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HEPATOPROTECTIVE EFFECT OF LOW DOSE OF VITAMIN A ON THE LIVER IN TOXIC DOSE OF METHAMPHETAMINE INDUCED ADULT MALE WISTAR RATS

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ABSTRACT

Methamphetamine (METH), is a potent central nervous system stimulant associated with severe toxic effects on multiple organs, including the liver. Vitamin A, particularly in its active form retinol, plays a significant role in various physiological functions, including vision, immune function, and skin health. This study evaluated the protective role of low-dose vitamin A on the liver of adult male Wistar rats exposed to methamphetamine. Twenty rats were randomly divided into four groups (n=5) and received the following as follows: group A (control) feed and water only, group B (METH-only; 20mg/kgbw), group C (vitamin A-only; received 0.7mg/kgbw), while group D (METH + vitamin A). All the experimental groups were fed with water and feed. All treatments were administered orally using intubation method for 28 consecutive days. Twenty-four hours (24) after the last administration, animals were sedated and sacrificed; the liver tissues were harvested, fixed in 10% neutral formal-saline and processed for histological examination using Haematoxylin and Eosin (HandE) staining. Body weight analysis revealed weight loss of meth-intoxicated Wistar rats. Relative liver weight analysis revealed increase in meth exposed Wistar rats. Activities of serum levels of AST and ALT in the methamphetamine-treated group indicated hepatotoxicity and histological result showed notable structural degeneration in the liver tissues. However, counter administration with low-dose vitamin A appeared to protect and regenerate hepatocellular architecture and counteract methamphetamine-induced liver toxicity. The study, therefore, validates the hepatotoxicity of methamphetamine on the liver and the potential hepatoprotective benefits of vitamin A through its antioxidant and anti-inflammatory characteristics.

KEYWORDS

Hepatoprotective, Vitamin A, Toxic dose, Methamphetamine and Wistar rats.

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INTRODUCTION

Background of the study

Methamphetamine is an addictive and potent stimulant and its use is associated with a range of

physical and mental health harms, overdose, and mortality (Christopher *et al*, 2021)[1].

Methamphetamine (METH) is an illicit psychostimulant that is abused throughout the world. (Subramaniam Jayanthi, *et al*, 2021)[2].

Methamphetamine is a powerful, highly addictive stimulant that affects the central nervous system. It takes the form of a white, odorless, bitter-tasting crystalline powder that easily dissolves in water or alcohol (Chomchai *et al*, 2015)[3]. Methamphetamine use is associated with numerous adverse effects, including the generation of reactive oxygen species (ROS), oxidative stress, accelerated aging, apoptosis, and necrosis. It can be ingested orally, intravenously, or through a combination of both methods, rapidly entering the bloodstream and spreading throughout the body, with major organs like the lungs, brain, liver and kidneys absorbing significant amounts. METH induces hepatotoxicity through intricate pathways, including the disruption of liver metabolic processes, the generation of oxidative stress and the elevation of body temperature. It has been associated with liver damage, potentially accelerating hepatic apoptosis by disrupting essential biological functions such as cell division and the cell cycle (Nawar. *et al*, 2024)[4].

Vitamin A, particularly in its active form retinol, plays a significant role in various physiological functions, including vision, immune function and skin health. In the brain, Vitamin A is involved in the regulation of neuronal differentiation, synaptic plasticity, and neuro-protection. Retinoic acid, a metabolite of Vitamin A, acts on the brain through retinoic acid receptors (RARs) and retinoid X receptors (RXRs), influencing gene expression and neural signaling (Shao *et al,* 2016)[5]. Retinoic acid has been shown to protect against neuro-degeneration and oxidative stress, which are often implicated in the neurotoxicity induced by drugs like methamphetamine. The protective effects of Vitamin A are thought to occur through its antioxidant properties, as it helps reduce the production of reactive oxygen species (ROS) and enhances the brain's repair mechanisms (Fassbinder *et al*, 2018)[6]. Therefore, this study aims to evaluate the hepatoprotective effect of low dose of vitamin A on the liver in Toxic dose of methamphetamine induced adult male Wister rats.

MATERIAL AND METHODS

Location of the Study

This study was carried out at the Animal House of the College of Health Sciences, Nnamdi Azikiwe University, Nnewi Campus, Anambra State Nigeria.

Ethical Approval

Ethical approval was obtained from the Ethical Committee, Faculty of Basic Medical Sciences, College of Health Sciences, Nnamdi Azikiwe University.

Materials of the Study

During this investigation, the following materials were utilized. Twenty-four adult Wistar rats, Iron cages with iron nettings, sawdust (litters), Animal feed (grower and finisher mash), laboratory coat and gloves, dissecting kit, one stopwatch, digital video recorder, measuring cylinder, weighing balance, water bath, sample bottle, 10% Neutral Buffered Formalin (Sodium Phosphate Monobasic 4.0gm, Sodium Phosphate Dibasic 6.5gm, Formaldehyde 37% 100.0ml, Distilled Water 900.0ml), Cotton and anaesthesia (chloroform), Graded Alcohol (50%,70%,95% and absolute alcohol), Glass slides and slide rack, Hot plate, Xylene, Paraffin wax, Embedding plate and pot, Deepex (DPX) Mountant, Hematoxylin and eosin, Coverslips, Light Microscope, Orbit shake, Diamond pencil, Rotatory microtome, Ethanol for tissue processing, Micropipette, Specimen labels and bottles, Trays, Paraffin dispenser, Cassette and slide storage, Pipette tips (various sizes), Knife sharpener, Notebook and biro.

Procurement and Housing of Experimental Animals

Twenty-four (24) adult Wistar rats weighing 180-250kg were procured from Research Enterprise Farm, University of Ibadan, Oyo State. Perspex cages were used to house four (4) groups of six (6) animals each for routine experiments. Each cage had a wire gauze top for cross-ventilation. The animals were allowed for two weeks for acclimatization under normal temperatures (27-30^{o}) at the Animal House of the Basic Medical Sciences. Nnamdi

Azikiwe University, Nnewi Campus. They were fed ad libitum with water and Grower mesh.

Procurement of Methamphetamine

Methamphetamine was procured from the locals and authenticated at the Department of Industrial Chemistry Nnamdi Azikiwe University Awka Anambra State.

Experimental Design and Protocols

Twenty four male adult rats were randomly grouped into Four groups (n=6)

Group A was control group which received feed and water only

Group B were administered 20mg/kgbw of Methamphetamine

Group C were administered 0.7mg/kgbw of Vitamin A (low dose)

Group D were administered 20mg/kgbw oft Methamphetamine + 0.7mg/kgbw of Vitamin A (low dose)

Administration was done orally using oral gavage method. All experimental protocols were observed under strict supervision, the experiment lasted for 28 days and methamphetamine administration was done daily.

Termination of Treatment

Twenty-four hours (24) after the last administration, the animal were weighed first using a-weighing balance to get the final weight before the animals were sacrificed. The animals were anesthetized with chloroform, blunt scissors were used to make a midline incision along the abdomino-pelvic region in each rat to avoid damage to the visceral organs. The rats were dissected lying on their back, abdomen facing upwards and limbs pinned laterally to the board for easy dissection. The liver was traced, harvested and examined macroscopically for any lesions or abnormalities. The liver was weighed and then fixed in 10% formalin to maintain normal physiological conditions and for the interest of histological investigations in the histology laboratory of Anatomy Department, Nnamdi Azikiwe University, Nnewi campus.

Tissue Processing

For easy study of sections under a microscope, the tissues were passed through several processes of fixation, dehydration, clearing, infiltration, embedding, sectioning and staining.

Fixation

The essence of fixation is to preserve the various constituents of the cells in a life-like state and to prevent autolytic changes and putrefaction. Fixation was carried out in 10% Neutral Buffered Formalin (Sodium Phosphate Monobasic 4.0gm, Sodium Phosphate Dibasic 6.5gm, Formaldehyde 37% 100.0ml, Distilled Water 900.0ml). The tissues remained in the fluid for 48 hours. After fixation, the tissues were washed overnight under stream tap water to remove any surplus fixatives.

Dehydration

Dehydration of the fixed tissues was done to remove water and other substancxes. This was carried out in different percentages of alcohol 50%, 70% and 95% absolute. In each grade of alcohol, tissues were changed twice for two (2) hours and one (1) hour for each change.

Clearing

The tissues were then cleared in two changes of xylene for two hours to remove the absolute alcohol that was used to dehydrate the tissues thereby replacing the absolute alcohol in the tissues with xylene. Xylene is usually miscible withxxx absolute alcohol and paraffin wax; therefore, xylene was used as the clearing agent. After clearing, infiltration was carried out.

Infiltration

The tissues were transferred to two changes of molten paraffin wax for 2 hours each. I ensured that the amount of wax was 25-50 times the volume of the tissue. Infiltration was carried out to replace xylene in the tissue spaces with molten paraffin wax. The temperature of the paraffin was kept at 60^{o}C.

Embedding

The tissues were embedded by submerging them in two changes of molten paraffin wax contained in cassette metal moulds at a constant temperature of 52-60^{o}C in an oven of paraffin wax for 2 hours each time. The tissues were well-oriented in the moulds to ensure the presentation of the desired parts of the tissues to be examined in the tissue sections.

Sectioning

This is the process by which a thin slice of the tissue of about 4µm thick is made using a rotatory microtome (Leica RM 2125 RST).

Staining

Hematoxylin and Eosin Staining (H&E)

Sections were dewaxed using xylene for one (1) minute and then rehydrated by alcohol through descending grades of ethyl alcohol and thereafter washed in distilled water. The sections were stained with Hematoxylin for twenty (20) minutes and differentiated with 2% acid alcohol for two (2) seconds. The acid alcohol was washed off with tap water and the sections passed through running tap water for ten (10) minutes to regain the blue colour. The sections were counterstained in 1% aqueous eosin for thirty (30) seconds and were dehydrated through ascending grades of ethyl alcohol, cleared in xylene and mounted using DPX. After which, the sections were viewed under a light microscope.

Data Analysis

Data was analysed using the SPSS version 27.0.1 software package. Mean and standard deviation were obtained, and one-way analysis of variance (ANOVA) was used to compare values between groups. Data was expressedx as Mean + Standard Deviation (SD) and then considered statistically significant when $P < 0.05$.

RESULTS AND DISCUSSION

Physical and Behavioral Changes

At the beginning of the experiments, all the animals looked healthy and agile. During the two weeks of acclimatization, their stools were normal. On administration of Methamphetamine, varying gradations of toxicity were observed. Generally, the signs of toxicity observed include. Bulging of the eyes, Staggering / loss of balance, Aggressiveness These signs were not observed following administration of Vitamin A.

Discussion of Findings

Methamphetamine is recognized as a potent central nervous system stimulant, often employed as a secondary treatment for conditions like attention deficit hyperactivity disorder and obesity, though its primary association is with recreational drug use. Its discovery dates back to 1893 when it was identified as comprising two chemical subgroups. dextromethamphetamine and levomethamphetamine (Radfar and Rawson, 2014)[7]. By 1919, methamphetamine emerged as a derivative of amphetamine in Japan and later gained attention in the 1930s in the United States for its uses as a bronchial inhaler, nasal decongestant, and obesity treatment. However, due to its neurotoxic properties and potential for abuse, its prescription is restricted. Safer alternatives with comparable efficacy are now preferred, leading to limited medical use of methamphetamine in the United States. Illicit production and trafficking of methamphetamine, both racemic and its individual enantiomers, have led to its classification as a Schedule II controlled substance by both U.S. and international authorities (Cisneros and Ghorpade, 2014)[8].

Body Weight Change

The analysis of body weight changes among the experimental groups reveals important physiological effects of methamphetamine induced and the modulating role of vitamin A. The final body weight of Groups C and D, which received vitamin A alone and methamphetamine + vitamin A, respectively, showed a statistically significant increase ($P < 0.05$) in relative to the control group (Group A). This observation suggests that vitamin A supplementation promoted weight gain, functioning as a dietary supplement that supports normal metabolic activity and growth.

This result aligns with the findings of Jeyakumar *et al*, (2015)[9], who demonstrated that vitamin A-enriched diets increased body weight and adiposity in both lean and obese Wistar rats. Their study attributed this effect to the up regulation of genes involved in lipid storage and energy metabolism, including PPAR-γ and lipoprotein lipase, without any increase in food intake. These findings suggest that vitamin A enhances growth and energy storage efficiency, which may explain the significant weight gain in Groups C and D.

In contrast, Group B, treated with methamphetamine alone, exhibited a significantly lower final body weight ($P < 0.05$) compared to the control groups. The weight change for Group B also showed a

statistically significant decrease when compared to Groups A. This reduction is consistent with the anorectic and catabolic effects of methamphetamine, which include appetite suppression, increased energy expenditure, and reduced food intake. Previous studies have similarly reported body weight loss in methamphetamine-treated rodents. For example, Krawattanapirom *et al*, (2021)[10] observed a marked decrease in body weight in rats following repeated administration of methamphetamine, attributing the loss to reduced appetite, metabolic disturbances, and increased oxidative stress. Additionally, methamphetamine is known to activate the hypothalamic-pituitary-adrenal (HPA) axis, leading to increased cortisol levels, muscle catabolism and energy imbalance-all contributing to weight loss.

The contrasting outcomes between Group B and Groups C and D further highlight the potential protective effect of vitamin A against methamphetamine-induced metabolic stress. The normalization or enhancement of body weight in Group D suggests that vitamin A may help restore appetite, modulate metabolism and reduce oxidative damage, thereby mitigating methamphetamine's weight-reducing effects.

Liver Weight Change

The findings from Table No.2 reveal a significant increase in the relative liver weight of Group B animals treated with methamphetamine ($p = 0.004$), compared to the control group (Group A) and the vitamin A-treated groups (Groups C and D). This elevation in liver-to-body weight ratio suggests pathological liver enlargement, commonly associated with hepatocellular injury, inflammation, or congestion.

Relative liver weight is a sensitive marker of organ toxicity, particularly in toxicological evaluations where absolute organ weights may not show meaningful differences due to changes in body weight. In this context, the increased liver weight in Group B is likely due to methamphetamine-induced hepatotoxicity, including inflammatory infiltration, cellular swelling, and vascular congestion, as observed in your histopathological data. This aligns with the study by Janthueng *et al*, (2023)[11], which reported that methamphetamine administration in rats caused liver enlargement and histological signs of chronic hepatitis, including inflammatory cell aggregation and central vein congestion.

Increased liver weight following methamphetamine exposure has also been observed by Ahmadi *et al*, (2020)[12], where multi-organ toxicity induced by chronic methamphetamine administration led to hepatomegaly and extensive histological damage. These findings support the notion that the elevated relative liver weight in Group B reflects pathological alterations, not physiological growth.

In contrast, Groups C and D, which received low-dose vitamin A alone or in combination with methamphetamine, showed no significant increase in relative liver weight compared to the control group. This suggests that vitamin A exerted a protective effect, mitigating methamphetamine-induced hepatic enlargement. The hepatoprotective and anti-inflammatory properties of vitamin A may have contributed to stabilizing liver architecture and preventing cellular edema or fibrosis, thereby maintaining normal liver mass. Similar results were reported by Momoh *et al*, (2020), where vitamin A treatment preserved liver morphology and organ weight in rats exposed to toxicants.

These observations reinforce the cytoprotective and antioxidant roles of vitamin A in preventing pathological organ hypertrophy caused by toxic drug exposure.

Liver Function Test

The biochemical analysis of serum enzyme activities in this study provides important insight into the hepatocellular effects of methamphetamine (METH) exposure and the potential protective role of low-dose vitamin A. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are commonly used biomarkers of liver function and hepatocellular integrity, while alkaline phosphatase (ALP) reflects biliary function and membrane transport.

In the current study, Group B (treated with methamphetamine alone) exhibited a significant increase in AST and ALT levels ($p < 0.05$) compared to the control group, which is indicative of methamphetamine-induced liver damage. Elevated transaminase levels suggest leakage of these enzymes from damaged hepatocytes into the

bloodstream, a hallmark of hepatocellular injury. This finding is consistent with previous studies, such as Akhter *et al*, (2019)[13], who reported significant elevations in ALT, AST and oxidative stress markers in rats administered "Yaba" (a form of methamphetamine), indicating liver damage and dysfunction (Akhter *et al*, Pharmacology Online, 2019)[13].

Furthermore, a study by Zhang *et al*, (2019)[14] also observed significantly elevated AST and ALT levels in rats following repeated administration of methamphetamine, correlating with histological evidence of hepatic injury and inflammatory cell infiltration. These enzyme alterations align with your histopathological findings in Group B, which showed features consistent with chronic hepatitis, such as intrahepatic inflammatory cell aggregates and vascular congestion.

Interestingly, the ALP activity in Group B was significantly decreased ($p < 0.05$) compared to the control. This is somewhat atypical, as ALP is often elevated in conditions involving cholestasis or biliary tract obstruction. However, reduced ALP levels may occur when hepatic enzyme synthesis is suppressed, potentially due to severe hepatocellular dysfunction or direct toxic effects on liver biosynthetic pathways. Pourahmad *et al*, (2011)[15] also observed a reduction in ALP activity in rats exposed to hepatotoxic agents, attributing the effect to disrupted enzyme production rather than biliary obstruction.

In contrast, Groups C and D, which were treated with low-dose vitamin A alone or in combination with methamphetamine, showed no significant differences or slight decreases in AST, ALT and ALP levels compared to the control group. These findings suggest a hepatoprotective role of vitamin A, likely mediated through its antioxidant, anti-inflammatory and cytoprotective properties. Vitamin A is known to scavenge reactive oxygen species (ROS) and enhance antioxidant enzyme activity, thereby mitigating oxidative stress-induced liver injury.

This result is in line with the work of Momoh *et al*, (2020), who demonstrated that vitamin A supplementation in rats exposed to gasoline vapors led to normalization of AST, ALT and ALP levels, as well as preserved liver histology. Similar protective effects of vitamin A have been documented in studies involving various hepatotoxic substances, highlighting its potential to stabilize hepatocyte membranes, reduce inflammation and prevent enzyme leakage.

Histological Findings

Histopathological findings of the present study indicated normal liver tissues in the control group A, as well as in groups C and D. In contrast, animals in group B that were administered methamphetamine showed severe hepatic degeneration, with marked aggregates of intrahepatic inflammatory cells (IHI) and vascular congestion (VC). These overall features are consistent with chronic hepatitis. This could be attributed to a methamphetamine-induced reduction in tissue soluble proteins and antioxidant enzyme activity, leading to increased oxidative stress and subsequent liver damage. This result agrees to Iraj Ahmadia and Hossein Foruozandeh, (2019)[16]. Who reported that Rats Treated with 4mg/kg of METH revealed degenerative changes such as portal inflammation, congestion, diffuse necrosis, vacuolization and hepatocytes edema.

The animals in group D gives a particularly interesting observation about the dynamics of reactions to the presence of various substances in our systems. On administration of Methamphetamine + low dose of Vitamin A, no toxicity changes were associated in physical and behavioral observation, there were body weight increase similar with the control, relative organ weight were statistically similar with the control and no histological lesions were observed in the liver tissue. By these observations, one may deduce that administration of low dose of vitamin A may boost the tolerance capacity for methamphetamine induced toxicity.

Thus, the hepatoprotective effect of vitamin A against methamphetamine induced liver recorded in the present study is attributed to their antioxidant and cytoprotective properties.

Toxicological evaluation of medicinal agents, including the determination of their median lethal dose (LD_{50}) and the absence of adverse histological changes or tissue degeneration, is crucial in

assessing their relative safety. A low dose of vitamin A has demonstrated a favorable safety profile and therapeutic potential. Due to its potent antioxidant properties, low-dose vitamin A helps to neutralize reactive oxygen species (ROS) and reduce oxidative stress - a key mechanism by which methamphetamine induces cellular injury and liver damage. By stabilizing cellular membranes, modulating inflammatory responses and supporting tissue regeneration, a low dose of vitamin A exhibits potential medicinal value in the prevention and management of methamphetamine-induced hepatic and systemic toxicity.

Table No.1: Comparison of mean initial and final body weight and weight change in all the groups (A, B, C, D)

S.No	Group	Initial Weight (G)	Final Weight (G)	p-value
1	A	130.40 ± 2.03	145.96 ± 0.02	0.001
2	B	136.20 ± 4.83	121.04 ± 6.01	0.007
3	C	135.94 ± 3.92	160.00 ± 1.09	0.000
4	D	135.90 ± 0.50	147.80 ± 0.92	0.001

Data was analyzed using Student dependent T-test and values were considered significant at P<0.05.

Table No.2: Comparison of mean relative liver weight for group A (control) and experimental groups (B, C and D)

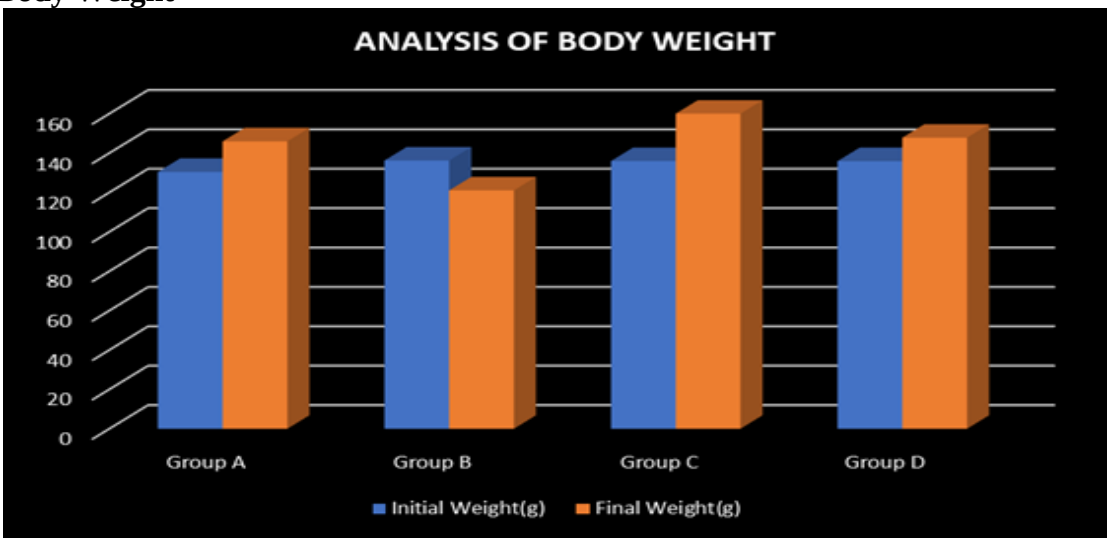
S.No	Group	Organ Weight	p-value	F-value
1	A	3.10 ± 0.00		
2	B	3.50 ± 0.07	0.004	22.082
3	C	3.20 ± 0.30		
4	D	3.25 ± 0.02		

Data was analyzed using One-way ANOVA followed by multiple comparison using LSD and data were considered significant at P<0.05.

Table No.3: Activities of Serum Levels of Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT) and Alkaline Phosphatase (ALP) in all the groups

S.No	Group	ALP (U/L)	ALT (U/L)	AST (U/L)
1	A	106.04 ± 0.27	29.20 ± 0.29	25.10 ± 0.76
2	B	79.00 ± 0.42	42.13 ± 1.32	37.49 ± 0.10
3	C	105.55 ± 0.01	29.02 ± 2.00	25.23 ± 0.03
4	D	104.76 ± 0.56	31.34 ± 2.23	27.14 ± 3.02
5	F-ratio	17.564	12.005	5.100
6	Prob. Of sig	<0.005	<0.005	<0.005

Analysis of Body Weight



Chat No.1: Representation of the Mean Initial and Final Body Weights of all the Groups

Analysis of Liver Weight

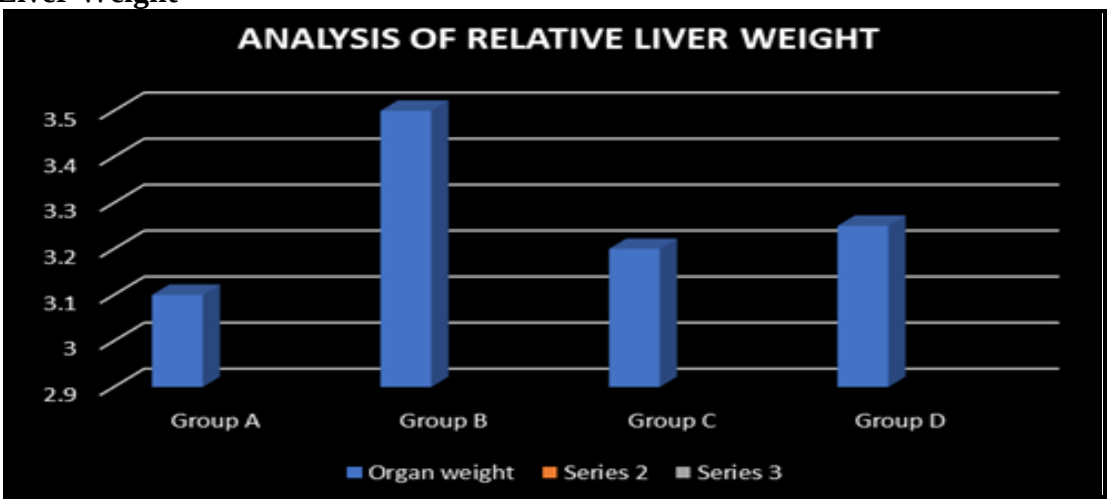


Chart No.2: Mean Relative Liver Weight for Groups A, B, C and D

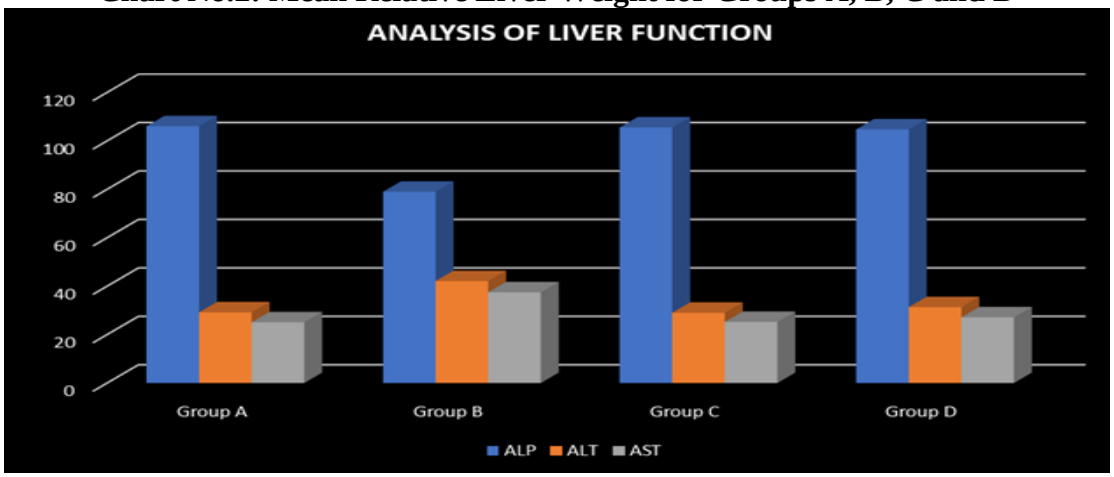
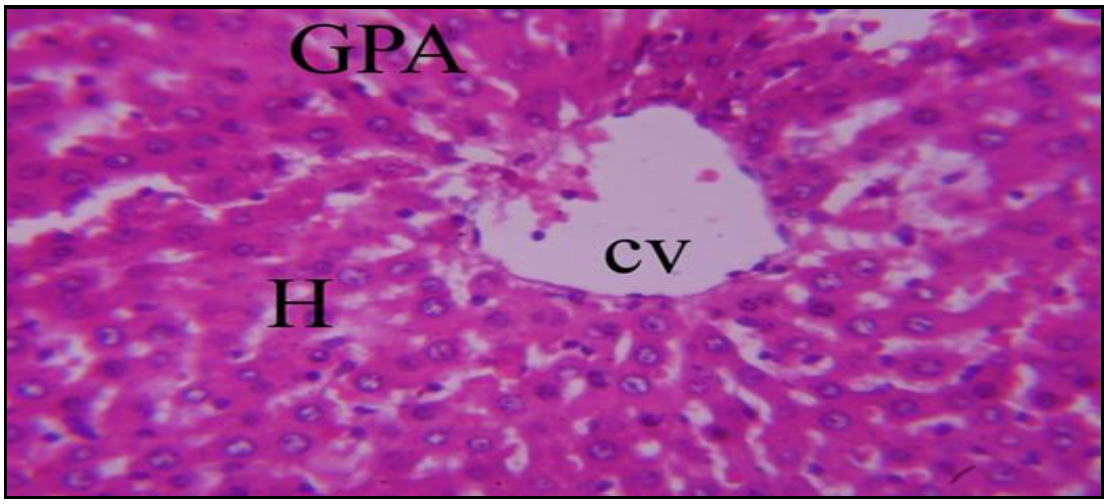
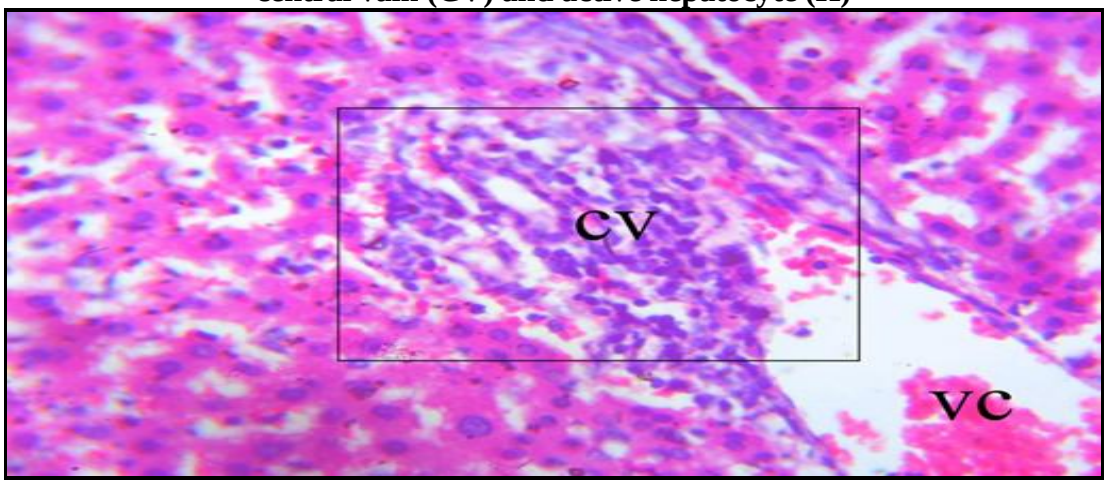


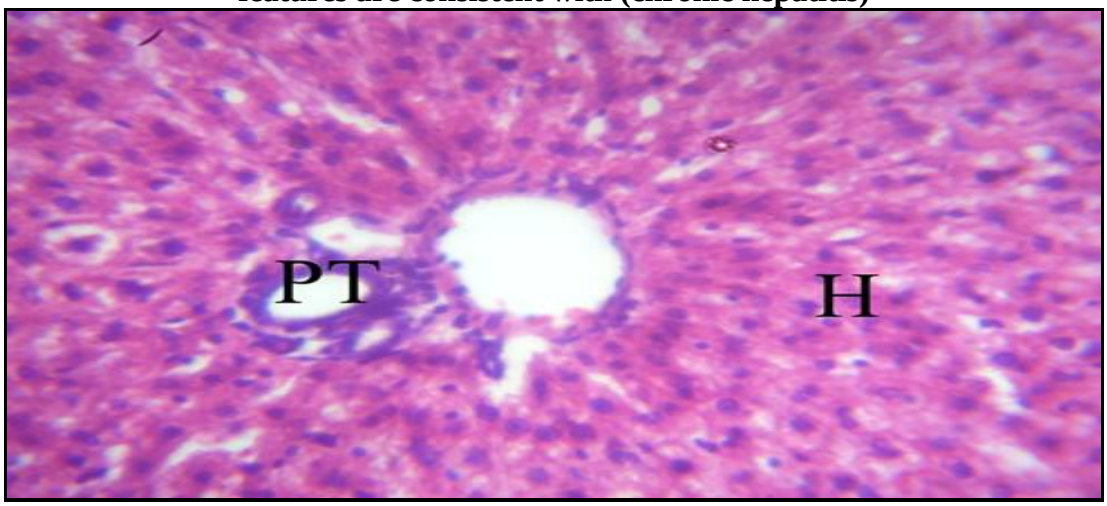
Chart No.3: Representation of Activities of Serum Levels of Aspartate aminotransferase (AST), Alanine aminotransferase (ALT) and Alkaline phosphatase (ALP)



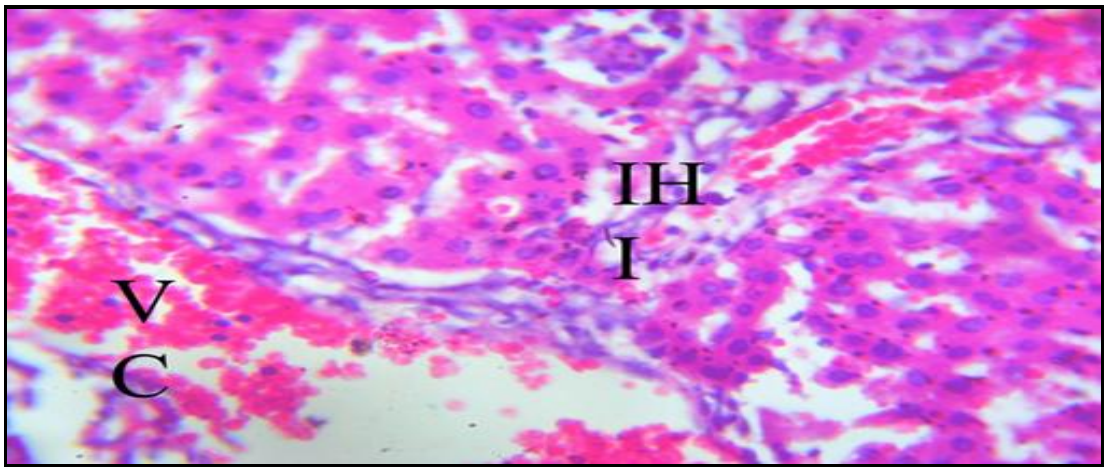
Graph No.1: Group A section of liver (×400) (H/E) shows well perfused normal hepatic tissue with central vain (CV) and active hepatocyte (H)



Graph No.2: Group B section of liver induced with meth only (×400) (H/E) shows severe degeneration with severe aggregate of intra hepatic inflammatory (IHI) and vascular congestion (VC) The overall features are consistent with (chronic hepatitis)



Graph No.3: Group C section of liver administered with vit A low dose (×400) (H/E) shows active hepatic tissue with portal traid (PT) and active hepatocyte (H)



Graph No.4: Group D section of liver induced with meth and treated with low dose of vit A (×400) (H/E) shows mild regeneration with moderate intra hepatic inflammatory (IHI) and moderate vascular congestion (VC)

CONCLUSION

The findings of this study indicate that low dose vitamin A did not induce adverse effects on key liver function biomarkers, including serum levels of AST, ALT and ALP and no histopathological lesions were observed in the liver tissues of treated rats. Moreover, low dose vitamin A demonstrated a protective effect against methamphetamine-induced hepatic toxicity in adult Wistar rats. Given the physiological and structural similarities between rat and human tissues, these results suggest that low dose vitamin A may offer therapeutic potential in mitigating methamphetamine-induced organ damage in humans.

RECOMMENDATIONS

This study has provided valuable insights into a possible means of preventing tissue damage caused by methamphetamine exposure. It is recommended that further investigations be conducted to evaluate the efficacy of low dose vitamin A in counteracting methamphetamine-induced toxicity, not only in the liver but also across other organ systems. While the present study focused on hepatic tissues, the potential protective effects of vitamin A should be assessed in other vital organs such as the spleen, heart, lungs and brain, which are also known targets of methamphetamine toxicity.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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