AKI and 68.75% had metabolic acidosis.

Although hemodialysis and other extracorporeal removal methods are performed for a limited number of toxins, they are very important and can save patients' lives and eliminate the effects of poisoning. Our study at the Loghman Hakim Center showed that methanol, multidrug and opioid (methadone & opium) poisoning are the most common causes of hemodialysis. Further studies (even case reports) on other toxins are recommended to increase the scope of knowledge about these methods and their effectiveness.

Limitation

One major constraint of this study was the inadequate documentation of certain laboratory information.

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Conflict of interest: None to be declared.

References

1. Shannon MW, Borron SW, Burns MJ, Haddad LM, Winchester JF. Haddad and Winchester's clinical management of poisoning and drug overdose: Saunders/Elsevier; 2007.
2. Al-Jelaify M, AlHomidah S. The individualized management approach for acute poisoning. Advances in pharmacological and pharmaceutical sciences. 2021;2021:1-5.
3. Otten EJ. Goldfrank's Toxicologic Emergencies, by Lewis S. Nelson, Mary Ann Howland, Neal A. Lewin, Silas W. Smith, Lewis R. Goldfrank, and Robert S. Hoffman. New York, McGraw-Hill Education 2019, 2070 pages, $245.79. Elsevier; 2020.
4. Arasu R, Jegatheesan D, Sivakumaran Y. Overview of hemodialysis access and assessment. Canadian Family Physician. 2022;68(8):577-82.
5. Ronco C, Bellomo R. Hemoperfusion: technical aspects and state of the art. Critical care. 2022;26(1):1-12.
6. King JD, Kern MH, Jaar BG. Extracorporeal removal of poisons and toxins. Clinical journal of the American Society of Nephrology. 2019;14(9):1408-15.
7. Abel JJ. On the removal of diffusable substances from the circulating blood by means of dialysis. Trans Ass Am Physicians. 1913;28:51.
8. Kyle LH, Jeghers H, Walsh WP, Doolan PD, Wishinsky H, Pallotta A. The application of hemodialysis to the treatment of barbiturate poisoning. The Journal of Clinical Investigation. 1953;32(4):364-71.
9. Schreiner GE. The role of hemodialysis (artificial kidney) in acute poisoning. AMA Archives of Internal Medicine. 1958;102(6):896-913.
10. Palmer BF. Effectiveness of hemodialysis in the extracorporeal therapy of phenobarbital overdose. American journal of kidney diseases. 2000;36(3):640-3.
11. Quintero Parra N, Wurgaft Kirberg A, Orellana Araya YV, Arellano Lorca J, Rojas Wettig L, Pefaur Penna J. Haemodialysis management for salicylate intoxication. Nefrología (English Edition). 2009;29(2):182-3.
12. Lavergne V, Nolin TD, Hoffman RS, Roberts D, Gosselin S, Goldfarb DS, et al. The EXTRIP (EXtracorporeal TReatments in poisoning) workgroup: guideline methodology. Clinical Toxicology. 2012;50(5):403-13.
13. Arelin V, Schmidt JJ, Kayser N, Kühn-Velten WN, Suhling H, Eden G, et al. Removal of methadone by extended dialysis using a high cut-off dialyzer: implications for the treatment of overdose and for pain management in patients undergoing light chain removal. Clinical nephrology. 2016;85(6):353-7.
14. Ghannoum M, Hoffman RS, Gosselin S, Nolin TD, Lavergne V, Roberts DM. Use of extracorporeal treatments in the management of poisonings. Kidney International. 2018;94(4):682-8.
15. Yaxley J, Scott T. Dialysis and extracorporeal therapies for enhanced elimination of toxic ingestions and poisoning. Therapeutic apheresis and dialysis. 2022;26(5):865-78.
16. Majidi M, Delirrad M, Yousefpour A, Mehrno M. An Investigation of Intoxicated Patients who Underwent Hemodialysis: A-five Year Cross-sectional study. Asia Pacific Journal of Medical Toxicology. 2021;10(4):128-33.
17. Delirrad M, Mohammadi AB. New methanol poisoning outbreaks in Iran following COVID-19 pandemic. Alcohol and Alcoholism (Oxford, Oxfordshire). 2020:0-.
18. Mehrpour O, Sadeghi M. Toll of acute methanol poisoning for preventing COVID-19. Archives of toxicology. 2020;94(6):2259-60.
19. Iranpour P, Firoozi H, Haseli S. Methanol poisoning emerging as the result of COVID-19 outbreak; radiologic perspective. Academic radiology. 2020;27(5):755-6.
20. Shokoohi M, Nasiri N, Sharifi H, Baral S, Stranges S. A syndemic of COVID-19 and methanol poisoning in Iran: Time for Iran to consider alcohol use as a public health challenge? : Elsevier; 2020. p. 25-7.
21. Mousavi-Roknabadi RS, Arzhangzadeh M, Safaei-Firouzabadi H, Mousavi-Roknabadi RS, Sharifi M, Fathi N, et al. Methanol poisoning during COVID-19 pandemic; A systematic scoping review. The American journal of emergency medicine. 2022;52:69-84.
22. Najari F, Baradaran I, Najari D. Methanol poisoning and its treatment. Int J Med Toxicol Forensic Med. 2020;10(1):26639.
23. Nekoukar Z, Zakariaei Z, Taghizadeh F, Musavi F, Banimostafavi ES, Sharifpour A, et al. Methanol poisoning as a new world challenge: A review. Annals of medicine and surgery. 2021;66:102445.
24. Hassanian-Moghaddam H, Zamani N, Roberts DM, Brent J, McMartin K, Aaron C, et al. Consensus statements on the approach to patients in a methanol poisoning outbreak. Clinical toxicology. 2019;57(12):1129-36.
25. Kute VB, Godara SM, Shah PR, Gumber MR, Goplani KR, Vanikar AV, et al. Hemodialysis for methyl alcohol poisoning: A single-center experience. Saudi Journal of Kidney Diseases and Transplantation. 2012;23(1):37.
26. Darracq MA, Cantrell FL. Hemodialysis and extracorporeal removal after pediatric and adolescent poisoning reported to a state poison center. The Journal of Emergency Medicine. 2013;44(6):1101-7.
27. Hassanian-Moghaddam H, Nikfarjam A, Mirafzal A, Saberinia A, Nasehi AA, Masoumi Asl H, et al. Methanol mass poisoning in Iran: role of case finding in outbreak management. Journal of public health. 2015;37(2):354-9.
28. Gagnon DJ, Jwo K. Tremors and agitation following low-dose intravenous hydromorphone administration in a patient with kidney dysfunction. Annals of Pharmacotherapy. 2013;47(7-8):e34-e.
29. Ghasemi S, Izadpanahi S, Yaghoubi MA, Brent J, Mehrpour O. Methadone associated long term hearing loss and nephrotoxicity; a case report and literature review. Substance Abuse Treatment, Prevention, and Policy. 2019;14(1):1-5.

Review
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The Synthetic Cannabinoids

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Abstract

Synthetic cannabinoids are defined as psychoactive substances that trigger the endocannabinoid system. Despite attempts to utilize some of their effects for therapeutic purposes, they are predominantly used as recreational drugs. In the past decade, their recreational use has increased more than other psychoactive substances in Europe and the United States. In Turkey, they are referred to as "Bonzai" or "Jamaika." Additionally, factors such as stronger effects compared to cannabis, cost-effectiveness, easy accessibility, and evasion of standard drug tests contribute to the growing use of synthetic cannabinoids. This paper aims to examine the structure and toxicology of synthetic cannabinoids, along with diagnosis and treatment, in line with current literature.

Keywords: poisoning; emergency medicine; synthetic cannabinoids; Δ9-THC; tetrahydrocannabinol

Introduction

Natural cannabis (Δ9-THC, tetrahydrocannabinol) is derived from the Cannabis Sativa plant[1]. Δ9-tetrahydrocannabinol (Δ9-THC), the main psychoactive component of marijuana, binds to endocannabinoid system receptors. Synthetic cannabinoids (SCs) stimulate the endocannabinoid system more intensely and briefly than natural cannabinoids[2].

Δ9-THC was first synthesized by Gaoni and Mechoulam in 1964 (3). Since 2008, 209 species of SCs have been identified in European Union (EU) countries. In 2019, they accounted for 60% of the psychoactive substance market. SC consumption is common among individuals aged 15-34 in the EU[2].

Due to structural differences among SCs and their short plasma half-lives, their detection is challenging. Continuous emergence of new SCs often leads to underestimation of their prevalence, posing a problem for countries[4].

SCs dissolve in organic solvents. It can be mixed with herbs such as mint and thyme. It is sold on the internet or other means under various packaging and names[2]. SCs are usually inhaled. It can also be consumed orally as a tablet powder herbal mixture[5,6].

Physicochemical Properties

In their pure form, synthetic cannabinoids (SCs) are odorless and appear as white or yellowish crystalline powders. They are soluble in organic solvents and alcohols (such as ethanol, methanol, acetone, isooctane, ethyl acetate, acetonitrile) but have low solubility in water[7].

Structurally, they are generally divided into four components: nucleus, tail, binder, and attached groups. Various analytical methods can be employed to detect and quantify SCs. The gold standard method combines gas chromatography-mass spectrometry (GC-MS). Techniques such as nuclear magnetic resonance (NMR) or infrared spectroscopy, gas chromatography combined with flame ionization detection, and liquid chromatography-mass spectrometry (LC-MS) can also be utilized[7,8].

The chemical classification of SCs can be as follows[9];

1. Classic cannabinoids: Tetrahydrocannabinol, other chemical components of marijuana, and their structurally similar synthetic analogs (e.g., AM-411, AM-906, HU-210, O-1184).

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2. Non-classic cannabinoids: Cyclohexylphenols or 3-aryl-cyclohexanols (e.g., CP55,244, CP-55,940, CP-47,497).
3. Hybrid cannabinoids: Combinations of structural features of classic and non-classic cannabinoids (e.g., AM-4030).
4. Aminoalkylindoles, further categorized into: (a) Naphthoylindoles (e.g., JWH-015, JWH-018, JWH073, JWH-081, JWH-122, JWH-200, JWH-210, JWH398) (b) Phenylacetylindoles (e.g., JWH-250, JWH-251) (c) Benzoylindoles (e.g., pravadoline, AM-694, RSC-4) (d) Naphthylmethylindoles (e.g., JWH-184) (e) Cyclopropylindoles (e.g., UR-144, XLR-11) (f) Adamantylindoles (e.g., AB-001, AM-1248) (g) Indole carboxamides (e.g., APICA, STS-135) (h) Indole carboxylates.
5. Eicosanoids: Endocannabinoids like anandamide and their synthetic analogs (e.g., Metanandamide).
6. Others: Encompasses other structural types such as diarylpyrazoles (e.g., RimonabantR), naphthoylpyrroles (e.g., JWH-307), naphthylmethylindenes (e.g., JWH176), and indazole carboxamides (e.g., APINACA).

Pharmacodynamic Effects

The main receptors of the endocannabinoid system are G protein-coupled receptors. The pharmacology of synthetic cannabinoids (SC) is similar to Δ9-THC, and they similarly affect cannabinoid receptors 1 and 2 (CB1R and CB2R). While Δ9-THC exhibits partial agonist effects on receptors, SCs exert full agonist effects. For this reason, SCs lead to higher psychoactive effects and more undesirable effects[10].

Activation of CB1R inhibits adenylate cyclase activity, leading to a decrease in cyclic adenosine monophosphate (cAMP)10. Additionally, CB1R activation induces the activation of the mitogen-activated protein kinase (MAPK) family, including signal-regulated extracellular kinases 1 and 2 (ERK1/2), by the βγ subunits. Phosphorylation of CB1R by G protein receptor kinases (GRKs) following activation may induce the translocation of β-arrestin 1 and 2 to the cell membrane, leading to desensitization and internalization of CB1R, which has been reported to be associated with the development of tolerance[11].

SCs can also modulate signaling pathways independently of CBRs. For example, it has been reported that aminoalkylindole derivatives, arylpyrazole derivatives, and synthetic analogs of phytocannabinoids target transient receptor potential cation channel subfamily V member 1 (TRPV1). It has been found that the desensitization of these channels by WIN55,212-2 promotes analgesic effects[12].

SCs primarily target the brain and modulate neurotransmitter signaling along with other processes.

Ossato and colleagues have shown that SCs facilitate dopamine release in the striatum and nucleus accumbens, resulting in a psychostimulant effect in mice dependent on CB1R activation. Since the ventral tegmental area and nucleus accumbens, along with the medial forebrain bundle connecting both regions, are key structures of the brain's reward circuitry, dopamine neural firing induced by SCs in these regions enhances reward response, thus explaining the addictive potential of these substances[13].

It has also been reported that SCs are more effective than Δ9-THC in inhibiting glutamatergic synaptic transmission14.

It has been shown that SCs suppress glutamate and γ-aminobutyric acid (GABA) release in mice by activating presynaptic CB1Rs in Purkinje cells[15].

Yano and colleagues have shown that SCs may target serotonin receptors independently of CBR activation[16].

Clinical and Therapeutic Aspects

SCs are primarily consumed via inhalation, resulting in rapid absorption by the alveoli. They quickly reach peak concentrations in the blood, and their effects are immediately noticeable. Their half-lives are short[10]. The high lipophilicity of most SCs allows them to bind extensively to plasma proteins, which can lead to increased distribution volumes[17].

SCs are also metabolized to more hydrophilic compounds via conjugation with sulfate and/or glucuronic acid to facilitate renal excretion. The presence of SC metabolites in urine makes it a preferred sample for SC detection. However, before analysis, urine must undergo β-glucuronidase treatment to separate conjugate metabolites10.

SC users often seek some of the known psychotropic effects of the drug, such as increased relaxation, heightened well-being, and social disinhibition, which typically occur immediately after consumption.

Considering the widespread distribution of cannabinoid receptors in the body, SCs can target different organs. They can trigger adverse effects in cardiovascular, digestive, dermatological, ophthalmological, neurological, pulmonary, and hepatic systems. Acute poisonings have been particularly associated with neurological perturbations, including short-term memory loss, flashbacks, and suicidal ideation, among other cognitive impairments[5].

Neurological symptoms include delirium, confusion, hallucinations, agitation, panic attacks, and convulsions. Chronic SC consumption is also associated with an increased risk of developing neuropsychiatric disorders.

Psychotic symptoms are common following SC use. While these are typically transient (lasting only a few hours), they can lead to prolonged psychotic episodes in individuals with no history of psychosis.

New third-generation fluorinated SCs have been shown to induce reduced motor activity and impaired sensorimotor responses, hypothermia, and increased pain threshold against harmful mechanical and thermal stimuli in mice[18].

SCs also target the human cardiovascular system, leading to increased heart rate, tachycardia, and, in the most severe cases, myocardial infarction or stroke[19].

Severe poisonings have been associated with rhabdomyolysis, liver and kidney toxicity, and failure.

Lung injuries (e.g., pneumothorax, pneumomediastinum) are also common and can be attributed to direct local injuries caused by SCs or impurities in SC mixtures, often requiring oxygen support[4,20].

SC withdrawal can also lead to adverse symptoms such as restlessness, headache, irritability, drug cravings, hypertension, nausea, tremors, diaphoresis, and nightmares. Seizures and cardiovascular arrest may occur in more severe cases[21,22].

Poisonings from SCs, whether taken alone or in conjunction with other recreational substances or prescription drugs, are often observed. Fatal poisonings resulting in cardiac arrest, drowning, multiple organ failure, suicide, or traumatic accidents can also occur.

Emergency indoles, indole carboxylates, and indazole carboxamides are the SCs most frequently mentioned in death reports.

Establishing a direct correlation between SCs and cause of death is often challenging because the lack of appropriate reference standards generally hinders the accurate identification and quantification of SCs found in biological samples. Additionally, post-mortem blood concentrations can vary depending on factors such as the type of SC, individual characteristics, and the time elapsed since death.

Most mild SC poisonings require only symptomatic treatment on an outpatient basis, while severe poisonings (e.g., seizures, severe agitation, neuropsychiatric complaints, arrhythmias, stroke, severe dyspnea) result in hospitalization.

The treatment of acute SC poisoning typically involves intensive monitoring and supportive therapy[23-26].

Intravenous fluids are commonly administered to expand the circulatory system volume, control vomiting, and prevent dehydration and renal failure.

Benzodiazepines are the first-line treatment to reduce sedation, anxiety, and agitation, although psychiatric evaluation and antipsychotic administration are often necessary[26,27].

Intubation and mechanical ventilation may be required in severe cases.In cases of oral ingestion, gastric lavage and ingestion of activated charcoal may be necessary depending on the amount of SC ingested and the time elapsed since ingestion[22].

Aksel and colleagues have identified a new treatment called intravenous lipid emulsion (ILE) for SC poisonings, showing promising results as an effective antidote for lipophilic drugs such as SCs, improving recovery from cardiovascular collapse and reversing neurological symptoms caused by these drugs[28]. ILE sequesters drugs in the intravascular space and distributes lipid-soluble drugs into the circulation phase, reducing their concentrations and toxicities.

Withdrawal symptoms from SCs are managed with benzodiazepines, antiemetics, and other symptomatic treatments[29].

Because adolescents and young adults (including women of reproductive age and pregnant women) are the primary users of SCs, the impact of SC use on neurodevelopment represents a fundamental concern. SCs modulate the endocannabinoid system, which is involved in various biological processes, including cell fate and neurogenesis mechanisms (e.g., neuronal differentiation, migration, maturation, synaptic pruning)[30,31].

Due to their high lipophilicity, SCs can easily pass through the placental barrier and reach embryonic tissues[32]. The connection between exposure to SCs prenatally and postnatally and neurogenesis dysfunction is strongly supported by preclinical studies.

Mereu and colleagues demonstrated that daily administration of the CB1R agonist WIN55,212-2 (0.5 mg/kg) to pregnant rats resulted in impaired memory retention capacity in offspring aged 40 and 80 days. These effects were accompanied by a decrease in presynaptic glutamate release in the hippocampus and changes in hippocampal long-term potentiation associated with learning and memory consolidation[33].

Pinky and colleagues reported that the same SC (WIN55,212-2) administered to pregnant rats at a dose of 2 mg/kg body weight daily significantly altered various biochemical markers in adolescent offspring, including a reduction in oxidative stress and apoptotic marker levels and an increase in mitochondrial function in the cerebellum (a brain region playing a significant role in learning and motor function). Interestingly, while GluA1 levels (a significant subtype of glutamate receptor) and tyrosine hydroxylase activity were unaffected, total monoamine oxidase (MAO) activity decreased significantly in the cerebellum, supporting the idea that SCs affect monoamine neurotransmitter levels in this brain region[34].

Numerous in vitro studies have also revealed the crucial role of CBR stimulation in modulating neurogenic processes[35,36]. Kim and colleagues observed that the SC (300 nM WIN55,212-2) significantly inhibited new synapse formation in rat hippocampal neurons obtained from 17-day-old embryos by inhibiting forskolin-induced cAMP elevation. Interestingly, WIN55,212-2 did not block effects induced by a membrane-permeable cAMP analog, suggesting that it inhibits new synapse formation by preventing cAMP synthesis rather than actions downstream of cAMP (e.g., neurotransmitter release)[37].

Jiang and colleagues reported that chronic treatment of neural stem cells isolated from E17 Long Evans rat embryos with 100 µg/kg HU-210 supported neuronal proliferation via ERK pathway activation but did not support differentiation. They associated this effect with the anxiolytic and antidepressant-like effects of HU-210[38].

Miranda and colleagues demonstrated that chronic exposure to SCs during neurogenesis promoted early neuronal and glial differentiation in human-induced pluripotent stem cells and led to abnormal functioning of voltage-gated calcium channels in newborn neurons when stimulated by extracellular potassium[39].

Evaluating the consequences of prenatal and postnatal SC exposure on human neurodevelopment is challenging. This is because cognitive, motor, and behavioral parameters can only be evaluated retrospectively, and various confounding factors can lead to significant differences in outcomes. Thus, isolating the direct consequences of SC use without interpretational bias is hindered[39-41]. Therefore, data on perinatal SC-associated toxicity are limited to only a few case studies reporting no mortality or morbidity characteristics in newborns.

Epigenetic disturbances have been reported in the brain and peripheral organs following exposure to Δ9-THC[42]. Several studies have reported the epigenetic mechanistic consequences of SC exposure[43]. Ibn Lahmar Andaloussi and colleagues observed an increase in global DNA methylation in the prefrontal cortex and transcription of DNA methyltransferase 1 (DNMT1) and 3 (DNMT3) in adolescent male rats exposed to WIN55,212-2 for one week. They suggested that these epigenetic modifications contributed to the anxiogenic-like effects observed in exposed rats and their offspring[44].

Tomas-Roig and colleagues observed that long-term administration of WIN55,212-2 during adolescence increased anandamide levels and promoted DNA hypermethylation in the intragenic region of the intracellular signal modulator Rgs7 (an intracellular antagonist of GPCR signaling). It was found that this altered the expression of Rgs7 in adulthood45. Application of HU-210 to female rats during pregnancy and for 14 days after birth has been shown to alter microRNA expression in the left hemisphere of the entorhinal cortex, a brain region associated with schizophrenia[46].

Therapeutic Potential

Accumulated findings have revealed the therapeutic potential of the endocannabinoid system, leading to the consideration of cannabinoids as candidate agents for treating various disorders[47]. Indeed, synthetic analogs of Δ9-THC, such as dronabinol and nabilone (Marinol and Cesamet, respectively), have been approved by the U.S. Food and Drug Administration as adjunct analgesics for alleviating chemotherapy-induced nausea and vomiting or chronic pain when first-line antiemetics fail[48]. Additionally, nabiximols, marketed as Sativex, which is a standardized combination of synthetic Δ9-THC and cannabidiol in equal amounts, has shown moderate evidence for treating spasticity associated with multiple sclerosis[47]. However, efforts to develop SC-based therapeutic agents have largely been halted due to adverse events associated with CB1R activation triggered primarily in the central nervous system[49].

The ability of SCs to bind to CB2Rs suggests the safe targeting of the endocannabinoid system due to its potential to modulate inflammatory processes. For instance, it has been shown that WIN55,212-2 suppresses nitric oxide production, TNF-α release, and the formation of CXCL10, CCL2, and CCL5 chemokines in IL-1-stimulated astrocytes[50]. However, the discovery of the endocannabinoidome has further complicated the signaling events triggered by SCs, thus limiting their potential therapeutic applications[49].

Conclusions

Research on the biological significance of the endocannabinoid system has greatly expanded in recent years, with synthetic cannabinoids (SCs) playing an important role as research tools to understand how this system regulates fundamental biological processes. However, the widespread recreational use of SCs has become a significant public health and social concern.

The ability of SCs to interact with cannabinoid receptors (CBRs), namely CB1R, CB2R, and non-CBRs (e.g., TRPV, GPR55, PPARs, 5-HT receptors), and the biased agonism of SCs upon binding to CBRs, increase the complexity of the signaling pathway network modulated by these substances, hindering the understanding of such signal modulation.

Furthermore, since the targets of SCs are widespread throughout the body, their effects and adverse outcomes extend to all major organs and tissues. The toxicology of SCs is generally uncertain because (a) toxic effects may be associated not only with SC itself but also with other toxic substances present in SC herbal mixtures; (b) various confounding factors (e.g., genetic, environmental, frequency/type of SC used) can influence their effects; (c) in vitro effects vary depending on the cell model and experimental design (e.g., concentration, time point, exposure protocol); and (d) only a few studies have addressed the toxicological effects of SCs at biologically relevant concentrations.

Modulation of mitochondrial function and activity by SCs and induction of apoptotic signaling have been shown as significant mechanisms underlying the toxicity of these substances.

Additionally, the contribution of SC-associated neurodevelopmental/neuropsychiatric disorders to neurogenesis is likely, which is particularly concerning given that adolescents and young adults are the main users of SCs. SCs may also interfere with epigenetic mechanisms and promote epigenetic changes that can predispose individuals to different pathologies inherited by their offspring. Interestingly, while the therapeutic value of SCs has been demonstrated with the clinical use of synthetic Δ9-THC analogs to treat chemotherapy-induced nausea and vomiting, evidence for their potential use in other

therapeutic applications remains lacking. Understanding the pharmacological and toxicological mechanisms underlying the short- and long-term consequences of SC use and how they may affect consumers' health and quality of life, as well as improving the interpretation of clinical/pathological findings related to SCs, is of great importance, and further research in this area is warranted.

Synthetic cannabinoids (SCs) are designed to mimic the effects of Δ9-tetrahydrocannabinol (Δ9-THC) but exhibit stronger potency and efficacy at cannabinoid receptors.

Recreational SC use is globally prevalent and often associated with acute poisoning and death reports.

SCs trigger a complex signaling pathway network contributing to the modulation of fundamental biological processes by targeting both cannabinoid and non-cannabinoid receptors.

Given their high metabolic rates and the lack of appropriate reference standards for main compounds and related metabolites, timely detection and quantification of SCs in biological samples continue to be a challenge for forensic toxicologists/pathologists.

SCs induce numerous adverse outcomes that are more severe and longer-lasting across different organ systems than those induced by Δ9-THC.

Chronic SC use and/or use, particularly by vulnerable groups (e.g., adolescents and young adults), may promote the onset of neurodevelopmental/neuropsychiatric disorders (e.g., psychosis, autism spectrum) in the long term, for example, by disrupting proper neurogenesis or causing epigenetic changes.

SCs have been proposed as candidate agents for several different therapeutic applications, but there is currently little evidence regarding their therapeutic potential beyond the treatment of chemotherapy-induced nausea and vomiting.

Further research is needed to elucidate the key mechanisms underlying the short- and long-term effects mediated by SCs, which will help reduce the misuse of SCs by high-risk groups.

References

1. Aşıcıoğlu FJYNP-AMSK. Yeni nesil psiko-aktif maddeler. 2013:3-5.
2. Drugs EMCf, Addiction D. Perspectives on drugs: synthetic cannabinoids in Europe. Publications Office of the European Union Luxembourg; 2017.
3. Gaoni Y, Mechoulam RJJotAcs. Isolation, structure, and partial synthesis of an active constituent of hashish. 1964;86(8):1646-7.
4. Mills B, Yepes A, Nugent KJTAjotms. Synthetic cannabinoids. 2015;350(1):59-62.
5. Lafaye G, Karila L, Blecha L, Benyamina AJDicn. Cannabis, cannabinoids, and health. 2017;19(3):309-16.
6. Solimini R, Busardo FP, Rotolo M, Ricci S, Mastrobattista L, Mortali C, et al. Hepatotoxicity associated to synthetic cannabinoids use. 2017;21.
7. Tettey JN, Crean C, Rodrigues J, Yap TWA, Lim JLW, Lee HZS, et al. United Nations Office on Drugs and Crime: recommended methods for the identification and analysis of synthetic cannabinoid receptor agonists in seized materials. 2021;3:100129.
8. Liu CM, Jia W, Meng X, Hua ZDJJoFS. Identification and quantification of 10 indole/indazole carboxamide synthetic cannabinoids in 36 herbal blends by gas chromatography□mass spectrometry and nuclear magnetic resonance spectroscopy. 2021;66(6):2156-66.
9. Tettey JNA, Crean C, Rodrigues J, Angeline Yap TW, Lee Wendy Lim J, Shirley Lee HZ, et al. United Nations Office on Drugs and Crime: Recommended methods for the Identification and Analysis of Synthetic Cannabinoid Receptor Agonists in Seized Materials. Forensic Science International: Synergy. 2021;3:100129.
10. Alves VL, Gonçalves JL, Aguiar J, Teixeira HM, Câmara JSJCRiT. The synthetic cannabinoids phenomenon: from structure to toxicological properties. A review. 2020;50(5):359-82.
11. Patel M, Manning JJ, Finlay DB, Javitch JA, Banister SD, Grimsey NL, et al. Signalling profiles of a structurally diverse panel of synthetic cannabinoid receptor agonists. 2020;175:113871.
12. Ruparel NB, Patwardhan AM, Akopian AN, Hargreaves KMJMp. Desensitization of transient receptor potential ankyrin 1 (TRPA1) by the TRP vanilloid 1-selective cannabinoid arachidonoyl-2 chloroethanolamine. 2011;80(1):117-23.
13. Oleson EB, Cheer JFJCSHpim. A brain on cannabinoids: the role of dopamine release in reward seeking. 2012;2(8):a012229.
14. Brown TM, Brotchie JM, Fitzjohn SMJJoN. Cannabinoids decrease corticostriatal synaptic transmission via an effect on glutamate uptake. 2003;23(35):11073-7.
15. Irie T, Kikura-Hanajiri R, Usami M, Uchiyama N, Goda Y, Sekino YJN. MAM-2201, a synthetic cannabinoid drug of abuse, suppresses the synaptic input to cerebellar Purkinje cells via activation of presynaptic CB1 receptors. 2015;95:479-91.
16. Yano H, Adhikari P, Naing S, Hoffman AF, Baumann MH, Lupica CR, et al. Positive allosteric modulation of the 5-HT1A receptor by indole-based synthetic cannabinoids abused by humans. 2020;11(10):1400-5.
17. Lobato-Freitas C, Brito-da-Costa AM, Dinis-Oliveira RJ, Carmo H, Carvalho F, Silva JP, et al. Overview of synthetic cannabinoids ADB-FUBINACA and AMB-FUBINACA: clinical, analytical, and forensic implications. 2021;14(3):186.
18. Canazza I, Ossato A, Vincenzi F, Gregori A, Di Rosa F, Nigro F, et al. Pharmaco-toxicological effects of the novel third-generation fluorinate synthetic cannabinoids, 5F-ADBINACA, AB-FUBINACA, and STS-135 in mice. In vitro and in vivo studies. 2017;32(3):e2601.
19. Gurney S, Scott K, Kacinko S, Presley B, Logan BJFSR. Pharmacology, toxicology, and adverse effects of synthetic cannabinoid drugs. 2014;26(1):53-78.
20. Tatusov M, Mazer-Amirshahi M, Abbasi A, Goyal MJTAJoEM. Clinical effects of reported synthetic cannabinoid exposure in patients admitted to the intensive care unit. 2019;37(6):1060-4.
21. Martinotti G, Santacroce R, Papanti D, Elgharably Y, Prilutskaya M, Corazza OJC, et al. Synthetic cannabinoids: psychopharmacology, clinical aspects, psychotic onset. 2017;16(5):567-75.

22. Cooper ZD. Adverse Effects of Synthetic Cannabinoids: Management of Acute Toxicity and Withdrawal. Current psychiatry reports. 2016;18(5):52.
23. Mills B, Yepes A, Nugent K. Synthetic Cannabinoids. The American journal of the medical sciences. 2015;350(1):59-62.
24. Riederer AM, Campleman SL, Carlson RG, Boyer EW, Manini AF, Wax PM, et al. Acute Poisonings from Synthetic Cannabinoids - 50 U.S. Toxicology Investigators Consortium Registry Sites, 2010-2015. MMWR Morbidity and mortality weekly report. 2016;65(27):692-5.
25. Armenian P, Darracq M, Gevorkyan J, Clark S, Kaye B, Brandehoff NP. Intoxication from the novel synthetic cannabinoids AB-PINACA and ADB-PINACA: A case series and review of the literature. Neuropharmacology. 2018;134(Pt A):82-91.
26. Müller HH, Kornhuber J, Sperling W. The behavioral profile of spice and synthetic cannabinoids in humans. Brain Research Bulletin. 2016;126:3-7.
27. Tsatsakis A, Docea AO, Calina D, Tsarouhas K, Zamfira LM, Mitrut R, et al. A Mechanistic and Pathophysiological Approach for Stroke Associated with Drugs of Abuse. Journal of clinical medicine. 2019;8(9).
28. Aksel G, Güneysel Ö, Taşyürek T, Kozan E, Çevik Ş E. Intravenous Lipid Emulsion Therapy for Acute Synthetic Cannabinoid Intoxication: Clinical Experience in Four Cases. Case reports in emergency medicine. 2015;2015:180921.
29. Armenian P, Darracq M, Gevorkyan J, Clark S, Kaye B, Brandehoff NP. Intoxication from the novel synthetic cannabinoids AB-PINACA and ADB-PINACA: A case series and review of the literature. Neuropharmacology. 2018;134:82-91.
30. El Marroun H, Brown QL, Lund IO, Coleman-Cowger VH, Loree AM, Chawla D, et al. An epidemiological, developmental and clinical overview of cannabis use during pregnancy. Preventive Medicine. 2018;116:1-5.
31. Cristino L, Bisogno T, Di Marzo V. Cannabinoids and the expanded endocannabinoid system in neurological disorders. Nature reviews Neurology. 2020;16(1):9-29.
32. Dong C, Chen J, Harrington A, Vinod KY, Hegde ML, Hegde VL. Cannabinoid exposure during pregnancy and its impact on immune function. Cellular and molecular life sciences : CMLS. 2019;76(4):729-43.
33. Mereu G, Fà M, Ferraro L, Cagiano R, Antonelli T, Tattoli M, et al. Prenatal exposure to a cannabinoid agonist produces memory deficits linked to dysfunction in hippocampal long-term potentiation and glutamate release. Proceedings of the National Academy of Sciences of the United States of America. 2003;100(8):4915-20.
34. Pinky PD, Majrashi M, Fujihashi A, Bloemer J, Govindarajulu M, Ramesh S, et al. Effects of prenatal synthetic cannabinoid exposure on the cerebellum of adolescent rat offspring. Heliyon. 2021;7(4):e06730.
35. Alexandre J, Carmo H, Carvalho F, Silva JP. Synthetic cannabinoids and their impact on neurodevelopmental processes. Addiction biology. 2020;25(2):e12824.
36. Oudin MJ, Gajendra S, Williams G, Hobbs C, Lalli G, Doherty P. Endocannabinoids regulate the migration of subventricular zone-derived neuroblasts in the postnatal brain. The Journal of neuroscience : the official journal of the Society for Neuroscience. 2011;31(11):4000-11.
37. Kim D, Thayer SA. Cannabinoids inhibit the formation of new synapses between hippocampal neurons in culture. The Journal of neuroscience : the official journal of the Society for Neuroscience. 2001;21(10):Rc146.
38. Jiang W, Zhang Y, Xiao L, Van Cleemput J, Ji SP, Bai G, et al. Cannabinoids promote embryonic and adult hippocampus neurogenesis and produce anxiolytic- and antidepressant-like effects. The Journal of clinical investigation. 2005;115(11):3104-16.
39. Miranda CC, Barata T, Vaz SH, Ferreira C, Quintas A, Bekman EP. hiPSC-Based Model of Prenatal Exposure to Cannabinoids: Effect on Neuronal Differentiation. Frontiers in molecular neuroscience. 2020;13:119.
40. Scheyer AF, Melis M, Trezza V, Manzoni OJJ. Consequences of Perinatal Cannabis Exposure. Trends in neurosciences. 2019;42(12):871-84.
41. Wu CS, Jew CP, Lu HC. Lasting impacts of prenatal cannabis exposure and the role of endogenous cannabinoids in the developing brain. Future neurology. 2011;6(4):459-80.
42. Szutorisz H, Hurd YLJN, Reviews B. High times for cannabis: Epigenetic imprint and its legacy on brain and behavior. 2018;85:93-101.
43. Gomes TM, da Silva DD, Carmo H, Carvalho F, Silva JPJPR. Epigenetics and the endocannabinoid system signaling: An intricate interplay modulating neurodevelopment. 2020;162:105237.
44. Andaloussi ZIL, Taghzouti K, Abboussi OJIJoDN. Behavioural and epigenetic effects of paternal exposure to cannabinoids during adolescence on offspring vulnerability to stress. 2019;72:48-54.
45. Tomas-Roig J, Benito E, Agis-Balboa R, Piscitelli F, Hoyer-Fender S, Di Marzo V, et al. Chronic exposure to cannabinoids during adolescence causes long-lasting behavioral deficits in adult mice. 2017;22(6):1778-89.
46. Hollins S, Zavitsanou K, Walker F, Cairns MJTp. Alteration of imprinted Dlk1-Dio3 miRNA cluster expression in the entorhinal cortex induced by maternal immune activation and adolescent cannabinoid exposure. 2014;4(9):e452-e.
47. Whiting PF, Wolff RF, Deshpande S, Di Nisio M, Duffy S, Hernandez AV, et al. Cannabinoids for medical use: a systematic review and meta-analysis. 2015;313(24):2456-73.
48. de Vries M, van Rijckevorsel DC, Wilder-Smith OH, van Goor HJEoop. Dronabinol and chronic pain: importance of mechanistic considerations. 2014;15(11):1525-34.
49. Cristino L, Bisogno T, Di Marzo VJNRN. Cannabinoids and the expanded endocannabinoid system in neurological disorders. 2020;16(1):9-29.
50. Sheng WS, Hu S, Min X, Cabral GA, Lokensgard JR, Peterson PKJG. Synthetic cannabinoid WIN55, 212-2 inhibits generation of inflammatory mediators by IL-1β-stimulated human astrocytes. 2005;49(2):211-9.

Case Report
Eurasian Journal of Toxicology

A Contrary Case in the Literature: Hepatotoxicity Following Mallow Consumption

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Abstract

Mallow (Malva neglecta Wallr, M.sylvestris L.) is a plant species, it's key constituents include mucilage, pectins, glycosides, and flavonoids. The plant is believed to possess antimicrobial, antioxidant, anti-inflammatory, anti-ulcerogenic, hepatoprotective, anti-urolithiasis, anti-cholinesterase, and angiotensin-converting enzyme (ACE) inhibitory effects, as well as inhibition against alpha-amylase, alpha-glucosidase, and pancreatic lipase. Despite all the reported hepatoprotective and antioxidant effects of mallow, the elevation in liver function test values in our case is quite remarkable and contradicts the information available in the current literature.

Keywords: Mallow, poisoning, hepatotoxicity, emergency medicine

Introduction

Mallow (Malva neglecta Wallr, M.sylvestris L.) is a plant species, either annual or perennial, commonly found along roadsides, disturbed areas, and gardens. Its leaves, seeds, and roots are utilized for various purposes. Key constituents include mucilage, pectins, glycosides, and flavonoids[1]. The plant is believed to possess antimicrobial, antioxidant, anti-inflammatory, antiulcerogenic, hepatoprotective, anti-urolithiasis, anticholinesterase, and angiotensin-converting enzyme (ACE) inhibitory effects, as well as inhibition against alpha-amylase, alpha-glucosidase, and pancreatic lipase. In traditional medicine, it is employed for the treatment of gastritis, gastric ulcers, cough, bronchitis, and pharyngitis[2].

In this report, we aim to present a case of acute abdominal pain following the ingestion of mallow, leading to an elevated liver function test (LFT) not previously reported in the literature. The patient was admitted with a preliminary diagnosis of toxic hepatitis.

Case Report

A 70-year-old male patient presented to our emergency department with abdominal pain. Vital signs were within normal limits. Physical examination revealed tenderness in the epigastric and right upper quadrant of the abdomen. Electrocardiogram (EKG) showed a normal sinus rhythm with no ischemic changes. Laboratory investigations disclosed elevated liver function tests (LFTs) with ALT: 437 U/L (normal range: 5-40 U/L), AST: 727 U/L (normal range: 5-40 U/L), Total Bilirubin: 3.70 mg/dL (normal range: 0.2-1.2 mg/dL), and Direct Bilirubin: 1.50 mg/dL (normal range: 0-0.5 mg/dL). Other investigations, including cardiac markers (Troponin I), were within normal limits.

Upon further inquiry into the patient's medical history related to liver function, it was revealed that the patient had consumed mallow weed that he had personally gathered during his evening meal and had not ingested mushrooms or any other medication. Additional tests, including coagulation studies and hepatitis markers, were within normal limits.

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The patient was admitted to the Gastroenterology service with a diagnosis of toxic hepatitis.

Discussion

While the botanical names for mallow are Malva neglecta Wallr and M. sylvestris L.3, it is referred to by various regional names such as "kömeç" and "tolik." Locally, it is believed to be effective in the treatment of mumps, rheumatic diseases, and tonsillar conditions. The plant is commonly boiled as a whole and applied as a poultice to the affected area after being prepared into a paste, which is then wrapped. Additionally, the local community incorporates mallow in salads and various dishes. The flower and leaves of the plant are also boiled, strained, and the resulting liquid is either consumed directly or mixed with honey after being dried4. In our case, mallow was consumed in the form of a cooked dish, equivalent to one portion.

Mallow is utilized in traditional medicine for the treatment of various conditions, including hypertension, atherosclerosis, and liver diseases. The flowers of the plant contain a variety of compounds such as flavonol glycosides, gossypitrin, missetin, quercetin, luteolin glycoside, anthocyanin, sabdaretin, hibisketrin, luteolin, luteolin glycoside, flavonoid, and chlorogenic acid. Among these, polyphenols, anthocyanins, and flavonoids exhibit antioxidant effects by scavenging free radicals and reactive oxygen species, inhibiting xanthine oxidase, enhancing antioxidant enzyme activity, and reducing lipid peroxidation[3].

Several studies have reported the antihypertensive effects of mallow. This effect has been linked to vasodilation and diuretic effects, inhibition of calcium entry, blockade of angiotensin 1 (AT1) receptors, and ACE inhibition[3].

In various studies utilizing extracts derived from the flowers, leaves, and seeds of mallow, it has been observed that it reduces oxidative stress and eliminates free radicals. Additionally, its antioxidant activity and anti-apoptotic effects have been reported to protect cells from cytotoxicity[3]. It was determined that there was no specific therapeutic intent in the ingestion reported in our case.

Mallow, in its infusion form and extract, has been traditionally used in medicine and as a food source for an extended period, generally considered safe. The limited information available in the current literature supports this. No cases of side effects or poisoning have been reported following oral consumption of mallow in the existing literature[3].

Despite all the reported hepatoprotective and antioxidant effects of mallow, the elevation in liver function test values in our case is quite remarkable and contradicts the information available in the current literature.

In the literature, it has been demonstrated that mallow is safe and not toxic at doses below 200 mg/kg[3]. Based on the statements of the patient and their relatives, we believe that the intake in our case, with an approximate weight of 80 kg, did not exceed this toxic threshold.

A study conducted by Aktürk et al. investigated the knowledge of medical students regarding plant identification, revealing that mallow was one of the least known plants among the students[5]. As clinicians who greeted, assessed, and managed the patient, we initially did not consider that mallow could have a toxic effect. In this regard, we share the belief that both medical students and healthcare professionals, particularly regarding medicinal and traditionally used aromatic plants, may lack sufficient knowledge in this field.

In a study investigating mallow's antimicrobial activities and product contamination, which is one of the reasons for its use in folk medicine, it was observed that mallow obtained from the herbalist had little effect against the tested standard and clinical strains. Additionally, the study revealed that mallow, especially, harbored microorganisms above the limit of 10^2 cfu/mg. These organisms were identified as Coagulase-negative Staphylococcus species, Enterobacteriaceae species, and Pseudomonas aeruginosa6. In another study conducted by Kara et al., it was reported that mallow was effective against H. pylori, Bacillus subtilis, and K. pneumoniae but not effective against Enterobacter cloacae, P. aeruginosa, and Candida albicans[3]. The presence of numerous aerobic bacteria and fungi on mallow suggests a potential risk of health issues for those using these plants. However, in our case, we do not consider the acute hepatotoxicity to be of microbial origin.

Conclusion

Despite the well-known hepatoprotective and antioxidant effects of mallow, the reasons for causing hepatotoxicity in our patient remain unclear and could not be definitively identified by us, contrary to the information in the literature. It is possible that our patient may have ingested a different plant, mistakenly thinking it was mallow, or that other wild/toxic plants may have been mixed in with the known mallow. Nevertheless, even a plant that can be characterized as safe and liver-friendly should be kept in mind by clinicians that, albeit rarely, it may exhibit contrary effects in some individuals.

References

1. Hakan Ö, Çoban F, Bouljak M. Doğu Anadolu Bölgesinin Önemli Tıbbi-Aromatik Bitkileri. Erciyes Tarım ve Hayvan Bilimleri Dergisi. 2020; 3(1):16-23.
2. Al-Snafi A. Medical benefit of Malva neglecta -A review. IOSR Journal Of Pharmacy. 2019; 9(6): 60-67.
3. Örs Y, Baldemir A. Kayseri Aktarlarında Satılan Ebegümeci (Malva Sylvestris L) Örneklerinin Avrupa Farmakopesi'ne

Uygunluğunun Araştırılması (tez). Erciyes Üniversitesi Eczacılık Fakültesi. 2013.

4. Akan H. Adıyaman merkezi ve Narince köyünün etnobotanik açıdan araştırılması. Bitlis Eren Üniversitesi Fen Bilimleri Dergisi, 2015; 4(2):219-248.
5. Aktürk Z, Dağdeviren N, Yıldırım T, Yılmazer AZ, Bulut FG, Subaşı B. Tıp öğrencileri bitkileri ne kadar tanıyor? Tıp Fakültesi birinci ve altıncı sınıf öğrencileri arasında bitkilerin ve sağlıktaki kullanım alanlarının bilinme durumu. Genel Tıp Dergisi. 2006; 16(3): 101-106.
6. Döşler S, Özdemir R, Yılmaz F. Bazı Bitki Ekstrelerinin Antimikrobiyal Etkilerinin Araştırılması. Türk Farmakope Dergisi. 2019; 4(3): 17-28.

Case Report

Eurasian Journal of Toxicology

One Night of Fun, One Lifetime of Effects: MDMA and Sympathomimetic Syndrome

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Abstract

Sympathomimetic syndromes are rare medical conditions involving complex clinical pictures caused by substances that have a stimulatory effect on the sympathetic nervous system or have similar effects to the sympathetic nervous system. In this case report, the clinical manifestations of sympathomimetic syndromes, the diagnostic process, treatment strategies and the difficulties encountered especially in emergency medicine will be reviewed.

Keywords: Critical care, Emergency department, Sympathomimetic syndrome

Introduction

Sympathomimetic syndromes are rare medical conditions involving complex clinical pictures caused by substances that have a stimulatory effect on the sympathetic nervous system or have similar effects to the sympathetic nervous system[1-4]. These syndromes are caused by the use of substances that enhance or mimic the effects of the sympathetic nervous system by binding to adrenergic receptors in the body1-3. Sympathomimetics can trigger a range of symptoms and signs with serious effects on respiration, circulation and the central nervous system[1-3,5].

Sympathomimetic syndromes include rare and complex clinical conditions that can often be difficult to understand1-5. These conditions can arise from a variety of causes including drug abuse, suicide attempts, chemical exposure or toxic interactions[5,6].

In this case report, the clinical manifestations of sympathomimetic syndromes, the diagnostic process, treatment strategies and the difficulties encountered especially in emergency medicine will be reviewed.

Case Report

The patient, a 31-year-old male, known to be in good general health, presented to the emergency department after using a synthetic drug called ecstasy (3,4-metilenedioksi-N-metilamfetamin [MDMA]) by his friends. The patient was brought to the emergency room by his relatives after rapidly increasing anxiety, agitation, high fever and sweating after ecstasy use. On physical examination, the patient's consciousness was alert and oriented, but a rapid pulse and high blood pressure were detected. The vital signs of the patient at the time of arrival to the emergency room were Blood Pressure Arterial: 160/95 mmHg, Pulse rate: 130 beats/minute, Respiratory Rate: 22/minute, Oxygen Saturation measured by pulse oximeter: 99% and the patient's temperature was 38,4 degrees Celsius. Eye examination revealed mydriasis, bilateral direct and indirect light reflexes were normal. Agitated behavior and excessive muscle movements were also noted. Respiratory rate and depth of respiration increased. Liver function tests, renal function tests and complete blood count were within normal limits. There was no acidosis in blood gas.

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It was evaluated that the patient developed sympathomimetic syndrome related to the ecstasy (MDMA) he had used.

The patient was given 20 mg diazepam and 150 cc saline per hour. The patient was followed up in the emergency department for approximately 16 hours. His complaints regressed. The patient was consulted to Psychiatry and discharged with recommendations.

Discussion

Sympathomimetics are substances that have a stimulant effect on the sympathetic nervous system and can cause symptoms such as increased heart rate, elevated blood pressure and extreme agitation[1,2,3]. The observed symptoms and physical examination findings point to this diagnosis.

The patient requires urgent medical intervention and stabilization of vital signs should be aimed first5. The patient's pulse rate, blood pressure and respiratory rate should be closely monitored and supportive treatment should be given when necessary[4].

There is no specific antidote for MDMA intoxication or a treatment protocol that provides the opposite effects[2,7]. Therefore, treatment management is based on symptom-oriented supportive therapies. Sedative drugs and methods to reduce agitation should be preferred to control the patient's agitation and excessive muscle movements.

If necessary, the patient may need to be transferred to an intensive care unit depending on the clinical condition and severity of symptoms. However, obtaining detailed information about the substance the patient is using and the process of use will help to determine the best possible treatment strategy.

In this case report, a patient admitted to the hospital due to MDMA use, which can cause sympathomimetic syndromes, is analyzed. It was emphasized that sympathomimetics can lead to serious clinical findings by stimulating the sympathetic nervous system[1-3].

MDMA is a synthetic drug used for recreational purposes that is thought to increase emotional bonding[1-3,7]. However, overdose and abuse can lead to the formation of sympathomimetic syndromes and life-threatening clinical pictures. Therefore, the importance of raising drug awareness in the society, awareness-raising studies on drug abuse and preventive measures should be emphasized.

Conclusion

This case underscores the critical importance of recognizing and managing sympathomimetic syndromes, particularly those induced by substances like MDMA. The presented patient's clinical course highlights the significance of prompt medical intervention, vital sign stabilization, and symptom-oriented supportive therapies. In emergency settings, healthcare providers should prioritize detailed substance use history, enabling tailored treatment strategies. The lack of a specific antidote for MDMA reinforces the need for a vigilant and multidisciplinary approach. Beyond individual cases, this report emphasizes the broader societal necessity for increased drug awareness, educational initiatives on substance abuse, and proactive preventive measures.

References

1. Kalant H. The pharmacology and toxicology of "ecstasy" (MDMA) and related drugs. CMAJ. 2001 Oct 2;165(7):917-28. PMID: 11599334; PMCID: PMC81503.
2. Steinkellner T, Freissmuth M, Sitte HH, Montgomery T. The ugly side of amphetamines: short- and long-term toxicity of 3,4-methylenedioxymethamphetamine (MDMA, 'Ecstasy'), methamphetamine and D-amphetamine. Biol Chem. 2011 Jan;392(1-2):103-15. doi: 10.1515/BC.2011.016. PMID: 21194370; PMCID: PMC4497800.
3. Jansen KL, Theron L. Ecstasy (MDMA), methamphetamine, and date rape (drug-facilitated sexual assault): a consideration of the issues. J Psychoactive Drugs. 2006 Mar;38(1):1-12. doi: 10.1080/02791072.2006.10399822. PMID: 16681170.
4. King A, Dimovska M, Bisoski L. Sympathomimetic Toxidromes and Other Pharmacological Causes of Acute Hypertension. Curr Hypertens Rep. 2018 Feb 24;20(1):8. doi: 10.1007/s11906-018-0807-9. PMID: 29478133.
5. Chan TC, Evans SD, Clark RF. Drug-induced hyperthermia. Crit Care Clin. 1997 Oct;13(4):785-808. doi: 10.1016/s0749-0704(05)70369-9. PMID: 9330841.
6. Brown H, Pollard KA. Drugs of Abuse: Sympathomimetics. Crit Care Clin. 2021 Jul;37(3):487-499. doi: 10.1016/j.ccc.2021.03.002. PMID: 34053702.
7. Shannon M. Methylenedioxymethamphetamine (MDMA, "Ecstasy"). Pediatr Emerg Care. 2000 Oct;16(5):377-80. doi: 10.1097/00006565-200010000-00022. PMID: 11063374.

Letter to Editor

Eurasian Journal of Toxicology

Effects of Microplastics on Mental Health

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Abstract

The impact of microplastics on mental health is an emerging area of research, and the medical literature points to potential neurobehavioral effects. Studies have shown that exposure to microplastics can lead to changes in behavior, neurotoxicity, and cognitive impairments in animal models. Although these findings from animal studies suggest a possible link between microplastic exposure and mental health outcomes, it is important to note that research in this area is still limited and more studies are needed to understand the mechanisms and consequences for human health.

Keywords: Environment, microplastics, mental health, toxicology

Dear Editor,

Microplastics are small plastic particles typically defined as less than 5 mm in diameter. They are caused by the breakdown of larger plastic debris, the release of plastic fibers from textiles, and microbeads used in personal care products. Microplastics are ubiquitous in a variety of environments, including marine and freshwater systems, soil, and the atmosphere. They can enter plant and animal tissues and have also been detected in human tissues such as lungs, brain, feces, placenta, and blood. The presence of microplastics in the environment and their potential to enter the food chain raises concerns about their impact on human health; however, direct clinical evidence of adverse effects is currently limited[1]. The impact of microplastics on the blood-brain barrier (BBB) is an emerging area of concern; there is evidence to suggest that some micro- and nanoplastics can cross the BBB and cause neurotoxic effects. Studies have shown that polystyrene nanoparticles (PS-NPs) can penetrate the BBB, increase its permeability, and accumulate in the brain, leading to microglia activation and potential neuronal damage. Nanoparticles, especially smaller sized ones, reach the brain and interact with the lipid bilayers of the BBB. Additionally, exposure to microplastics has been associated with oxidative stress, inflammation, and disruption of tight junction proteins such as zona occludens 1 (ZO-1) in brain microvascular endothelial cells, which are integral to BBB integrity[2]. Chronic exposure to microplastics has also been linked to cognitive deficits and memory impairments in animal models, suggesting potential neurotoxic effects. Additionally, size-dependent effects of microplastics have been observed; smaller particles cause more significant disturbances in the nervous system, including changes in neurotransmitter levels[2].

The relationship between microplastics and psychiatric disorders is an emerging area of research, and several studies suggest a potential link. Microplastics have been shown to accumulate in various tissues, including the brain, and are associated with neurotoxicity and behavioral changes in animal models. For example, polystyrene microplastics (PS-MPs) have been reported to cause anxiety-like behavior in mice; evidence points to gut microbiota dysbiosis, metabolic disorder, and activation of inflammatory pathways in the brain as potential mechanisms[3]. Additionally, prenatal and postnatal exposure to microplastics has been associated

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with the development of autism spectrum disorder (ASD)-like traits in mice, suggesting a potential risk factor for ASD4. Moreover, exposure to microplastics is linked to impairments in neuronal arborization and dendritic spine density in the prefrontal cortex of mice; this may have effects on cognitive and emotional regulation. Additionally, studies have shown that microplastics can increase amyloid-beta peptide aggregation and increase neurotoxicity associated with Alzheimer's disease pathology[5].

While these findings from animal and in vitro studies suggest a potential relationship between microplastics and psychiatric disorders, it is important to note that the direct applicability and clinical significance of these findings to human health requires further investigation. The mechanisms it may contribute to are areas of active research. Therefore, current understanding of the relationship between microplastics and psychiatric disorders is still evolving, and further research is needed to establish causality and understand the underlying biological processes.

References

1. Jung YS, Sampath V, Prunicki M, Aguilera J, Allen H, LaBeaud D, et al. Characterization and regulation of microplastic pollution for protecting planetary and human health. Environmental Pollution. 2022; 315: 120442.
2. Li C, Chen X, Du Z, Geng X, Li M, Yang X, et al. Inhibiting ferroptosis in brain microvascular endothelial cells: A potential strategy to mitigate polystyrene nanoplastics–induced blood–brain barrier dysfunction. Environmental Research. 2024; 250: 118506.
3. Li G, Liu X, Sun X, Huang L, Kuang W, Ou J, et al. Polystyrene microplastics induce anxiety via HRAS derived PERK-NF-κB pathway. Environment international. 2024; 185: 108543.
4. Zaheer J, Kim H, Ko IO, Jo EK, Choi EJ, Lee HJ, et al. Pre/post-natal exposure to microplastic as a potential risk factor for autism spectrum disorder. Environment International. 2022; 161: 107121.
5. Gou X, Fu Y, Li J, Xiang J, Yang M, Zhang Y. Impact of nanoplastics on Alzheimer 's disease: Enhanced amyloid-β peptide aggregation and augmented neurotoxicity. Journal of Hazardous Materials. 2024; 465: 133518.