Evaluation of the Protective Effect of Tomato Seed Aqueous Extract on Statin Drug Induced Liver Damage of Albino Rats

Nkiruka Millicent Amadi*, Amarachukwu Perpetua Ugwoke, Nonyelum Vivian Anoh

Department of Medical Laboratory Science, Enugu State University of Scence and Technology, Enugu State, Nigeria

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ABSTRACT

Statins (simvastin) are among the drug most commonly used for lowing blood cholesterol, but sometimes associate with adverse effects. Tomato seed extract has been found to exert hepatoprotective effect through its anti-inflammatory and bioactive properties. The aim of the study was carried out to evaluate the protective effect of tomato seed extract on the stastin induce liver damage of albino rats damaged. Twenty-five (25) albino rats weighing 150-200 grams were used, and grouped into five groups of five animals each. The experimental group (1-3) was induced with orally stastin 100mg/kg b.wt for 14 days and then varying doses of 200 mg, 300mg, 400mg, of tomato seed extract for 14 days respectively. Group 4 (negative control) received orally statins 100mg/kg b.wt for 14 days only while group 5 (normal control) received only food and water. Animal treatment was conducted for 28days before sacrifice. Blood samples for biochemical analysis were collected through retro-orbital puncture and the liver tissue excised for histological analysis.

Results: There was significant elevation of the liver enzyme parameters, ALT, AST, and ALP among medium and high dose extract treatment groups. Histomorphological examination revealed that the low dose exerted a significant healing effect than the higher doses. **Tomato seed extract hepatotoxic protective effect appeared to be dose dependent in the experimental studies.**

Keywords: Statins, Hepatoprotective, Tomato Seed, Albino rats

INTRODUCTION

Background of the study

Statins, also known as **HMG-CoA reductase inhibitors**, are widely prescribed as lipid lowering agents that inhibit the cholesterol synthesis (Istvan et al., 2001). Clinical evidence demonstrates that statin therapy effectively reduces **low-density lipoprotein cholesterol** (LDL-C) levels by 20–50%, triglyceride concentrations by 10–20%, and modestly increase serum **high-density lipoprotein cholesterol** (HDL-C) levels by 5–10% (Taylor et al., 2013). Despite these benefits, the potential impact of statins on **liver function** remains area of active investigation, where both hepatotoxicity and therapeutic effects are being explored (Björnsson, 2017). Russo reported 22 cases of statin-associated drug-induced liver injury (DILI) from a prospective registry of 1,188 patients (2004–2012). Most cases were female (68%), time from statin start to symptom onset varied widely (34 days to 10 years; median 155 days). Histomorphological patterns suggested multiple mechanisms. Some patients progressed to chronic liver disease, predominantly with an autoimmune phenotype (Russo et al, 2014) Furthermore, statins may reduce hepatic inflammation by inhibiting of small guanosine triphosphate hydrolases (GTP) binding proteins thereby lowering oxidative stress. (Chong et al, 2015). Atorvastatin and simvastatin (statins) 80mg/kg/b.wt dissolved in distilled water by oral gavage for 12 weeks respectively induced hepatic injury in rats (Adly et al, 2019). Also some animal studies link high dose statins to liver tumors. Yet, clinical trials suggest reduction in liver cancers with statins. (McGlynn et al, 2015).

Tomato seeds are rich in antioxidants (lycopene, phenolics, flavonoids) and unsaturated fatty acids, which help reduce oxidative stress, inflammation, and hepatic lipid accumulation supporting liver health (Sahin et al, 2010;

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Allaqaband et al , 2022). Studies reported that low to moderate doses (200–250 mg/kg body weight) of tomato seed extract consistently improved liver enzyme profiles, reducing ALT, AST, and ALP levels (Sahin et al., 2010; Al-Jameel, 2014). Moreover, Sharaf et al. (2015) reported that extremely high doses (1000 mg/kg) of tomato seed extract elevated oxidative stress markers, suggesting that excessive intake may overwhelm the liver's antioxidant capacity. Although the potential impact of tomato seed extract doses on hepatic function remains incompletely understood, current evidence of toxicity is limited.

Problem Statement

Statins are established as effective lipid lowering agents, with proven benefits in reducing cardiovascular risk through modulation of cholesterol and triglyceride levels. While clinical studies have reported instances of hepatotoxicity, the mechanisms underlying these effects and their relevance to long-term therapy are still debated. Experimental models, particularly in rats, provide a valuable platform for investigating both the therapeutic and adverse hepatic consequences of statin administration. At the same time, **liver disease burden** continues to rise globally, accounting for millions of deaths annually. Despite the widespread use of statins, their role in modulating liver disease progression, whether protective or harmful remains unclear. This gap highlights the necessity of systematic research into the **hepatotoxicity** and potential therapeutic effects of statins in experimental models. Understanding these dual aspects could inform clinical practice, guide safer use of statins in populations at risk of liver disease, and contribute to strategies aimed at reducing the global burden of hepatocellular disorders.

Significant of the study

Tomato seeds are a valuable source of diverse bioactive compounds are rich in **antioxidants** such as lycopene, phenolics, and flavonoids, they play a crucial role in neutralizing free radicals, thereby reducing oxidative stress and preventing hepatocellular damage. In addition, the presence of **flavonoids** has been associated with anti-inflammatory and anti-carcinogenic properties, as these compounds modulate cellular signaling pathways and inhibit the production of pro-inflammatory cytokines. Tomato seeds also contain **unsaturated fatty acids,** which help lower hepatic lipid accumulation and improve liver function, reducing the risk of fatty liver disease. Importantly, the synergistic effects of these bioactive molecules extend beyond liver protection, offering potential in the prevention of chronic diseases. Evidence further suggests that whole tomato products, including seeds, demonstrate stronger protective effects against cancer compared to purified lycopene alone, underscoring the importance of the natural food matrix in enhancing bioactivity. Collectively, these findings highlight tomato seeds as a promising natural intervention with antioxidant, anti-inflammatory, and disease-preventive properties.

Justification of study

The liver is a vital organ for metabolism, storage, and excretion, yet it is highly vulnerable to drug-induced damage. Tomato seeds contain carotenoids such as lycopene with strong antioxidant properties that may protect liver against hepatic injury. Studying the effects of tomato seed constituents on a drug damaged liver is therefore justified, as it may reveal natural hepatoprotective mechanisms and potential dietary interventions for liver health.

Aim of Study

The overall aim of this research is to evaluate the protective effect of tomato seed extract on statin induced liver damage on albino rats.

Objectives of study

The study aims of the study the following specific objectives;

To examine the most effective dose concentration of aqueous tomato seed extract on statin induced liver injury of albino rats.

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To evaluate some biochemical effect of aqueous tomato seed extract on albino rats with induced Statin liver damage

To determine histomorphological effect of tomato seed extract on statin induced the liver damage of albino rats.

Hypothesis

Null Hypothesis (H_0): Tomato seeds extract therapy has no significant effect on **hepatic injury** in experimental rat models.

Alternative Hypothesis (H_1): tomato seed therap extract administration significantly reduces hepatotoxic effects, reflected in altered liver enzyme levels and histological changes in experimental rat models compared to untreated controls.

LITERATURE REVIEW

The human liver filters off all the blood in the body and breaks down poisonous substances, such as alcohol and drugs. It also aids in the production of bile, conversion of excess glucose into glycogen for storage, and bilirubin clearance. The type of damage caused by the statin is a drug-induced liver injury (DILI), it is one of the most common and significant causes of acute liver failure and acute hepatitis (Devarbhavi et al, 2021). It progresses from steatosis, which is a non-alcoholic fatty liver disease, to cirrhosis and hepatocellular carcinoma (Devarbhavi et al, 2023).

Types of Hepatotoxicity

Drug-induced liver injury (DILI): The most common, responsible for up to **50% of acute liver failures** worldwide. Caused by prescription drugs, over-the-counter medications, or herbal supplements.

Alcohol-induced hepatitis: Often progresses to cirrhosis in chronic or heavy alcohol use.

Chemical-induced hepatitis: Exposure to industrial or environmental toxin such as CCl_4 and vinyl chloride.

Nutritional/supplement-related: Excessive intake of vitamin A, bodybuilding supplements, or contaminated and unregulated herbal remedies.

Common Causes of Liver Injury

Medications: Acetaminophen, NSAIDs (diclofenac, ibuprofen), Antibiotics (e.g., amoxicillin-clavulanate, isoniazid, nitrofurantoin), Statins (atorvastatin, simvastatin), Chemotherapy and immunotherapy drugs overdose usually result in mild, transient enzyme elevations leading cause of acute liver failure.

Symptoms of Hepatic Injury

Early signs: Fatigue, nausea, abdominal pain, loss of appetite.

Advanced signs: Jaundice (yellow skin/eyes), dark urine, itchy skin, ascites (fluid buildup), confusion (encephalopathy).

Severe cases: Vomiting blood, delirium, bruising, coma which may indicate acute liver failure.

Diagnosis of Hepatic Injury

Blood tests: Liver function tests (ALT, AST, ALP, bilirubin).

Imaging: Image viewing through CT, MRI, ultrasound to assess liver structure.

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Biopsy: Liver tissues are sometimes needed to confirm cause.

Pattern classification:

Hepatocellular injury leads to elevated ALT/AST.

Cholestatic injury causes high ALP.

Mixed injury result in both elevated.

Prevention & Management

Monitoring liver enzymes (ALT, AST, ALP, bilirubin) during drug therapy and follow drug prescription.

Avoiding excessive alcohol and unregulated supplements intake.

Overdose uses of antidotes like N-acetylcysteine or acetaminophen.

Ensure occupational safety to limit chemical or toxin exposures

Severe cases: Liver transplantation may be required.

National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) (2024).

STATIN

In 2014, Russo reported a total of 22 cases involving statin use in a prospective registry of 1188 patients with drug-induced liver injury between 2004 and 2012. Of these patients, the majority were female (68%), with a varied latency of onset from 34 days to 10 years (median 155 days) associated with a variety of cellular injury mechanisms. Interestingly, they reported that the condition of four of these patients progressed to chronic liver disease, mainly of the autoimmune phenotype (Russo et al, 2014).

Their beneficial effects, including reduction of mortality and cardiovascular events, have been established in randomized clinical trials. (Mary et al, 2014).

In mouse models, statins inhibit angiogenesis (formation of new blood cells) and growth of hepatocellular carcinoma (Tijeras-Raballand et al, 2010).

Treatment of dyslipidemic patients with a combination of statins, which inhibit endogenous cholesterol synthesis, and ezetimibe, a cholesterol uptake inhibitor, to reduce plasma low density lipoprotein cholesterol levels, improved hepatic steatosis. (Nakade et al, 2017)

The observational study reported only one case of rhabdomyolysis and one case of muscle weakness amongst 20,000 patients treated with a type of statin. (Yokote et al, 2011).

Hepatotoxicity of Statins

Several studies have investigated the hepatotoxic effects of statins in rat models. Statins can induce liver enzyme alterations, indicating potential liver damage. For instance, a study by Nakahara et al, 2002 reported that high doses of atorvastatin caused significant increases in serum Alanine aminotransferase (ALT) and Aspartate aminotransferase (AST) levels in rats, markers indicative of liver injury.

Mechanisms of Liver Injury

The mechanisms by which statins might induce liver injury include oxidative stress and mitochondrial dysfunction. A study by Bhardwaj and Khanna demonstrated that simvastatin induced oxidative stress in rat

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liver tissues, leading to increased lipid peroxidation and reduced levels of antioxidant enzymes. This oxidative stress can result in hepatocyte apoptosis and necrosis (Bhardwaj et al, 2016).

Dose-Dependent Effects

Dose- dependent report indicated that rats administered with high doses of lovastatin showed significant liver histopathological changes, including hepatocyte ballooning and inflammation, compared to those given lower doses (Zhang et al, 2008).

Protective Effects and Benefits

Some studies suggest that statins may also have hepatoprotective effects at lower doses or in certain pathological conditions. For instance, research by Basiglio et al, 2010 indicated that atorvastatin could reduce liver fibrosis and inflammation in a rat model of non-alcoholic steatohepatitis potentially through anti-inflammatory and antifibrotic mechanisms.

TOMATOES:

Scientific Classification

Botanical Taxonomy

Kingdom: Plantae

Order: Solanales

Class: ***Magnoliopsida***

Family: Solanaceae (nightshade family)

Genus: *Solanum*

Species: *Solanum lycopersicum* (domesticated tomato)

(Integrated Taxonomic Information System, 2024).

Ethobotanical survery

There are many tomato species, only two are considered edible: Solanum pimpinellifolium and Solanum lycopersicum var. cerasiforme (the cherry tomato) (De Broglie et al., 2005).

The cultivated tomato is Solanum lycopersicum. Its closest wild relative is Solanum pimpinellifolium, differing by only 0.6% of nucleotide base pairs (Tomato Genome et al, 2012). The wild tomatoes are generally small compared to the domesticated ones.

Tomato specie of *Solanum lycopersicum*.

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Nutritional Composition of Tomato Seeds:

Tomato seeds are rich in bioactive compounds that contribute to their nutritional value, including:

Proteins: Tomato seeds are a notable source of protein, which contains essential amino acids vital for human health (Periago, 2008).

Lipids: The seeds contain significant amounts of lipids, particularly unsaturated fatty acids such as oleic acids, which are beneficial for cardiovascular health (Silva et al, 2019).

Fibers: They are also rich in dietary fibers, which supports digestive health and can help in controlling blood sugar levels (Silva et al, 2019).

Also, tomatoes contain a lot of nutrients for example, vitamin C, Lycopene, Carotenoid. Due to their antioxidant properties, lycopene and other carotenoids are said to protect against carcinogenesis by preventing oxidative damage in DNA and proteins through antioxidant mechanisms (Basu et al, 2007).

Mechanisms of Action of tomato seeds

Antioxidant Defense: At optimal doses, the antioxidants in tomato seeds reduce markers of oxidative stress, by neutralizing free radicals and enhancing the liver's defense system preventing liver cell damage (Sharaf et al, 2015).

Anti-inflammatory Effects: Tomato seeds can reduce pro-inflammatory cytokines in the liver, for example Interleukin-6, reducing inflammation and promoting liver health (Morsi et al, 2012).

Lipid Metabolism: Tomato seeds, through their high unsaturated fatty acid content, can influence lipid metabolism by preventing the accumulation of fats in the liver, through breakdown of fats, and thus protecting against non-alcoholic fatty liver disease (Morsi et al, 2012).

Modulation of apoptosis: Tomato seed studies have been shown to balance apoptosis by reducing the expression of pro-apoptotic factors, such as Bax and increasing anti-apoptotic factors like Bcl-2. This balance helps protect the liver from premature death that can be caused by inflammation, oxidative stress (Aydemir et al, 2012).

MATERIALS AND METHOD

Animal procurement

Twenty-five (25) albino rats weighing between 150–200 g were obtained from the ESCOM animal house. The animals were acclimatized for 14 days prior to experimentation.

Housing and acclimatization

Rats were housed in a well-ventilated iron cage under controlled environmental conditions. The room was maintained at a constant temperature of 25 ± 3 °C with a 12-hour light/dark cycle. All animals had free access to water and were fed a standard commercial chow diet throughout the study.

Ethical Approval

The experiment was conducted in accordance with institutional guidelines and ethical standards for the use of animals [ESUT/AREC/0225/09/20170300181721MLS].

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Sample collection and Preparation of tomato seed aqueous extract

The tomatoes were locally sourced at Ogbete market, Enugu North local government area of Enugu State, The tomato seeds were collected from fresh tomatoes, air dried and ground into a fine powdery form using blender.

250 grams of the ground tomato seeds were mixed with 1000 ml of water. The mixtures were left in the fridge at a temperature of 10°C for 24 hours before filtrations. The mixture was filtered using muslin cloth and Whatman No. 1 filter paper. Crude extra was stored in plastic air tight container and placed in refrigerator set at 4^0C until needed (Oliveira et al, 2009)

Drug procurement

Statin (simvastatin) used was purchased at Open heaven pharmaceutical store at Park Avenue GRA.

Study design

The rats in group 1 to 5 were weighed after purchase, prior to experiment day 0

Type: Experimental, randomized controlled trial (the animal experiment was conducted for 28days)

Duration: 4 weeks

Subjects: Twenty- five (25) healthy albino rats, weighing 150-200 grams..

Animal Inducement method

The statins 100 mg/ kg body weight was intraperitoneal administered daily for 14 days. (Nagaska, 2012 ; Bahrami, 2010; Adly, et al, 2019 modifications)

Experimental design

After the acclimatization period, the animals were randomly distributed into five groups, each consisting of five rats

Groups	**Treatments**
Group 1	Food, water,100mg/ kg b. wt of statins for 14days and then treated with low dose (200 mg/kg b.wt) of Solanum lycopersicum for 14 days
Group 2	Food, water, 100 mg/ kg b.wt stastins for 14days and then treated with moderate dose (300 mg/kgb.wt) of solanum lycopersicum for 14days
Group 3	Food, water and 100 mg/ kg b.wt of statins for 14days and then treated with high dose (400mg/kgb.wt) for 14 days
Group 4	Food, water and statin 100 mg/ kg b.wt (Control) for 14 days only
Group 5	Food and water (Normal control)

Sample and Specimen Collection

Blood samples were collected through retro-orbital plexus and the rats were sacrificed under Chloroform anesthesia at the end of the treatments. The organs (liver) were carefully excised among the all the groups using standard technique.

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Histological Sample Analysis

The excised tissue was fixed in 10% formal saline and taken to the laboratory for tissue processing. The tissue harvested were processed through dehydration, clearing, impregnation in wax, embedding, sectioning, staining with hematoxylin and eosin stain, mounted and analyzed photomicrography under the microscope.

Scoring: Histological lesions were graded using a semi- quantitative scoring systems as follows;

Score	Parameter
0	Normal
1	Mild changes
2	Moderate changes
3	Severe changes

(Suzuki et al, 1993)

Biochemical Analysis

Serum was obtained from the blood samples collected and used in analysis of liver enzyme parameters, ALT, AST, ALP.

Statistical Analysis

The data generated from the experiment results were analyzed for statistical significance using Tukey's post-hoc multiple comparison test, P values < 0.05, were considered statistically significant.

RESULTS

Table 1. Effect of Tomato Seed Extract on Alanine Aminotransferase (ALT) Activity in Statin-Induced Hepatotoxicity in Albino Rats

Group	**ALT (u/l)**
Low dose	112.40 ± 6.06^{a}
Medium	110.63 ± 17.83^{a}
High dose	134.47 ± 22.33^{a}
Control	140.30 ± 6.95^{a}
Normal control	106.67 ± 10.51^{a}
***F* (4, 10)**	2.0037
***p*-value**	*0.1683*

Values are mean ± SD (n = 3). Means that do not share a superscript letter differ significantly (p < 0.05, Tukey HSD).

Description of Table 1 and Figure 1

As presented in Table 1 and Figure 1, serum ALT activity did not differ markedly among the experimental groups. The statins-treated control group recorded a mean ALT of 140.30 ± 6.95 u/l, while the low-dose, medium-dose, and high-dose extract groups recorded means of 112.40 ± 6.06 u/l, 110.63 ± 17.83 u/l, and 134.47 ± 22.33 u/l, respectively. The normal control group had the lowest numerical ALT (106.67 ± 10.51 u/l). ANOVA revealed no statistically significant difference among the groups ($F = 2.0037$, $p = 0.1683$). These data indicate that, at the doses tested, tomato seed extract did not produce a significant shift in ALT, and statins administration alone did not induce a pronounced ALT elevation under the conditions of this study.

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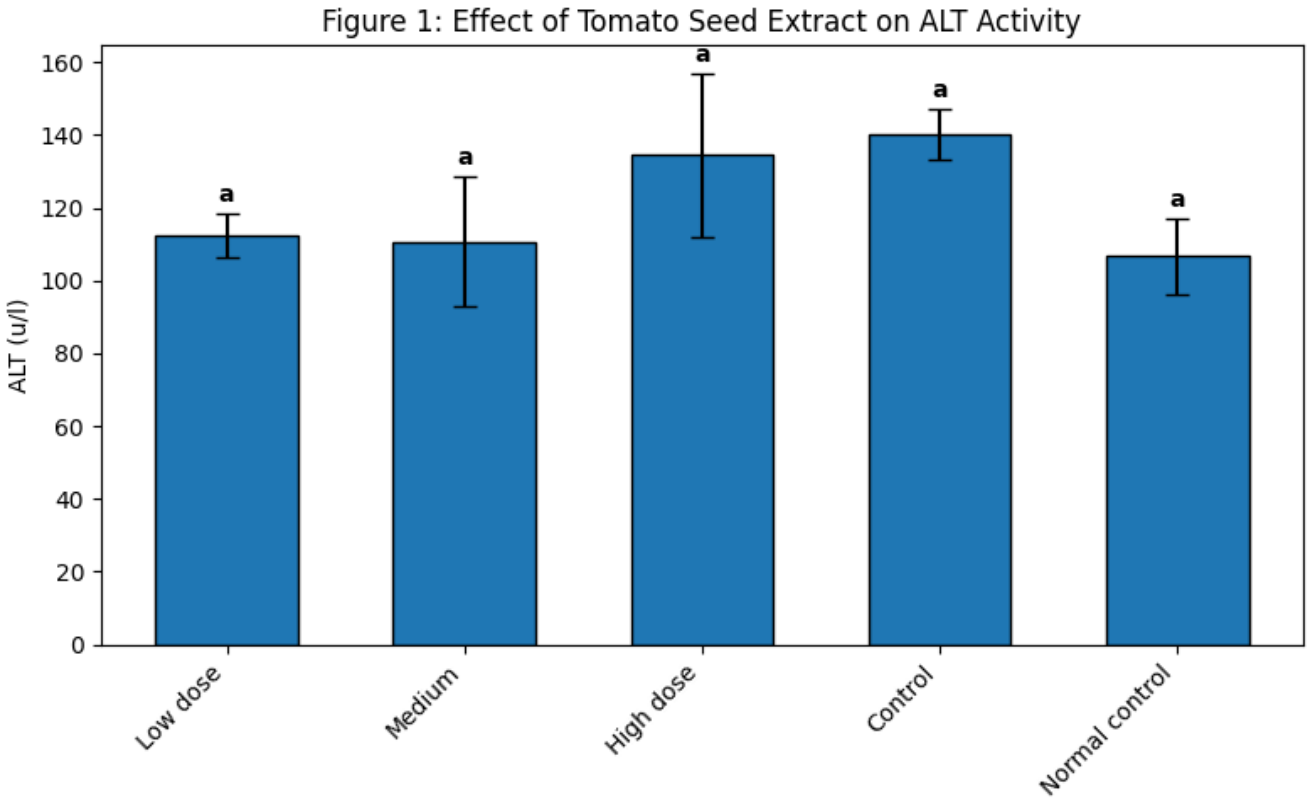
Figure 1. Effect of Tomato Seed Extract on Alanine Aminotransferase (ALT) Activity in Statin-Induced Hepatotoxicity in Albino Rats



Bars represent Mean ± SD (n = 3). Bars with different superscript letters differ significantly at $p < 0.05$ using Tukey's post-hoc multiple comparison test.

Table 2. Effect of Tomato Seed Extract on Aspartate Aminotransferase (AST) Activity in Statin-Induced Hepatotoxicity in Albino Rats

Group	**AST (u/l)**
Low dose	179.91 ± 1.35^{a}
Medium	252.21 ± 9.54^{b}
High dose	190.61 ± 53.83^{ab}
Control	252.44 ± 17.85^{b}
Normal control	176.00 ± 14.56^{a}
***F* (4, 10)**	4.9026
***p*-value**	*0.0183**

Values are mean ± SD (n = 3). Means that do not share a superscript letter differ significantly ($p < 0.05$, Tukey HSD).

Description of Table 2 and Figure 2

As shown in Table 2 and Figure 2, serum AST activity varied significantly across the experimental groups. Statin administration (control) caused a pronounced elevation in AST (252.44 ± 17.85 u/l) relative to the normal control (176.00 ± 14.56 u/l) and low-dose extract groups (179.91 ± 1.35 u/l). The medium-dose group (252.21 ± 9.54 u/l) remained similarly elevated, while the high-dose extract (190.61 ± 53.83 u/l) produced an intermediate AST level that did not differ significantly from either the normal or the control groups. One-way ANOVA confirmed a significant overall effect ($F = 4.9026$, $p = 0.0183$). These findings point to a dose-dependent hepatoprotective effect of tomato seed extract, with the high dose partially attenuating statin-induced hepatocellular enzyme leakage.

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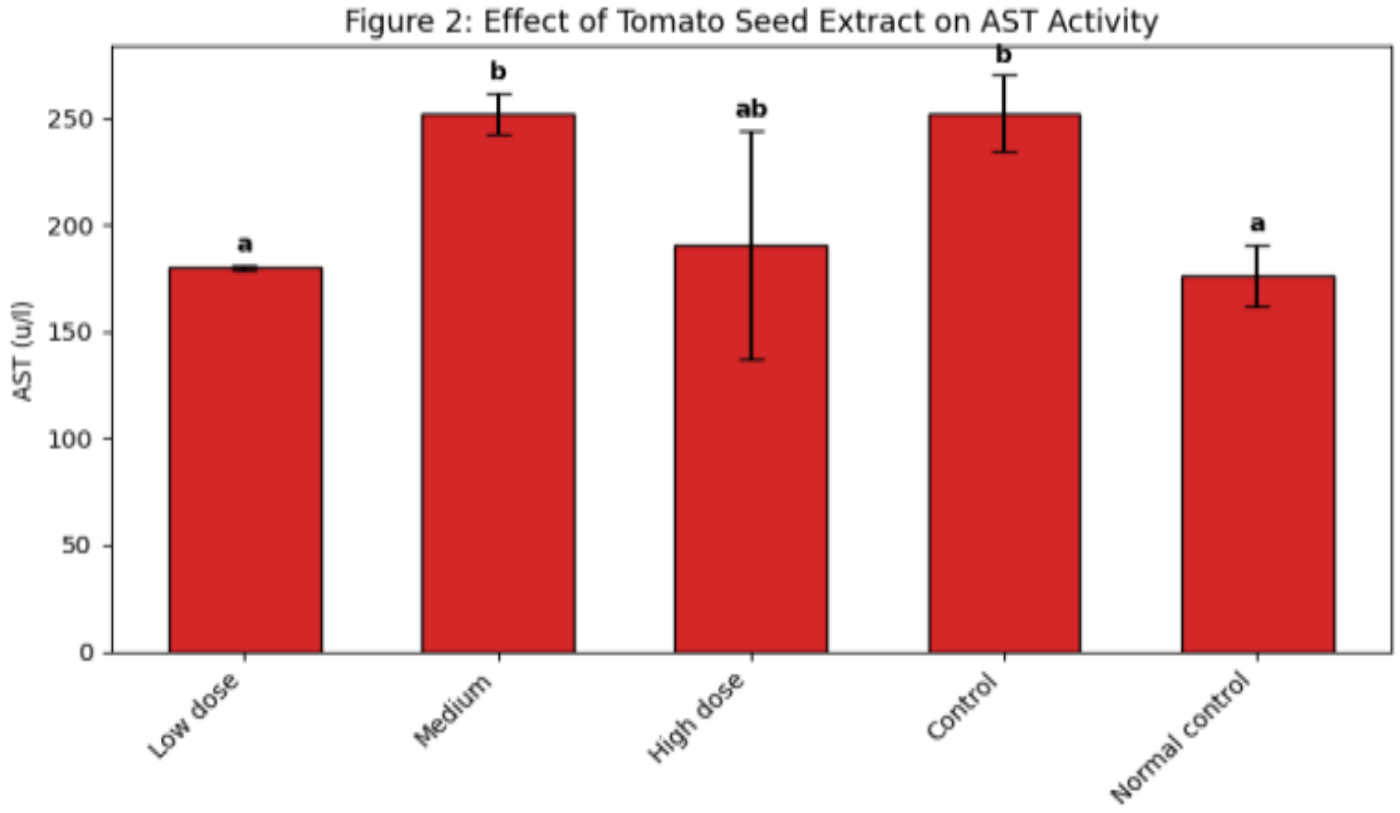
Figure 2. Effect of Tomato Seed Extract on Aspartate Aminotransferase (AST) Activity in Statin-Induced Hepatotoxicity in Albino Rats



Bars represent Mean ± SD (n = 3). Bars with different superscript letters differ significantly at $p < 0.05$ using Tukey's post-hoc multiple comparison test.

Table 3. Effect of Tomato Seed Extract on Alkaline Phosphatase (ALP) Activity in Statin-Induced Hepatotoxicity in Albino Rats

Group	**ALP (u/l)**
Low dose	406.31 ± 66.28^{a}
Medium	394.12 ± 44.40^{a}
High dose	375.18 ± 89.06^{a}
Control	484.39 ± 18.87^{a}
Normal control	370.13 ± 43.47^{a}
***F* (4, 10)**	1.3750
***p*-value**	*0.3097*

Values are mean ± SD (n = 3). Means that do not share a superscript letter differ significantly ($p < 0.05$, Tukey HSD).

Description of Table 3 and Figure 3

As displayed in Table 3 and Figure 3, serum ALP activity followed a numerical pattern similar to that of the transaminases but did not reach statistical significance. The statin-control group exhibited the highest mean ALP (484.39 ± 18.87 u/l), whereas the normal control (370.13 ± 43.47 u/l) and the extract-treated groups (low dose 406.31 ± 66.28 u/l; medium dose 394.12 ± 44.40 u/l; high dose 375.18 ± 89.06 u/l) recorded lower values. Analysis of variance yielded $F = 1.3750$, $p = 0.3097$, indicating no statistically significant difference among the groups. Thus, tomato seed extract did not significantly alter ALP activity, suggesting that statin-induced hepatobiliary stress, if any, was not sufficient to produce a detectable rise in this marker under the conditions tested.

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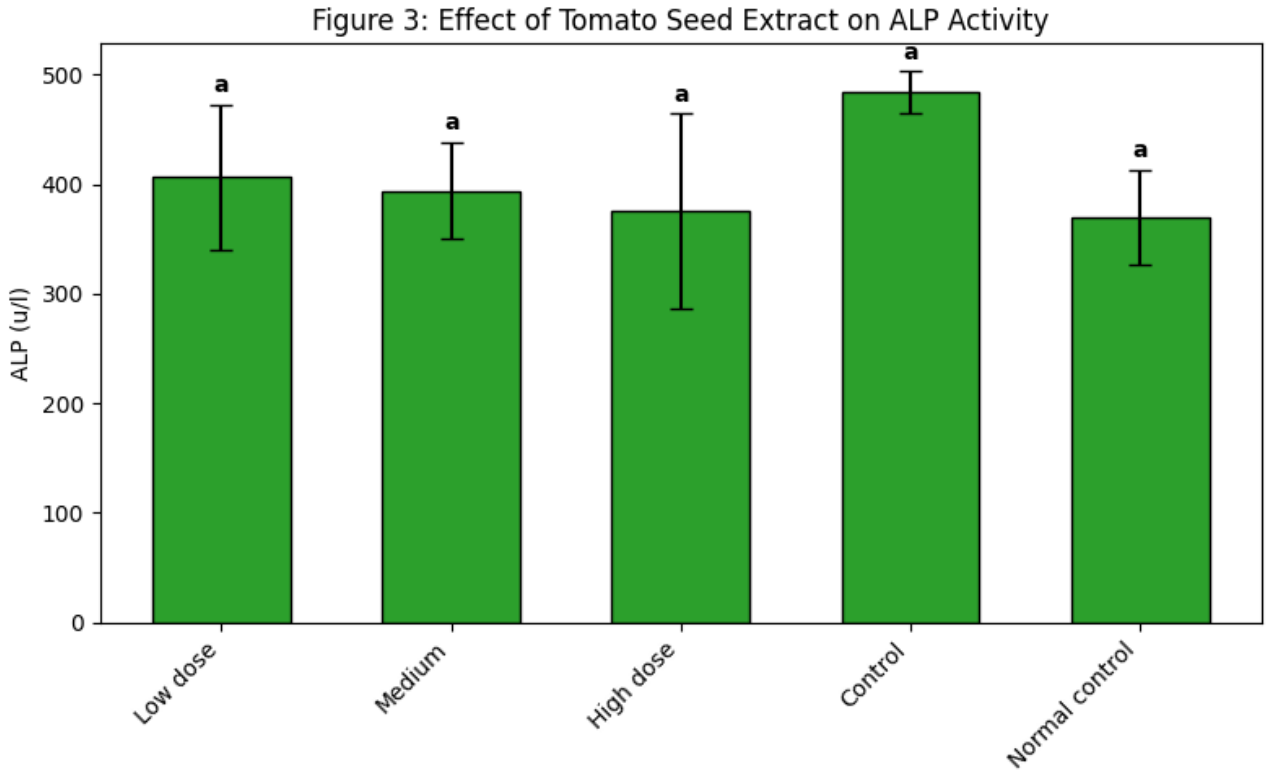
Figure 3. Effect of Tomato Seed Extract on Alkaline Phosphatase (ALP) Activity in Statin-Induced Hepatotoxicity in Albino Rats



Bars represent Mean ± SD (n = 3). Bars with different superscript letters differ significantly at $p < 0.05$ using Tukey's post-hoc multiple comparison test.

Table 4. Effects of Tomato Seed Extract on Serum Liver Enzyme Markers (ALT, AST, and ALP) in Statin-Induced Hepatotoxicity in Albino Rats

Group	ALT (u/l)	AST (u/l)	ALP (u/l)
Low dose	112.40 ± 6.06^{a}	179.91 ± 1.35^{a}	406.31 ± 66.28^{a}
Medium	110.63 ± 17.83^{a}	252.21 ± 9.54^{b}	394.12 ± 44.40^{a}
High dose	134.47 ± 22.33^{a}	190.61 ± 53.83^{ab}	375.18 ± 89.06^{a}
Control	140.30 ± 6.95^{a}	252.44 ± 17.85^{b}	484.39 ± 18.87^{a}
Normal control	106.67 ± 10.51^{a}	176.00 ± 14.56^{a}	370.13 ± 43.47^{a}
***F* (4, 10)**	2.0037	4.9026	1.3750
***p*-value**	*0.1683*	*0.0183**	*0.3097*

*Values are mean ± SD (n = 3). Superscript letters indicate Tukey groupings within each column. F- and p-values correspond to one-way ANOVA for each parameter. *p < 0.05.*

Description of Table 4 and Figure 4

Table 4 and Figure 4 provide a consolidated view of the serum liver enzyme profile. Statin administration (Control) consistently produced the highest or near-highest values for all three enzymes, most notably AST, which was significantly elevated relative to the normal control and low-dose groups ($p < 0.05$). The high-dose tomato seed extract partly reversed this trend, bringing AST to an intermediate level (190.61 ± 53.83 u/l) that was no longer significantly different from normal. ALT and ALP showed similar numerical patterns but failed to reach statistical significance ($p = 0.1683$ and $p = 0.3097$, respectively). The grouped summary confirms a dose-dependent hepatoprotective tendency of the extract, most clearly evident in the attenuation of AST activity.

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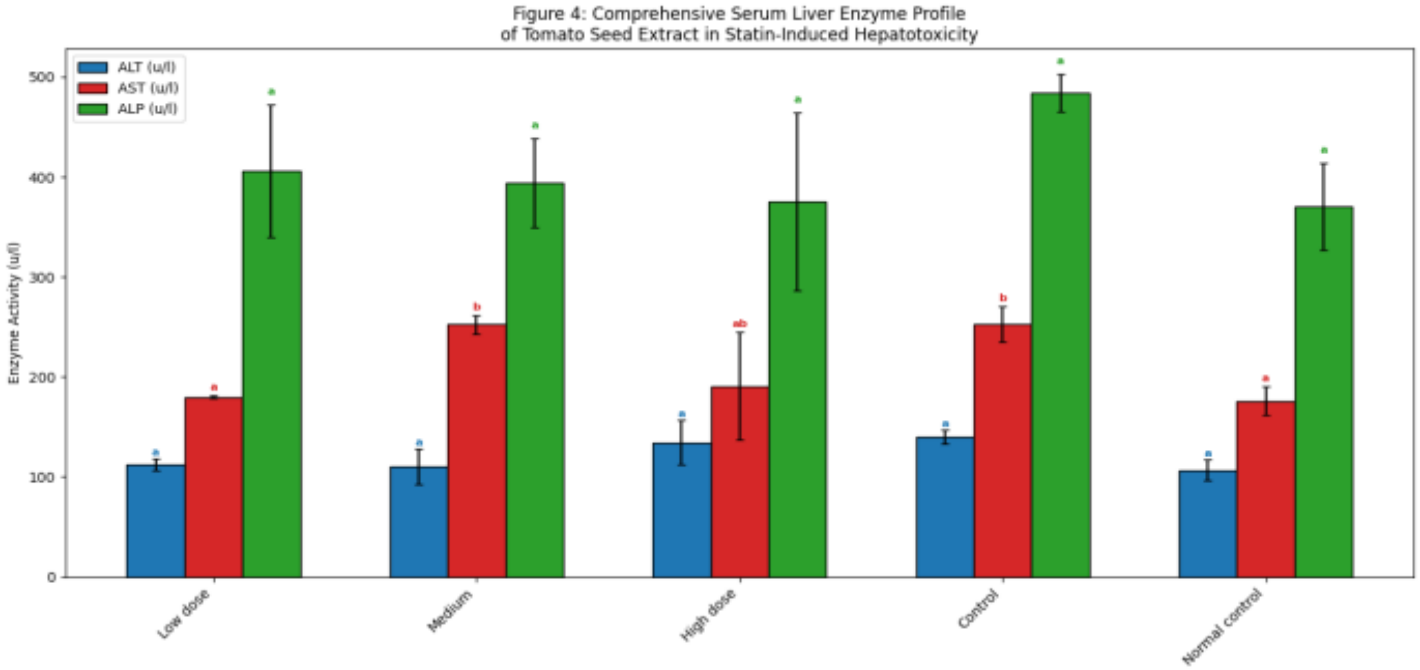
Figure 4. Effects of Tomato Seed Extract on Serum Liver Enzyme Markers (ALT, AST, and ALP) in Statin-Induced Hepatotoxicity in Albino Rats



Bars represent Mean ± SD (n = 3). Bars with different superscript letters differ significantly at $p < 0.05$ using Tukey's post-hoc multiple comparison test. Colour coding: ALT = blue, AST = red, ALP = green.

Photomicrography

Table 5. Semi quantitative histological scores of types of hepatic injuryon liver sections from statin treated albino rats pretreated with tomato seed extract

Group	Histopatholgy results			
	Inflammation	Necrosis	Eroded hepatocyte	Widened sinusoidal spaces
Group 1 (Low dose)	0 (0 - 0)^{a}	0 (0 - 0)^{a}	0 (0 - 0)^{a}	0 (0 - 0)^{a}
Group 2 (Medium)	1 (0 - 1)^{ab}	2 (1 - 3)^{bc}	2 (1 - 3)^{b}	0 (0 - 1)^{ab}
Group 3 (High dose)	2 (2 - 3)^{bc}	0 (0 - 1)^{ab}	1 (1 - 1)^{ab}	0 (0 - 1)^{ab}
Group 4 (Control)	3 (2 - 3)^{c}	2 (2 - 3)^{c}	0 (0 - 1)^{a}	2 (1 - 2)^{b}
Group 5 (Normal control)	0 (0 - 0)^{a}	0 (0 - 0)^{a}	0 (0 - 0)^{a}	0 (0 - 0)^{a}
H (4)	12.86	12.04	8.73	10.91
p-value	0.012*	0.017*	0.068	0.028*

*Values are expressed as median (range). Scores: 0 = Normal, 1 = Mild, 2 = Moderate, 3 = Severe. Different superscript letters within a row indicate significant differences ($p < 0.05$) based on Dunn's post-hoc test following a significant Kruskal–Wallis test. *$p < 0.05$.*

Description of Table 5

As presented in Table 5, liver sections from the normal control and low dose groups displayed no histopathological abnormalities (score 0 for all parameters). The statin-only control group exhibited marked hepatic injury, with significantly elevated median scores for inflammation (3, range 2–3), necrosis (2, range 2–3), and widened sinusoidal spaces (2, range 1–2) relative to normal and low-dose groups ($p < 0.05$). Eroded hepatocyte did not differ significantly among groups ($p = 0.068$).

Pre-treatment with tomato seed extract attenuated some aspects of statin-induced damage. The low-dose group remained histologically indistinguishable from the normal control across all parameters. In the high-dose

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group, inflammation remained elevated and did not differ significantly from the control, whereas necrosis was significantly reduced to a level comparable with normal controls. The medium-dose group showed intermediate scores, with necrosis remaining significantly elevated relative to normal. Widened sinusoidal spaces were largely absent in all extract-treated groups.

These findings indicate that tomato seed extract partially protected the liver from statin-induced histological injury, with the most complete preservation of normal architecture observed at the low dose. The high dose selectively reduced necrosis without fully suppressing inflammation, suggesting a differential effect of the extract on distinct pathological processes

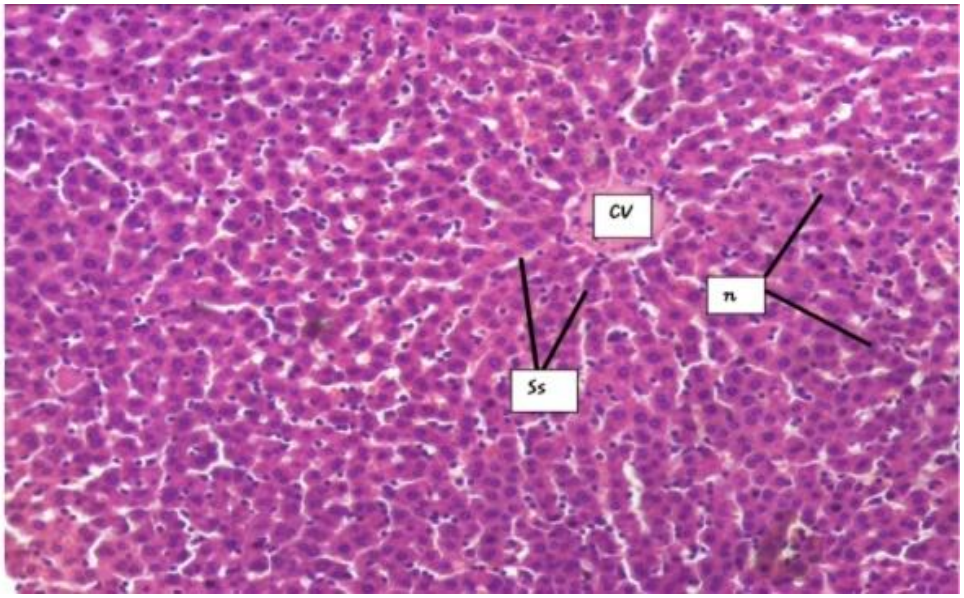

FIG I- Light photomicrograph of Liver section from rat treated with low dose of Solanum lycopersicum seed extract (Group 1) after liver injury induction with statin showing intact tissue parenchyma. The hepatocytes (nH- normal hepatocytes) around the central veins (CV), portal tracts and mid-zonal areas appear intact with no obvious lesion, indicating the protective effect of Solanum lycopersicum seed extract on hepatic tissue at low dose (200 mg/kg b.wt) (Stain: Haematoxylin & Eosin; Mag: x100)

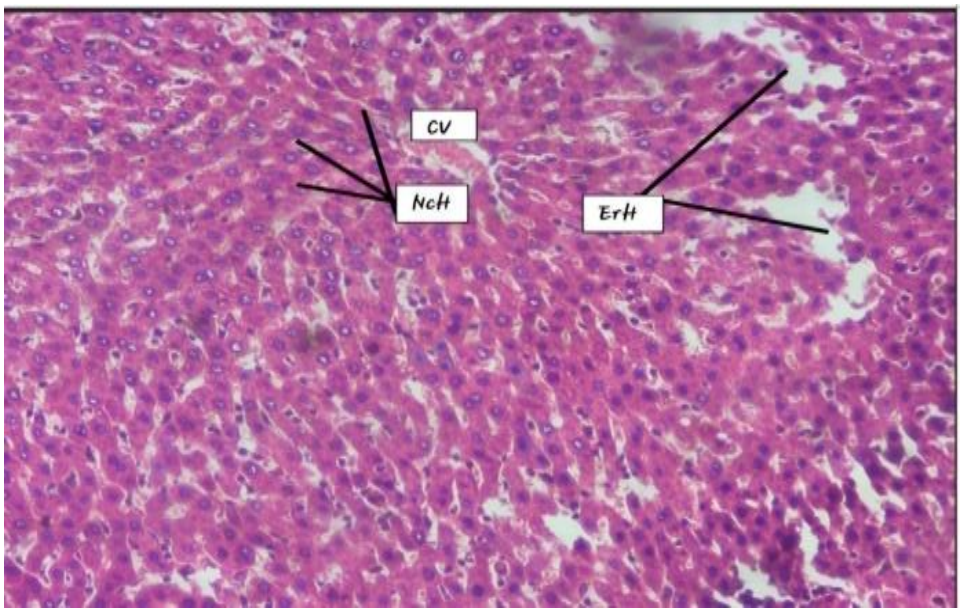

FIG II- Light photomicrograph of Liver section from rat treated with medium dose of Solanum lycopersicum seed extract (Group 2) after liver injury induction with statin showing some obvious histo-morphological alterations; Some hepatocytes are eroded around the mid-zonal region (ErH) while some hepatocytes are necrotic (NcH) around the central vein (CV), (Stain: H&E; Mag: 100)

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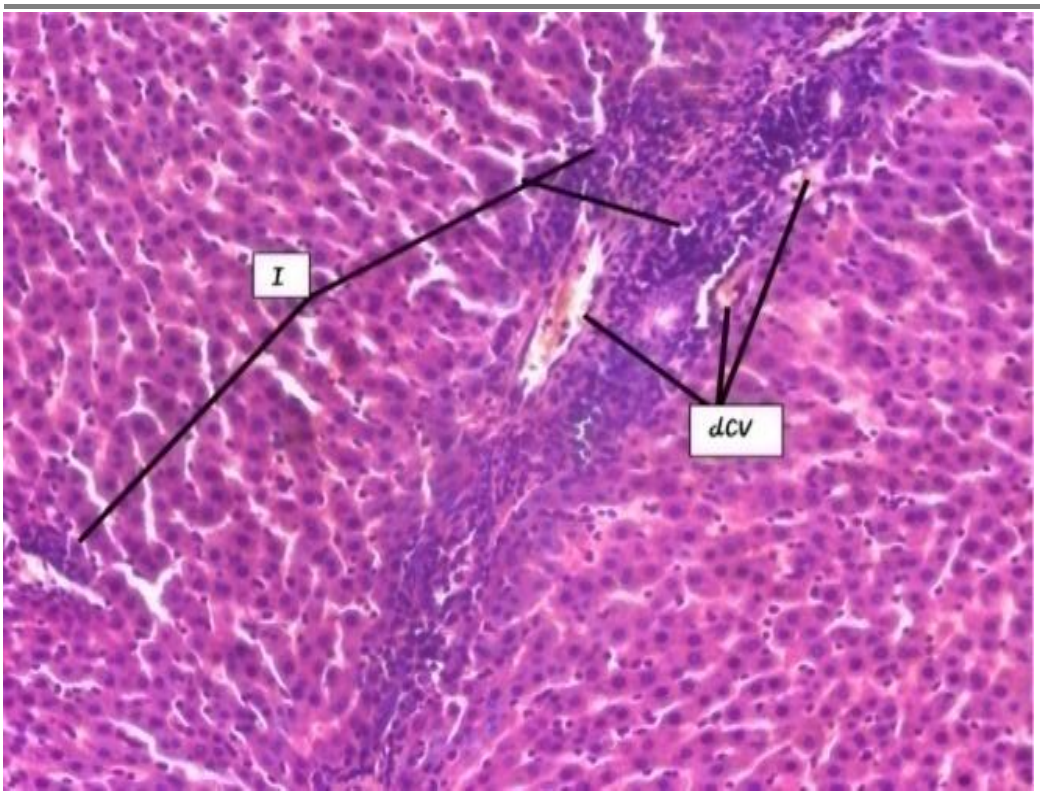

FIG III- Light photomicrograph of Liver section from rat treated with high dose of Solanum lycopersicum seed extract (Group 3) after liver injury induction with Statin showing some obvious histo-morphological alterations; disruption of the central veins (dCV) and marked inflammatory cellular infiltration (Stain: H&E; Mag: 100)

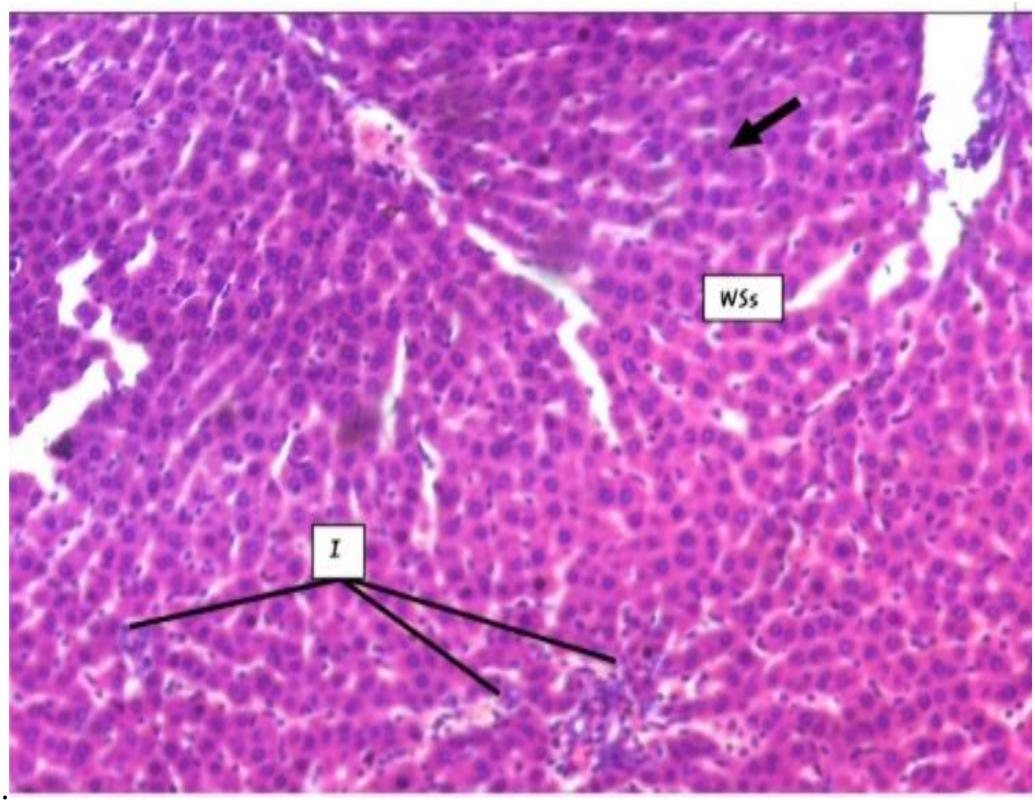

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FIG IV- Light photomicrograph of Liver section from rat treated with 100 mg/kg Statin only (Negative Control-group 2) showing some obvious histo-architectural alterations. Features observed include: marked inflammatory cellular infiltration (Ic); necrotic hepatocytes (thick arrow) and widened sinusoidal spaces (WSs). (Stain: Haematoxylin & Eosin; Mag: x100)

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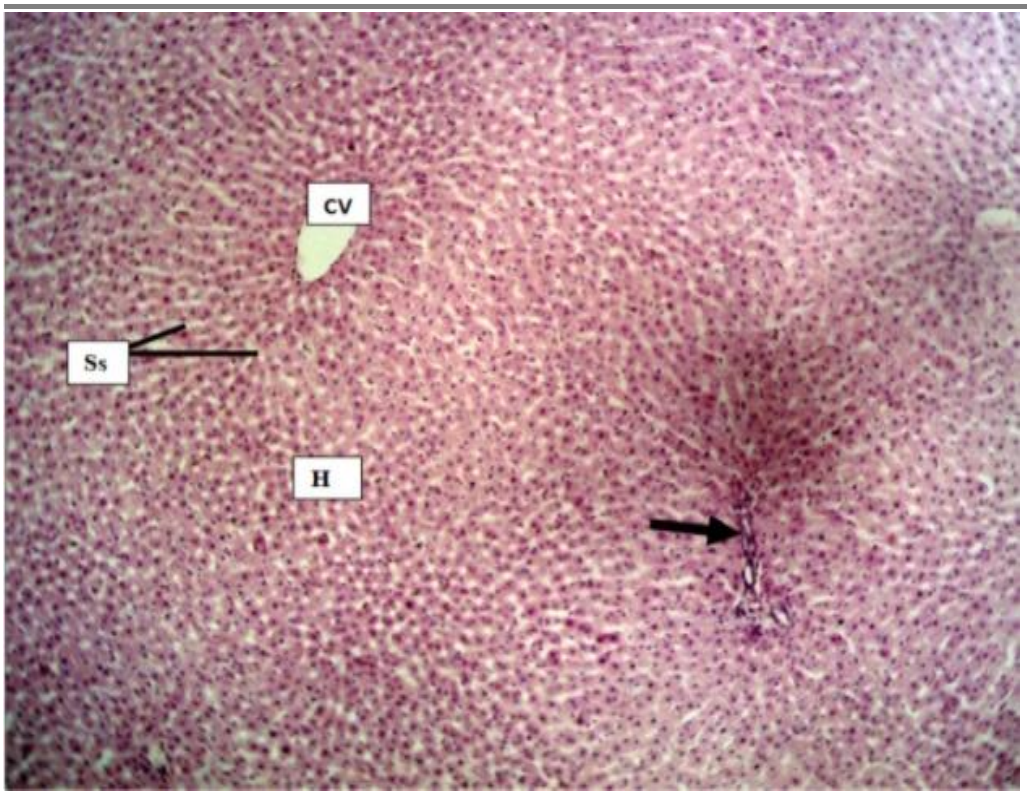

FIG V- Light photomicrograph of Liver section from normal control rat (Group 1) showing normal histo-architecture of the hepatic tissue. Normal features observed include; central veins (CV), hepatocytes (H), portal tract (arrow) and sinusoidal spaces (Ss) appear normal. (Stain: Haematoxylin & Eosin; Mag: x100)

DISCUSSION, CONCLUSION AND RECOMMENDATION

The hepatoprotective properties of tomato seed extract are attributed to its high content of **bioactive compounds**, which enhance the liver's antioxidant defense mechanisms. Previous studies support these findings. Ahmed and Ali (2018) reported improved liver enzyme profiles in rats treated with tomato seed extract, with significant reductions in alanine aminotransferase (ALT) and aspartate aminotransferase (AST), both markers of liver injury. Similarly, tomato extracts at 30 mg/kg body weight demonstrated hepatoprotective effects, significantly lowering liver enzyme activities (Uchendu et al., 2018). At doses, such as 80 mg/kg, phytochemical agents provided strong protection against drug-induced hepatotoxicity (Buabeid, 2024).

Dose-dependent effects evident were observed in the study, though was in concordance with studies reported that low to moderate doses (200–250 mg/kg body weight) of tomato seed extract consistently improved liver enzyme profiles, reducing ALT, AST, and ALP levels (Sahin et al., 2010; Al-Jameel, 2014). However, doses of tomato seed extract from the study produced mixed outcomes. While antioxidant properties initially provided hepatoprotection at low doses, excessive intake led to increased oxidative stress and potential liver damage due to over accumulation of bioactive compounds. These results were in agreement with Sharaf et al. (2015) reported that extremely high doses (1000 mg/kg) of tomato seed extract elevated oxidative stress markers thus, suggesting that excessive intake may overwhelm the liver's antioxidant capacity.

Histological examinations further reinforced these biochemical findings. Zhang et al. (2019) observed reduced inflammation and necrosis in liver tissues of rats treated with tomato seed extract 200mg/kg.b.wt compared to untreated controls, indicating preservation of tissue structure and function. Nonetheless, the partial protective effect observed in this study may be influenced by factors such as extraction methods, bioavailability of active compounds, dosage, administration route, and the specific pathways affected by statins. Longer study durations and advanced experimental models may provide deeper insights into these mechanisms. The findings emphasize the complexity of liver injury mechanisms and the potential role of dietary phytochemicals in mitigating statin-induced hepatotoxicity.

Conclusion

This study demonstrates that **tomato seed extract** possesses hepatoprotective properties, particularly at low doses, by reducing liver enzyme activity, inhibiting lipid peroxidation, and preserving tissue integrity. However, medium and high doses may paradoxically increase oxidative stress, highlighting the influence of dose optimization. Tomato seeds, with their rich composition of antioxidants, flavonoids, and unsaturated fatty acids, represent a promising natural intervention for liver protection

Future research should explore different extraction methods, varied dosages, and the combined use of whole tomato components—including pulp and skin—to maximize therapeutic benefits. Clinical trials will be essential to validate these protective effects in humans and to establish tomato seed extract as a complementary strategy alongside conventional pharmacological therapies.

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