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Original Research Article

Potential restorative effect of silymarin on liver histoarchitecture on paracetamol-induced in, hepatotoxicity in adult albino rats

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ABSTRACT

Background: Paracetamol is one of the most common pain relievers you'll find in any medicine cabinet. Worldwide its often used for fevers or everyday aches without a second thought. But while it's generally safe, taking too much can seriously harm the liver, something many might not realize. Otherwise, natural remedies offer potential remedies like silymarin, an extract from milk thistle. This herbal compound isn't just a supplement; studies suggest it fights oxidative stress and even helps repair damaged cells. Objective: To determine the histo-restorative effects of different doses of silymarin milk thistle on liver histo-architecture on paracetamol-induced hepato-toxicity among adult albino rats.
Methods: a total of 24 rats, splitting them into four groups. One group got a high, toxic dose of paracetamol alone; another stayed untreated as a control. The remaining rats were all given paracetamol first to induce liver injury, then divided into three subgroups receiving low, medium, or high doses of silymarin. After the treatment period, their liver tissues were extracted and studied under a microscope, using standard staining techniques to assess any recovery.
Results: High dose of paracetamol induced liver toxicity. Upon administration of high dose of silymarin milk thistle, there was histo-restoration of liver architecture with evenly distribution of hepatocytes and reduction and vacuolation of the central vein in relation to the control group.
Conclusions: These findings showed that high dose (600 mg/kbwt) of silymarin milk thistle was found to have restorative effects and restored the liver histo-architecture to near normal.

Keywords: Hepato-restorative, Liver histo-architecture, Paracetamol hepato-toxicity, Silymarin milk thistle

INTRODUCTION

Paracetamol is an accessible first-choice analgesic that can be obtained with or without prescription as an over-the-counter drug. It is the most preferred non steroidal analgesic since it tolerable to most of the individuals. Unlile other steroidal analgesic associated with renal, gastrointestinal, and cardiovascular side effects, especially in older people with multiple co-morbidities, paracetamol has always been the drug of choice. It is usually considered safe when the daily intake does not exceed 4 g per day.[1]

There has been a steady increase in liver toxicities worldwide from various causes such as alcohol and drugs. This has led to increased morbidity and mortality in the general population with approximately 30% from drug induced hepatotoxicty.[2] These drugs are either prescribed or found over the counter. Due to chronic pains from work related musculoskeletal disorders such as low back pain and muscle aches, there is a steady increase in the use of paracetamol as an antipyretic and for management of fevers in children.[3] In the COVID-19 pandemic alone, studies indicate that there was an increase of 150% in its consumption during the pandemic to manage chronic pain

and pyrexia that was a common symptom of the COVID-19 virus.[4]

Paracetamol toxicity has been found to be caused by a single high dose ingestion or after it has been chronically ingested. Furthermore, studies have also shown that an advanced age of more than 80 years, low body weight of less than 50 kg, underweight or persons with a small frame, patients with malnutrition and poor dietary habits, prolonged exposure more than 3 days and daily dose more than 3 gm have been asscoiated with paracetamol toxicity or in alcohol intake even when administered at a therapeutic dose.[5-7]

With increasing effects of hepatotoxic effects from either alcohol or drug induced aetiologies, liver damage presents with histological and functional changes. These include changes in the hepatic architecture disaorganization that present with vacualation of hepatocytes, congestion of the central vein, congestions of the portal area, dilatations of the sinusoids or even obliteration of the sinusoids and increasing number of kuppfer cells that line the blood sinusoids.[8] These changes due to the injuries to the hepatocytes and bile duct cells causes accumulation of bile acid within the liver causing liver damage.[9,10]

Prolonged use of paracetamol or at high doses causes oxidative metabolites N-acetyl-para-benzoquinone mine (NAPQI) to cause the liver cells to be under oxidative stress. This therefore will cause the hepatocellular mitochondria to burst leading to free oxygen radicals and nitrogen ions to cause necrosis of hepatocellular cells leading to liver damage.

Silymarin milk thistle is an edible plant as either vegetable or roasted seeds in most parts of the world that has been found to have hepatoprotective properties on the liver. Silymarin is the main ingredient in the plant effective in treating various liver diseases, hepatitis, blood lipids, diabetes, cardiovascular diseases and cancer with its highest concentration in its seeds and stem.[11]

These anti-oxidant properties of silymarin have been found to greatly reduce free radicals that are produced secondary to metabolism of toxic substances such as paracetamol and alcohol thereby improving the integrity of the mitochondria and maintaining redox balance and modulates enzymes associated with the development of cellular damage, fibrosis and cirrhosis thereby maintaining liver function.[12] Silymarin also increases hepatic glutathione which will promote the antioxidant defence of the liver.[13]

Studies have shown that silymarin can prevent direct formation of free radicals, or prevent free radical formation by inhibiting the enzymes that cause oxidative stress in the mitochondria. The inhibition of those free radicals helps in the protection of Kupffer cells in the liver. It also has free radical scavenging activity and prevents formation of enzymes responsible for production of free radicals in the cell thus maintaining an optimal redox state.[14]

METHODS

The study was conducted between May 2023 to July 2023 at the school of Biomedical Sciences of Maseno University. It's located along the equator in Kisumu County Western part of Kenya. All experimental studies appertaining feeding, weighing and administration of drugs were done at the animal house within the school.

Study subjects

This study was conducted on pure bred albino rats of the species of *Rattus norvegicus* from a pure colony of both sexes sourced from the School of Biomedical Sciences of Maseno University, Kisumu, Kenya. The albino weighing between 240 gm and 280 gm. The animals were fed with standard rodent pellets obtained from Unga Feeds Limited Kisumu city and water ad libitum. They were then put in cages and left to acclimatize for 5 days before the commencement of the study. All protocols for humane handling of the animals were strictly adhered to.

Experimental design

This study followed a post-test only true experimental design. A total of 24 animals were randomly assigned to different groups using simple random sampling. The groups were structured as follows:

Group A (control): received no drug treatment- only standard food and water.

Group B (paracetamol-only): administered a high dose of paracetamol (750 mg/kg body weight) daily for five days.

Group C (low-dose silymarin- SIL-G1): given the same high dose of paracetamol for five days, followed by a low dose of silymarin milk thistle (200 mg/kg body weight) for the remaining study period.

Group D (medium-dose silymarin- SIL-G2): treated with the high paracetamol dose for five days, then a medium dose of silymarin (400 mg/kg body weight).

Group E (high-dose silymarin- SIL-G3): received the initial five-day paracetamol regimen, followed by a high dose of silymarin (600 mg/kg body weight).

Sample size determination and sampling technique

A total number of 24 rats were sampled for this experiment. The sampled size was arrived at using modified resource equation method" of which there was no previous research done to determine the standard deviation.[15]

Drug acquisition and dose determination

The paracetamol tablets (500 mg tablets) were obtained from Litein Central Chemist, Kericho- Kenya while the silymarin milk thistle tablets were obtained from Dynapharm Kenya Limited-Nakuru, Kenya. They were prepared by dissolving in water for injection before use. To induce liver toxicity, paracetamol a high dose paracetamol (750 mg/kbwt) was administered for five days.

Procedure for drug administration

The drugs were administered orally where they were dissolved in water for injection. Paracetamol was used to induce hepatotoxicity and silymarin milk thistle was used as a curative/ restorative drug. For the paracetamol-only control group and the experimental group, they were given high dose paracetamol once daily for five days. Thereafter, those in the experimental group were given varying doses of silymarin according to the different groups.

Each albino rat was held and wrapped using a table towel to avoid the animal from soiling the primary researcher's garments. The animal was held behind the neck region with one hand. After that, the rat was put to resting position to lie on the researcher with its mouth put to face forward. The gastric gavage needle was gently inserted into the albino rat's mouth while gently to manoeuvring it through the esophageal constrictors and finally through the cardiac sphincter. Eventually the paracetamol dose was eventually deposited into the rat's stomach. The gastric gavage needle was removed slowly and gently to avoid injuring the animal.

Procedure for anesthetizing of albino rats

Concentrated chloroform was opened into a heavy tight fitting bell jar. The albino rats were euthanized by being put into the bell jar for approximately 3-5 minutes. After being euthanized they were removed from the tight fitted lid jar and put on the dissecting board and well mounted using mounting pins to lie of the rear side facing supine.

Figure 1: Albino rats being euthanized by being put into the bell jar for approximately 3-5 minutes.

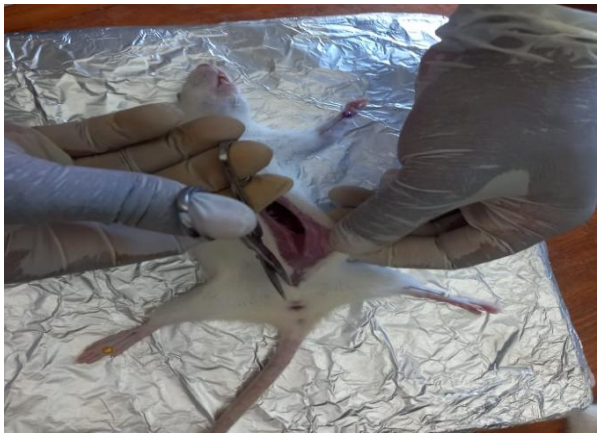

Figure 2: Albino rat mounted on a dissecting board while facing supine.

Picture 3: Liver harvested from the albino rat

Histological analysis

The rats in the control group and paracetamol-only group were anaesthetized on day 5 by using concentrated chloroform and the liver specimens were harvested. The rats in the experimental group were anaesthetized on day 21 by using concentrated chloroform and the liver specimens were harvested. Histo-architectural studies were done, where histological processing and staining using the H and E technique were done and studied under a microscope (Olympus BP).

The liver tissue excised underwent fixation using formaldehyde solution for a period of 24 hours thereafter they were immersed in ascending strengths of alcohol from 50%, 60%, 70%, 80%, 90% up to 100% for a period of one hour in each concentration to be dehydrated.

After dehydration, it was cleared with xylene and infiltrated using paraffin wax for 12 hours at 56°C and then positioned longitudinally and paraffin wax used to embed it onto the wooden blocks. The surplus wax was removed till there was full exposure of the whole length of the liver tissue. Thin longitudinal sections of 5 µm thickness were obtained by cutting using a Leitz sledge rotary microtome with those longitudinal sections left to float on water at 370 to stretch the liver sections. These cut longitudinal sections

were sticked onto the glass slide and applied using a micro-dropper as a thin film onto the glass slide and left to dry in an oven of temperature 370 for 24 hours. Thereafter staining using hematoxylin and eosin (H and E) was done.

Procedures for photography

The slides that were prepared for histological study were secured on the microscope's stage. The fine and coarse adjustment knobs of the microscope were adjusted to obtain a clear focus of the image to be photographed and magnified appropriately. Photograph images of the regions under focus were taken and photographs obtained were stored in a computer and a flash disc. The photograph images taken were then uploaded and carefully labelled using the Adobe fireworks Programme. A LABOMED IV 3200 fitted with digital camera was used for photomicrography.

RESULTS

Histological changes on the liver when administered with hepatotoxic dose of paracetamol

The liver histological slides of the paracetamol only group were compared with the control group. The sinusoids, hepatocytes, central part and the central vein were observed.

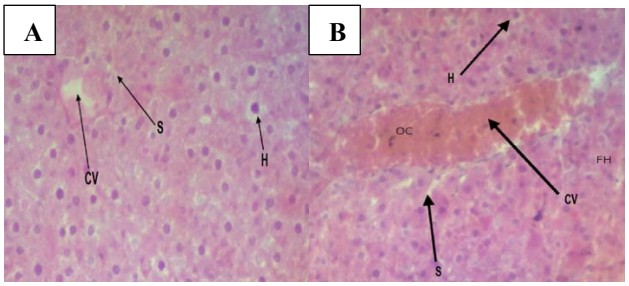

Figure 4: Photomicrographs of the control group and the paracetamol only group after staining with hematoxylin and eosin (H and E); A) control group B) paracetamol only group

Key: CV-Central vein, S- sinusoid, H- hepatocyte, OC-Occlusions, FH- Focal Hemorrhage.

The control group (Figure 4A) had evenly distributed hepatocytes, normal sinusoidal dilatation and visible central vein. The paracetamol only group (Figure 4B) group had dilated central vein, dilated sinusoids, focal areas of hemorrhage and atrophied hepatocytes. It also presented with occlusions in central veins and numerous Kupffer cells.

Histo-morphological changes on the liver on paracetamol induced hepatotoxicity following administration of different doses of silymarin

The histological slides of the silymarin intervention groups were examined. The central vein, sinusoids and the hepatocytes were compared among the silymarin intervention groups with those of the control group.

The central veins and sinusoids were dilated in the paracetamol only group, medium dose and low dose group as compared to the high dose SIL group. There was also reduction in size of the hepatocytes in the paracetamol only group, medium dose SIL and low dose SIL group as compared to the High dose SIL group and control group that had normal hepatocytes. The low dose SIL had dilated hepatocytes, vocal areas of hemorrhage. The central veins of the paracetamol only group, medium dose SIL and low dose SIL group had also been occluded while High dose SIL had evenly distributed hepatocytes and no dilated sinusoids (Figure 5C). This could be due to the hepatotoxic effects of paracetamol on the liver cells that causes these changes in the central vein. The occlusion in these groups could also be due to the hemorrhage brought about by the reactive oxygen and protein radicals within the liver affecting the normal liver functions. The focal areas of necrosis and hemorrhages is possibly due to the increase in the toxic levels of NAPQI triggering the necrotic changes.

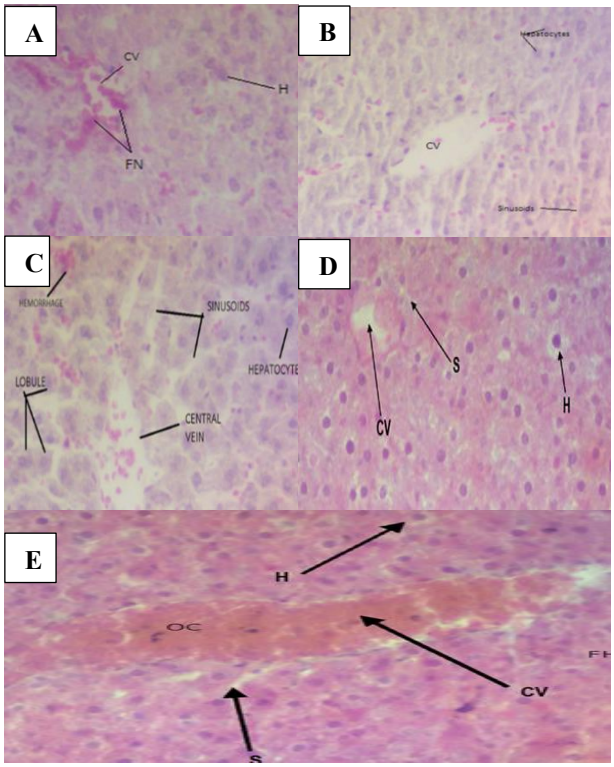

Figure 5: Photomicrographs of the control group compared to paracetamol only group and silymarin intervention groups that were treated with different doses of silymarin milk thistle and stained with H and E.

A) low sil. group; B) medium sil. group; C) high sil. group. Key: H and E- hematoxylin and eosin. CV-central vein, S- sinusoid, H-hepatocyte, DS- dilated sinusoids, MV- mild vacuolation, N-nucleus, FN- focal necrosis, NH- normal hepatocytes, OC-occlusions, FH- focal hemorrhage. D. control group; E. paracetamol only group. Key: H and E- hematoxylin and eosin. CV- central vein, S- sinusoid, H- hepatocyte, DS- dilated sinusoids, MV- mild vacuolation, N- nucleus, FN- focal necrosis, NH- normal hepatocytes, OC- occlusions, FH- focal hemorrhage.

The control group and the high dose SIL group had normal central vein, evenly distributed normal hepatocytes, normal arrangements and dilations of sinusoids as compared to the low dose, medium dose SIL groups and the paracetamol only group. The liver histo-architecture of the high dose SIL group and the control group had similar histological presentations of the sinusoids, hepatocytes and central vein illustrating restoration on high dose silymarin (Figure 5). These changes observed in these two groups could be due to the restorative effects of high dose of silymarin milk thistle on the liver that restores the normal liver histo-architecture and restores normal functioning.

Table 1: Table of results.

Group	Result
Group A- control group	They had normal and evenly distributed hepatocytes, normal arrangements and sinusoidal dilatation and visible central vein.
Group B- paracetamol only group	The group had dilated central vein, dilated sinusoids, focal areas of hemorrhage and atrophied hepatocytes visualized within the liver parenchyma. It also presented with occlusions in central veins and numerous Kupffer cells.
Group C- low dose silymarin group	The central veins and sinusoids were dilated. There was also reduction in size of the hepatocytes. Visualized dilated and unevenly hepatocytes, vocal areas of hemorrhage. The central veins had also been occluded. The focal areas of necrosis and hemorrhages within the parenchyma
Group D- medium dose silymarin group	The central veins and sinusoids were dilated. There was also reduction in size and distribution of the hepatocytes. Dilated hepatocytes with vocal areas of hemorrhage. Occlusions of the central veins. The focal areas of necrosis and hemorrhages
Group E- high dose silymarin group	Had normal hepatocytes which were evenly distributed. There were no dilated sinusoids. Presented with normal central vein patency. Liver parenchyma presented with normal arrangements and dilations of sinusoids.

DISCUSSION

Paracetamol is one of the most commonly accessible over-the-counter drugs used to manage pain and its overdose and abuse have been associated with liver damage.[16] According to the histo-morphologic findings in this study, the paracetamol only group was found to have areas of hemorrhagic necrosis with the presentation of vacuolated hepatocytes, deranged and dilated sinusoids, pockets of foci areas of hemorrhage, and abnormally high numbers of Kupfer cells, while those of the control group had a normal arrangement of sinusoids, normal hepatocytes and no areas of necrosis. These morphological changes could have been due to an increase in NAPQI in the liver tissue, causing damage and disruption in cytoplasmic organelles. This could have a negative effect in the normal liver physiology and cause deranged liver biochemical markers causing further liver damage. These changes also in the liver parenchyma could lead to mitochondrial dysfunction thus affecting the ATP generation in the cells causing necrotic cell death.[17] A study by Manal and Emal on the effects of paracetamol on liver histology of adult rabbits also observed necrosis, vacuolization of hepatocytes with irregular nuclei and the presence of abnormally high Kupfer cells on administration of high-dose paracetamol.[18] In addition, a study on histopathological changes in acetaminophen-induced liver injury in Wistar albino mice, reported focal points of hemorrhagic necrosis on the liver, which could be due to inflammatory responses at these hepatotoxic levels, as was observed in the current study.[19]

Paracetamol toxicity in the liver of rats have also indicated to cause centrilobular necrosis in the hepatocytes. This could be as a result of the toxic metabolite of paracetamol NAPQI within the cells inducing oxidative stress and cellular necrosis. This study also exhibited distortion in the histoarchitecture of the hepatocytes and were in tandem with other studies that found out that the hepatocytes exhibited degeneration with further dilation, congestion and hemorrhage of the central vein.[20-22]

Silymarin milk thistle an edible herb, is believed to have antioxidant, radical scavenging, and regulation of glutathione levels properties. It has been used over time in treating various conditions, including stomach upset, liver and kidney problems; however, its pharmacokinetics and pharmacodynamics have not been well documented. In this current study, different doses of silymarin milk thistle (high dose of SIL: 600 mg/kbwt, medium dose of SIL: 400 mg/kbwt, low dose of SIL: 200 mg/kbwt) were administered to the silymarin interventional group.

On the histo-architectural findings of the silymarin intervention groups, the low-dose SIL group was found to have some aspects of sinusoidal dilatations, vacuolated hepatocytes and areas of focal necrosis, which could be due to the minimal impact of silymarin on the liver cell. The medium-dose SIL group had relatively normal hepatocytes with mild dilation of sinusoids and minimal focal areas of necrosis. The high-dose SIL group had minimal cell damage, possibly due to the changes brought about by the high dose of silymarin that might have possibly counteracted the hepatotoxicity (Figure 5). These

changes in the liver parenchyma in the three groups could possibly be due to the varying doses of silymarin, thus affecting the levels of glutathione and reducing the levels of reactive superoxides and anions, which eventually affect the liver histology. These findings could also be due to the neutralization of free oxygen radicals and nitrosative stress from the liver bringing about these changes.

Various literature reviewed indicated that administration of silymarin milk thistle at varying doses posed varying changes in its restorative impact. It was noted that restorative effect of silymarin on nonalcoholic fatty liver disease (NAFLD) or cirrhosis varied based on the type, stage, and severity of the illness. However, for optimum results, high dosage of silymarin was found to have good prognosis on administration post liver cirrhosis or nonalcoholic fatty liver disease.[23]

From different literature reviewed, a study on streptozotocin-induced diabetic rats found that silymarin and silybinin caused repair on the histoarchitectural damaged pancreatic islets of Langerhans and normalization of arrangements of acinar cells, and improvements on beta cells.[24] A study by Zuzana et al, recorded that during concurrent administration of silymarin and acetaminophen in Wistar rats, silymarin protected the liver tissue from damage and necrosis, noting that it had antioxidant properties.[25] Other studies observed that administration of silymarin and vitamin C led to a reduction of reactive oxygen species, bringing about normalization of the liver histo-architecture on acetaminophen-induced liver damage in Wistar rats, concurring with this study that there are restorative effects brought about by administration of silymarin milk thistle.[26]

The high silymarin milk thistle group was largely comparable with the control group as it had fairly even distribution of the hepatocytes, minimal to no occlusions of the central vein and almost identical to normal liver histoarchitecture. This finding exhibits that silymarin has regenerative properties and improvement of the hepatocytes to near normal liver histology as compared to those that didn't receive any treatment of the silymarin.[27]

CONCLUSION

Silymarin milk thistle was found to have histo-restorative effects on paracetamol induced hepatotoxicity at a high dose (600 mg/kbwt). This led to normalization of liver histo-architecture and restoration of the liver histological presentation of the hepatocytes, central vein and sinusoids to near normal at high dose as compared to low dose silymarin.

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