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Histomorphological Effects of Crack Cocaine on the Liver of Wistar Rats

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Abstract

Cocaine (koe kane') is a potent local anesthetic that appears to act by inhibition of voltage-gated sodium channels, increasing the threshold for electric excitability of nerve axons and thus decreasing neuroconduction. In the central nervous system, cocaine appears to block both norepinephrine and serotonin reuptake. The aim of this study is to determine the histological effect of crack cocaine on the liver of adult albino wistar rat. A total of forty (40) adult Albino Wistar rats of comparable sizes were used for this study. They were divided into four equal groups (A – D) with ten (10) rats each. Group A served as the control and the rats were given distilled water and feed only. In addition to feed and water, groups B rats were given 0.5ml (100mg) *crack cocaine extract* and *crack cocaine extract,* group C rats were given 2ml (200mg) *crack cocaine extract*, and group D rats were given 5ml (300mg) *crack cocaine extract* respectively. The drug administration was given daily for 14 days (2 weeks) and the weights of both the test and control animals was monitored before and after administration of *crack cocaine extract*. The administration of the *crack cocaine* extracts was given orally. After the administration, the rats were put under light chloroform anaesthesia and the liver were obtained. ANOVA was used to analyze the results of the weight and differences was considered significant at $p<0.05$ level of confidence. All data was expressed in table as mean ± standard deviation (SD). The results of this study show presence of bridging necrosis and portal fibrosis in the liver histology of test wistar rats administered with crack cocaine at 200 and 300mg when compared with the non-cocaine administered group also a non-significant variation was observed in the body weight of control and test groups across the groups. In conclusion, the use of cocaine can lead to significant and harmful effects on liver histology, resulting from a combination of factors related to the drug's pharmacological actions, metabolism, and physiological responses. These changes stem from cocaine's vasoconstrictive properties, generation of reactive metabolites, direct toxic effects, and interactions with other substances.

Keywords: Crack, Cocaine, Histology, Liver, Wistar Rats.

INTRODUCTION

Cocaine (koekane') is a potent local anesthetic that appears to act by inhibition of voltage-gated sodium channels, increasing the threshold for electric excitability of nerve axons and thus decreasing neuroconduction. In the central nervous system, cocaine appears to block both norepinephrine and serotonin reuptake. High doses produce euphoria followed by withdrawal symptoms, leading to a repeated desire to restart it and great abuse potential (Farooque, Okorie, Kataria, Shah & Bollampally, 2020). Chronic use is associated with irritability, paranoia, violence and drug seeking behavior. Cocaine is one of the most addictive medications known. For this reason, cocaine is listed as a Schedule I drug, indicating that it has high abuse potential and no current medical usefulness. Cocaine

abuse is relatively common; an estimated 600,000 Americans regularly abuse cocaine (Mash, 2019).

Cocaine is a benzoid acid ester that that was originally used as a local anesthetic, but is no longer used because of its potent addictive qualities. When given in high doses systemically, cocaine has mood elevating effects that have led to its widescale abuse. High doses of cocaine can be associated with toxic reactions including hyperthermia, rhabdomyolysis, shock and acute liver injury which can be severe and even fatal (Rai & Tewari, 2018).

Cocaine crosses the blood-brain barrier via a proton-coupled organic cationantiporter and (to a much lesser extent) via passive diffusion. Cocaine acts as an indirect sympathomimetic by blocking the dopamine transporter inhibiting reuptake of dopamine from the synaptic cleft into the pre-synaptic axon terminal; the higher dopamine levels in the synaptic cleft increase dopamine receptor activation in the post-synaptic neuron, which drives the effects of euphoria and arousal. Cocaine also blocks the serotonin transporter and norepinephrine transporter, inhibiting reuptake of serotonin and norepinephrine from the synaptic cleft into the pre-synaptic axon terminal and increasing activation of serotonin receptors and norepinephrine receptors in the post-synaptic neuron, contributing to the modulation of consciousness, emotions, and movements that characterize cocaine exposure (Oung, Kremer, Amara, Zaidi & Koslowski, 2022).

Cocaine can be addictive due to its effect on the reward pathway in the brain. A single dose of cocaine induces tolerance to the drug's effects. After a short period of use, dependence is likely. Abstention from cocaine after chronic use results in drug withdrawal, with symptoms that may include depression, decreased libido, decreased ability to feel pleasure and subjective fatigue (Beiser & Yaka, 2019). Cocaine's use increases the overall risk of death and particularly the risk of trauma, and infectious diseases, such as blood infections and AIDS. It also increases risk of stroke, heart attack, cardiac arrhythmia, lung injury (when smoked), and sudden cardiac death. Illicitly sold cocaine is commonly adulterated with local anesthetics, levamisole, cornstarch, quinine, or sugar, which can result in additional toxicity. The Global Burden of Disease study found that cocaine use caused around 7300 deaths in 2007 (Farrell *et al.,* 2019).

The liver is an organ present in vertebrates and some other animals. It plays a major role in metabolism and has a number of functions in the body, including glycogen storage, decomposition of red blood cells, plasma protein synthesis, and detoxification. This organ also is the largest gland in the human body. It lies below the diaphragm in the thoracic region of the abdomen. It produces bile, an alkaline compound which aids in digestion, via the emulsification of lipids. It also performs and regulates a wide variety of high-volume biochemical reactions requiring very specialized tissues (Hamada, 2020). Medical terms related to the liver often start in hepato- or hepatic from the Greek word for liver, hēpar (ήπαρ).

Crack cocaine abuse has emerged as a pressing public health challenge worldwide, giving rise to a range of detrimental consequences for individuals and society. While the neurological and cardiovascular impacts of crack cocaine have been extensively investigated, its potential effects on peripheral organs, particularly the liver, have not received proportionate attention. The liver, a vital organ with essential roles in metabolism, detoxification, and physiological regulation, may play a pivotal role in the overall health implications of drug abuse (Abadie & Dombrowski, 2020). Therefore, there exists a critical need to delve into the histological alterations that crack cocaine could induce in the liver of adult albino Wistar rats, shedding light on an aspect of drug abuse that remains understudied.

Despite the significant body of research on the effects of crack cocaine, our comprehension of how it affects the histological structure of the liver is notably incomplete. Given the central importance of the liver in maintaining bodily homeostasis, exploring potential changes in its cellular and morphological composition resulting from crack cocaine abuse holds substantial importance (Bauer, 2019). Notably, the utilization of animal models, such as adult albino Wistar rats, provides a controlled environment to study drug-induced changes, offering insights that can inform our understanding of potential human responses.

Scientifically, investigating the histological effects of crack cocaine on the liver contributes to the advancement of pharmacology, toxicology, and substance abuse research (Lau, & Lau, 2021). The outcomes can broaden our understanding of how illicit substances interact with various organs, opening doors for further research and innovative approaches to addressing substance abuse-related health challenges. By uncovering novel insights into the liver's response to crack cocaine at a cellular level, this research ultimately serves the dual purpose of expanding scientific knowledge and informing practical solutions to mitigate the adverse effects of drug abuse.

MATERIALS AND METHODS

Study Area

This study was carried out in Ekpoma, the administrative headquarters of Esan West Local Government Area of Edo State, Nigeria. The area proper lies between latitude 6^0 45 North of Equator and longitudes 6^0 5 and 6^0 8' East of the Greenwich Meridian. Ekpoma area falls within the rain forest/savannah transitional zone of south western Nigeria. Ekpoma has a population of 172, 400 people.

Majority of people in this area are civil servants, traders, business men and women, transporters, farmers, teachers/lecturers and students by occupation. Ekpoma is made up of many quarters, including Eguare, Iruekpen, Emaudo, Ujolen, Ihumudumu, Illeh, Uke, Uhiele, Ujemen, Ukpenu, Egoro, Emuhi, Igor and Idumebo (National Population Commission, 2012).

Experimental Animals/Housing Condition

Forty (40) Adult Albino Wistar rats of comparable sizes and weights were procured from the animal house and transferred to the experimental site where they were allowed two (2) weeks of acclimatization. They were housed in well-ventilated labeled wooden cages at the site of the experiment. The cages were designed to secure the animals properly especially from wild animals/insects and cleaned daily. During this period of acclimatization, the rats were fed growers' mash and water. Animals were maintained and experimental procedures complied with the guide for care and use of laboratory animals (National Research Council, 1985).

Experimental Design

A total of forty (40) adult Albino Wistar rats of comparable sizes were used for this study. They were divided into four equal groups (A – D) with ten (10) rats each. Group A served as the control and the rats were given distilled water and feed only. In addition to feed and water, groups B rats were given 100mg *crack cocaine extract* and *crack cocaine extract*, group C rats were given 200mg *crack cocaine extract*, and group D rats were given 300mg *crack cocaine extract* respectively. The drug administration was given daily for 14 days (2 weeks) and the weights of both the test and control animals was monitored before and after administration of *crack cocaine extract*. After the administration, the rats were put under light chloroform anaesthesia and the liver were obtained. ANOVA was used to analyze the results of the weight and differences was considered significant at $p<0.05$ level of confidence. All data was expressed in table as mean ± standard deviation (SD).

Animal Grouping

The experimental animals were separated into four groups (A – D). Group A had ten rats (n = 10) while groups B – D had ten rats (n = 10) each using 4 big cages to house them. Group A served as the control and received only the normal feed (grower's mash) and water with no administration of *crack cocaine extract*, while Group B, C and D received different doses of *crack cocaine extract* and were equally fed with grower's mash and water.

Study Duration

The preliminary studies, animal acclimatization, drug procurement and preparation, actual animal experiment and evaluation of results, lasted for a period of three months. However, the actual experiment lasted for lasted for four (4) weeks: two weeks of acclimatization and two weeks administration of *crack cocaine extract* to the test animals.

Collection and Identification of Plant Materials

Fresh prepared aqueous *crack cocaine extract* were collected from a health facility. The aqueous *extracts* were identified and authenticated by experts.

Preparation of Plants Extract

The powder *crack cocaine* was weighed using the electric weighing scale and 100g was dissolved in 1 litre of distilled water and stirred at intervals for 24 hours (1 day). This was later reconstituted to give the required doses of 0.5ml (100mg), 2ml (200mg) and 5ml (300mg) used in the present study.

Administration of Substance

Crack cocaine extracts was prepared to prepare the doses of 0.5ml, 2ml and 5ml respectively for the experiment. The administration of the *crack cocaine* extracts was given orally as follows:

Group A (Control) received only normal feed (growers' mash) and distilled water daily for 28days.

Group B received 0.5ml of *crack cocaine* extracts, feed and distilled water daily for 28days.

Group C received 2ml of *crack cocaine* extracts, feed and distilled water daily for 28days.

Group D received 5ml of *crack cocaine* extracts, feed and distilled water daily for 28days.

Ethical Approval

Ethical approval for the use and collection of samples from laboratory animals was obtained from the Ethics and Review Committee, College of Medical Sciences, Ambrose Alli University, Ekpoma.

Sample Collection and Analysis

Weight was measured before and after acclimatization. Similar weight measurements were done at the end of the treatment periods and the average weight recorded accordingly. Furthermore, the liver of each rat was obtained at the end of the experiment under chloroform anaesthesia and fixed in 10% formalin for histological processing.

Processing Schedule

The tissues were processed according to standard histological procedures. The fixed plastic cassette tissues in 10% formalin were automatically processed by passing them through different grades of alcohol as follows:

70% alcohol	2hrs
80% alcohol	2hrs
90% alcohol	2hrs
90% alcohol	2hrs
95% alcohol	2hrs
Absolute	2hrs
Xylene 1	2hrs
Xylene II	2hrs

Molten paraffin wax 1	2hrs
Molten paraffin Wax II	2hrs

After the last timing, the tissues were removed from their plastic cassettes and placed at the centre of the metallic tissue mould and then filled with molten paraffin wax. They were left to solidify after which they were placed in the refrigerator at 5°C for 15 minutes. After the blocks were cool in the refrigerator for the time stated above, the blocks were removed from the metallic case using a knife and after which the paraffin wax at the side of the blocks were removed. The blocks were trimmed and cut serially at 3nm on a rotary microtome. The sections were floated in water bath at 55°C and picked up by the use of a clean frosted end slides. The frosted end slides were placed on the hot plate for 40 minutes for adequate attachment of the sections on the slides after which the sections were de-waxed, hydrated, air dried and stored in a slide box ready for staining.

Staining Procedure

Sections for general tissue structure were stained using Haematoxylin and Eosin staining technique.

1. The sections were de-waxed in 3 changes of xylene 5 minutes
2. The sections were hydrated through descending grades of alcohol (absolute, 95%, 80% and 70%).
3. The sections were stained in Harris haematoxylin 5 minutes
4. The sections were rinsed in running tap-water to remove excess stain
5. The sections were differentiated in 1% acid alcohol 3 seconds
6. The sections were blued in running tap water 10 minutes
7. The sections were counterstained with 1% eosin 1 minute
8. Sections were finally rinsed in water, dehydrated in ascending grades of alcohol (70%, 80, 95% and absolute)
9. The sections were cleared in xylene, air-dried and mounted with dibuthylphthalate propylene xylene (DPX) (Armstrong *et al.,* 2007).

The slides were examined under a light microscope at x100 magnification and photomicrographs were taken.

Data Analysis

All results were expressed as mean ± standard deviation (X ± SD). The obtained data was subjected to statistical analysis using SPSS (version 21). The test groups' values were compared with the values of the control group using One-way analysis of variance (ANOVA) at 95% level of confidence. Values of $P< 0.05$ were considered significant.

RESULTS

Body Weight Changes of Rats at Various Intervals

Table 1 shows the body weight changes of rats in the test and control groups. The results were presented in mean ± standard deviation. At every stage of the weight determinations, the control group (Group A) presented body weight gain at first, second, third and final week after acclimatization, while the test groups (B, C and D) presented body weight loss in the different weeks after acclimatization respectively. Though, the difference in weight didn't show any significant difference ($p>0.05$) within the test groups, group D was observed to have a higher weight reduction, followed by group C and B respectively. The body weight of control animals (group A) before acclimatization and before sacrificing was 205.50±0.50g and 245.25±0.50g. Similarly, the body weight of the test animals in group B before acclimatization and before sacrificing was 215.50±1.00g and 200.55±2.22g, group C was 210.40±1.29g and 195.25±3.24g, group D was 225.55±1.41g and 190.25±2.45g respectively.

Table 1: Body Weight Changes of Rats at Various Intervals

Weight (g)	Control (n = 10)	B (100mg) (n = 10)	C (200mg) (n = 10)	D (300mg) (n = 10)
WBA	210.50±0.50	220.50±1.00	215.40±1.29	230.55±1.41
WAA	220.65±0.50	217.75±1.50	210.50±0.42	225.45±1.20
W2WK	225.45±0.50	215.25±1.35	205.85±1.50	215.50±1.84
W3WK	240.15±1.71	210.50±1.50	205.50±1.15	205.35±2.55
FW	250.25±0.50	205.55±2.22	200.25±3.24	195.25±2.45

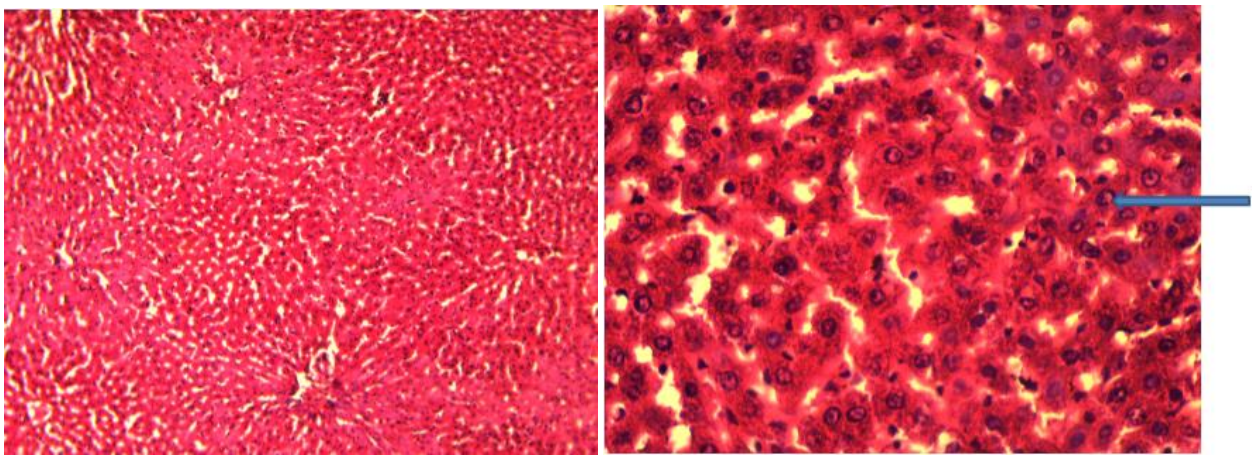
KEY: WBA: Weight before acclimatization; **WAA:** Weight after acclimatization, **W2WK:** Weight at second week of *cocaine* extracts; **W3WK:** Weight at third week of *cocaine* extracts, **FW:** Final weight before sacrificing; Values are mean ± Standard deviation; Wt= weight (Grams); **n:** Number of sample.

Table 2: Summary micrograph table

	Findings
Group A	Liver shows Normal Hepatocytes
Group B	Liver Shows Normal Hepatocytes
Group C	Liver shows Areas of Bridging Necrosis
Group D	Liver shows Areas of Bridging Necrosis

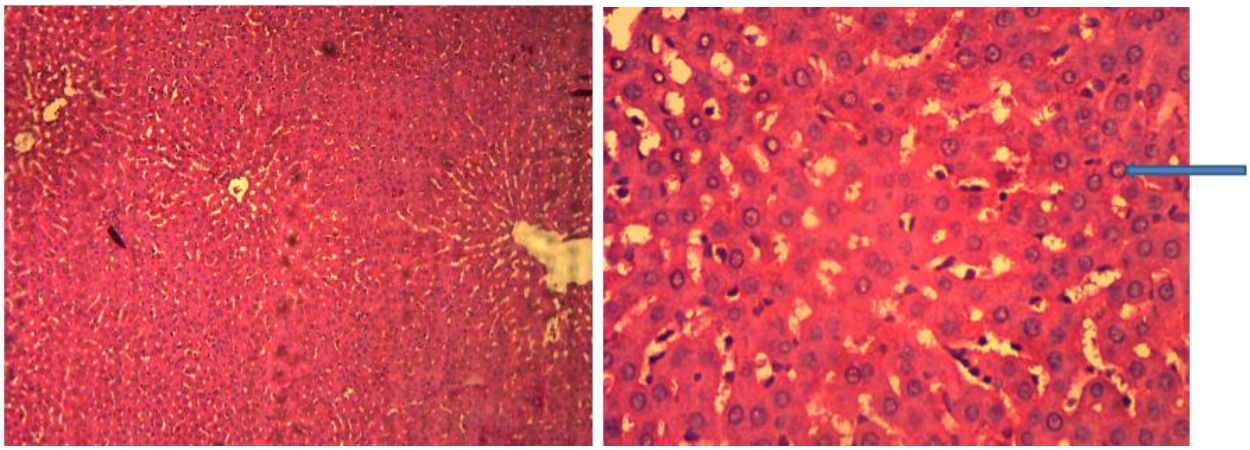
Key:

Group A (Control) received only normal feed (growers' mash) and distilled water daily for 28days.
Group B received 0.5ml of *crack cocaine* extracts, feed and distilled water daily for 28days.
Group C received 2ml of *crack cocaine* extracts, feed and distilled water daily for 28days.
Group D received 5ml of *crack cocaine* extracts, feed and distilled water daily for 28days.



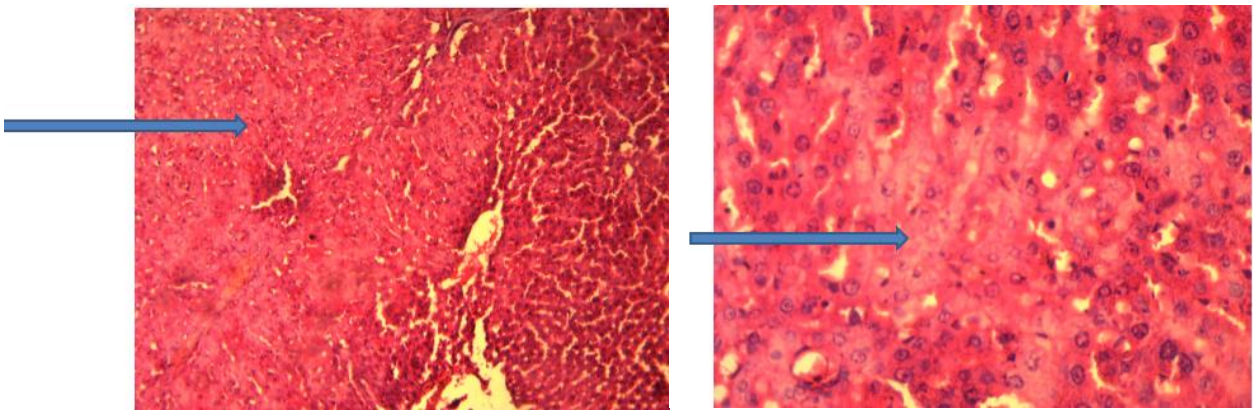
LIVER CONTROL X100

Plate 1: Liver Control: Section of the Liver Shows Normal Hepatocytes (Arrow) HandEX400



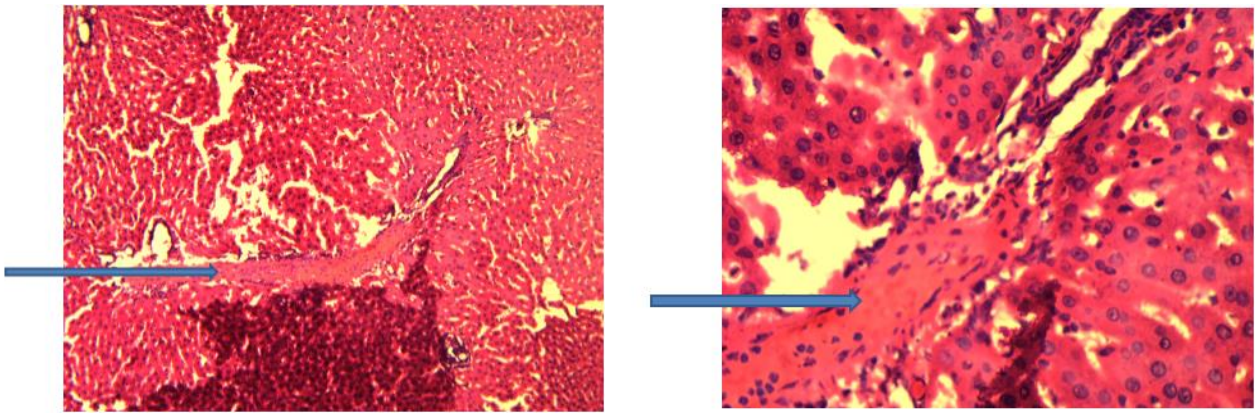
LIVER A X100

Plate 2: Liver B: Section of the Liver Shows Normal Hepatocytes (Arrow) HandEX400



LIVER B X100

Plate 3: Liver C: Section of the liver Shows Areas of Bridging Necrosis (Arrow)



LIVER C X100: PORTAL FIBROSIS

Plate 4: Liver DX400: Section of the Liver Shows Areas of Bridging Necrosis (Arrow) HandEX400

DISCUSSION

Cocaine, one of the earliest drugs used by man, is popular because of its tremendous stimulant and euphoriant effects. The most recent surge in usage in the past 10 to 15 yr relates to a greater awareness of the drug and its effects, its greater availability and lower relative cost. Consequently, more reports are seen in the literature concerning cocaine, its toxic effects and organ-system injuries, most notably those affecting the central nervous system (seizures, psychoses, hallucinations, strokes), the cardiac system (dysrhythmias, myocardial infarction) and the neuromuscular system (rhabdomyolysis) (Mottram, 2018).

Cocaine being a powerful stimulant drug can have various effects on the body, including potential impacts on body weight. Cocaine is known to suppress appetite. When individuals use cocaine, they often experience reduced feelings of hunger and may go for extended periods without eating. This appetite-suppressing effect can lead to rapid weight loss over time. This general belief does not resonate with the findings of this study, the findings of this study as observed in table 1 observed a non-statistically significant alterations in the test groups administered with varying dosage of cocaine when compared with the control group (Wood, Pyper & Casali, 2022). The findings of this study contradict the findings of Calderon-Garcia *et al.,* (2022), whose findings on "The skinny on cocaine: insights into eating behavior and body weight in cocaine-dependent men" observed a significant reduced fat mass of cocaine subjects when compared with non-drug using peers and stated that the weight changes in cocaine users reflect fundamental perturbations in fat regulation.

Cocaine-related liver injury was first described in studies of animals by Ehrlich in 1890; extensive experimental studies have been published since interest in the drug increased in the 1970s. Hepatotoxicity in man was first suggested in 1967 by Marks and Chapple, whose study of 89 heroin and cocaine users showed abnormal liver test results in approximately two thirds of the group. In some instances, enzyme levels returned to normal in hospitalized patients, but rebounded after they were discharged and probably returned to using drugs; however, factors such as multiple drug use precluded convincing documentation of cocaine-related liver cell injury in these patients. It's important to note that the effects of cocaine on liver histology can vary depending on factors such as the dose and duration of use, individual susceptibility, and any pre-existing liver

conditions. Chronic and heavy cocaine use can increase the risk of more severe liver damage (Carulli & Verhaagen, 2021). The findings of this study further proves that the administration of cocaine extract causes physiological and morphological damages to the liver as observed in the histological examination of group B and C. The aforementioned findings observed in this study resonates with the findings of Capaldo *et al.,* (2018) whose findings observed extensive centrilobular and midzonal necrosis in three cases and panlobular necrosis in two others of cocaine-using individuals. A mild lymphocytic infiltrate with bile duct proliferation was present in each specimen. Another study by Roque Bravo *et al.,* 2022 also aligns with the findings of this study, in Roque Bravo *et al.,* (2022) study, the dose – dependent administration of cocaine resulted in Portal tract with mild mononuclear cell infiltration and nonnecroticperiportal hepatocytes, Perivenular and midzonal regions exhibiting coagulative-type necrosis and Periportal hepatocytes with microvesicular fatty change. The reason for the histological alteration could be attributed to the fact that Cocaine metabolism generates reactive oxygen species (ROS) and free radicals. These molecules can induce oxidative stress, causing damage to liver cells (hepatocytes) and contributing to inflammation and tissue injury (Georgieva, Karamalakova, Miteva, Abrashev & Nikolova, 2021).

CONCLUSIONS

In conclusion, the use of cocaine can lead to significant and harmful effects on liver histology, resulting from a combination of factors related to the drug's pharmacological actions, metabolism, and physiological responses. Cocaine-induced changes in liver histology can include hepatocellular damage, oxidative stress, inflammation, steatosis (fat accumulation), and disruptions in liver function. These changes stem from cocaine's vasoconstrictive properties, generation of reactive metabolites, direct toxic effects, and interactions with other substances. While the impact of cocaine on the brain and cardiovascular system is often highlighted, it is crucial to recognize that the liver is also vulnerable to the damaging effects of this powerful stimulant. The liver's role in metabolizing drugs, including cocaine, makes it susceptible to tissue damage and dysfunction, which can have long-term consequences on overall health.

- The most effective way to prevent the harmful effects of cocaine on liver histology is to avoid using the drug altogether. Recognize the risks associated with cocaine use and make a commitment to prioritize health and well-being.
- Individuals should educate each other's about the potential consequences of cocaine on liver health. Understanding the risks can serve as a strong deterrent to using the drug.
- Individuals with history of cocaine usage should schedule regular medical check-ups to monitor liver function and overall health. Detecting any early signs of liver dysfunction can allow for timely intervention and management.
- Adoption of a healthy lifestyle that includes regular exercise, a balanced diet, and stress-reduction techniques. A healthy lifestyle can support overall well-being and potentially minimize the impact of substance abuse on the body.
- Individuals should avoid combining cocaine with other substances, including alcohol. The combined use of multiple substances can increase the risk of liver damage and other health complications.
- Individuals trying to overcome substance abuse should consider joining support groups or seeking counseling to address the psychological and emotional factors that contribute to substance abuse. Connecting with others who are going through similar challenges can be beneficial.

REFERENCES

- Abadie, R., & Dombrowski, K. (2020). "Caballo": risk environments, drug sharing and the emergence of a hepatitis C virus epidemic among people who inject drugs in Puerto Rico. *Harm Reduction Journal*, *17*, 1-11.
- Bauer, I. (2019). Travel medicine, coca and cocaine: demystifying and rehabilitating Erythroxylum–a comprehensive review. *Tropical diseases, travel medicine and vaccines*, *5*(1), 20.
- Beiser, T., & Yaka, R. (2019). The role of oxidative stress in cocaine addiction. *Journal of Neurology & Neuromedicine*, *4*(1).
- Farooque, U., Okorie, N., Kataria, S., Shah, S. F., & Bollampally, V. C. (2020). Cocaine-induced headache: a review of pathogenesis, presentation, diagnosis, and management. *Cureus*, *12*(8).
- Farrell, M., Martin, N. K., Stockings, E., Bórquez, A., Cepeda, J. A., Degenhardt, L., ... & McKetin, R. (2019). Responding to global stimulant use: challenges and opportunities. *The Lancet*, *394*(10209), 1652-1667.
- Hamada, H. (2020). Molecular and cellular basis of left–right asymmetry in vertebrates. *Proceedings of the Japan Academy, Series B*, *96*(7), 273-296.
- Lau, W. Y., & Lau, W. Y. (2021). Hemilivers, Sections (Sectors), Segments. *Applied Anatomy in Liver Resection and Liver Transplantation*, 7-20.
- Mash, D. C. (2019). 6.2 NEUROPSYCHIATRIC CONSEQUENCES OF CHRONIC COCAINE ABUSE. *Drug Abuse Handbook*, 412.
- Oung, S. W., Kremer, N., Amara, S. B., Zaidi, A., & Koslowski, T. (2022). Protonation and orientation: a computational approach to cocaine diffusion through a model membrane. *Physical Chemistry Chemical Physics*, *24*(23), 14219-14227.
- Rai, S. K., & Tewari, A. K. (2018). Dual role of drugs: beneficial and harmful aspects. In *Synthesis of Medicinal Agents from Plants* (pp. 305-332). Elsevier.