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"Pharmacological Evaluation of the Hepatoprotective Potential of Herbal Extract in Thioacetamide-Induced Liver Injury."

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INTRODUCTION

The liver plays a central role in metabolism and detoxification, making it highly vulnerable to chemical-induced damage. Continuous exposure to toxins, drugs, and environmental pollutants often leads to liver injury, fibrosis, and cirrhosis. Thioacetamide (TAA) is a well-established hepatotoxin that induces liver damage through oxidative stress, inflammation, and necrosis, closely mimicking human liver disorders.
Tinospora cordifolia exhibits significant hepatoprotective activity against thioacetamide (TAA)-induced liver injury through its antioxidant, anti-inflammatory, and anti-apoptotic properties. TAA is metabolized in the liver to reactive intermediates that generate excessive reactive oxygen species (ROS), leading to lipid peroxidation, oxidative stress, hepatocyte necrosis, and fibrosis. Bioactive phytoconstituents of Tinospora cordifolia, including alkaloids, diterpenoid lactones, glycosides, polysaccharides, and phenolic compounds, enhance endogenous antioxidant defense by increasing the activities of superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and reduced glutathione (GSH), while reducing malondialdehyde (MDA) levels. The extract also suppresses inflammatory mediators such as tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), interleukin-6 (IL-6), and inhibits activation of the NF-κB signaling pathway, thereby
minimizing inflammatory cell infiltration and hepatocellular damage.

Furthermore, Tinospora cordifolia reduces hepatocyte apoptosis by modulating Bax/Bcl-2 expression and caspase-3 activation, while promoting regeneration of liver cells and preserving normal hepatic architecture. These combined mechanisms contribute to the normalization of liver function biomarkers (ALT, AST, ALP, and bilirubin), attenuation of fibrosis, and restoration of liver tissue integrity in TAA-induced experimental liver injury.
Drug-induced liver injury (DILI) is one of the most common causes of liver dysfunction worldwide. Among the drugs associated with hepatotoxicity, antitubercular medications such as isoniazid (INH) and rifampicin (RIF) are frequently implicated. These drugs are widely used for the treatment of tuberculosis (TB), but prolonged use can lead to significant liver damage (Pal etal., 2010). Therefore, the search for effective hepatoprotective agents has gained considerable attention.
Medicinal plants have been used for centuries in traditional medicine for the treatment of liver disorders. Herbal extracts contain bioactive compounds such as flavonoids, phenolics, alkaloids, tannins, and terpenoids that possess antioxidant, anti- inflammatory, and hepatoprotective properties. The present study aims to evaluate the hepatoprotective potential of a selected herbal extract against isoniazid and rifampicin-induced liver injury (Rana et al., 2010).

Need of the Work

Liver diseases are a major global health concern, contributing significantly to morbidity and mortality due to their progressive nature and limited curative treatment options. Hepatic injury often progresses from mild inflammation to fibrosis, cirrhosis, and eventually liver failure if not properly managed. Among the various experimental models used to study liver damage, thioacetamide (TAA)-induced hepatotoxicity is widely accepted because it closely mimics human liver fibrosis through mechanisms involving oxidative stress, inflammation, hepatocellular necrosis, and activation of fibrogenic pathways such as TGF-β1/Smad signaling.

Tinospora cordifolia (Guduchi) is a highly valued medicinal plant in traditional Ayurvedic medicine and is known for its broad pharmacological activities, including immunomodulatory, antioxidant, anti-inflammatory, antidiabetic, and hepatoprotective effects. Its phytochemical profile includes alkaloids, glycosides, diterpenoid lactones, steroids, and phenolic compounds, which are believed to contribute to its therapeutic potential. Although several studies have reported the general hepatoprotective effects of T. cordifolia, there is still a lack of detailed understanding regarding its precise molecular mechanisms, particularly in relation to TAA-induced liver injury and associated pathways such as oxidative stress regulation, inflammatory cytokine suppression (TNF-α, IL-6), apoptosis modulation (Bax, Bcl-2, caspases), and fibrotic signaling (TGF-β1, α-SMA).

DRUG PROFILE

Tinospora cordifolia [37]:
Common Name(s): Amrita, Giloe, Giloya, Guduchi, Gulancha, Heartleaf moonseed.
Color: Greyish
odour: odourless
Test: Mucilaginous, bitter

LITERATURE REVIEW:

Sr. No.	Article Name	Authors	Journal	Year	Description
1	Phytochemical constituents and protective efficacy of *Schefflera arboricola* leaves extract against thioacetamide-induced hepatic encephalopathy in rats	El-Hagrassi A.M. et al.	*Biomarkers*	2022	Methanolic extract (100 & 200 mg/kg) significantly reduced ALT, ALP, ammonia, MDA, TNF-α, IL-1β, and IL-6 levels while increasing GSH. Histopathology confirmed reduced liver and brain damage, indicating strong hepatoprotective and anti-inflammatory activity.
2	Thioacetamide-induced acute liver toxicity in rats treated with *Balanites roxburghii* extracts	Talluri M.R., Tadi R.S., Battu G.R.	*Journal of Acute Disease*	2016	Hydroalcoholic extract showed strong antioxidant activity and dose-dependent hepatoprotection. Significant restoration of AST, ALT, ALP, bilirubin, and total protein was observed, with maximum protection at 500 mg/kg, confirming non-toxicity and hepatoprotective potential.
3	Hepatoprotective role of *Vitex negundo* and *Caesalpinia sappan* in thioacetamide-induced liver injury in rats	Kadir F.A.A.	*University of Malaya (PhD Thesis)*	2014	Ethanolic extracts of *Vitex negundo* and *Caesalpinia sappan* significantly reduced TAA-induced liver cirrhosis. Extracts improved liver enzymes, antioxidant status, histopathology, and downregulated fibrotic markers (TGF-β1, α-SMA, MMPs), showing antioxidant and antifibrotic mechanisms.
4	Protective effect of *Pisonia aculeata* on thioacetamide-induced hepatotoxicity in rats	Anbarasu C., Rajkapoor B., Bhat K., Giridharan J., Amuthan A.A., Satish K.	*Asian Pacific Journal of Tropical Biomedicine*	2012	TAA caused significant elevation of AST, ALT, ALP, bilirubin, GGTP, and lipid peroxidation with reduced antioxidant enzymes. Treatment with *Pisonia aculeata* extract (250 & 500 mg/kg) restored biochemical and antioxidant parameters near normal, showing hepatoprotective activity comparable to silymarin.

AIM:

4.1 "Pharmacological Evaluation of the Hepatoprotective Potential of Herbal Extract in Thioacetamide-Induced Liver Injury."

OBJECTIVE:

1. To induce liver injury in rats using a standardized thioacetamide (TAA) hepatotoxicity model.
2. To evaluate the hepatoprotective effect of theherbal extract through liver function biomarkers (ALT, AST, ALP, bilirubin, LDH, TC, TG).
3. To assess oxidative stress parameters-MDA, SOD, Catalase, and GSH in liver tissue.
4. To analyze inflammatory markers such as TNF-α, IL-1β, and nitric oxide to determine anti-inflammatory activity.
5. To examine histopathological changes in liver tissue and compare the efficacy of the herbal extract with a standard hepatoprotective drug.

Plan of work :

Outline of the Proposed Research Work (Chapter Scheme):

Sr. No	Research Work	Tentative Time (Months)
1	Literature Survey	1
2	Pilot dose finding of plant extract	1
3	TAA Induction model Standardization	1
4	In-vivo study treatment	2
5	Biochemical & molecular assays	2
6	Result, Discussions and conclusion	2
6	Data compilation and thesis writing	1

Methodology/ Laboratory Work:

Paracetamol-induced hepatotoxicity in laboratory animals: Experimental designs:
The animals were divided randomly into groups with six rats per group as follows:
Group I: Normal group: The rats will receive only vehicle (Distilled water) for 56 days.
Group II: Vehicle control: The rats receive Thioacetamide (200 mg/kg) for 56 days.
Group III: Silymarin (50) group: The rats receive Thioacetamide (200 mg/kg) for 56 days. They will be pre- treated with Silymarin at a dose of 50 mg/kg, p.o., for 56ays.
Group IV: *Tinospora cordifolia* (75) group: The rats will receive Thioacetamide (200 mg/kg). They will be pre- treated with *Tinospora cordifolia* at a low dose of 125 mg/kg, p.o for 56 days.
Group V: *Tinospora cordifolia* (150) group: The rats will receive Thioacetamide (200 mg/kg). They will be pre-treated with *Tinospora cordifolia* at a low dose of 200 mg/kg, p.o for 56 days.
Group VI: *Tinospora cordifolia* (300) group: The rats will receive Thioacetamide (200 mg/kg). They will be pre- treated with *Tinospora cordifolia* at a low dose of 200 mg/kg, p.o for 56 days.



Preparation of test drug solution:

Drug solution of *Tinospora cordifolia* was prepared by using distilled water a vehicle

Route of administration:

In the pylorus ligation- and acetic-induced peptic ulcer model, the solution of *Tinospora cordifolia* was administered per oral (p.o.) route.

Preparation of Standard drug solution:

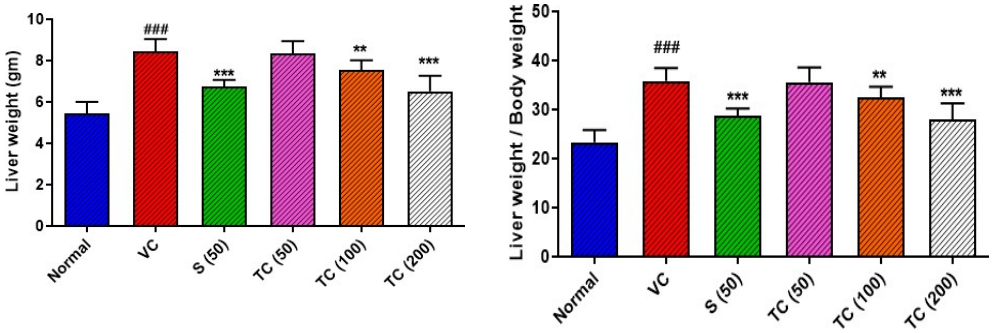
Drug solution of Silymarin was prepared by using distilled water as a vehicle

Parameter for assessment of the effect of *Tinospora cordifolia* on Thioacetamide -induced hepatotoxicity in rats:

Body weight
Liver Weight
Liver weight /Body Weight
AST
ALT
ALP
Albumin
Total bilirubin
LDH
Anti-oxidant activity (Total protein, MDA, CAT, GSH and SOD) in hepatic tissue
Molecular Markers (TNF-α, IL-1β, Nitric oxide)
Histopathology of hepatic tissue

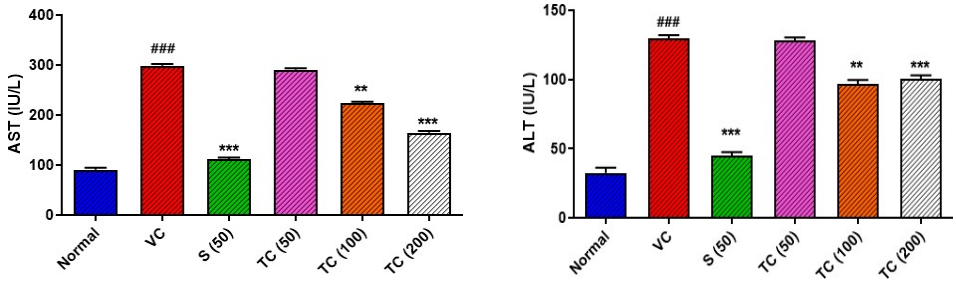
Effect of *Tinospora cordifolia* on Thioacetamide induced alteration in absolute liver weights

Time (in days)	Absolute liver weight (gm) and Relative liver weight - Mean ± SEM					
	Normal	Vehicle Control	Silymarin (50 mg/kg)	TC (50 mg/kg)	TC (100 mg/kg)	TC (200 mg/kg)
Liver weight (gm)	5.44 ± 0.23	8.43 ± 0.25$^{###}$	6.74 ± 0.14***	8.33 ± 0.25	7.55 ± 0.19**	6.53 ± 0.31***
Liver weight / Body weight	23.41 ± 1.00	35.87 ± 1.09$^{###}$	28.75 ± 0.60***	35.61 ± 1.22	32.43 ± 0.92**	27.93 ± 1.38***



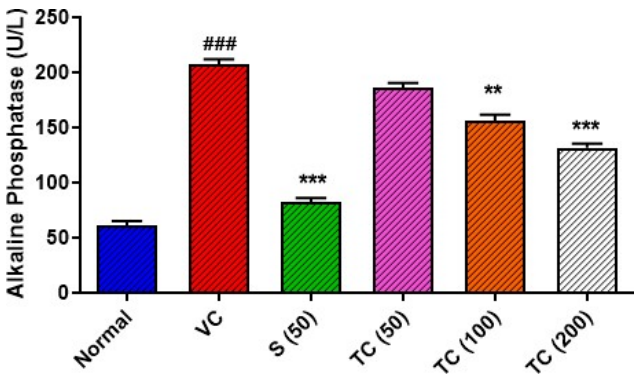
Effectof *Tinospora cordifolia* on Thioacetamide -induced alteration in AST and ALT levels

Parameter	AST (IU/L) and ALT (IU/L) - Mean ± SEM					
	Normal	Vehicle Control	Silymarin (50 mg/kg)	TC (50 mg/kg)	TC (100 mg/kg)	TC (200 mg/kg)
AST (IU/L)	91.2 ± 2.78	298.8 ± 2.08###	112.3 ± 1.47***	29070 ± 1.54	223.8 ± 1.49**	165.2 ± 1.29***
ALT (IU/L)	32.7 ± 2.11	129.70 ± 1.78###	44.8 ± 2.18***	128.3 ± 1.36	96.8 ± 1.29**	100.7 ± 1.18**



Effectof *Tinospora cordifolia* on Thioacetamide -induced alteration in ALPlevel

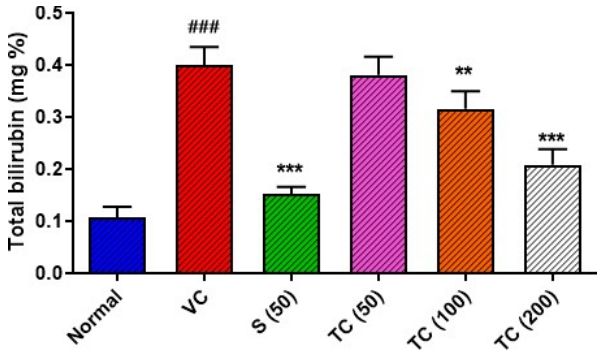
Alkaline Phosphatase (U/L) - Mean ± SEM					
Normal	Vehicle Control	Silymarin (50 mg/kg)	TC (50 mg/kg)	TC (100 mg/kg)	TC (200 mg/kg)
61.5 ± 2.43	209.80 ± 2.42###	79.7 ± 1.49***	176.70 ± 3.11	154.8 ± 4.58**	126.00 ± 2.63***



When compared to normal group, administration of INH+RIF cased a significant increase ($P < 0.001$) in vehicle control group. Treatment with silymarin (50 mg/kg) for 56th days significantly reduced ALP levels ($P < 0.001$) compared with vehicle control group. Similarly, *Tinospora cordifolia* at 200 mg/kg administered over 8th days also resulted in a significant decrease in ALP levels ($P < 0.001$) compared with vehicle control group. *Tinospora cordifolia* at 50 mg/kg and 100 mg/kg did not produce statistically significant reductions in ALP levels when compared to the vehicle control group.

Effect of *Tinospora cordifolia* on Thioacetamide -induced alteration in total levels

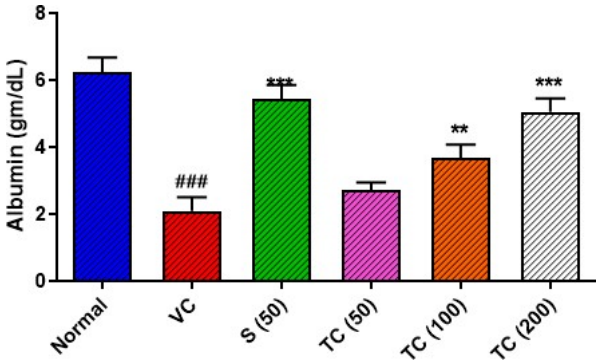
Parameter	Total bilirubin (mg %) and Direct bilirubin (mg %) - Mean ± SEM					
	Normal	Vehicle Control	Silymarin (50 mg/kg)	TC (50 mg/kg)	TC (100 mg/kg)	TC (200 mg/kg)
Total bilirubin (mg %)	0.10 ± 0.021	0.40 ± 0.03###	0.15 ± 0.014***	0.38 ± 0.034	0.31 ± 0.033**	0.20 ± 0.030***



Administration of INH+RIF caused significant increased ($P < 0.001$) in total and direct bilirubin levels in vehicle control group when compared to normal group on day 8. Treatment with silymarin (50 mg/kg) for 56th day resulted in a significant decrease in both total and direct bilirubin levels ($P < 0.001$) compared with vehicle control group. Similarly, *Tinospora cordifolia* at 200 mg/kg also produced a significant reduction in in both total and direct bilirubin levels ($P < 0.001$) compared with vehicle control group. *Tinospora cordifolia* at 50 mg/kg and 100 mg/kg did not result in a statistically significant decrease in bilirubin levels compared to the vehicle control group.

Effect of *Tinospora cordifolia* on Thioacetamide-induced alteration in albumin level

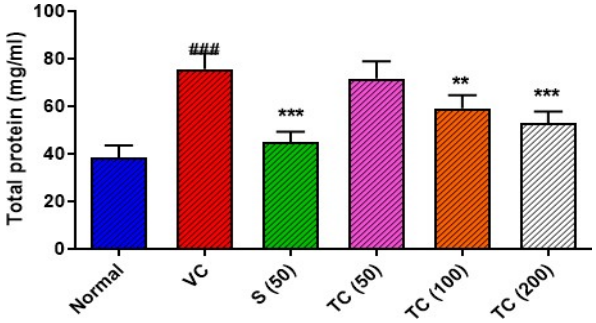
Albumin (gm/dL) - Mean ± SEM					
Normal	Vehicle Control	Silymarin (50 mg/kg)	TC (50 mg/kg)	TC (100 mg/kg)	TC (200 mg/kg)
6.24 ± 0.44	2.10 ± 0.4###	5.44 ± 0.41***	2.70 ± 0.23	3.68 ± 0.39**	5.04 ± 0.40***



The albumin level in the vehicle control group was found to be significantly ($P < 0.001$) decrease in normal group. The treatment Silymarin (50 mg/kg) significantly increases albumin levels ($P < 0.001$) as compared to vehicle control group. Similarly, *Tinospora cordifolia at* 200 mg/kg administered over 56th days produced a significantly increases in albumin levels ($P < 0.001$) vehicle control group. *Tinospora cordifolia* at 50 mg/kg and 100 mg/kg did not result in significant improvement in albumin levels after 56th days of treatment.

Effect of *Tinospora cordifolia* on Thioacetamide-induced alteration in hepatic total protein level

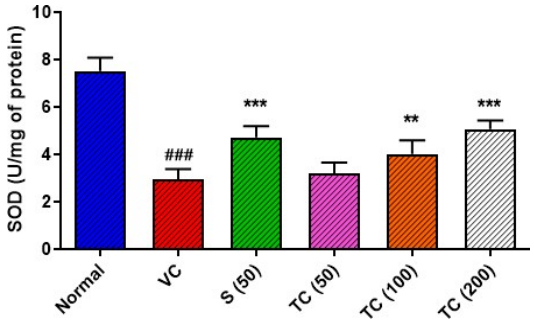
Hepatic total protein (mg/gm) - Mean ± SEM					
Normal	Vehicle Control	Silymarin (50 mg/kg)	TC (50 mg/kg)	TC (100 mg/kg)	TC (200 mg/kg)
38.47 ± 2.11	75.73 ± 2.72$^{###}$	45.16 ± 1.72***	71.77 ± 2.92	58.15 ± 2.11**	53.11 ± 1.95***

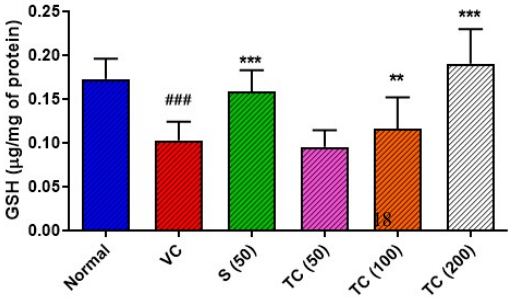


The hepatic total protein level significantly increases ($P < 0.001$) in the vehicle control group compared to the normal group. Treatment with silymarin (50 mg/kg) for 56th days significantly decrease hepatic total protein levels ($P < 0.001$) compared to the vehicle control group. *Tinospora cordifolia* at 200 mg/kg significant decrease in hepatic total protein levels ($P < 0.001$) compared to the vehicle control group.

Effect of *Tinospora cordifolia* on Thioacetamide -induced alteration in hepatic SOD and GSH level

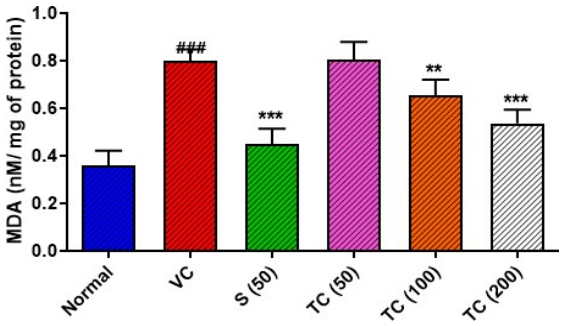
Parameter	Hepatic SOD (U /mg of protein) and GSH µg/mg of protein) levels - Mean ± SEM					
	Normal	Vehicle Control	Silymarin (50 mg/kg)	TC (50 mg/kg)	TC (100 mg/kg)	TC (200 mg/kg)
SOD (U/mg of protein)	7.5 ± 0.22	2.94 ± 0.18$^{###}$	4.72 ± 0.19***	3.18 ± 0.19	4.01 ± 0.23**	5.07 ± 0.14***
GSH (µg/mg of protein)	0.17 ± 0.02	0.10 ± 0.02$^{###}$	0.15± 0.02***	0.09 ± 0.01	0.11 ± 0.03**	0.19 ± 0.03***

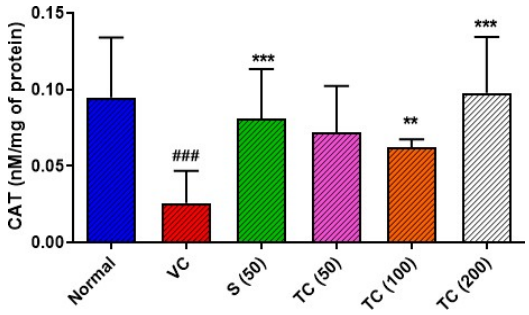




Effectof *Tinospora cordifolia* on Thioacetamide-induced alteration in hepatic MDAand CAT level

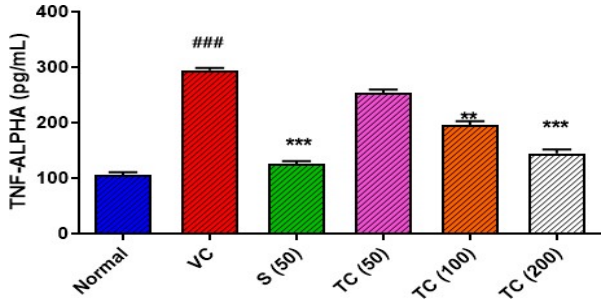
Parameter	Hepatic MDA and CAT (nM/mg of protein), - Mean ± SEM					
	Normal	Vehicle Control	Silymarin (50 mg/kg)	TC (50 mg/kg)	TC (100 mg/kg)	TC (200 mg/kg)
MDA (nM/mg of protein)	0.33 ± 0.02	0.76 ± 0.02###	0.42 ± 0.02***	0.79 ± 0.03	0.65 ± 0.02	0.53 ± 0.02***
CAT (nM/mg of protein)	0.095 ± 0.015	0.026 ± 0.008###	0.081± 0.013***	0.072 ± 0.012	0.062 ± 0.02	0.098 ± 0.01***





Effect of *Tinospora cordifolia* on Thioacetamide-induced alteration in hepatic TNF-Alpha level

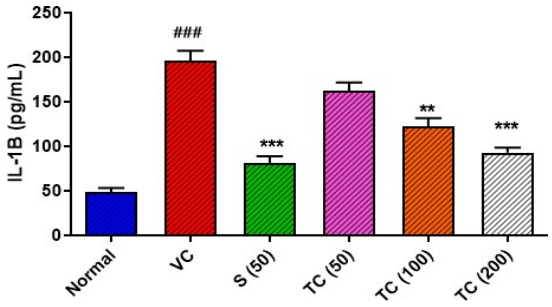
Parameter	**Hepatic TNF-ALPHA (pg/ml), - Mean ± SEM**					
	Normal	Vehicle Control	Silymarin (50 mg/kg)	TC (50 mg/kg)	TC (100 mg/kg)	TC (200 mg/kg)
TNF-ALPHA (pg/ml)	105.8 ± 2.01	295.2 ± 1.51###	125.8 ± 2.13***	254.0 ± 2.42	195.5 ± 2.99**	145.2 ± 2.72***



There was significant increase in hepatic TNF-ALPHA levels in vehicle control group as compared to normal group. When compared to the vehicle control group, silymarin (50 mg/kg) treatment for 56 days resulted in a significant decrease in both TNF-ALPHA levels ($P < 0.001$). *Tinospora cordifolia* at 200 mg/kg for 56 days showed a significant decrease in both TNF-ALPHA levels ($P < 0.001$). *Tinospora cordifolia* at 50 mg/kg and 100 mg/kg did not produce any significant reduction in hepatic MDA and NO levels after 7 days of treatment when compared to the vehicle control group.

Effect of *Tinospora cordifolia* on Thioacetamide-induced alteration in IL-6 level

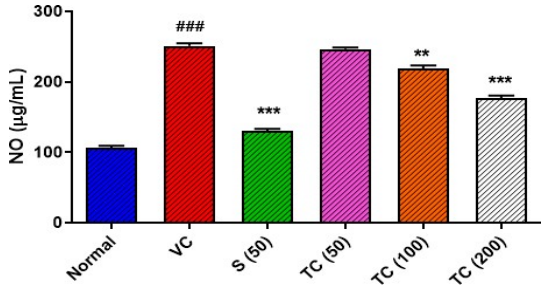
Parameter	Hepatic TNF-ALPHA (pg/ml), - Mean ± SEM					
	Normal	Vehicle Control	Silymarin (50 mg/kg)	TC (50 mg/kg)	TC (100 mg/kg)	TC (200 mg/kg)
IL-6 (pg/ml)	48.67 ± 1.9	196.7 ± 4.41###	81.33 ± 3.18***	162.5 ± 3.8	122.5 ± 3.8	93 ± 2.36***



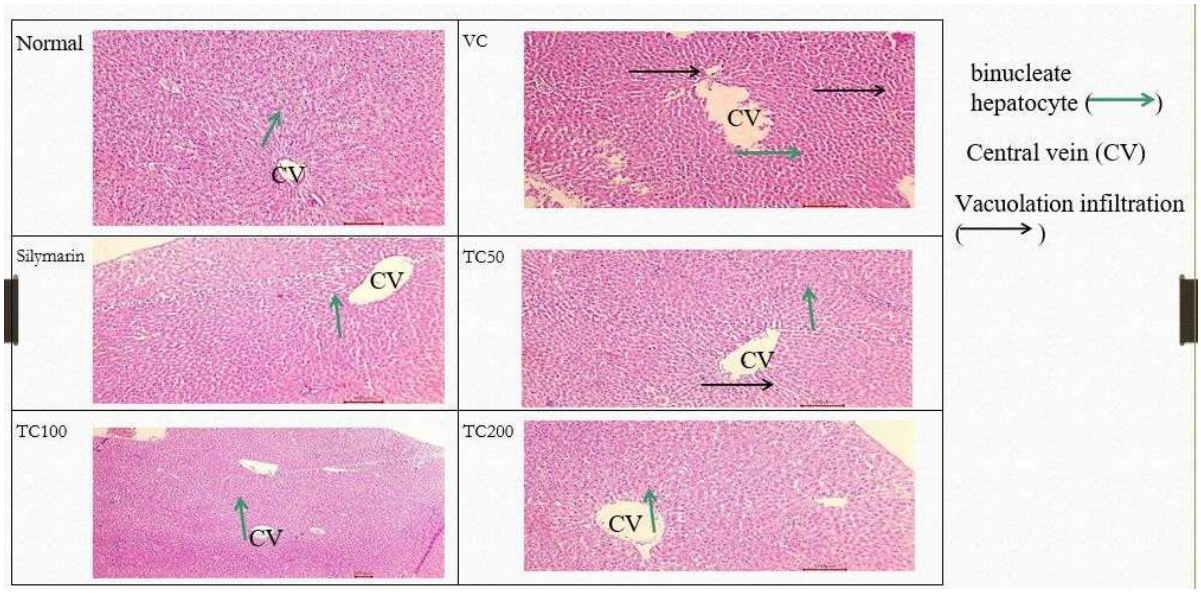
There was significant increase in hepatic IL-6 levels in vehicle control group as compared to normal group. When compared to the vehicle control group, silymarin (50 mg/kg) treatment for 7 days resulted in a significant decrease in IL-6 levels ($P < 0.001$). *Tinospora cordifolia* at 200 mg/kg for 7 days showed a significant decrease in IL-6 levels ($P < 0.001$). *Tinospora cordifolia* at 50 mg/kg and 100 mg/kg did not produce any significant reduction in hepatic IL-6 levels after 28 days of treatment when compared to the vehicle control group.

Effect of Tinospora cordifolia on Thioacetamide-induced alteration in hepatic NO level

Parameter	Hepatic nitric oxide (µg/ml) - Mean ± SEM					
	Normal	Vehicle Control	Silymarin (50 mg/kg)	TC (50 mg/kg)	TC (100 mg/kg)	TC (200 mg/kg)
Nitric oxide (µg/ml)	106.70 ± 1.05	251.40 ± 1.54###	131.0 ± 1.09***	246.9 ± 0.85	219.0 ± 1.87**	176.6 ± 1.78***



There was significant increase in hepatic NO levels in vehicle control group as compared to normal group. When compared to the vehicle control group, silymarin (50 mg/kg) treatment for 7 days resulted in a significant decrease in NO levels ($P < 0.001$). *Tinospora cordifolia* at 200 mg/kg for 7 days showed a significant decrease in both MDA and NO levels ($P < 0.001$). *Tinospora cordifolia* at 50 mg/kg and 100 mg/kg did not produce any significant reduction in hepatic NO levels after 8 days of treatment when compared to the vehicle control group.



Histopathological scoring

Group	Vesicular Fat	Inflammatory infiltration	Plasma cells	Congestion	Edema	Vacuolization	Pyknosis	Necrosis
Normal	+	0	0	+	0	+	0	0
Vehicle Control	++++	++++	++++	++++	+++ +	+ + + +	+++	++++
Silymarin (25 mg/kg)	+	++	++	++	+	+	0	+
Tinospora cordifolia (50 mg/kg)	+++	++	++	++	++	+ +	++	++
Tinospora cordifolia (100 mg/kg)	++	++	++	+++	+	+ +	++	++
Tinospora cordifolia (200 mg/kg)	+	0	0	++	0	+	0	+

Discussion:

The present study demonstrated that the selected herbal extract possesses significant hepatoprotective activity against thioacetamide (TAA)-induced liver injury in experimental animals. TAA-induced hepatotoxicity was characterized by elevated serum liver enzymes (ALT, AST, and ALP), reduced total protein and albumin levels, oxidative stress, and marked histopathological alterations, including hepatocellular degeneration, necrosis, inflammatory cell infiltration, and congestion. Treatment with the herbal extract significantly ameliorated these biochemical and histological changes, indicating restoration of liver function and preservation of hepatic architecture. The hepatoprotective effect is likely mediated through multiple mechanisms, including scavenging of reactive oxygen species, inhibition of lipid peroxidation, enhancement of endogenous antioxidant defenses such as superoxide dismutase (SOD), catalase (CAT), and reduced glutathione (GSH), suppression of inflammatory mediators, stabilization of hepatocyte membranes, and promotion of liver cell regeneration. These beneficial effects are attributed to the presence of bioactive phytochemicals, including flavonoids, phenolic compounds, tannins, and other natural antioxidants. Overall, the findings support the therapeutic potential of the herbal extract as a natural hepatoprotective agent for the management of chemically induced liver injury and provide a scientific basis for further studies aimed at identifying its active constituents, elucidating their molecular mechanisms, and evaluating their long-term safety and clinical efficacy.

Conclusion:

The results of the present investigation demonstrate that the selected herbal extract possesses significant hepatoprotective activity against thioacetamide-induced liver injury. The extract effectively reduced hepatic damage by improving serum biochemical markers and preserving the normal histological architecture of the liver. The hepatoprotective effect is most likely mediated through antioxidant, anti-inflammatory, and membrane-stabilizing mechanisms, which minimize oxidative stress and prevent hepatocellular damage. Overall, the study concludes that the herbal extract has considerable potential as a natural hepatoprotective agent. These findings provide scientific evidence supporting its traditional use in the treatment of liver disorders. However, further investigations are required to isolate and characterize the active phytoconstituents, elucidate their precise molecular mechanisms, evaluate long-term safety, and conduct clinical studies to confirm efficacy in humans. Such studies may contribute to the development of safe, effective, and affordable plant-based therapies for the prevention and treatment of liver diseases.

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