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COMPARATIVE EVALUATION OF HEPATOPROTECTIVE ACTIVITY OF HERBAL AND UNANI FORMULATION, ON AMOXICILLIN/CLAVULANIC ACID-INDUCED LIVER INJURY IN WISTAR RATS

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ABSTRACT

Liver damage is a significant global health concern, and the use of herbal remedies as a balancing and alternative approach to liver disorders has grown in favor. A review of liver injury and the roles played by herbal remedies in its administration, together with any potential advantages, difficulties, and future directions, are provided in this abstract. Treatments for liver injury that are often used in medicine include immunosuppressive drugs, antiviral drugs, lifestyle changes, and surgery. This study was undertaken to examine the hepatoprotective activity of inducing drug amoxicillin/clavulanic acid and treatment of herbal protective drug jigreen , liv 52, and Silymarin. The hepatoprotective effects of various herbs and natural substances are combined in these formulations. It is postulated that Liv.52 and Jigreen, given their makeup, may have antioxidant qualities following the damage caused by amoxicillin/clavulanic acid. It is hypothesized that Liv.52 and Jigreen, due to their traditional use for liver health and the hepatoprotective qualities of their herbal components, may have antioxidant benefits. To elucidate the underlying mechanisms and evaluate the potential clinical consequences of Jigreen and Liv.52 as antioxidants, more research is required. Extensive experimental and clinical research is required to support this theory and provide evidence on the function of these formulations in enhancing liver health and thwarting oxidative stress.

KEYWORDS: hepatotoxicity, Amoxicillin/Clavulanic acid, Liv.52, Jigreen, Silymarin,

INTRODUCTION

Liver is a dark brown tissue with many crucial functions in the body. It weighs about 3 pounds. About 2% of an adult's body weight is made up of it... Blood supply to the liver holds about 13% and many drugs and other substances pass through the liver to metabolize and detoxify them. That's the reason that the liver is exposed to different types of drugs. (Juza, Pauli, et al., 2014).[28] the liver is anatomically alienated in distinct lobes (Four). Right, one is split by the quadrate and caudate lobes and is larger than the left lobe. (Ahluwalia N, Naseeruddin et al., 2022).[3]

Lymphatic vessels

The portal tracts contain the shortest divisions of the hepatic artery, biliary tree, and portal vein, which travel in tandem. Blood enters the liver's sinusoidal capillaries and passes via the hepatic artery and portal vein branches before arriving at the terminal hepatic venule. (Babu et al; 2014).[8] Concurrently, bile generated by hepatocytes travels in the opposite direction through bile canaliculi and into the bile ductules of the triad. This coordinated movement allows for the exchange of nutrients, waste products, and bile within the liver.

Hepatic Sinusoid

The hepatic sinusoid, a tiny blood channel, houses an amputation from the hepatic artery to the hepatic portal vein. The sinusoidal in Zone 1 are smaller than those in Zone 2, and the size of the sinusoids changes depending on how close they are to the portal triad. Kupffer cells make up the majority of them. local liver macrophages, and are devoid of a basement membrane. Hepatocyte plates surround and surround the endothelial cells that border the sinusoids. Blood plasma is found in the area of disease, sometimes referred to as the perisinusoidal, which is located between the hepatocytes and the lining of the vessels' cells. It displays the type III collagen fibers that comprise the liver's reticular architecture as well as the fat-storing hepatic stellate cells. (Gibert-Ramos et al.[19]

Biliary System

The bile produced by the hepatocytes is received by the duct system that starts in the bile canaliculi and ends in the common bile duct. A liquid is retained in the gallbladder between meals and used during meals in the duodenum to help with the absorption of dietary fats and oils as well as to flush the body of bile waste. The gallbladder can only hold a maximum of 30 to 60 mL of bile at a time, compared to the liver's daily output of up to 1200 mL. Consequently, the reabsorption of water and electrolytes by the epithelial cells via active sodium ion transport processes regulates the amount of bile in the gallbladder, permitting the residual biliary components to concentrate in the gallbladder, including bile salts, cholesterol, and bilirubin.

(Hundt, et al., 2017).[22]
In a liver many type of cell are work
Hepatocyte's cell,
Endothelial cell,
kuffer cell, or hepatic stellate cell.

Cells of the Liver

Hepatocytes

Polyhedral epithelial cells called hepatocytes make up 70% of the hepatic parenchyma. They connect the several hepatic zones in cords or rows that are 30 to 40 m wide. (Cullen; 2016).[16] Hepatocytes are rich in enzymes and perform a multitude of metabolic, endocrine, and secretory functions in the liver. They contain a variety of cell organelles, including as the energy-producing mitochondria, and a sophisticated system for the Golgi system's secretion and excretion. They also have a framework of filamentous proteins that act as the cell's scaffolding. This framework is composed of microfilaments, microtubules, and intermediate filaments. The hepatocyte's sinusoidal side makes direct touch with the blood plasma. (Ksheminska, 2005; et al.)[32] At that point, the plasma membrane expands widely or can significantly increase the region of contact. The cell membrane is altered at its biliary side to create bile canaliculi, which allow bile to drain into the biliary tree. Desmosomes and other adhering regions of the plasma membrane bring it into lateral contact with neighboring hepatocytes.

Endothelial Cells

Hepatocytes and sinusoidal endothelial cells are divided by the liver's Disse gap. These cells lack intercellular junctions and a basement membrane but have multiple fenestrations, or pores. These features allow for direct communication between the blood within the sinusoidal space, the space of Disse, and the hepatocyte membranes. A high filtration capacity is made possible by the bidirectional flow of fluids and solutes between the blood and the hepatocytes, including compounds with both low and high molecular weight. The bile duct cleaning and metabolic processes depend heavily on the liver sinusoidal endothelial cells. They participate in endocytosis and the metabolism of several macromolecules, such as extracellular matrix elements, glycoproteins, lipoproteins, and inert colloids.

Kupffer Cells

The liver's Kupffer cells contain the majority of the body's resident tissue macrophages. Pathogens arriving through the portal or artery circulation are carefully positioned within the hepatic sinusoid and adhered to the sinusoidal wall in order to be phagocytized. Through endothelial fenestrations or gaps, they can directly interact with hepatocytes, pit cells, endothelial cells, and hepatic stellate cells (HSC). They are the first line of defense for the digestive tract against immunoreactive chemicals and are essential for the removal of endotoxins that are consumed through the portal circulation. They are also responsible for eliminating hemoglobin and senescent red blood cells.

Hepatic Stellate Cells

Hepatic stellate cells (HSC) are sinusoidal liver cells that are in close proximity to the endothelial cells in the Disse space. They are also referred to as fat-storing cells or Ito cells. They are modest in stature and contain large amounts of lipid droplets rich in vitamin A. They generate five to eight percent of all liver cells. (R. a. B. Bataller, D.A., 2009)[41] They stop producing retinoids, grow bigger, produce more pseudopodia, become mobile, and transdifferentiate into myofibroblasts when stimulated. Myofibroblasts have two distinguishing features: they grow actin fibers that contribute to their ability to contract and significantly increase their endoplasmic reticulum to produce ECM components. (Bataller & Brenner, 2005).[5]

Functions of liver

The liver is a vital organ that performs a number of functions, including metabolism, Detoxification of drugs, production of bile and other important proteins, storage of glycogen etc. one of the liver's crucial roles include oxidation of lipids which eventually leads to packaging of the excess lipids molecules for the secretion and storage specially in adipose tissues. The bile produces inside liver get stored ion the gall bladder and when needed it secrete out to carry out essential function of fat digestion. Many proteins that are found in the blood stream are produced in the liver.(Trefts et al., 2017).[48]

Additionally, the liver is crucial to the identifying process and detection of pathogens that enter through the gut or portal circulation, which delivers numerous bacteria and viruses into the liver. Liver provide excellent immune response and protect the body and there is a balance in immune respose and the tolerance which is crucial for liver health.(Kubes & Jenne, 2018).[29]

MATERIALS AND METHODS

Chemicals and reagents

amoxicillin / clavulanic acid (gifted sample by R.V. northland Institute Laboratory), liv.52 and jigreen syrup

purchased by Apollo pharma Ltd, silymarin gifted sample from zenith nutrition and all other components, such as chemicals as well as reagents were used in the current study were analytical kind and came from dependable vendors like Sigma-Aldrich along with SDFCL and SISCO. Amoxicillin / clavulanic acid is precise to the rodents as orally. Amoxicillin / clavulanic acid was given for 21 days 30 minutes beginning at a measurement of 60 mg/kg body weight. Of conduct tests. Liv -52 and jigreen 1.0ml/kg in a day and each silymarin contained 50 mg/kg & excipients and tablets were powdered & blended in with clean 0.9 %W/V ordinary saline. It was controlled to rodents with orogastric taking care of cylinder at a dose of 50mg/kg body w.t for 21 days & 2-hrs before the beginning of behavioral experiments.

Animal research protocol

Wistar albino rats weighing 150-170 gm were used. Seven days were spent acclimating the animals before the study. Thirty male albino rats (Wistar strain) with weights of about 150-170 gm were obtained from the primal house facility of R. V. Northland Institute Dadri, Greater Noida. The animals were acclimatized for one week and than separated and divided into five groups. The animals were caged in standard cages (29 cm X2 mc X14 cm), maintained on red feed pellets, and tap water available in water bottles with stainless steel nozzles by random sampling method. All of the animals were housed in good, industry-standard conditions in the lab, such as 12 hours of light and 12 hours of darkness, regulated room temperature of around 25°C, and maintained relative humidity of approximately 50. All of the animals were fed commercial pellet food made by Golden Feeds in Mehrauli, New Delhi, as well as unlimited amounts of water. All the experimental studies will be conducted under CPCSEA and IAEC guidelines. The choice of this animal model allows researchers to study the physiological responses to silymarin in a controlled and standardized manner. Approval no. RVNI/IAEC/22-23/02.

Experimental plan

Thirty animals were separated into 5 groups of 6 animals each for 21 days and they got therapy to participate in the following in vivo hepatoprotective investigations, which are described below.

Total no. of animals 6 × 5 = 30

Group A: Rats used as controls were given daily doses of 1 ml/day Normal saline p.o.

Group B: The rats were fed regular food and water and given single dose of toxicant amoxicillin / clavulanic acid 60 mg/kg, p.o.

Group C: Rats were fed daily with amoxicillin / clavulanic acid 60mg/kg, p.o. + Liv-52 1.0ml/kg, p.o)

Group D: Rats were given amoxicillin / clavulanic acid 60mg/kg, p.o. + Jigreen 1.0ml/kg, p.o)

Group E: Rats were given daily standard drug amoxicillin / clavulanic acid 60 mg/kg, p.o. + Silymarin 50mg/kg, p.o).

From day 1 to day 21, the vehicle or medication treatments were given orally following an hour-long concomitant dose of amoxicillin / clavulanic acid. The rats were kept on a regular diet and given unlimited access to water during the medication treatment period. At the end of the experiment, memory and behavioral tests were performed, then the rats were decapitated and the brain was excised and dissected into two halves. The one half will be used for the estimation of biomarker/biochemical parameters. The homogenate was then centrifuged at 1800xrpm for 10 minutes, and subjected to estimation of various biochemical parameters. The other half's brain tissues were kept in a 10% formalin solution for Histopathological studies.

Biochemical estimation

To study the liver function, the transaminase enzymes in serum performed by AST (SGOT),[11] ALT (SGPT)[11] and ALP (Bowers & Mccomb, 1972)[14] and Total Bilirubin (endrassik, L. and Gróf, 1938)[15] levels in the serum were examined using a spectrophotometer.

And also performed Antioxidant Enzymes in Liver Homogenate Tissue Glutathione (Reduced GSH Level) (Sedlak & Lindsay, 1968),[44] Catalase (Greenwald, 1985)[10], Estimation Of Superoxide Dismutase (SOD) test (Marklund & Marklund, 1974).[38]

Histopathological Studies

Method: Eosin – Hematoxylin (Belur, B., N. Kandaswamy, 1990).[9]

After sacrificing the animal, the liver was removed, washed → ice-cold normal saline → dried. This was then preserved in 10% formalin saline. Tissue was then stained by Eosin-Hematoxylin stains and paraffin sections of liver tissue was studies to determine the degree to which free radicals have damaged tissue and the impact of the Amoxicillin-Clavulanate and comparison will be made against different test substances.

Statistical Analysis

Data displaced as mean ± standard error mean (SEM) (n = 5). Groups of data → compared with one-way ANOVA. Values are considered significant if $p < 0.05$.

RESULTS

Biochemical Estimations in Serum

1. Effect of Liv52 and jigreen on alanine aminotransferase (ALT) against standard drug silymarin with inducing agent Amoxicillin-Clavulanic acid

The data were represented and standard. Comparisons of different participating groups were performed using one-way ANOVA followed by Tukey´s test comparison test. All *P* expressed in range $P < 0.05$ is considered significant. The data were investigated using the graph-pad v-9.5.

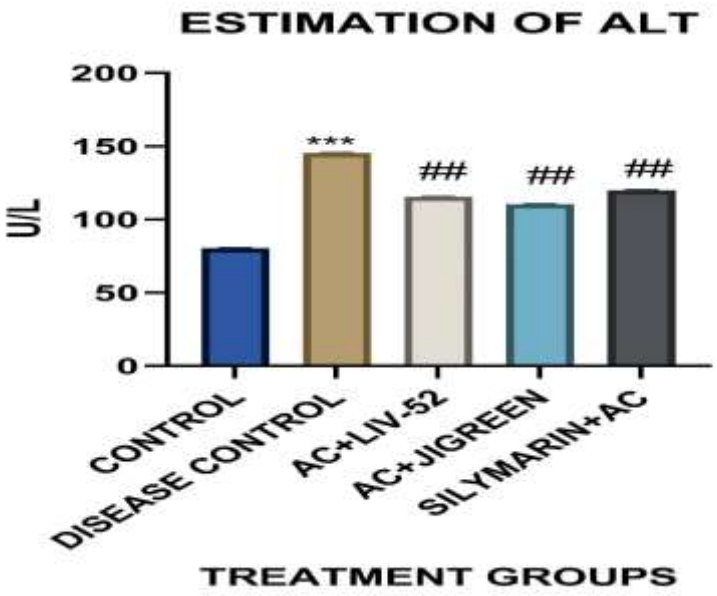


Figure 1: Results are mean±SEM and;n=5 viewing ***P<0.001(Control vs Disease control);$^{\#\#}$P<0.01(Disease control vs AC+LIV.52);$^{\#\#}$P<0.01(Disease control vs AC+Jigreen);$^{\#\#}$P<0.01(Disease control vs Silymarin + AC);applying ANOVA(one way) through Tukey´s test.

2. Effect of Liv52 and jigrin on alanine aspartate transaminase (AST) against standard drug silymarin with inducing agent Amoxicillin- Clavulanic acid

The data were represented and standard. Comparisons of different participating groups were performed using one-way ANOVA followed by Tukey´s test comparison test. All *P* expressed in range *P* < 0.05 is considered significant. The data were investigated using the graph-pad v-9.5.

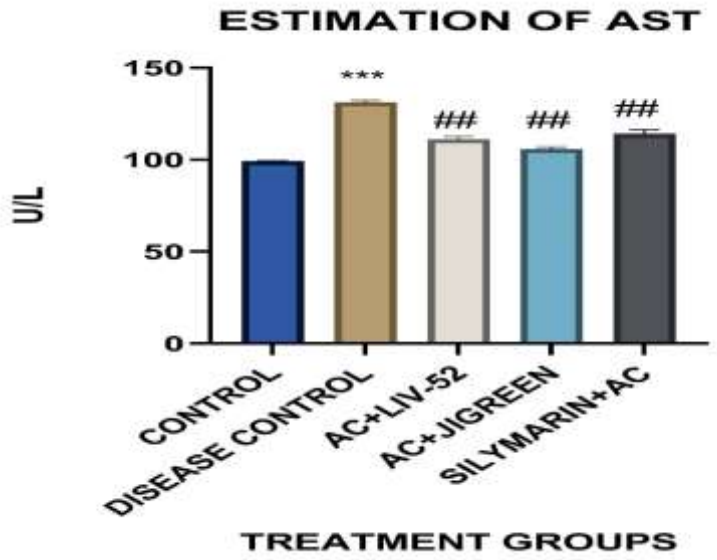


Figure 2: Results are mean±SEM and;n=5 viewing ***P<0.001(Control vs Disease control);##P<0.01(Disease control vs AC+LIV.52);##P<0.01(Disease control vs AC+Jigreen);##P<0.01(Disease control vs Silymarin + AC);applying ANOVA(one way) through Tukey´s test.

3. Effect of Liv52 and jigreen on alanine alkaline phosphatase (ALP) against standard drug silymarin with inducing agent Amoxicillin- Clavulanic acid

The data were represented→mean and standard. Comparisons of different participating groups were performed using one-way ANOVA followed by Tukey´s test comparison test. All *P* expressed in range *P* < 0.05 is considered significant. The data were investigated using the graph-pad v-9.5.

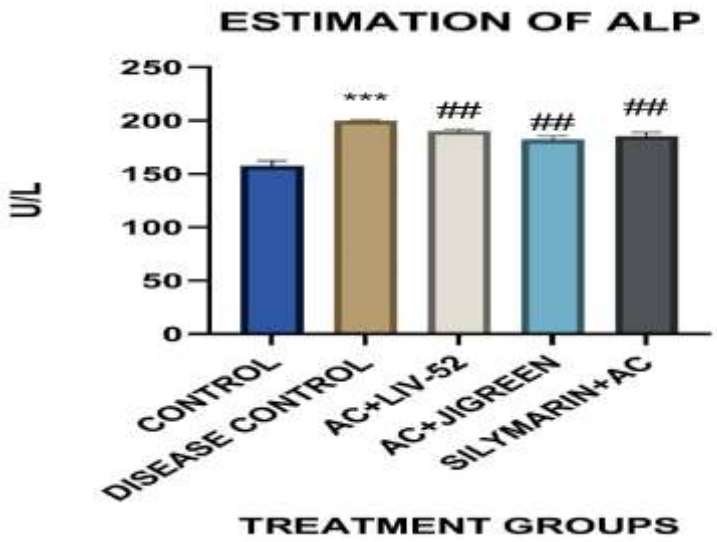


Figure 3: Results are mean±SEM and;n=5 viewing ***P<0.001(Control vs Disease control);$^{\#\#}$P<0.01(Disease control vs AC+LIV.52);$^{\#\#}$P<0.01(Disease control vs AC+Jigreen);$^{\#\#}$P<0.01(Disease control vs Silymarin + AC); applying ANOVA(one way) through Tukey´s test.

4. Effect of Liv52 and jigreen on alanine Alkaline Total bilirubin against standard drug silymarin with inducing agent Amoxicillin- Clavulanic acid

The data were represented→mean and standard. Comparisons of different participating groups were performed using one-way ANOVA followed by Tukey´s test comparison test. All *P* expressed in range $P < 0.05$ is considered significant. The data were investigated using the graph-pad v-9.5.

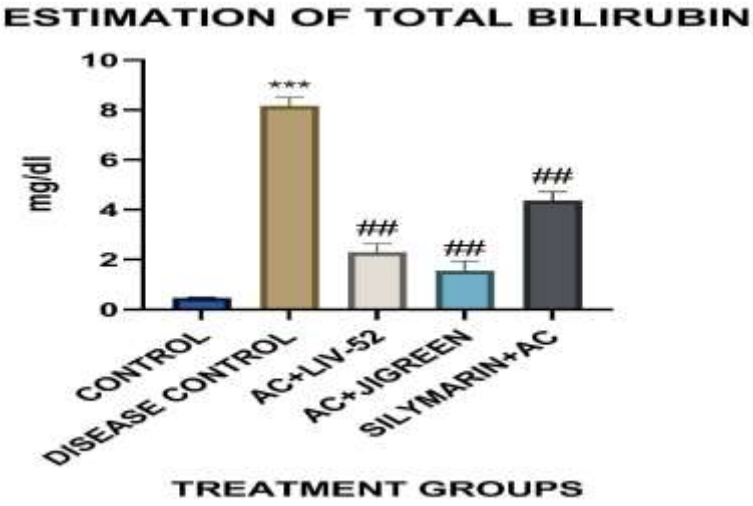


Figure 4: Results are mean±SEM and;n=5 viewing ***P<0.001(Control vs Disease control);$^{\#\#}$P<0.01(Disease control vs AC+LIV.52);$^{\#\#}$P<0.01(Disease control vs AC+Jigreen);$^{\#\#}$P<0.01(Disease control vs Silymarin + AC); applying ANOVA(one way) through Tukey´s test.

Table 1: Biochemical Estimations in Serum.

GROUPS	(ALT) U/L	(AST) U/L	(ALP) U/L	Total bilirubin mg/dl
Control	80.3±0.30	99.2±0.28	157.6±4.41	0.4±0.18
Disease Control	145.4±0.51***	131.3±0.84***	199.8±1.62***	8.1±0.33***
AC+ LIV-52	115.5±0.37$^{\#\#\#}$	111.1±1.27$^{\#\#}$	190.1±2.10$^{\#\#}$	2.3±0.34$^{\#\#}$
AC + JIGREEN	110.5±0.35$^{\#\#\#}$	105.8±0.99$^{\#\#}$	182.1±3.38$^{\#\#}$	1.5±0.39$^{\#\#}$
Silymarin + AC	119.9±0.52$^{\#\#\#}$	114.1±2.05$^{\#\#}$	185.2±3.65$^{\#\#}$	3.9±0.35$^{\#\#}$

Biochemical estimations in tissue

1. Effect of Liv52 and jigreen on Total protein against standard drug silymarin with inducing agent Amoxicillin- Clavulanic acid

The data were represented→mean and standard. Comparisons of different participating groups were performed using oneway ANOVA followed by Tukey´s test comparison test. All *P* expressed in range $P < 0.05$ considered significant. The data were investigated using the graph-pad v-9.5.

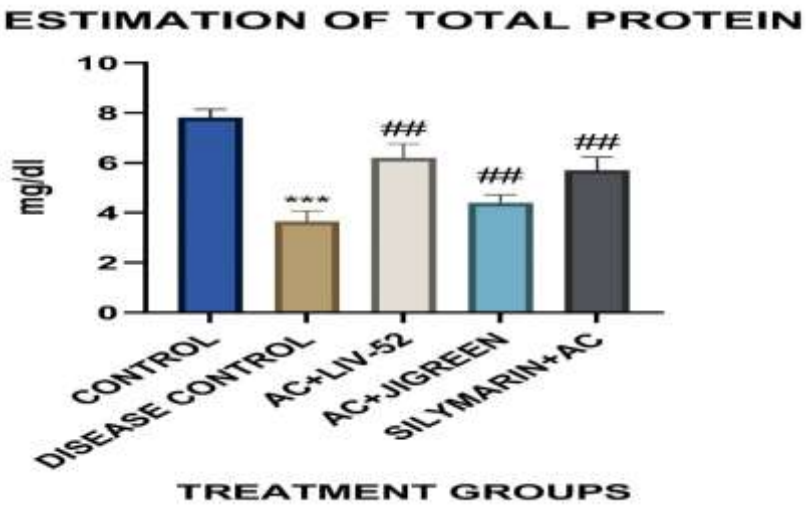


Figure 5: Results are mean±SEM and;n=5 viewing ***P<0.001(Control vs Disease control);$^{\#\#}$P<0.01(Disease control vs AC+LIV.52);$^{\#\#}$P<0.01(Disease control vs AC+Jigreen);$^{\#\#}$P<0.01(Disease control vs Silymarin + AC);applying ANOVA(one way) through Tukey´s test.

2. Effect of Liv52 and jigreen on SOD against standard drug silymarin with inducing agent Amoxicillin- Clavulanic acid

The data were represented→mean and standard. Comparisons of different participating groups were performed using oneway ANOVA followed by Tukey´s test comparison test. All *P* expressed in range $P < 0.05$ is considered significant. The data were investigated using the grap-pad v-9.5.

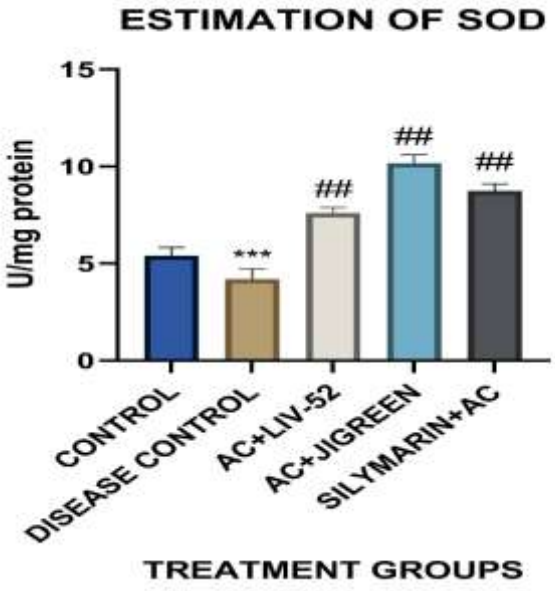


Figure 6: Results are mean±SEM and;n=5 viewing ***P<0.001(Control vs Disease control);$^{\#\#}$P<0.01(Disease control vs AC+LIV.52); $^{\#\#}$P<0.01(Disease control vs AC+Jigreen);$^{\#\#}$P<0.01(Disease control vs Silymarin + AC); applying ANOVA(one way) through Tukey´s test.

3. Effect of Liv52 and jigreen on GSH against standard drug silymarin with inducing agent Amoxicillin- Clavulanic acid

The data were represented→mean and standard. Comparisons of different participating groups were performed using oneway ANOVA followed by Tukey´s test comparison test. All *P* expressed in range $P < 0.05$ is considered significant. The data were investigated using the graph-pad v-9.5.

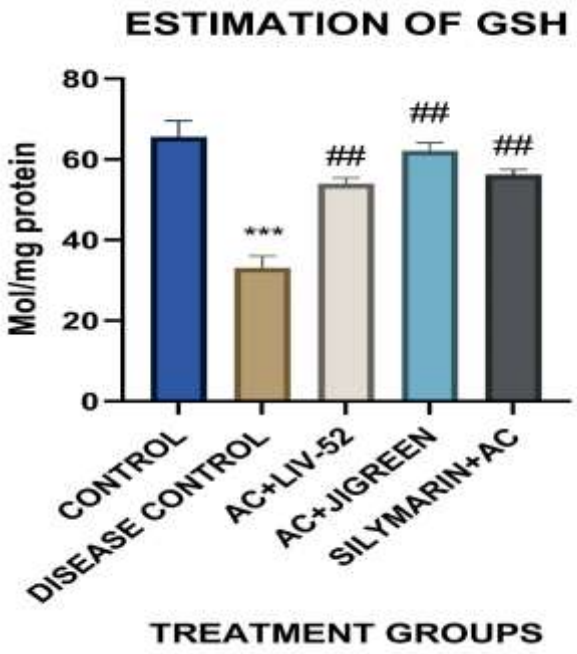


Figure 7: Results are mean±SEM and;n=5 viewing ***P<0.001(Control vs Disease control);$^{\#\#}$P<0.01(Disease control vs AC+LIV.52);$^{\#\#}$P<0.01(Disease control vs AC+Jigreen);$^{\#\#}$P<0.01 (Disease control vs Silymarin + AC); applying ANOVA(one way) through Tukey´s test.

4. Effect of Liv52 and jigreen on Catalase against standard drug silymarin with inducing agent Amoxicillin- Clavulanic acid

The data were represented as mean and standard. Comparisons of different participating groups were performed using one-way ANOVA followed by Tukey´s test comparison test. All *P* expressed in range $P < 0.05$ is considered significant. The data were investigated using the graph-pad v-9.5.

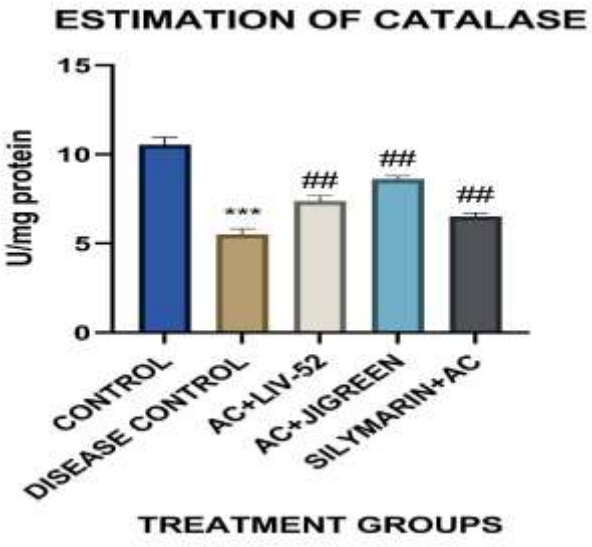


Figure 8: Results are mean±SEM and;n=5 viewing ***P<0.001(Control vs Disease control);$^{\#\#}$P<0.01(Disease control vs AC+LIV.52);$^{\#\#}$P<0.01(Disease control vs AC+Jigreen);$^{\#\#}$P<0.01(Disease control vs Silymarin + AC); applying ANOVA(one way) through Tukey´s test.

Table 2: Biochemical Estimations in Tissues.

GROUPS	Total protein mg/dl	SOD U/mg protein	GSH mol/mg protein	Catalase U/mg protein
Control	7.1±0.33	5.4±0.40	65.6±3.91	10.5±0.39
Disease Control	3,6±0.43***	4.2±0.52***	33.1±2.92***	5.5±0.31***
AC+ LIV-52	6.2±0.56##	7.6±0.28##	53.9±1.42##	7.3±30##
AC + JIGREEN	4.4±0.32##	10.1±0.41##	62.1±1.91##	8.6±0.17##
Silymarin + AC	5.7±0.54##	8.7±0.35##	56.2±1.26##	6.5±0.19##

Histological examination

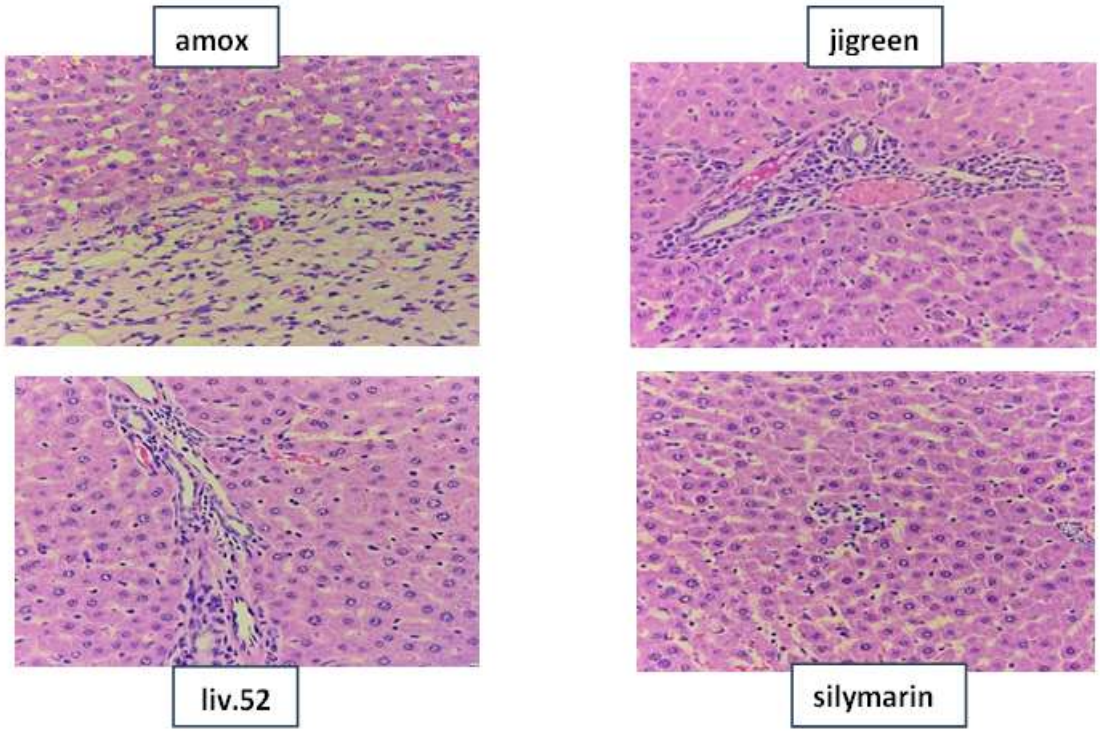
1.) Group 1 normal saline (control)- The section examined shows maintained lobular architecture with trabecularly arranged hepatocytes with maintained polarity.

2.) Group 2 Amoxicillin/clavulanic acid (Disease Control)- Section examined shows maintained lobular architecture with trabecularly arranged hepatocytes with maintained polarity. Hepatocytes are polygonal, having eosinophilic cytoplasm, round to oval nucleus with coarse chromatin and conspicuous nucleoli. Sinusoides are dilated at places with extravasated RBCs. Few central veins are dilated. A single large nodule is seen comprising of fibrocollagenous tissue with moderate inflammatory cell infiltrate, fibrosis and interspersed blood vessels. No necrosis, biliary cell damage and fatty change seen (H&E, 400X).

3.) Group 3 Jigreen- Section examined shows maintained lobular architecture with trabecularly arranged hepatocytes with maintained polarity. Hepatocytes are polygonal, having eosinophilic cytoplasm, circular to oval nucleus with noticeable nucleoli and granular chromatin. Moderate inflammation in portal triad region and focal areas of lobular inflammation seen. Sinusoides and few central veins are dilated. No necrosis, biliary cell damage and fatty change seen (H&E, 400X).

4.) Group 4 Liv 52- Section examined shows maintained lobular architecture with trabecularly arranged hepatocytes with maintained polarity. Hepatocytes are polygonal, having eosinophilic cytoplasm, round to oval nucleus with coarse chromatin and conspicuous nucleoli. At places portal triad shows mild inflammatory cell infiltrate. Few central veins are dilated. No necrosis, biliary cell damage and fatty change seen (H&E, 400X).

5.) Group 5 Silymarin - Section examined shows maintained lobular architecture with trabecularly arranged hepatocytes with maintained polarity. Hepatocytes are polygonal, having eosinophilic cytoplasm circular to oval nucleus with noticeable nucleoli and granular chromatin. Moderate inflammation in portal triad and mild lobular inflammation seen. Sinusoides and few central veins are dilated. No necrosis, biliary cell damage and fatty change seen (H&E, 400X).



DISCUSSION

The present study titled "Comparative Evaluation of Hepatoprotective Activity of Herbal And Unani Formulation, on Amoxicillin/Clavulanic acid Induced Liver Injury in Wistar Rats.

In the current investigation, we found that Amoxicillin Clavulanic Acid could harm Wistar rats' livers when administered orally. This was demonstrated by the discovery that liver enzymes, in particular AST, ALT, and ALP, had significantly elevated when compared to the control group. Additionally, it should be mentioned that both Total and Direct Bilirubin were discovered to have significantly higher levels.

After establishing liver injury therapeutic evaluation was done and different treatment options were scheduled. The treatment included an ayurvedic polyherbal preparation Liv-52, another polyherbal preparation of Unani system Jigreen was also used along with standard drug Silymarin The whole idea of the exercise was to establish a comparative trial of different drug for similar time line.

The results indicated that liv.52 and jigreen were deceptively brilliant in decreasing the liver injury caused by the drug treatment. They decreased AST, ALT and ALP values with time. It was also found that they were able to decreased Total Bilirubin.

It was also observed that liv.52 and jigreen were also able to decrease the oxidative stress exerted by the drug induced liver injury. This was established by the reduction in SOD, Catalase, GSH, value which was found to be increased by Amoxicillin treatment.

CONCLUSION

In this study evaluated the hepatoprotective effects of two herbal formulations, Liv.52 and Jigreen, against liver injury induced by Amoxicillin-clavulanic acid in Wistar rats. The experiment demonstrated that Amoxicillin-clavulanic acid administration led to liver injury, as evidenced by elevated levels of liver enzymes and bilirubin. However, both Liv.52 and Jigreen showed significant hepatoprotective effects, effectively reducing the liver injury markers and oxidative stress. These findings suggest that these herbal formulations could be potential candidates for managing liver illnesses and protecting the liver from drug-induced damage. Further research and clinical trials are necessary to validate these results and establish evidence-based guidelines for integrating herbal treatments into conventional therapeutic approaches for liver health.

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Conflict of Interest

The writers did not declare any potential conflicts of interest.

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