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RESEARCH ARTICLE

Protective potential of ginseng and silymarin on the liver and kidney of ethanol-treated mice (*Mus musculus*)

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ABSTRACT

Background: Alcohol use and abuse have been rampant worldwide, and therapeutic regimen has been sought for to ameliorate changes brought about by such. Herbal medicines have been mostly used due to their inherent properties and non-toxic effects in the body. **Aims and Objectives:** The objective of this study was to determine if ginseng and silymarin can provide protective effects to prevent liver fibrosis and renal destruction in mice (*Mus musculus*). **Materials and Methods:** Thirty laboratory mice were randomly placed in six groups, each with five mice. Treatments were introduced for the next 3 weeks (21 days). Food pellets were mixed with 0.10 mL silymarin or 0.10 mL ginseng with 20% ethanol v/v water was given. Group 1 was given local food pellets and mineral water, Group 2 was given local food pellets and 20% ethanol, Group 3 given ginseng food pellets and mineral water, Group 4 given silymarin food pellets and mineral water, Group 5 given ginseng food pellets and 20% ethanol, and Group 6 given silymarin food pellets and 20% ethanol. At the end of the treatment period, the mice were sacrificed through cervical dislocation, and the liver and kidneys were extracted and processed for histological analysis. **Results:** Both liver and kidneys showed extensive damage in the group treated with 20% ethanol. Silymarin and ginseng were both able to protect the liver, though there were more protective effects when treated with silymarin as compared to ginseng. **Conclusion:** It can be concluded that silymarin and ginseng may have protective effects against hepatic and renal insults and damage.

KEY WORDS: Ethanol; Ginseng; Hepatoprotection; Nephroprotection; Silymarin

INTRODUCTION

The liver is one of the biggest organs in our body,[1] and one of its main function is to filter the blood coming from the digestive tract, before passing it to the rest of the body.[2] The liver also detoxifies chemicals and metabolizes drugs,[3] secretes bile and gets reabsorbed back to the intestine,[2] and makes proteins important for blood clotting, and other functions.[4] Specifically, it is one of the organs that regulate some factors and metabolic functions to maintain homeostasis.[5]

One reason for liver damage can be due to excess intake of alcoholic beverages. This happens because people get addicted to alcohol for the reason that alcohol targets the reward system of the brain.[6] The disease that can be attained from too much intake of alcohol is called liver fibrosis, which can lead to cirrhosis if the damage is not tended to.[7] Alcohol is absorbed into the bloodstream from the stomach, and all blood from the stomach or sometimes the intestine passes through the liver first before circulating through the body. The liver has enzymes, which can break down alcohol into other chemicals then later on broken down again into water and carbon dioxide. This is then brought out of the body through urine. Even though the body has this function, it can only process a

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certain amount of alcohol per hour and exceed that limit can damage the liver.[2] The liver is said to have a self-restorative property although it is not enough to bring back the liver to its cured stage. Certain medicines are available that further restore the liver and may help prevent liver disorder.

The kidney has multiple functions. First, it regulates fluid and electrolyte balance by filtration, secretion, and re-absorption. Second, the kidney is an endocrine organ; therefore, it activates both erythropoietins for the production of red blood cells, and vitamin D, which regulates calcium metabolism. Aside from that, it also produces renin in the afferent arteriole, which affects various aspects of water and electrolyte homeostasis.[3]

Milk thistle is a plant native to Europe[8] and a flavonoid complex called silymarin can be extracted from the seeds of milk thistle and is believed to be the biologically active component. Milk thistle provides protection to liver cells by stabilizing and guarding the cell membranes. It alters the structure of the outer cell membrane so as to prevent the penetration of liver toxins into the interior cell. Silymarin exerts its powerful antioxidant properties by combining and neutralizing harmful free radicals resulting from metabolic processes and the process of detoxification.[9] Milk thistle helps repair damaged cells and generate new ones when needed. It accomplishes this by stimulating vital protein synthesis through the enzyme RNA polymerase I. Silibinin may be the agent of this process, functioning by imitating a steroid hormone.[10]

The importance of this study is that it will be able to give out information if ginseng and silymarin have the capacity to give enough prevention of liver fibrosis and kidney disease or renal destruction**.** In this study, the alcohol will be given to the mice along with the ginseng and silymarin, which is said to have preventive and protective effects.

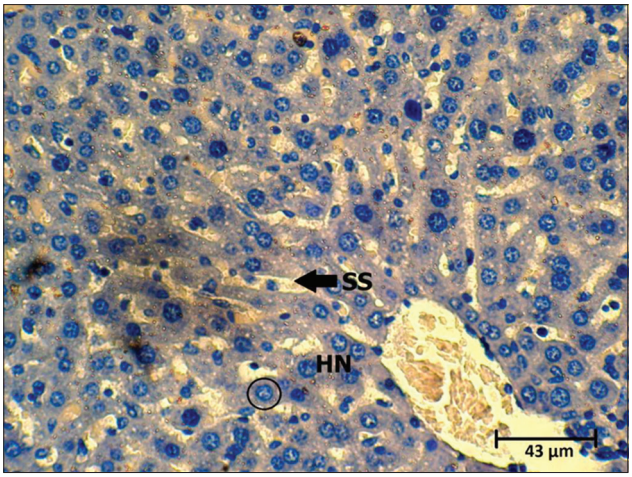

Figure 1: *Mus musculus* liver from the negative control group. Radial arrangement of the hepatocytes could be seen, as well as the hepatic SSs. No enlargement of hepatocytes. SS: Sinusoid, HN: Hepatocyte nucleu

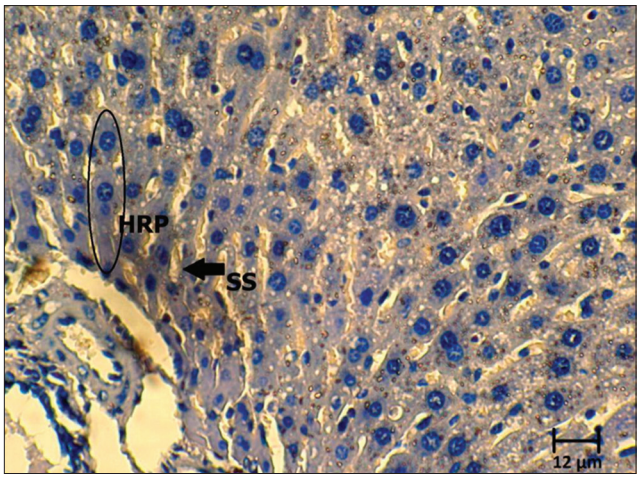

Figure 3: *Mus musculus* liver, which is induced with 20% ethanol and ginseng. It shows radial arrangement of the hepatocytes. SSs are present although almost obliterated. SS: Sinusoids, HRP: Radial pattern of hepatocytes

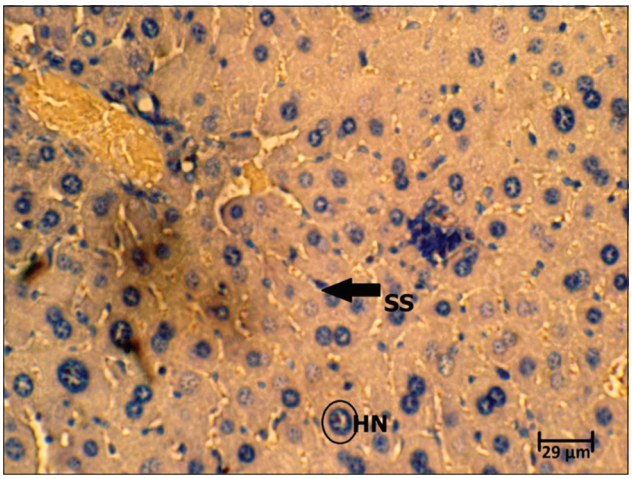

Figure 2: *Mus musculus* liver cross-section which was induced with 20% ethanol. It shows disorientation of the hepatocytes. Some nucleus is enlarged, and some are disintegrating. Hepatocytes are inflamed in which SSs became obliterated. SS: Sinusoids, HN: Hepatocyte nucleus

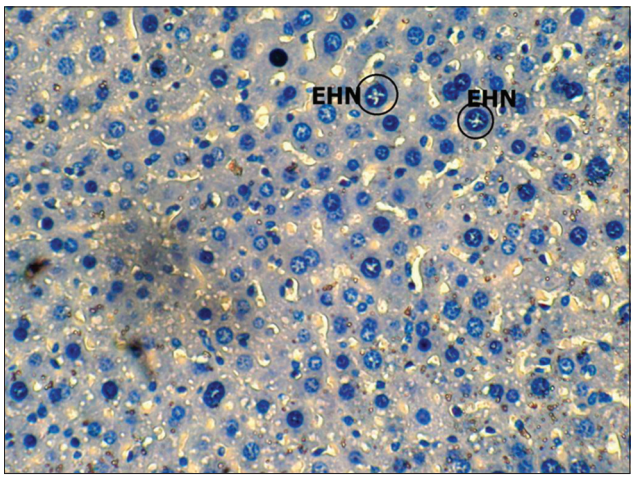

Figure 4: *Mus musculus* liver, which is induced with 20% ethanol and ginseng. It shows radial arrangement of the hepatocytes. SSs are present although almost obliterated. EHN: Enlarged hepatic nucleus, SS: Sinusoids

MATERIALS AND METHODS

A total of 30 6–7-week-old ICR male mice with an average weight of 25 g were obtained from the Bureau of Animal Industry, Department of Agriculture, Republic of the Philippines were used in the experiment. The mice were randomly placed into six groups [Table 1]. The mice were acclimatized for 7 days before the start of the experiment proper. During the acclimatization period, the mice were given untreated food pellets and mineral water only. The mice were housed in the Animal House of the Biology Department, De La Sall University with an average temperature of 22°C, relative humidity of 72, and a 12 h light:12 h dark cycle. The succeeding experiments described below have been approved

Table 1: Assigned treatments for each group

Group	Treatment
Group 1: Sham control	Local food pellets with mineral water
Group 2: Negative control	Local food pellets with 20% ethanol in mineral water
Group 3: Ginseng	0.10 mL ginseng mixed with local food pellets with mineral water
Group 4: Silymarin	0.10 mL silymarin mixed with local food pellets with mineral water
Group 5: Ginseng with ethanol	0.10 mL ginseng mixed with local food pellets with 20% ethanol mineral water
Group 6: Silymarin with ethanol	0.10 mL silymarin mixed with local food pellets with 20% ethanol mineral water

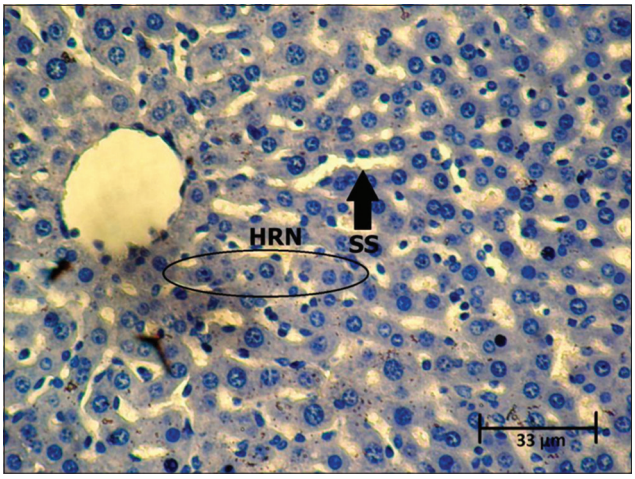

Figure 5: *Mus musculus* liver treated with 20% ethanol and silymarin. It shows the radial pattern of the hepatocytes. SSs can be clearly detected. No change in size in the nucleus occurred ×400. SS: Sinusoid. HRP: Radial pattern of hepatocytes

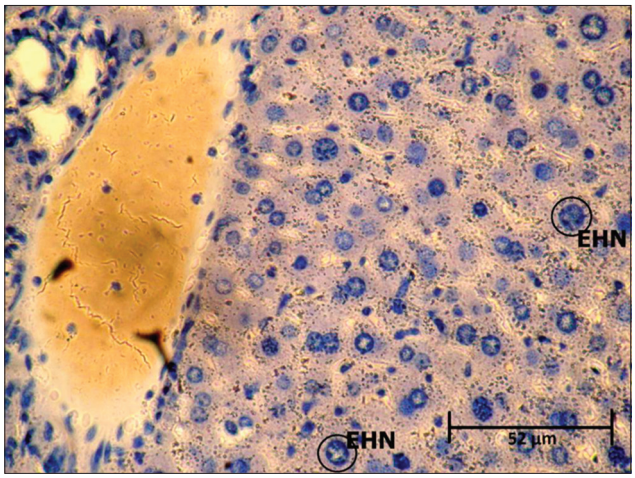

Figure 6: Liver of a *Mus musculus* fed with normal diet with the addition of ginseng. Radial pattern of the hepatocytes cannot be identified. SSs are obliterated. Some nucleus enlarged. EHN enlarged hepatic nucleus, SS: Sinusoids

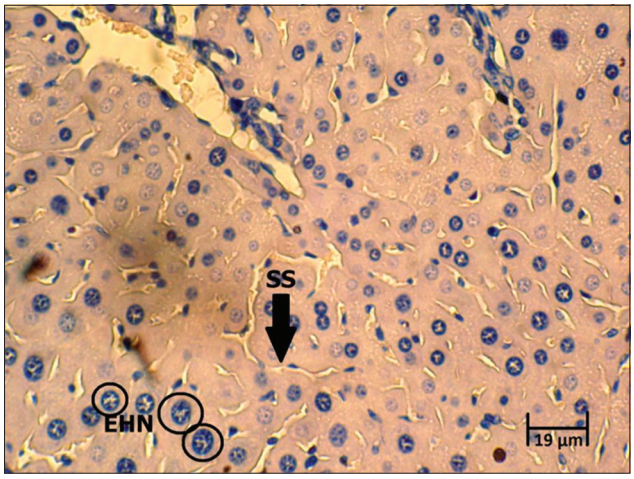

Figure 7: Liver of *Mus musculus* fed with normal diet with the addition of silymarin. SSs are present but are congested. Increase in nucleus size can be seen. SS: Sinusoid. EHN: Enlarged hepatic nucleus.

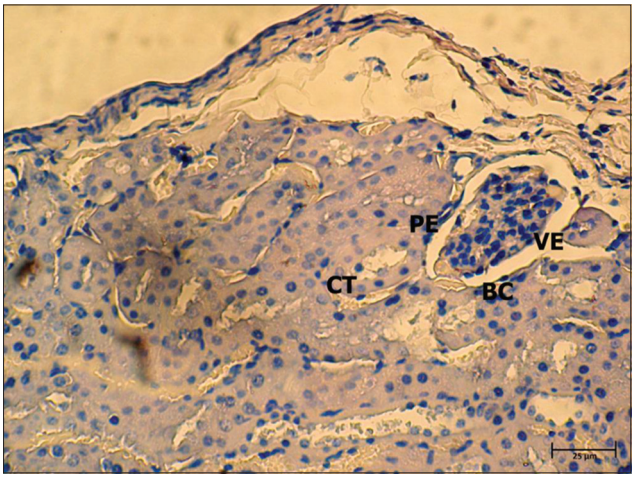

Figure 8: *Mus musculus* kidney wherein the mouse was given normal diet. CT surrounding the glomerulus are present. Glomerular space is present. Distinct space between the PE and VE is present. PE: Parietal epithelium, BC: Bowman's capsule, VE: Visceral epithelium, CT: Convoluted tubules

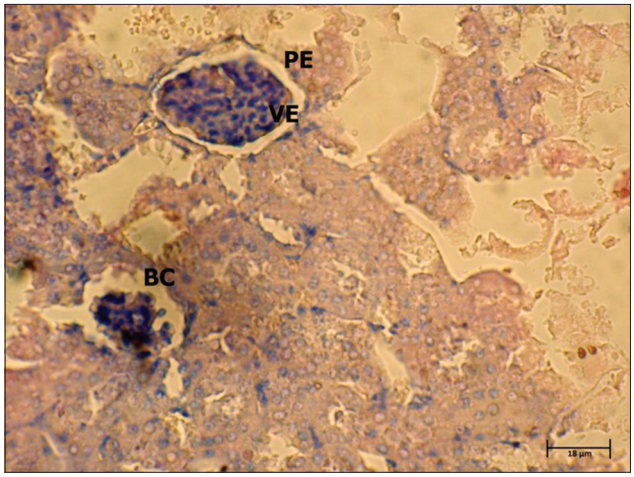

Figure 9: *Mus musculus* kidney induced with 20% ethanol. The CT are cloudy and hard to detect. Shrinkage in one of the GL shown can be seen. Distinct space between the PE and VE is present. PE parietal epithelium, BC: Bowman's capsule, VE: Visceral epithelium, CT: Convoluted tubules, GL: Glomeruli

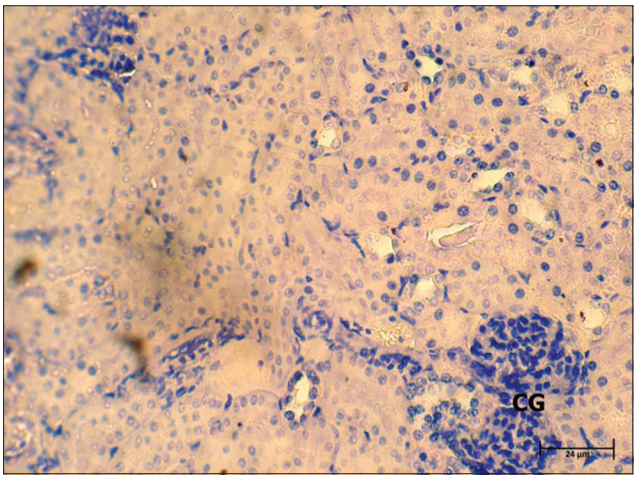

Figure 11: *Mus musculus* kidney wherein they were induced to 20% ethanol and their diets are mixed with ginseng. The CT are cloudy. The GL are disintegrated as well as their BS. CG: Converging glomeruli, BS: Bowman's space, CT: Convoluted tubules, GL: Glomeruli

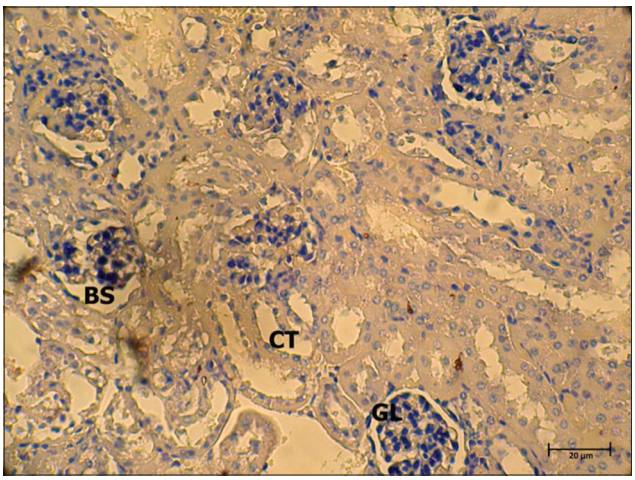

Figure 10: *Mus musculus* kidney wherein they were induced to 20% ethanol and their diets are mixed with silymarin. The CT are present along with GL. Some of the GL shrinked showed by an increase in BS some enlarged manifested by a decrease in BS, and some are normal. CT: Convoluted tubules, GL: Glomeruli, BS: Bowman's space

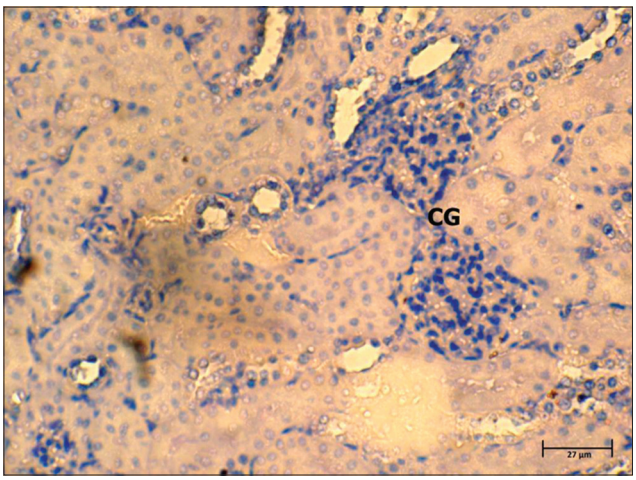

Figure 12: *Mus musculus* kidney wherein they were induced by 20% ethanol in their diets are mixed with ginseng. The CT appear to be cloudy. Two GL seem to be converging. CG: Converging glomeruli, GL: Glomeruli

by the Institutional Animal Care and Use Committee of the De La Salle University Manila.

Animals were treated for 21 days with the different treatments. On the 22nd day, the mice were sacrificed by cervical dislocation. The liver and kidneys of the mice were obtained and kept in separate containers with 10% formalin for slide preparation. Slides were processed using routine hematoxylin and eosin preparation and histological cross-sections of the liver and the kidney were performed under a light microscope.

RESULTS

Liver

Results of the sham control showed that there were no changes in the histological morphology of the liver. The hepatocytes manifested a usual radial pattern and no significant enlargement of the nucleus. The sinusoids (SSs) could also be distinguished [Figure 1].

Histology of the negative control group showed deterioration of the liver. Analysis shows the disorientation of the liver

hepatocytes from a once radial pattern. The nucleus size of some hepatocytes showed enlargements, and the sinusoidal spaces became obliterated [Figure 2]. Ethanol treatment for 21 days manifested severe damage of liver shown by the congestion of SSs.

To find out which drug could give a better protective effect on the liver, a group of mice were induced with 20% ethanol alongside with ginseng to test if ginseng has the capabilities to protect the liver from ethanol damage. The pictures below showed the difference between two areas of the liver wherein the presence of ginseng and ethanol brought about a partial obliteration of the SSs and hepatocyte damage. Figure 3 showed the presence of SSs while Figure 4 showed obliterated SSs.

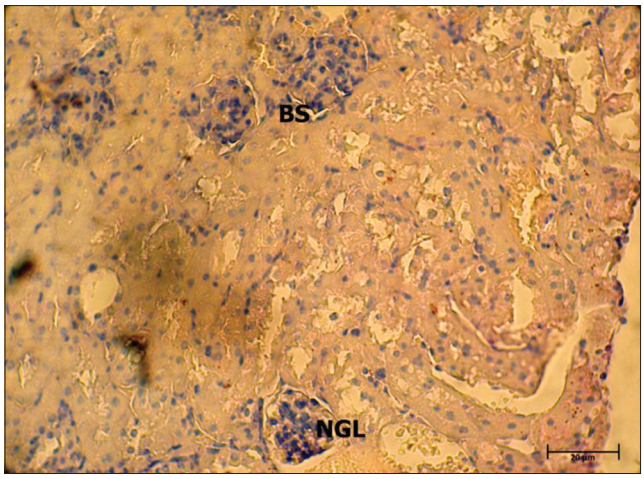

Figure 13: Kidney of *Mus musculus* fed with normal diet with the addition of silymarin. Congestion of the CT was seen. Both normal and damaged GL are present, which was manifested by the deterioration of the BS. BS: Bowman's space, NGL: Normal glomeruli, CT: Convoluted tubules, GL: Glomeruli

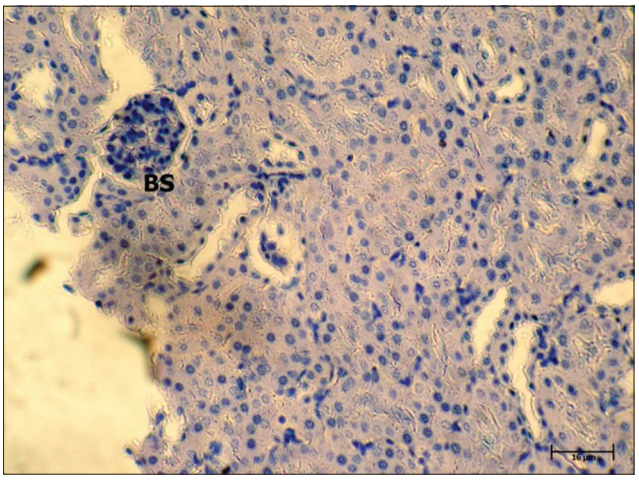

Figure 14: Kidney of *Mus musculus* fed with normal diet with the addition of silymarin. CT are cloudy. Normal glomerulus is present manifested by the BS although it is a bit narrowed. BS: Bowman's space, CT: Convoluted tubules

The result below showed that silymarin compared to ginseng had a better protective effect on the liver manifested by the presence of the SSs and the radial pattern of the hepatocytes on the picture below. There were no significant enlargements in the hepatic nuclei [Figure 5].

A group of albino mice were also given ginseng mixed with normal diet mixed without the presence of ethanol to find out if ginseng could carry out damage to the liver. The result below shows that addition of Ginseng to the normal diet of the albino mice obliterated the hepatic SSs. Enlargement in some nucleus was also detected in some areas [Figure 6].

Another group of albino mice were also given normal diet but mixed with silymarin. This would test if silymarin could induce damage to the liver in the absence of ethanol. In rats treated with silymarin, the liver showed mild congestion. The result below shows that there was an increase in the nucleus size of hepatocytes accompanied by a congestion of the SSs. The radial pattern of hepatocytes is also present [Figure 7].

Kidney

The proximal convoluted tubules (CT) can be detected as well as normal glomeruli (GL) manifested by the presence of the glomerular capsule. No sign of extensive damage could be seen in Figure 8.

Histology of the negative control kidney, which was induced to 20% ethanol, showed that the proximal CT are cloudy and hard to distinguish. Normal GL could be observed although there are some that disintegrated and others manifested a decrease in size [Figure 9].

Silymarin was also given to the diet of the albino mice along with the induction of 20% ethanol to test if Silymarin could also protect the kidney from damage aside from the liver when ethanol is induced. Accordingly, data here showed that

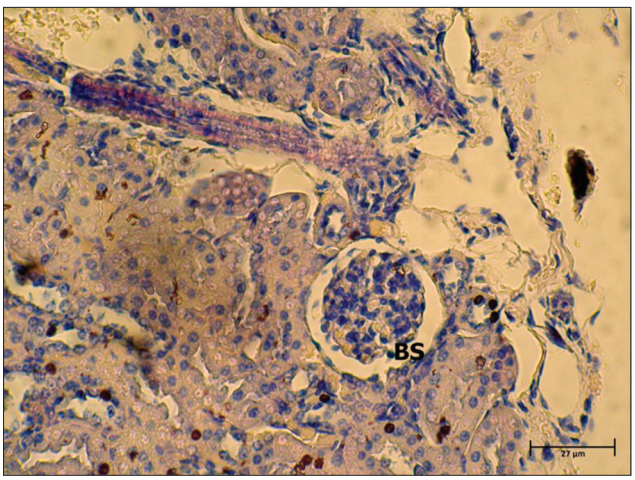

Figure 15: Kidney of *Mus musculus* fed with normal diet with the addition of ginseng. GL are normal which were manifested by the presence of BS. BS: Bowman's space, GL: Glomeruli

long-term ethanol treatment affects renal extramitochondrial metabolism in a similar way to that of the liver (Fernandez *et al*., 1998). The picture below shows that the GL are dominantly normal. The glomerular space (Bowman's capsule) is present, which separates the parietal and visceral epithelium (VE). Moreover, there are some that manifest shrinkage due to the increase in the Bowman's space (BS) [Figure 10].

Just like Silymarin, ginseng was also given to the diet of albino mice along with the intake of 20% ethanol to test if ginseng would strengthen the damage done by the 20% ethanol on the kidney or if it could have a protective mechanism against the damage dealt by the ethanol on the kidney. The results below show that the CT are cloudy and could be barely differentiated from one another. The GL are disintegrated and with the absence of the BS, two GL seemed to fuse [Figures 11 and 12].

Silymarin without the induction of ethanol was given to the mice to test if the usage of silymarin as a protective drug on the liver could give or induce a side effect on the kidney of the albino mice. The results show that the CT are cloudy and could hardly be detected. GL both with and without the presence of the BS could be seen in the picture below signifies that Silymarin intake could cause harm to the kidney [Figures 13 and 14].

Another group of albino mice was given ginseng, which was mixed with their normal diet. This is to test whether ginseng would do damage to the kidney. CT are present and are less cloudy compared to that of the silymarin group. Majority of the GL appeared to be normal due to the presence of the BS, which separates the parietal and VE [Figure 15].

DISCUSSION

The results of the study can be seen summarized in Tables 2 and 3. Based on the data presented, it can be seen the silymarin have more protective mechanisms than administration of ginseng in alcohol-induced hepatic and kidney problems.

From the data shown above, it is proven that the intake of at least 20% ethanol for 21 days could induce damage based on the negative control group. The intake of ethanol is absorbed by the blood and is then brought to the liver for metabolism. There were increases in the size of the nuclei and the obliteration of the SSs. The metabolism of ethanol-induced an oxidative damage to the liver, which was manifested by an increase in lipid peroxidation.[11] The synthesis of fatty acid is increased in the presence of ethanol, in which fat accumulates in the liver. Thus, a fatty liver is formed, which is the first stage to liver cirrhosis. This then could interfere with the transport of oxygen and nutrients to the liver cells. If this continues, it can lead to fibrosis or scarring. The third stage is liver cirrhosis in which cells harden and turns orange, aside from these they permanently lose their functions and die. Cirrhosis could not be reversed anymore but fibrosis can, through abstinence of ethanol. This, in turn, could have altered the morphological structure of the liver. The liver could only break down a certain amount of ethanol, and the excess could be the leading cause for the oxidative damage thus leading to the deterioration of the liver. The metabolism of ethanol requires NAD+ as a hydrogen acceptor to convert ethanol into acetic acid, this, in turn, slows down other mechanisms that require NAD+ when ethanol is taken in high amounts, and in turn affect other organs like the kidney. Positive control was then compared to the negative control, which was only given normal diet and it showed no signs of damage wherein the sizes of the nuclei are normal, and SSs are present.[3]

Silymarin gives the liver protection through many processes and mechanisms,[12] specifically due to its antioxidant effects against ethanol intoxication.[13] Several studies have demonstrated that diabetic patients with cirrhosis require insulin treatment because of insulin resistance. As chronic alcoholic liver damage is partly due to the lipoperoxidation of hepatic cell membranes, anti-oxidizing agents may be useful in treating or preventing damage due to free radicals.[14] Current knowledge of the role of oxidative stress in the pathogenesis of alcoholic liver disease (ALD), suggests that silymarin's pharmacological properties may have potential therapeutic value in ALD.[6] According to Asghar and Masood,[15] silymarin shows high antioxidant capacity compared to green tea and other standards, protects plasma lipids against oxidation, and scavenges free radicals. Silymarin gives hepatoprotection by acting through many

Table 2: Summary of results for the histopathological analysis of the liver

Group	Effect	Histopathological analysis
Group 1: Sham control	No damage	Radial pattern and SSs present
Group 2: Negative control	With damage	SSs are obliterated with an increase in the size of liver nucleus
Group 3: Ginseng	With damage	SSs are obliterated with an increase in the size of liver nucleus
Group 4: Silymarin	Mild damage	Mild congestion of hepatocytes
Group 5: Ginseng with ethanol	Partially protected the liver	Some areas where SSs and radial pattern are present
Group 6: Silymarin with ethanol	No damage seen	Radial patterns and SSs present

SS: Sinusoid

Table 3: Summary of results for the histopathological analysis of the kidney

Group	Effect	Histopathological analysis
Group 1: Sham control	No damage	Normal GL
Group 2: Negative control	With damage	Shrinkage of GL manifested by an increase in BS
Group 3: Ginseng	No damage	Normal GL are present
Group 4: Silymarin	With damage	Enlargement of GL manifested by decrease in BS
Group 5: Ginseng with ethanol	With damage	Obliteration of BS and fusion of GL
Group 6: Silymarin with ethanol	With partial protection	Both normal and shrinkage of GL are present

BS: Bowman's space, GL: Glomeruli

mechanisms, and it has been tested in several trials.[12] According to Shalan *et al*.,[13] the feeding of silymarin, which contains silybin restores the impaired function of the liver and normalizes lipid metabolism and inhibits atherosclerosis. Aside from these, silymarin provides protection to the cell membrane from radical-induced damage.[16] This could have been the reason why the morphology of the liver treated with silymarin seems to be the same that of the sham control. Although based from the results above, when there is an absence of ethanol, the intake of silymarin proved to induce mild damage manifested by congestion in the liver.

It was also observed that the intake of ginseng without the induction of ethanol was also able to induce damage to the liver. This was manifested by the obliteration of SSs, and the radial patterns of the hepatocytes were hard to detect due to the congestion. There were no specific literatures found indicating that silymarin or ginseng is a damage inducer to the liver. However, it is hypothesized that in the absence of ethanol, the active substance of the drugs administered had alcohol groups in their structures which could have been oxidized to formaldehyde and was the leading cause of the damage seen in the absence of ethanol. This could have been the reason for the change in morphology of the liver. In the consumption of ginseng along with the induction of ethanol, there was partial obliteration of the SSs. The damage dealt by the liver with ginseng and ethanol is not that severe compared to the positive control, meaning ginseng has a protective effect on the liver. According to Kim *et al*.,[17] they were able to confirm the antioxidant effects of ginseng manifested by a decrease in ROS which is the major contributor to oxidative stress which causes tissue damage by lipid peroxidation.[18] This increase in lipid peroxidation is normalized or decreased by the intake of ginseng and silymarin. It is proven from the data above that ginseng compared to silymarin have weaker protective and preventive effect on the liver. Ethanol is a possible risk factor for chronic kidney disease and has been linked to kidney disorders in clinical and animal studies.

The effects of ethanol in the liver that lead to mitochondrial alterations resulting in dull metabolic pathways such as gluconeogenesis and mitochondrial b-oxidation of fatty acids, also would be occurring in the kidney.[19] Intake of alcohol uses NAD+as hydrogen acceptors thus slowing other mechanisms that require NAD+. When this occurs, oxidation of lactate to pyruvate will be slower thus there would be an accumulation of lactate. Once there is a high concentration of lactate in blood, it competes with renal mechanisms in excreting uric acid. This could be the possible reason for the morphological disturbances in the kidney. It can be proven by the shrinkage or enlargement of the GL manifested by an increase or decrease in the BS, as well as the presence of a cloudy CT.[20]

CONCLUSION

The intake of silymarin and ginseng as a protective drug affected both the liver and the kidney. During the experiment, ethanol was given to the mice. In the negative control, it showed that when given 20% ethanol, the SSs are present but are congested. The nucleus was enlarged as well when treated with silymarin alone without the induction of ethanol, showed that the SSs were mildly congested. As for the kidney, when given 20% ethanol, it was seen that the GL shrunk. It was manifested by an increase in the BS. When treated with silymarin, the CT appeared to be partially cloudy as compared to the one induced with 20% ethanol. In the liver, when treated with ginseng, it did not show as much protective and preventive effect as silymarin. It is seen that it only affected the liver partially. The SSs were completely congested, and the nucleus was greatly enlarged. As for the kidney, the GL were greatly damaged when induced with alcohol. However, sinseng was not able to protect the kidney when it was given with ethanol. Based on the results of the experiments, it can be said that silymarin would have a more protective effect than ginseng both in the liver and the kidney.

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