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STUDY ON THE EFFECT OF ISILIN AND PELANGES ON LIVER AND KIDNEY FUNCTION ENZYMES AND DETERMINATION OF THE NO-OBSERVED-ADVERSE-EFFECT LEVEL (NOAEL)

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Abstract:

Background: The liver and kidneys are major organs responsible for the metabolism and excretion of xenobiotics, which makes them more susceptible to chemical toxicity. It is important to be able to assess therapeutic safety by characterizing the effects of new compounds on these organs.

Objective: The objective of the present study is to evaluate hepatorenal effects of two drugs in male albino mice (Pelanges and Isilin) some doses.

Methods: 15 healthy mice were randomly divided into five groups (n=3/group). Group 1 was treated with distilled water (control), Group 2 and 3 were administered Pelanges at doses of 0.05 ml/kg, and two different concentrations while Isilin in Groups IV & V at that dose level of drugs respectively. Treatments were performed for 30 consecutive days by gavage. At the end of experiment, blood was sampled for analysis of liver and kidney biomarkers as ALT, AST, ALP TSB BUN creatinine. Further, H & E staining was also carried out for histopathological examinations of hepatic and renal tissues.

Results: Biochemical analysis indicated that increased the dose of Isilin leads to increasing levels ALT, AST,ALP.TSB and BUN, creatinine in groups receiving this substance with significant differences at doses higher than those studied dosages. Only Pelanges-treated groups

were little off the control levels. Histologic results confirmed these findings, characterised by evident inflammatory infiltration in Isilin groups as well as glomerular atrophy and hepatic congestion. Pelanges clustering demonstrated slight or none tissue variation.

Conclusion: Isilin showed an unmistakable hepatorenal toxicity in a dose-dependent manner and Pelanges seemed to have no adverse effect under the present experimental conditions. These results underscore the need for dose consideration in therapeutic treatment development and support that Pelanges is relatively safe.

Keywords: Isilin, Pelanges, Liver Function, Kidney Function, ALT, AST, BUN, Creatinine, Histopathology, Toxicity, Mice Model.

Introduction

The liver and kidneys are two of the most vital organs in both humans and other creatures on which they exist, serving many important roles such as bio-metabolism, detoxification, homeostasis and removal of toxic substances among others [1]. The liver acts as a major metabolic organ, synthesising, converting and breaking down substances (both endogenous and exogenous) [1]. Likewise, kidneys are responsible for maintaining electrolyte balance, removing waste products from the body, and maintaining fluid homeostasis [2]. Disruptions to normal physiology of either the liver or kidneys can result in systemic toxicity and/or organ failure, emphasising the need for evaluating pharmacological agents' and nutrient supplementation products' safety profiles [3].

More types of medications from plant-derived to chemical to dietary supplements are being created and used more than ever before [4]. Many of these new medications can offer therapeutic benefits, however; these same medications may cause potential toxicity, particularly to the liver and kidney as both organs are principal players in drug breakdown and removal [5]. Therefore, the biochemical impact of many of these new medications on liver and kidney functions must be considered, especially after continual use [6].

Although the two new chemicals Isilin and Pelanges show some potential for positive health benefits (like better metabolic profiles and antioxidant activity), there is limited toxicology assessment data available at present [7]. Due to a lack of extensive scientific research on them, especially organ-specific safety studies, there are no current instances of these chemicals being approved for universal use in either clinical or commercial settings. Therefore, further investigation of the possible negative effects of these chemicals on both the liver and kidneys would be beneficial for determining safe dosage limits as well as establishing a No Observed Adverse Effect Level (NOAEL) –an important toxicological endpoint for risk assessment [8 , 9].

Biochemical measures such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP) and total serum bilirubin (TSB) are used to assess liver

function or the integrity of the hepatocyte cell. A rise in these levels may indicate liver injury or abnormal hepatic function. In addition, blood urea nitrogen (BUN), serum creatinine (CRE), total serum BUN and serum creatine values are routinely assessed during evaluation of renal function, to assess nephrotoxicity (damage) or the ability of the kidney to excrete certain substances. By consistently monitoring these biomarkers, one is capable of measuring the dose/response relationship of the therapeutic agent after exposure, as well as the ability to detect early effects following exposure, which are useful for toxicity assessment [12].

Lab rodents typically used in research include the albino mouse, since they are well-understood organisms with a known genetic background and have been studied extensively in relation to how pharmacology and toxicology can be applied to humans. Animal studies also provide researchers with an opportunity to administer test compounds in a controlled manner, repeat experiments, and establish a connection between biochemical evidence and dose-response or duration of exposure. [14].

Study Objective

The research aims to study the effects of Isilin and Pelanges on liver and kidney function enzymes in Albino mice while determining the No-Observed-Adverse-Effect Level (NOAEL) for both compounds.

Methodology

Animals and Experimental Design

The research involved fifteen healthy adult male Albino mice whose weight ranged from 225 grams. The research animals received standard laboratory care (22 ± 2°C temperature and 12-hour light/dark cycle) with unrestricted access to food and water. The researchers distributed fifteen mice into five groups which contained three animals in each group.

- Group 1 (Control) was given distilled water.
- Group 2: 0.05 ml/kg body weight of pelanges was administered to them.
- Group 3: 0.1 ml/kg body weight of pelanges was administered.
- Group 4: 0.05 ml/kg body weight of isilin was administered.
- Group 5: 0.1 ml/kg body weight of isilin was administered.

Dosing and Treatment Duration

The gavage needle gave all of the treatments by mouth once a day for thirty days in a row, from December 9 to January 9. The researchers figured out how much treatment each mouse needed based on its weight and then changed it every week to make sure the doses were always correct.

Sample Collection and Biochemical Analysis

The animals received humane euthanasia before the researchers ended the treatment period. Blood collection occurred through cardiac puncture before transferring the blood into plain

tubes for serum separation. The researchers used serum samples to conduct biochemical tests that measured liver and kidney function.

Biochemical Parameters

The evaluation of liver function involved quantifying serum concentrations of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and total serum bilirubin (TSB). To check how well the kidneys were working, they measured blood urea nitrogen (BUN), creatinine (CRE), and urea in serum.

Statistical Analysis

The obtained data were statistically analyzed using one-way analysis of variance (ANOVA) to determine the significance of differences between the groups. A p-value of less than 0.05 was considered statistically significant.

Results

Liver and Kidney Function Results

g4 and g5 were treated with Isilin and experienced a slight increase in their ALT levels compared to the control group (G1); while this increase in ALT levels is not statistically significant (such as with G5's mean ALT level of 58.07), there may be evidence of differing amounts of mild hepatotoxicity at larger doses. In contrast, G2 and G3 were treated with Pelanges; their ALT levels were similar to G1..

Table 1. Descriptive Statistics for ALT (Alanine Aminotransferase) Levels

Group	N	Mean	Std. Deviation	Std. Error
G1	3	51.0000	13.74773	7.93725
G2	3	51.3333	4.50925	2.60342
G3	3	51.2100	9.64365	5.56776
G4	3	56.7000	3.56791	2.05994
G5	3	58.0667	9.51963	5.49616

The table indicates a progression of increase in AST levels but Iselin treated subjects had the greatest AST levels amongst all treatment groups (G4 & G5), suggesting a dose-response relationship of hepatocellular toxicity. Conversely, Pelanges appeared to have some moderate variation from control but within a bounded range..

Table 2. Descriptive Statistics for AST (Aspartate Aminotransferase) Levels

Group	N	Mean	Std. Deviation	Std. Error
G1	3	105.6667	24.41994	14.09886
G2	3	108.6667	11.67619	6.74125
G3	3	113.6667	4.72582	2.72845
G4	3	132.1667	26.23077	15.14434
G5	3	139.8333	12.16566	7.02385

In Table 3 a marked elevation in ALP levels was found in Isilin groups (G4 and G5), suggesting potential biliary obstruction or increased liver stress. Pelanges-treated groups showed moderate increases but stayed closer to control values, indicating a milder effect.

Table 3. Descriptive Statistics for ALP (Alkaline Phosphatase) Levels

Group	N	Mean	Std. Deviation	Std. Error
G1	3	354.0000	98.78765	57.03508
G2	3	372.3333	57.76966	33.35333
G3	3	385.0000	93.06449	53.73081
G4	3	488.1333	52.52165	30.32339
G5	3	515.2667	30.54052	17.63258

From the results of table 4, it can be seen that Isilin has caused a marked elevation in the BUN levels of the Isilin treated animals, with G5 being the higher dosed group (G5) indicating a marked degree of kidney dysfunction in the Isilin treated group. When assessing Pelanges, the BUN levels of the Pelanges treated animals compared to the control were lower, thus indicating either a mild diuretic effect or the absence of nephrotoxicity at the doses assessed..

Table 4. Descriptive Statistics for BUN (Blood Urea Nitrogen) Levels

Group	N	Mean	Std. Deviation	Std. Error
G1	3	19.0000	1.21655	0.70238
G2	3	15.0667	0.77675	0.44845
G3	3	17.9333	2.91433	1.68259
G4	3	43.5967	4.50511	2.60103
G5	3	47.3967	5.34979	3.08870

In Table 5 serum creatinine levels increased in groups G4 and G5, reflecting impaired renal filtration likely due to Isilin. The increase was dose-dependent. Pelanges groups remained close to the control, suggesting low or no nephrotoxicity.

Table 5. Descriptive Statistics for CRE (Creatinine) Levels

Group	N	Mean	Std. Deviation	Std. Error
G1	3	0.2667	0.05508	0.03180
G2	3	0.2764	0.02309	0.01333
G3	3	0.2861	0.03055	0.01764
G4	3	0.3433	0.05132	0.02963
G5	3	0.3600	0.05292	0.03055

The significant increase in TSB levels of the Isilin-treated groups (G4 and G5), as noted in Table 6, suggests that there may be potential liver abnormalities or hemolysis taking place. None of the Pelanges groups exhibited a statistically significant difference from their respective control groups, thus suggesting that the Pelanges groups experienced minimal liver damage at the doses tested.

Table 6. Descriptive Statistics for TSB (Total Serum Bilirubin) Levels

Group	N	Mean	Std. Deviation	Std. Error
G1	3	0.4333	0.05774	0.03333
G2	3	0.4651	0.10346	0.05774
G3	3	0.4717	0.11547	0.06667
G4	3	0.6333	0.05774	0.03333
G5	3	0.6863	0.05974	0.03333

Histological Findings

Histological examination of the renal cortex from control group showed normal renal architecture (see image 1). The glomerulus appears to be intact and well defined with normal capillary loops; however, there are no signs of congestion, atrophy or increased numbers of cells. Proximal convoluted tubules have the typical brush border and possess an eosinophilic staining pattern for their cytoplasm and centrally located nucleus, suggesting they maintained their ability to absorb substances. The distal convoluted tubules are also well developed but their cytoplasm has a lighter appearance with open lumens. Other than this lack of cytoplasmic coloration, their histological features conform to the standard criteria established for their type of renal tubule. There were no signs of inflammation, necrosis or structural damage.

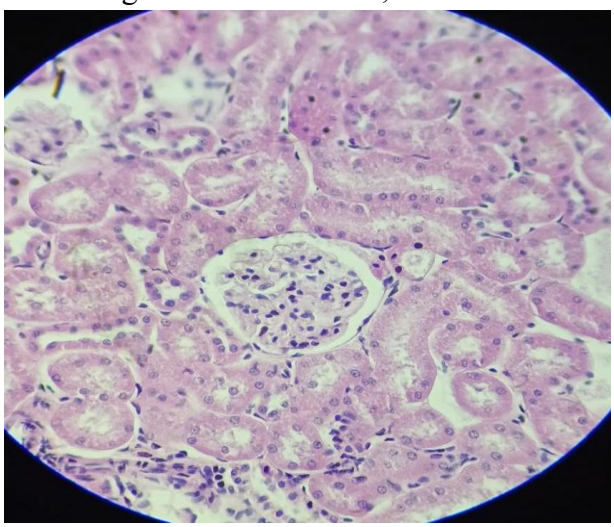

Image 1: Histological section of the renal cortex from the control group showing normal morphology of the glomerulus, proximal convoluted tubule, and distal convoluted tubule. Stained with H&E, magnification 400x.

The second group of kidney tissues were examined and show considerable infiltration of inflammatory cells into the kidney tissue. In the kidney tissues that contain immune cells, there has been an inflammatory response and is suggestive of the initiation of renal damage or irritation caused by potentially harmful substances. The presence of immune cells has caused damage to both the glomeruli and tubules. There are no predominant areas of necrosis or fibrosis at this time in the kidney tissue. There is mild to moderate levels of inflammation in the kidney tissue, which illustrates the effectiveness of the Group 2 treatment..

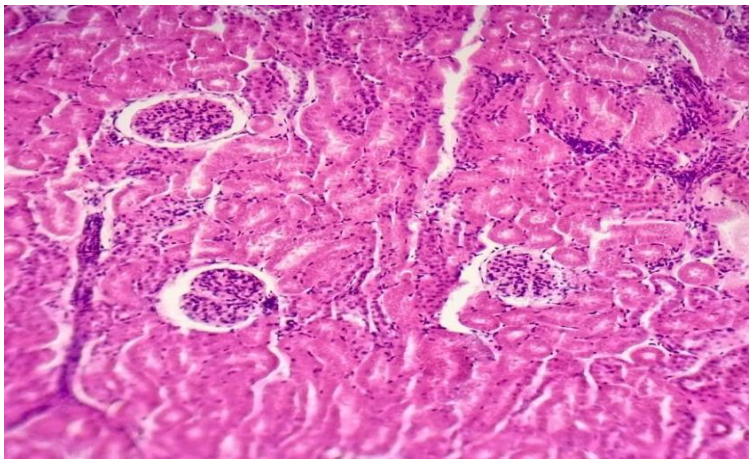

Image 2: Histological part of the renal from Group 2 demonstrating filtration of inflammatory cells. Stained with H&E and magnified 100x.

Kidneys from Group 3 (Image 3) have severe acute inflammation compared to kidneys in Group 2 (greater cell infiltration). The large number of cells present continues to cause tissue damage and indicate that an immune response is still ongoing. There is also structural damage caused by swelling with visible swelling and possible damage to glomeruli/tubules. All these changes indicate that treatment administered to Group 3 has resulted in greater nephrotoxicity/irritation..

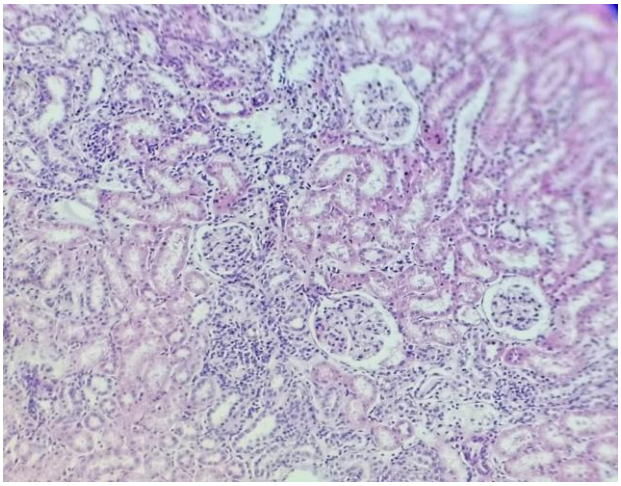

Image 3: Kidney part of a rat from Group 3 showing acute infiltration of inflammatory cells. Stained with H&E, magnification 100x.

Group 4's kidney tissue shows a high level of acute inflammation, indicating a significant inflammatory response. This indicates that the intervention used on this group has caused tremendous damage to their renals. The normal glomeruli and the tubules have been substantially damaged, presenting with very high cellular infiltrate and potentially developing edema. The observed changes within the histopathology indicate that these kidneys have become very toxic and that the immune response is effective..

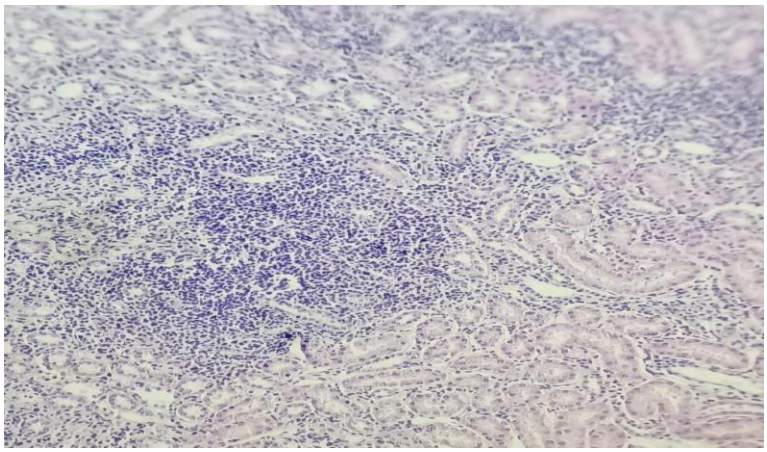

Image 4: Kidney part of a rat from Group 4 showing acute infiltration of inflammatory cells. Stained with H&E, magnification 100x.

Significant inflammatory cell infiltration is evident in the renal tissue from Group 5 (Image 5) with extensive glomerular atrophy. Therefore, there is considerable inflammation affecting the kidneys along with shrinking/breaking down of the glomerulus. Therefore, the kidneys are already damaged. The change to the normal renal architecture of both tubular (including collecting ducts) and glomerular structure suggests high levels of nephrotoxicity related to the increased dose given to Group 5. The results suggest that kidney function is impaired and there is ongoing pathological change..

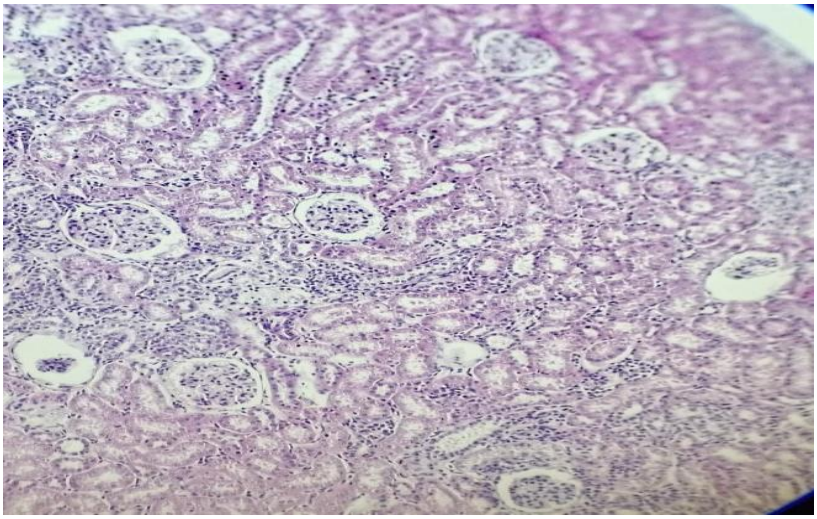

Image 5: Kidney part of a rat from Group 5 showing infiltration of inflammatory cells and glomerular atrophy. Stained with H&E, magnification 100x.

The control liver (Image 6) is characterized by a well formed central vein and a population of normal hepatocytes arranged in radiating plates about it. These hepatocytes have normal morphology (i.e., clear cytoplasm and centrally located nucleus) and demonstrate no signs of cellular injury from inflammation, necrosis or degeneration. As such, the histological appearance of this control liver is consistent with preservation of architecture/function with no exposure to toxic substances.

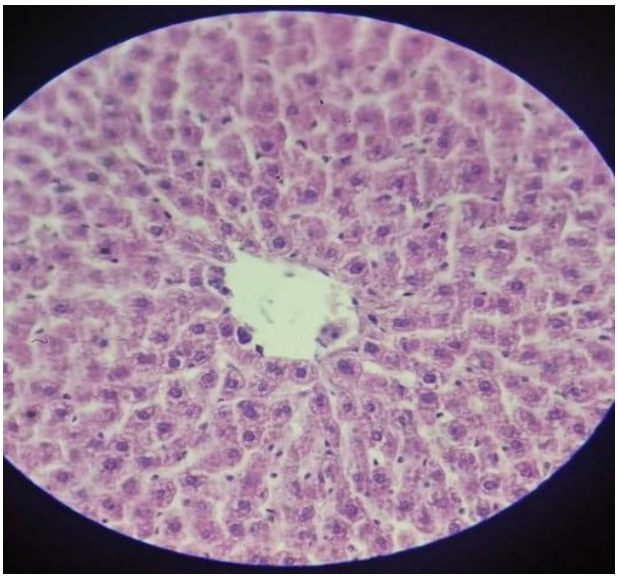

Image 6: Rat liver section from the control group showing the central vein surrounded by hepatocytes. Stained with H&E, magnification 100x.

The liver section demonstrates a mild infiltration of inflammatory cells, indicating a subtle immune response within the hepatic tissue. Hepatocytes maintain their general structure, but the presence of inflammatory cells suggests early or mild hepatic irritation or damage. No significant necrosis or fibrosis is evident, suggesting that liver injury is minimal or in the initial stages (Image 7).

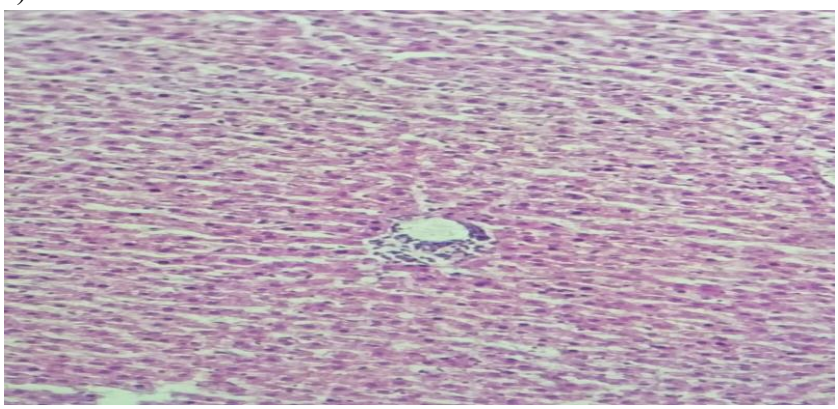

Image 7: Histological section of rat liver showing mild infiltration of inflammatory cells. Stained with H&E, magnification 100x.

In Group 3, liver tissue exhibits significant acute inflammatory response with significant infiltration by inflammatory cells. The degree of infiltration implies notable damage or irritation to the liver with loss of normal arrangement of hepatocytes. The degree of inflammatory response may suggest hepatotoxicity induced by treatment. There is no evidence of fibrosis observed but there were active signs of inflammation present in the tissue..

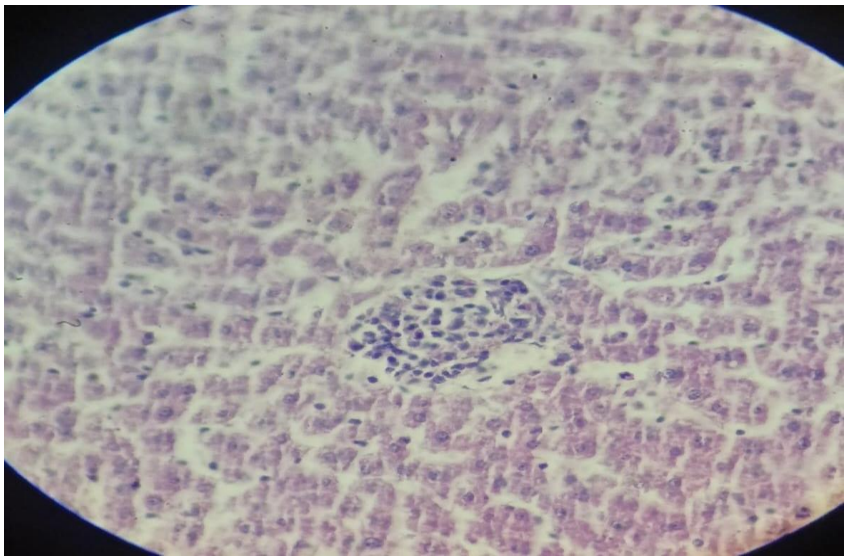

Image 8: Rat liver section from Group 3 showing acute infiltration of inflammatory cells. Stained with H&E, magnification 400x.

Image 9 demonstrates from the Group 4 liver sections that they exhibit some extent of vascular congestion with inflammatory cell infiltrations. They are minimally responding to the treatment's effect with minor impairment of blood flow and an early indication of inflammation. Furthermore, the hepatocytes themselves exhibit minimal alterations to their morphology; however, the congestion involved suggests that the liver tissue may be experiencing either a physical strain or irritation..

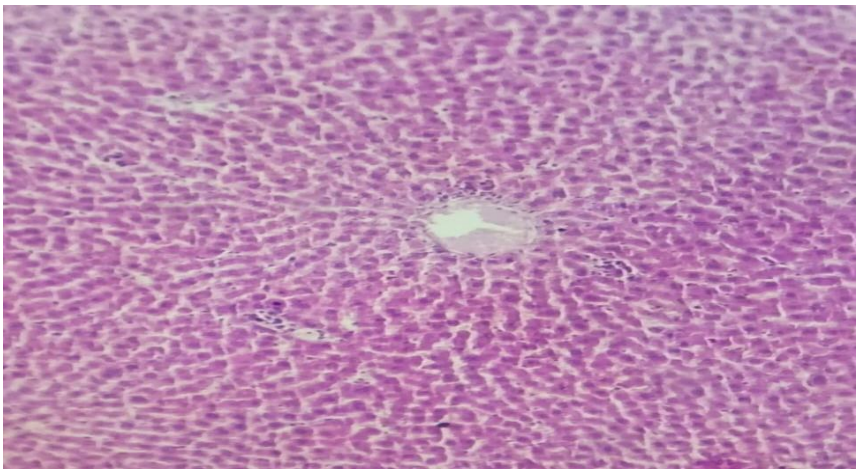

Image 9: Rat liver section from Group 4 showing mild congestion and infiltration. Stained with H&E, magnification 400x.

Liver cells from Group 5 (Image 10) demonstrate significant damage because of a substantial build up of acute inflammatory cells; therefore, we conclude that there was major liver dysfunction caused by the experimental/surgical treatment of this Group. In addition there are significant changes from normal hepatocyte architecture per cell from this group indicating active inflammation and probable early liver cell death.

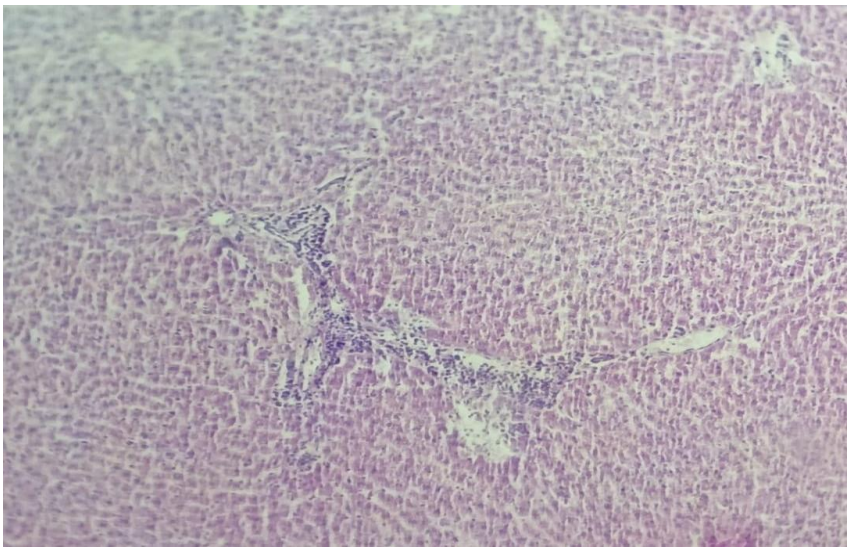

Image 10: Group 5 liver section showing acute infiltration of inflammatory cells. Stained with H&E, magnification 100x.

Discussion

In the biochemical analyses, it was determined that there was a dose-related liver and kidney disturbance due to Isilin administration. The ALT, AST, ALP and TSB levels were increased significantly in Groups 4 and 5 compared to Group 1 (control) with Group 5 consistently showing the greatest elevation in values. Elevated ALT and AST levels are classic indicators of liver cell injury as they will leak from the liver cells (hepatocytes) into the blood after the hepatocyte membrane has been damaged [15]. The very large increase in AST in particular in Groups 4 and 5 may also suggest that Isilin causes damage to the mitochondria of hepatocytes, because AST is located in both the cytoplasm and the mitochondria of hepatocytes [16].

The increased levels of ALP and total serum bilirubin in the same groups indicate dysfunction in bile drainage or further obstruction which are classic signs of cholestatic liver disease. This supports the conclusion that Isilin's effects on the liver at higher doses are likely caused by oxidative damage, mitochondrial injury, or immune-mediated mechanisms - similar to those found with drug-induced liver injury models.

In contrast to the animals treated with Pelanges (groups 2 and 3) demonstrated that the same hepatotoxicity markers, namely ALT, AST, ALP, TSB, exhibited results that were comparable with those from the control group; therefore, these data in groups 2 and 3 suggest that the doses of Pelanges evaluated, do not negatively impact liver function. The results also indicate that

Pelanges may be non-hepatotoxic or demonstrate mild antioxidant or anti-inflammatory activity that could, in part, prevent liver injury [19].

There was a marked increase in both BUN and creatinine (CRE) among animals treated with Isilin, particularly the G5 it indicates renal excretory function and glomerular filtration rate (GFR) were reduced as a consequence of nephrotoxicity [20]. These elevated levels may also represent acute tubular injury, decreased renal perfusion or direct glomerular toxicity. There appears to be a dose dependent pattern in terms of the elevations observed and supports the notion that the higher concentration of Isilin delivered greater damage to renal function, which may present similar characteristics to those associated with drug induced acute kidney injury (AKI) or hepatorenal-type syndrome due to the above mentioned [21].

BUN levels did not increase in the Pelanges groups and were instead at least stable and possibly lower than the control group; however, the creatinine levels were also stable. BUN levels could also demonstrate a diuretic effect of the test compound on the kidneys or provide evidence for renal safety with the test dose of the compound [22]. This renal effect is similar to the observations seen with other plant-based or natural products that have limited nephrotoxicity, or even provide some nephroprotective effects, when subjected to mild oxidative stress [23].

Histopathological examinations were similar to those of biochemistry. The renal cortex in control animals (shown in picture 1) had a normal appearance and was arranged as normal proximal and distal convoluted tubules (no signs of inflammation, necrosis, or distortion to the architecture). Therefore, these findings support normal morphology in the renal cortex [24].

Group two (image two) showed signs of acute immune response to Pelanges as demonstrated by the high number of infiltrating inflammatory cells into the renal interstitium. Group three had the highest level of inflammatory cell infiltration and known as being the location where acute inflammatory cell infiltration indicated moderate nephritic inflammation [25]. The renal tissue architecture of both groups displayed only minimal damage with no evidence of tubular necrosis or glomerular collapse [25].

Kidney specimens from Groups 4 and 5 exhibited marked acute inflammatory infiltration and Group 5 also demonstrated glomerular atrophy (see Images 4 and 5). The histopathologic findings are consistent with either acute interstitial nephritis or glomerulonephritis and correlate with the markedly elevated BUN and creatinine in both groups [24]. The severe renal injury resulting from Isilin administered to Group 5 is a consequence of cytotoxic and/or immunotoxic effects of Isilin and supports the conclusion that Isilin is nephrotoxic at higher doses [26].

Confirmation of the results previously reported in vivo was found with histological examination of liver sections. The liver from the control (Image 6) was histologically normal exhibiting normal (i.e., typical) architecture, which consisted of hepatocytes radiating outward from a central vein (i.e., typical portal triads), and free of inflammation, necrosis, and other gross pathological changes. Liver from Group 2 (Image 7) exhibited a combined minimal infiltration of inflammatory cells; therefore, little hepatic injury occurred as a result of Pelanges. In contrast, Histologically Group 3 (Image 8) exhibited more acute inflammation due to

significantly increased infiltration of inflammatory cells compared with Group 2 (but the architecture was relatively unaltered or intact compared with the control).

The Level of Sinusoidal Congestion and Inflammatory Infiltrate Observed in Test Group; Group 4 Mild Level of Congestion and Inflammatory Infiltrate (Figure 9) and Indicated Some Degree of Vascular Compromise to Hepatocytes and Indicated Some Level of Stress to Hepatocytes; Group 5 Moderate Level of Congestion and Inflammatory Infiltrate (Figure 10) and the Most Severe Hepatic Response with Severe Inflammatory Infiltrate and Disruption to the Hepatic Plates in the Liver Indicating Some Acute Hepatic Injury. Histopathology Findings Are in Close Correlation With Increasing ALT, AST, ALP as Well as TSB, Thus Supporting Evidence of Isilin's Hepatotoxicity, Especially at the Highest Dose That Was Tested. [28].

Conclusion

The biochemical and histological effects of Isilin indicate hepatotoxicity as well as nephrotoxicity in the experimental rat at low and high doses, while the results of Pelanges show that it has a more favourable safety profile than what was observed with Isilin, and caused very limited to moderate changes in histology, and very stable biochemical values. Therefore, these data require monitoring all herbal and/or synthetic compounds that are prescribed for therapeutic use to ensure that they are appropriate for the patient and that they are safe for use in all organs.

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