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RESEARCH ARTICLE

Assessment of Hepatoprotective Activity of Shirishadi Yoga in an Experimental Model of Acetaminophen-Induced Hepatotoxicity.

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Abstract: ***Background***: Acetaminophen-induced hepatotoxicity represents a significant global health concern. Shirishadi Yoga, a traditional Ayurvedic formulation containing herbs with Vishaghna (anti-toxic) properties, offers potential therapeutic benefits for drug-induced liver injury, yet systematic evaluation remains limited.***Objective:*** To assess the hepatoprotective effect of Shirishadi Yoga and compare its efficacy with silymarin as a reference standard against acetaminophen-induced hepatotoxicity in Sprague-Dawley rats.***Methods:*** Thirty-six male Sprague-Dawley rats were randomly divided into six groups (n=6): normal control, acetaminophen-induced hepatotoxicity (500mg/kg i.p.), silymarin treatment (100mg/kg twice daily), and three Shirishadi Yoga dose groups (low dose: 0.864ml/200g, normal dose: 1.728ml/200g, high dose: 2.592ml/200g body weight). Treatment and hepatotoxicity induction were administered simultaneously for six consecutive days. Biochemical parameters and histopathological examination were evaluated 24 hours post-treatment.***Results:*** Shirishadi Yoga demonstrated significant dose-dependent hepatoprotective effects. The normal dose group showed superior efficacy compared to silymarin in multiple parameters. SGOT levels were reduced from 186.6±5.785 IU/L (disease control) to 166.6±5.785 IU/L, SGPT from 148.83±8.91 IU/L to 118.96±3.00 IU/L, and ALP from 290±33.8 IU/L to 132.5±22.25 IU/L. Histopathological analysis revealed preserved hepatic architecture with minimal inflammatory infiltration.***Conclusion:*** Shirishadi Yoga exhibits potent hepatoprotective activity against acetaminophen-induced hepatotoxicity through its Vishaghna properties, with the normal dose demonstrating superior efficacy to silymarin in acetaminophen-induced liver damage.

Keywords: Shirishadi Yoga, hepatoprotective, acetaminophen, hepatotoxicity, Ayurvedic medicine, Vishaghna, Sprague-Dawley rats .

INTRODUCTION

Drug-induced liver injury (DILI) represents a major clinical challenge worldwide, with acetaminophen (APAP) overdose accounting for approximately 50% of all acute liver failure cases in developed countries (1). Acetaminophen hepatotoxicity involves the formation of N-acetyl-p-benzoquinone imine (NAPQI), a reactive metabolite produced through cytochrome P450 enzymes. Under normal therapeutic conditions, NAPQI is efficiently detoxified through glutathione conjugation. However, in overdose situations, glutathione depletion leads to NAPQI accumulation, causing severe liver damage (2)

The liver serves as a central hub for metabolism and detoxification, converting carbohydrates, proteins, and fats into energy, regulating blood glucose levels, synthesizing essential proteins including albumin and clotting factors, and producing bile for fat digestion. The hepatic detoxification process occurs through two enzymatic phases: Phase I reactions increase toxin reactivity, while Phase II reactions enhance water solubility for excretion (3)

Traditional Ayurvedic medicine provides valuable insights into hepatotoxicity through the concept of Gara Visha (concocted poison), defined as synthetic toxins resulting from mixing various inanimate and animate poisonous substances. Modern lifestyle factors including food adulteration, incompatible food combinations, and pharmaceutical agents exemplify contemporary manifestations of Gara Visha (4). These toxins, characterized as "Kalantaravipaki" due to their delayed manifestations, ultimately result in Srotorodha (channel obstruction) and Agnimandya (impaired digestive fire), disrupting Dhatuparinama (tissue metabolism) (5)

Agada Tantra, the toxicological branch of Ashtanga Ayurveda, addresses comprehensive toxicological management. Within this framework, acetaminophen-induced hepatotoxicity can be conceptually understood as a manifestation of Gara Visha, affecting Yakrita and Pliha (liver and spleen), which represent the Moolasthana (primary sites) of Raktavaha Srotas (circulatory channels) and control numerous Paittika and enzymatic activities (6)
Shirishadi Yoga represents a classical Ayurvedic formulation containing herbs with established Vishaghna properties documented in various Ayurvedic Samhitas.

This polyherbal preparation comprises Albizia lebbeck (Shirisha), Curcuma longa (Haridra), Berberis lycium (Daruharidra), Azadirachta indica (Nimba), and Rubia cordifolia (Manjishtha) in decoction form (7). Individual components have demonstrated hepatoprotective and antioxidant effects in previous studies, yet comprehensive evaluation of the complete formulation against acetaminophen-induced hepatotoxicity remains limited (8-10)

The present study aims to systematically assess the hepatoprotective efficacy of Shirishadi Yoga and compare its therapeutic potential with silymarin, the established hepatoprotective reference standard, using a well-characterized Sprague-Dawley rat model of acetaminophen-induced hepatotoxicity.

Aims and Objectives

- To assess the hepatoprotective effect of Shirishadi Yoga against acetaminophen-induced hepatotoxicity.
- To compare the hepatoprotective efficacy of Shirishadi Yoga with silymarin as a reference standard inacetaminophen-induced hepatotoxicity

MATERIALS AND METHODS

Materials

1. Test Drug: Shirishadi Yoga
2. Standard Drug: Silymarin
3. Animals: 36 male Sprague-Dawley (SD) rats
4. Toxicant: Acetaminophen

Test Drug: Shirishadi Yoga

Shirishadi Yoga is a traditional Ayurvedic formulation containing herbs with established Vishaghna properties documented in classical Ayurvedic Samhitas. The formulation includes Shirisha (Ch. Su. 4/16), Haridra (Ch. Su. 4/16), Daruharidra (Raj Nighantu Pippalyadi Varg 202), Nimba (Kaidev Nighantu Aushada Varga 883), and Manjishtha (Ch. Su. 4/16) in combined decoction form.

Table 1: Composition of Shirishadi Yoga

Ingredient	Scientific Name	Family	Part Used
Shirisha	Albizia lebbeck Benth.	Leguminosae	Bark
Haridra	Curcuma longa Linn.	Zingiberaceae	Rhizome
Daruharidra	Berberis lycium DC.	Berberidaceae	Root
Manjishtha	Rubia cordifolia Linn.	Rubiaceae	Root
Nimba	Azadirachta indica A. Juss.	Meliaceae	Leaf

Ingredients Of Shirishadi Yoga

Shirisha

Haridra

Daruharidra

Manjishtha

Nimba

Preparation of Shirishadi Yoga
Following classical Ayurvedic principles outlined in Sharangadhara Samhita, where no specific proportions are mentioned, all ingredients were taken in equal quantities as per the directive: "where no proportions are mentioned, all contents of yoga are to be taken in the same proportion" [(11).] Individual plant materials were separately powdered, and fine powders were thoroughly mixed to form a homogeneous mixture.

Shirishadi Yoga Kwatha Preparation: Fine powder of Shirishadi Yoga was processed according to classical methodology. One Pala of Dravya Churna was mixed with sixteen parts of water and boiled over Mridu Agni (gentle heat) until the liquid volume reduced to one-eighth part [(12).]

Standard Drug and Toxicant

Silymarin: Administered at 100mg/kg body weight, mixed in dimethyl sulfoxide (DMSO).[(13)]

Acetaminophen: Administered at 500mg/kg body weight intraperitoneally.[(14)]

Dose Calculation
Shirishadi Yoga Kwatha Dose Calculation:
Classical dose according to Sharangadhara Samhita: 2 Pala (96 ml)
Human dose of Shirishadi Yoga = 96 ml
Rat conversion factor (200g) = 0.0183
Standard rat dose = 96 ml × 0.018 = 1.728 ml/200g body weight (8.65 ml/kg body weight)
Dose Groups:

- **Low Dose:** 1 Pala equivalent = 0.864ml/200g body weight
- **Normal Dose:** 2 Pala equivalent = 1.728ml/200g body weight
- **High Dose:** 3 Pala equivalent = 2.592ml/200g body weight

Animals and Experimental Design

Thirty-six healthy male Sprague-Dawley rats were housed under standard laboratory conditions with access to standard pellet diet and water ad libitum. Experimental protocol was approved by the Institutional Animal Ethics Committee of CPCSEA. All the animals used in this study received human care in compliance with CPCSEA guidelines.

Table 2: Experimental Protocol

Group	Treatment	Number of Animals
Group 1	Normal Control	6
Group 2	Acetaminophen-induced Hepatotoxicity	6
Group 3	Acetaminophen + Silymarin (100mg/kg, twice daily)	6
Group 4	Acetaminophen + Shirishadi Yoga (Low Dose: 0.864ml/200g)	6
Group 5	Acetaminophen + Shirishadi Yoga (Normal Dose: 1.728ml/200g)	6
Group 6	Acetaminophen + Shirishadi Yoga (High Dose: 2.592ml/200g)	6

Administration Protocol

Route of Administration:

- *Shirishadi Yoga Kwatha* and silymarin: Oral administration using rat feeding tubes attached to syringes
- Acetaminophen: Intraperitoneal injection

Dosing Schedule: Test drugs, reference standard, and toxicant were administered simultaneously between 10:00-11:00 AM and 17:00-18:00 PM for 6 consecutive days. Both treatment and hepatotoxicity induction occurred concurrently in the acetaminophen-induced hepatotoxicity model.

Sample Collection and Processing

Twenty-four hours after the final treatment, animals were fasted overnight and sacrificed by CO_2 hypoxia followed by cervical dislocation. Blood samples were collected via retro-orbital puncture for biochemical evaluation. Samples were collected in microcentrifuge tubes, maintained at room temperature for 2 hours, then centrifuged at 5000 rpm for 10 minutes. Serum was aspirated and frozen at -80°C until analysis.

Liver tissues were carefully dissected, cleaned of extraneous tissues, blotted to remove blood stains, and weighed. Representative portions were preserved in 10% formalin solution for histopathological processing.

Biochemical Analysis

Biochemical parameters were estimated using an automated biochemical analyzer. The following liver function markers were assessed:

- SGOT (Serum Glutamic-Oxaloacetic Transaminase)
- SGPT (Serum Glutamic-Pyruvic Transaminase)
- Alkaline Phosphatase (ALP)
- Total Bilirubin
- Direct Bilirubin
- Total Protein
- Albumin

Histopathological Examination

Liver tissue samples were processed through standard histopathological techniques. Fixed tissues were processed to create paraffin blocks, sectioned using a microtome, and stained with haematoxylin and eosin. Histological analysis was performed under light microscopy at magnifications of 100x-400x.

Statistical Analysis

Data are expressed as mean ± standard deviation (SD). Statistical evaluation was performed using one-way ANOVA followed by Tukey's Multiple Comparison Test (post hoc analysis). All groups were compared with normal control, disease control, and silymarin standard groups using Sigma Stat 3 software package. Multiple comparison tests were performed only when p-values from one-way ANOVA were less than 0.05. Statistical significance was set at $p<0.05$

RESULTS

General Observations

No mortality was observed in any experimental group during the study period. No adverse effects were documented among the animals in terms of behavioral changes or clinical symptoms during the study duration.

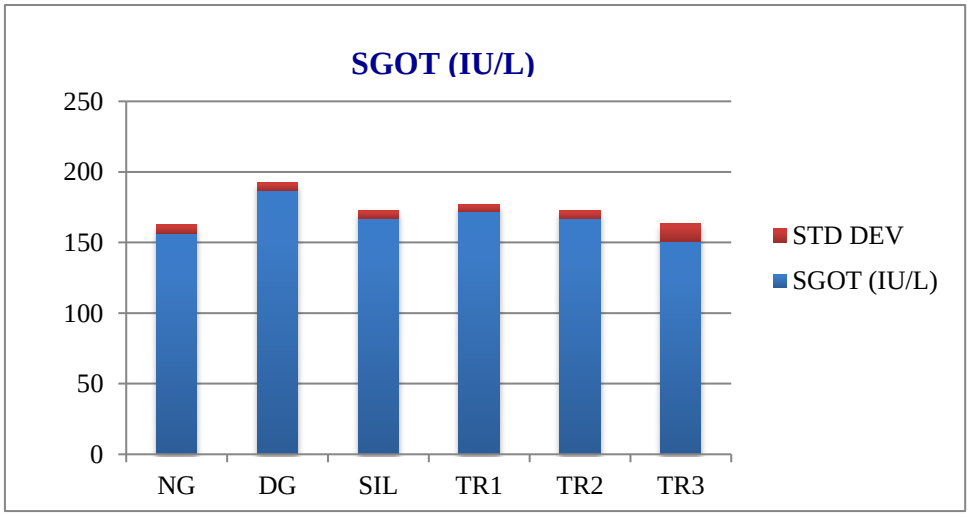
Biochemical Parameters

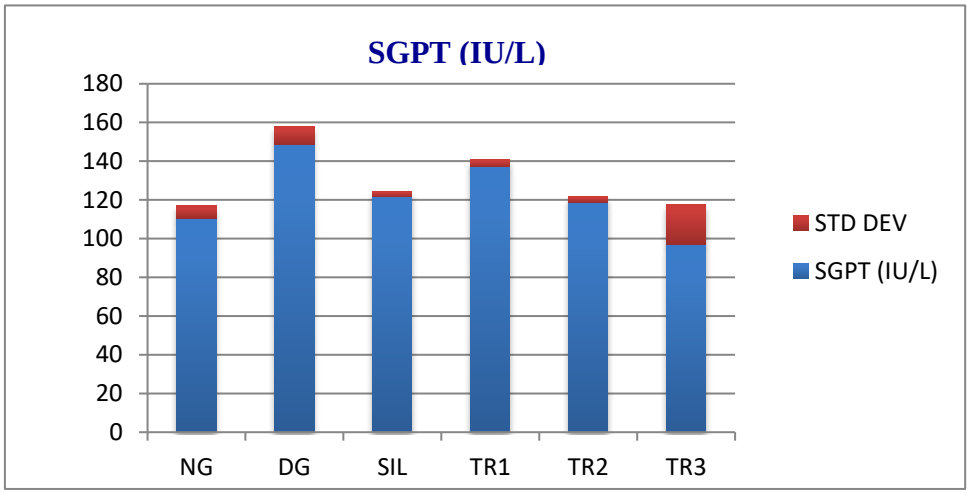
Table 3: Effect of Shirishadi Yoga on Biochemical Parameters

Group	SGOT (IU/L)	SGPT (IU/L)	Total Bilirubin (mg/dL)	Direct Bilirubin (mg/dL)	ALP (IU/L)	Albumin (g/L)
Normal Control	156.6±5.785	110.56±6.33	0.07±0.02	0.09±0.03	168.4±46.83	2.77±0.807
Acetaminophen Control	186.6±5.785	148.83±8.91	0.13±0.02	0.68±0.22	290±33.8	4.81±0.508
Shirishadi Yoga (Low Dose)	171.6±5.574	137.11±3.91	0.076±0.02	0.15±0.03	153.3±24.7	2.6±0.22
Shirishadi Yoga (Normal Dose)	166.6±5.785	118.96±3.00	0.073±0.02	0.10±0.04	132.5±22.25	2.87±0.24
Shirishadi Yoga (High Dose)	151.0±12.744	96.88±20.72	0.08±0.01	0.10±0.01	163.0±46.16	2.83±0.15
Silymarin	166.8±5.913	121.61±2.92	0.09±0.03	0.12±0.04	215.8±132.9	3.19±0.49

SGOT and SGPT Analysis

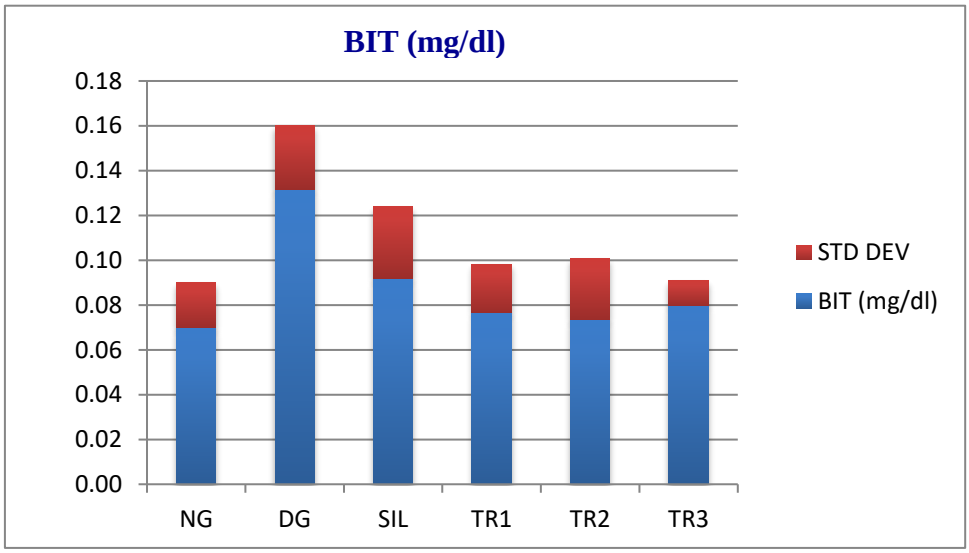
Acetaminophen administration significantly elevated serum transaminase levels, indicating hepatocellular damage. The disease control group showed significant increases in both SGOT (186.6±5.785 IU/L) and SGPT (148.83±8.91 IU/L) levels compared to normal controls. All *Shirishadi Yoga* treatment groups demonstrated dose-dependent protection, with the normal dose showing optimal hepatoprotective effects. Notably, *Shirishadi Yoga* normal dose demonstrated values nearly equivalent to the silymarin standard group, while the high dose group exhibited the most pronounced reduction in both transaminase levels.

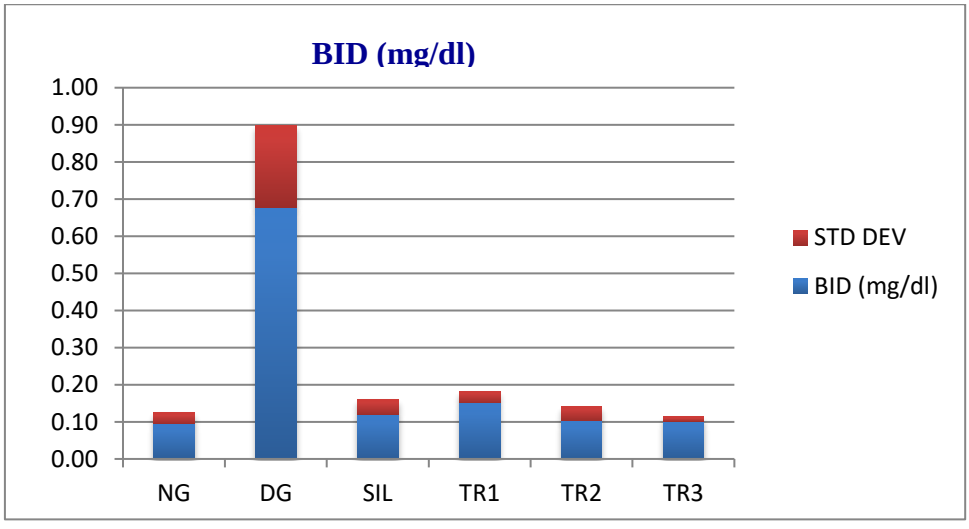




Bilirubin Analysis

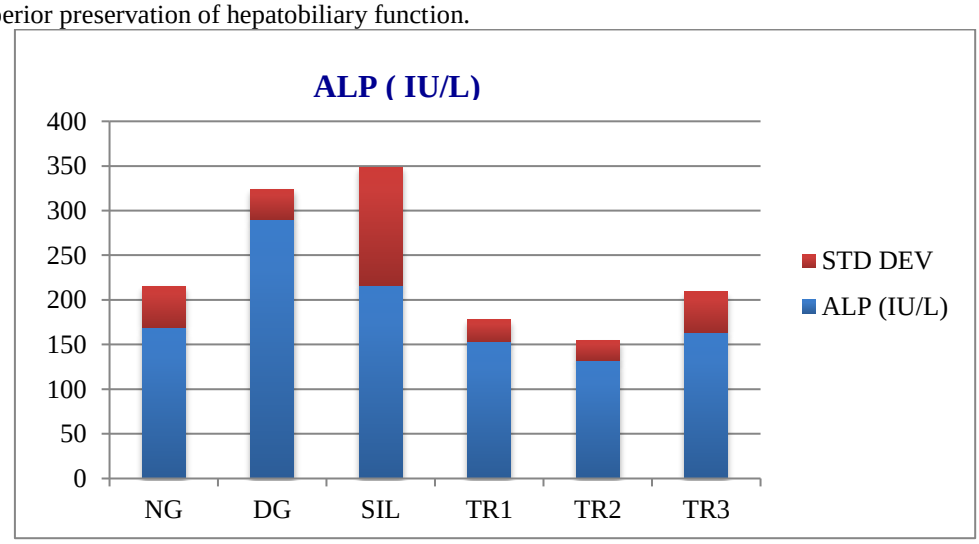
Acetaminophen toxicity resulted in significant elevation of both total (0.13±0.02 mg/dL) and direct bilirubin (0.68±0.22 mg/dL) levels compared to normal controls. All *Shirishadi Yoga* treatment groups effectively normalized bilirubin levels, with more pronounced effects observed compared to silymarin treatment. The test groups showed significant decreases in bilirubin values, while the silymarin standard group showed no evident decrease in total bilirubin levels.





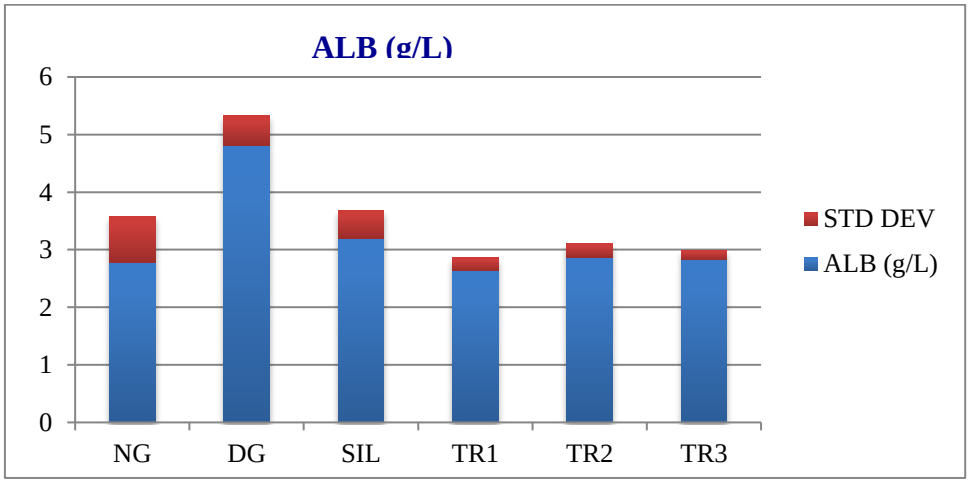
Alkaline Phosphatase Analysis

ALP levels were significantly elevated in the acetaminophen control group (290±33.8 IU/L), indicating hepatobiliary dysfunction. All *Shirishadi Yoga* dose groups and silymarin demonstrated decreased ALP values. Remarkably, *Shirishadi Yoga* normal dose (132.5±22.25 IU/L) showed more evident reduction compared to silymarin (215.8±132.9 IU/L), suggesting superior preservation of hepatobiliary function.



Protein Metabolism

Albumin levels were significantly elevated in the acetaminophen group (4.81±0.508 g/L) compared to normal controls (2.77±0.807 g/L). All Shirishadi Yoga dose groups effectively normalized albumin levels, with silymarin showing comparatively higher values among treated groups.



Histopathological Findings

Histopathology, derived from Greek words "histos" (tissue), "pathos" (suffering), and "logia" (study), represents the microscopic examination of tissues to study disease manifestations (15). Toxic chemicals can cause significant bodily harm, impacting various organs and systems, leading to cellular damage, metabolic dysfunction, and increased disease risks including cancer, neurological disorders, and liver diseases.

The liver maintains crucial roles in metabolism and detoxification as a central processing hub for nutrients and toxin neutralization. Acetaminophen hepatotoxicity involves predictable pathways within hepatocytes but presents variable clinical manifestations, making it a global concern requiring effective therapeutic interventions.

Normal Control Group

Liver sections revealed normal hepatic architecture with well-organized hepatocytes and normal vascular tissue in hepatic parenchyma without inflammatory or degenerative pathological changes.

Acetaminophen Control Group

Moderate degenerative changes were observed in hepatoparenchyma with cellular swelling. Hepatic necrotic changes with

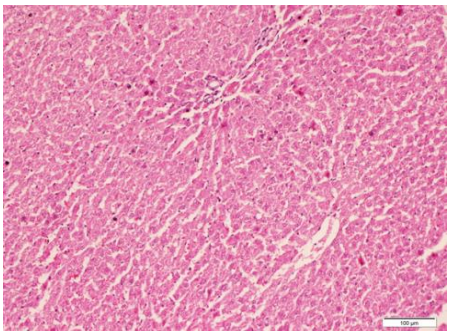
nuclear loss were noted, along with focal vascular congestion and hemorrhages in hepatic parenchyma.

Shirishadi Yoga Treatment Groups

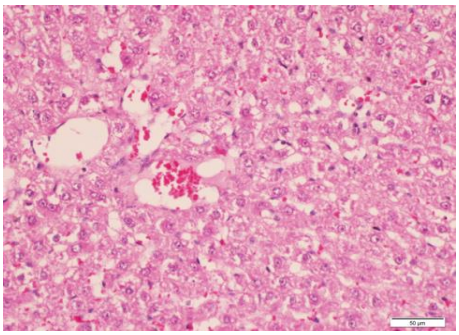
- **Low Dose:** Normal portal triads and central venous system with preserved hepatocytes. Sinusoidal space cells showed mild increase without inflammatory changes.
- **Normal Dose:** Normal portal triads and hepatic veins with normal hepatocyte structure. Minimal inflammatory changes were present.
- **High Dose:** Excellent preservation of hepatic architecture with normal hepatocytes, absence of inflammation, and no cellular swelling.

Silymarin Group

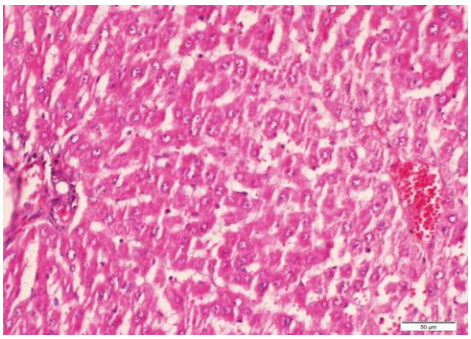
Liver sections showed residual injury markers with hepatocytes not optimally arranged in radial patterns. Mild inflammatory cell infiltrations were observed.



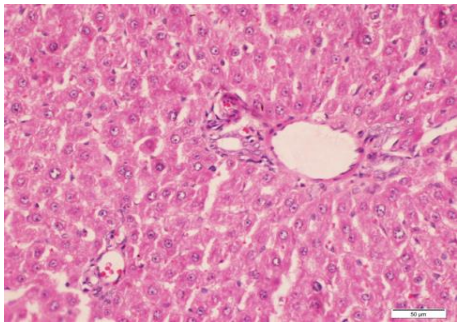
Normal Control



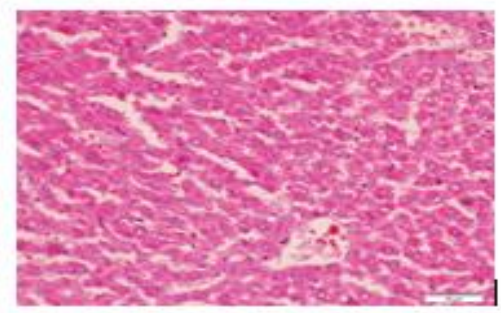
Disease Group



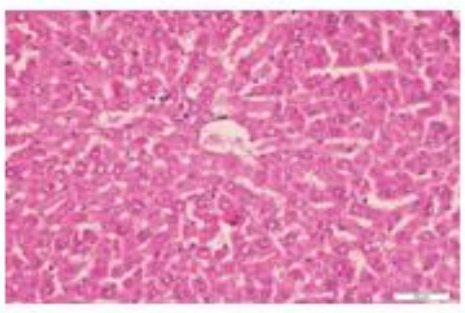
Silymarin



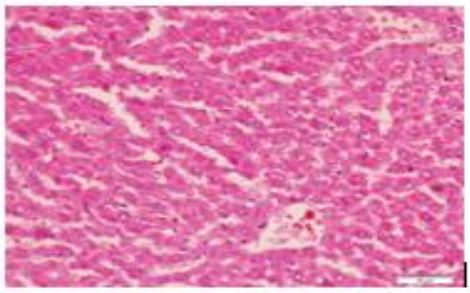
Shirishadi Yoga (Low Dose)



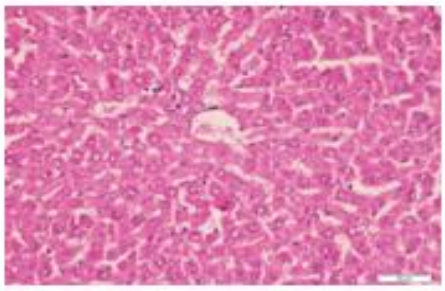
Shirishadi Yoga (Normal Dose)



Shirishadi Yoga (High Dose)



Shirishadi Yoga (Normal Dose)



Shirishadi Yoga (High Dose)

DISCUSSION

Ayurvedic Pharmacodynamics

The hepatoprotective efficacy of Shirishadi Yoga can be attributed to the synergistic effects of its constituent herbs, each contributing specific Ayurvedic properties:

Table 4: Pharmacodynamic Properties of Shirishadi Yoga Constituents

Drug	Rasa	Guna	Virya	Vipaka	Karma
Shirisha	Tikta, Katu, Kashaya	Laghu	Anusna	Katu	Vishaghna, Tridoshara, Shothahra
Haridra	Tikta, Katu	Laghu, Ruksha	Ushna	Katu	Kushthaghna, Vishaghna, Krimighna
Daruharidra	Tikta, Kashaya	Laghu, Ruksha	Ushna	Katu	Kandughna, Vishahara, Shophahara
Manjishtha	Tikta, Kashaya, Madhura	Guru, Ruksha	Ushna	Katu	Shothahara, Raktashodhaka, Rasayana
Nimba	Tikta, Kashaya	Laghu	Shita	Katu	Kaphapittahara, Vishahara, Krimighna

The collective formulation demonstrates predominant Katu, Tikta, Kashaya, and Madhura rasa with Katu Vipaka, Ushna Virya, and Laghu Ruksha Teekshna Guna, contributing to comprehensive anti-toxic properties including Vishaghna, Shothaghna, Krimighna, Deepana, Pachana, Vranahara, Garanashaka, and Raktashodhaka actions [16].

Physicochemical Evaluation

Physicochemical assessment plays an important role in determining the quality, purity, and authenticity of medicinal plant materials. The evaluation of physical and chemical parameters helps establish standardization criteria and ensures the reliability of herbal formulations. In the present study, various physicochemical parameters, including foreign matter, ash value, acid-insoluble ash, water-soluble extractive, moisture content, pH, and percentage loss on drying,wereanalyzed. These investigations were performed according to established guidelines recommended by the Government of India and the World Health Organization (WHO).

Phytochemical Analysis

The methanolic extract of Shirishadi Yoga was subjected to preliminary phytochemical investigation, which revealed the presence of alkaloids, tannins, steroids, flavonoids, polyphenols, saponins, glycosides, resins, phenolic compounds, and quinones. These phytoconstituents are known to possess a wide range of biological activities and may collectively contribute to the therapeutic efficacy of the formulation. Among them, polyphenols are particularly recognized for their strong antioxidant potential and have also been reported to exhibit antimicrobial, anti-inflammatory, antiviral, and chemoprotective properties. The synergistic action of these phytochemicals may be responsible for the observed pharmacological effects of Shirishadi Yoga.

Molecular Mechanisms

Literature reveals that various ingredients of Shirishadi Yoga possess antioxidant, immunomodulatory, anti-inflammatory, anti-ulcerative, and hepatoprotective properties. Shirishadi Yoga may exert hepatoprotective effects through multiple mechanisms:

1. **Prostaglandin Synthesis Inhibition:** Anti-inflammatory effects may prevent prostaglandin-mediated inflammatory cascades
2. **CYP450 Suppression:** Suppression of cytochrome P450 enzymes, particularly those involved in NAPQI production

3. **Glutathione Enhancement:** Increased synthesis of glutathione (GSH), providing enhanced cellular protection
4. These synergistic actions contribute to the overall hepatoprotective activity of Shirishadi Yoga ([17-19]).

Clinical Significance

The study results demonstrate that Shirishadi Yoga minimized drug-induced liver damage across all dose groups, with the normal dose showing superior efficacy compared to both low and high doses, and remarkably, superior performance compared to silymarin. Liver function test investigations revealed that Shirishadi Yoga normal dose effectively reversed hepatotoxicity markers.

CONCLUSION

After comprehensive evaluation of observations, statistical analysis, and literature review, the following conclusions were drawn:

- The study demonstrated that both Shirishadi Yoga and silymarin possess hepatoprotective and antioxidant activities against acetaminophen-induced hepatotoxicity
- Shirishadi Yoga effectively minimized drug-induced liver damage, with the normal dose proving more effective than both low and high doses
- Laboratory investigations confirmed that Shirishadi Yoga normal dose significantly reduced hepatotoxicity markers compared to silymarin
- Histopathological examination revealed that Shirishadi Yoga minimized inflammation, congestion, and necrosis of hepatocytes and associated blood vessels
- No adverse effects were observed among the experimental animals during the study period
- Statistical analysis conclusively demonstrated that the hepatoprotective activity of Shirishadi Yoga normal dose was superior to the standard drug silymarin in acetaminophen-induced liver damage
- These findings validate the traditional therapeutic use of Shirishadi Yoga for liver disorders and support its potential development as an effective hepatoprotective agent. The superior performance compared to silymarin suggests significant clinical potential for managing drug-induced hepatotoxicity through its comprehensive Vishaghna properties.

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Histopathological examination confirmed that Shirishadi Yoga minimized inflammation, congestion, and necrosis of hepatocytes and associated blood vessels. These findings indicate that Shirishadi Yoga is effective in both preventive and curative aspects of drug-induced liver damage.

Comparative Analysis with Silymarin

Statistical analysis clearly demonstrated that the hepatoprotective activity of Shirishadi Yoga normal dose was more effective than the standard drug silymarin in acetaminophen-induced liver damage. This superior efficacy suggests that the polyherbal formulation may offer broader therapeutic mechanisms compared to single-component treatments

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