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Hepatoprotective Activity Of Leaf Extracts From Tamarix Dioica Against Paracetamol Induced Hepatotoxicity In Swiss Albino Mices: A Systemic Review

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Abstract: -

Paracetamol (acetaminophen) is widely used as an analgesic and antipyretic drug, but overdose can cause severe hepatotoxicity due to the formation of a reactive metabolite, N-acetyl-p-benzoquinone imine (NAPQI), leading to oxidative stress and liver injury. The increasing prevalence of drug-induced liver damage has intensified the search for hepatoprotective agents from natural sources. Tamarix dioica, a halophytic shrub traditionally used in folk medicine, has shown promising hepatoprotective potential in recent experimental studies, particularly in murine models. This review summarizes and critically evaluates existing experimental data on the hepatoprotective effects of Tamarix dioica leaf extracts, with a focus on paracetamol-induced hepatotoxicity in Swiss albino mice. Mechanisms of action are explored, including antioxidant activity, enzyme normalization, and histopathological recovery. This review highlights Tamarix dioica as a potential natural therapeutic candidate for the prevention and treatment of drug-induced liver injury, warranting further investigation through clinical studies.

1. INTRODUCTION: -

Drug-induced liver injury (DILI) represents a major clinical challenge and is a leading cause of acute liver failure, especially in Western countries. It accounts for approximately 13% of cases of acute liver failure, with a significant number being attributed to over-the-counter medications such as acetaminophen (paracetamol) [1]. Hepatotoxicity may result from direct hepatocyte damage, mitochondrial dysfunction, oxidative stress, or immune-mediated responses, depending on the drug's properties and metabolic profile [2]. DILI is generally categorized into **intrinsic (predictable and dose-dependent)** and **idiosyncratic (unpredictable and dose-independent)** reactions. Paracetamol-induced liver toxicity falls under the intrinsic category and serves as a well-established model for hepatotoxicity in both clinical and experimental settings [3].

Paracetamol is widely used for its analgesic and antipyretic effects, but at supratherapeutic doses, it can lead to severe hepatotoxicity. The primary pathway of paracetamol metabolism involves conjugation with glucuronide and sulfate; however, a small proportion is metabolized by cytochrome P450 enzymes (mainly CYP2E1) to form **N-acetyl-p-benzoquinone imine (NAPQI)**, a highly reactive and toxic intermediate [4]. Under normal conditions, NAPQI is rapidly detoxified by conjugation with **glutathione (GSH)**. In overdose situations, glutathione stores are depleted, leading to accumulation of NAPQI, which binds covalently to cellular macromolecules, causes oxidative stress, and leads to mitochondrial dysfunction,

lipid peroxidation, and ultimately hepatocyte necrosis [5]. Histological features typically include centrilobular (zone 3) necrosis in the liver [6].

Given the limitations and potential side effects of synthetic hepatoprotective drugs such as **N-acetylcysteine (NAC)**, attention has increasingly turned toward **natural compounds** derived from plants and other natural sources for their liver-protective properties. These agents often exhibit **antioxidant**, **anti-inflammatory**, and **anti-apoptotic** activities, thereby attenuating hepatotoxic effects through multiple pathways [7]. For instance, plant-derived polyphenols, flavonoids, and terpenoids have shown promising hepatoprotective effects in various preclinical models of liver injury, including paracetamol-induced hepatotoxicity [8]. Exploring natural products not only provides alternative therapeutic options but may also lead to the development of novel pharmacological agents with improved safety profiles.

2. Botanical Description and Traditional Uses of *Tamarix dioica*

Taxonomy and Morphology

Tamarix dioica, commonly known as **jhau**, **lal jhau**, or **tamarisk**, is a halophytic shrub or small tree that belongs to the family **Tamaricaceae**. This species is native to arid and semi-arid regions of South Asia, particularly India, Pakistan, and Bangladesh, and is commonly found in riverine and saline environments [9]. It is one of the few species in its genus that is dioecious, meaning that male and female flowers grow on separate plants.

Taxonomic Classification:

- **Kingdom:** Plantae
- **Clade:** Angiosperms
- **Order:** Caryophyllales
- **Family:** Tamaricaceae
- **Genus:** *Tamarix*
- **Species:** *Tamarix dioica* Roxb. ex Roth

Morphologically, *T. dioica* is a woody plant reaching up to 3–6 meters in height. It has **slender, reddish-brown branches** with **minute, scale-like leaves** arranged alternately. The leaves are succulent and help the plant conserve water in saline conditions. The flowers are small, pink to reddish, and borne in slender spikes. These adaptations make it highly tolerant of saline, alkaline, and nutrient-poor soils [10].

Ethnomedicinal Relevance

In traditional medicine systems, including **Ayurveda** and **Unani**, *Tamarix dioica* has been used for its therapeutic potential in treating a variety of ailments. Various parts of the plant—particularly the **leaves, bark, and roots**—are used in indigenous practices for their **astringent**, **diuretic**, **antipyretic**, and **anti-inflammatory** properties [11].

Some traditional uses include:

- **Treatment of liver disorders:** Decoctions of the bark and leaves have been traditionally used to manage jaundice and other hepatic dysfunctions [12].
- **Gastrointestinal issues:** It is used for treating diarrhea, dysentery, and indigestion.
- **Wound healing and skin infections:** Topical applications of the paste or extracts are common in folk medicine.
- **Anti-inflammatory and febrifuge:** The plant has been used to reduce fever and inflammation.

These ethnomedicinal claims have prompted scientific interest in its potential pharmacological activities, particularly its hepatoprotective and antioxidant properties.

Phytochemical Profile:-

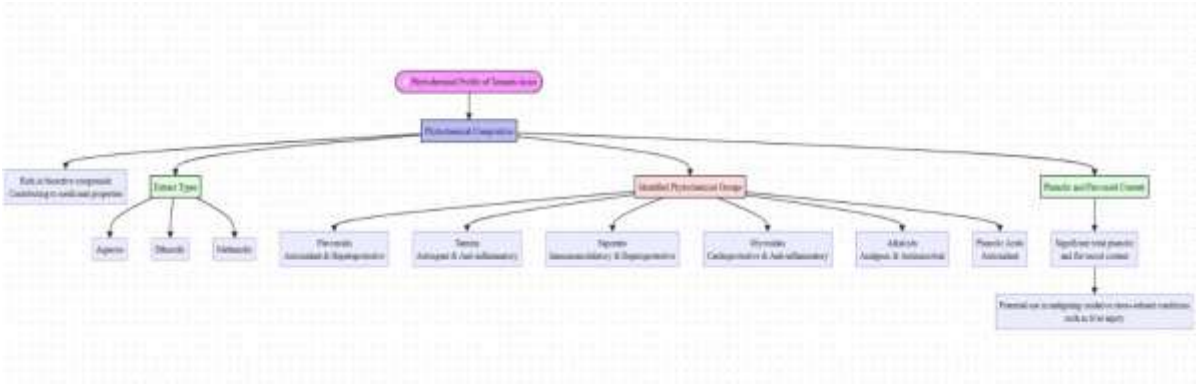
Preliminary phytochemical screening of *Tamarix dioica* has revealed a rich composition of **bioactive compounds** that may contribute to its medicinal properties [1]. The major phytochemical groups identified in various extracts (aqueous, ethanolic, methanolic) include:

- **Flavonoids** – e.g., quercetin and its derivatives, known for antioxidant and hepatoprotective effects [13].
- **Tannins** – contributing to astringent and anti-inflammatory properties.
- **Saponins** – known for immunomodulatory and hepatoprotective activities.

- **Glycosides** – which may exhibit cardioprotective and anti-inflammatory properties.
- **Alkaloids** – with reported analgesic and antimicrobial effects.
- **Phenolic acids** – such as gallic acid and ferulic acid, with strong antioxidant properties.

Studies have confirmed the presence of **significant total phenolic content (TPC)** and **total flavonoid content (TFC)**, which are associated with **free radical scavenging activity**, suggesting the potential use of *T. dioica* in mitigating oxidative stress-related conditions such as liver injury [14].

Fig: -1 Preliminary phytochemical screening of *Tamarix dioica*



3. Experimental Models for Studying Hepatotoxicity (*Tamarix dioica*)

Use of Swiss Albino Mice in Hepatoprotective Research:

Swiss albino mice are one of the most commonly used animal models in preclinical studies due to their genetic uniformity, ease of handling, rapid reproduction, and well-characterized physiology. These mice are particularly suitable for toxicological and pharmacological studies, including assessments of hepatoprotective agents [15]. Their metabolic pathways share key similarities with humans, allowing for extrapolation of hepatotoxic effects and protective responses.

In studies assessing the hepatoprotective activity of natural compounds like *Tamarix dioica*, Swiss albino mice serve as an ideal model because:

- They exhibit a **predictable response to hepatotoxins**, especially paracetamol (acetaminophen).
- Their small size and robust nature make them well-suited for repeated dosing and sample collection (e.g., serum liver enzymes, tissue histology).
- Established protocols exist for **dose optimization**, **toxicity monitoring**, and **biochemical evaluation** (e.g., ALT, AST, ALP, bilirubin levels) [16].

In experimental designs evaluating *Tamarix dioica*, mice are typically divided into groups receiving paracetamol alone or in combination with plant extracts. A significant decrease in liver enzymes and improvement in histopathological architecture in the treatment group suggests hepatoprotective activity [17].

Paracetamol-Induced Liver Injury Models:

Paracetamol-induced hepatotoxicity is a **well-established and widely used model** to study drug-induced liver injury and screen potential hepatoprotective agents. This model replicates the oxidative stress and hepatic necrosis observed in clinical overdose cases, providing a reliable system for preclinical research [18].

Mechanism in the model:

- High doses of paracetamol (>150 mg/kg in mice) are administered to induce liver injury.
- The toxic metabolite **NAPQI (N-acetyl-p-benzoquinone imine)** is generated via cytochrome P450 (CYP2E1).
- NAPQI depletes intracellular **glutathione (GSH)** and binds to cellular proteins, resulting in **oxidative stress**, **lipid peroxidation**, and **centrilobular hepatic necrosis** [19].

Key evaluation parameters include:

- **Biochemical markers**: ALT (alanine aminotransferase), AST (aspartate aminotransferase), ALP (alkaline phosphatase), total bilirubin, and GSH levels.

- **Histopathological examination**: Liver sections are stained (e.g., with hematoxylin and eosin) to assess necrosis, inflammation, and hepatocyte degeneration.
- **Oxidative stress assays**: Levels of malondialdehyde (MDA), superoxide dismutase (SOD), and catalase are also assessed.

When *Tamarix dioica* extracts are administered prior to or after paracetamol exposure in this model, studies have shown a **reduction in liver enzyme levels**, improved **antioxidant enzyme activity**, and **restoration of normal liver architecture**, indicating its **hepatoprotective potential** [20].

4. Hepatoprotective Effects of *Tamarix dioica* Leaf Extracts

In Vivo Studies Using Paracetamol-Induced Models:-

Several **in vivo experimental studies** have evaluated the hepatoprotective potential of *Tamarix dioica* leaf extracts using **paracetamol-induced liver injury models** in rodents, particularly rats and mice. In these models, hepatotoxicity is induced by administering a single high dose of paracetamol (typically 300–500 mg/kg in rats or 150–250 mg/kg in mice), followed by treatment with plant extracts [21].

One significant study by Gupta et al. (2017) demonstrated that methanolic leaf extracts of *T. dioica* significantly attenuated hepatic damage caused by paracetamol. The extract showed marked improvement in liver enzyme profiles, antioxidant enzyme activity, and histological architecture of the liver compared to the toxic control group [22].

The hepatoprotective effect is attributed primarily to the **antioxidant constituents** in the extract—mainly flavonoids and phenolic compounds—which combat oxidative stress, restore glutathione levels, and prevent cellular damage.

Dose-Dependent Effects and Administration Routes:-

The hepatoprotective efficacy of *Tamarix dioica* is often **dose-dependent**, with higher doses offering greater protection up to a threshold limit. Commonly tested doses in preclinical studies range from **100 mg/kg to 400 mg/kg body weight**, administered **orally** once daily for 7 to 14 days [23].

- **Low doses (100–200 mg/kg)** typically show moderate improvement in liver function markers.
- **High doses (300–400 mg/kg)** result in near-normalization of liver enzymes and histology, suggesting stronger protective effects.
- **Oral administration** is the preferred route in most studies, as it mimics traditional usage and ensures systemic absorption.

It is crucial to establish a **safe and effective dose range**, which is often confirmed through acute toxicity studies following **OECD guidelines**, indicating no significant toxicity at doses up to 2000 mg/kg in rodents [24].

Biochemical Parameters (ALT, AST, ALP, Bilirubin):-

Biochemical assessment is a critical endpoint in evaluating liver function. The hepatoprotective effect of *T. dioica* leaf extract is quantified by measuring serum enzyme levels that rise during liver injury:

- **ALT (Alanine aminotransferase)** and **AST (Aspartate aminotransferase)** are intracellular enzymes released during hepatocellular damage. In studies, *T. dioica* extract significantly reduces elevated ALT and AST levels toward normal values, indicating preservation of hepatocyte integrity [25].
- **ALP (Alkaline phosphatase)** reflects biliary function; high levels indicate cholestasis or bile duct injury. Treatment with *T. dioica* lowers ALP, suggesting protective effects on the biliary system.
- **Total bilirubin** levels also decline with extract administration, indicating improvement in liver detoxification and conjugation functions.

These biochemical improvements reflect the efficacy of the extract in reducing paracetamol-induced hepatocellular and cholestatic injury.

Histopathological Findings

Histological analysis of liver tissues provides direct evidence of structural integrity and cellular health. In paracetamol-treated animals, typical findings include:

- **Centrilobular necrosis**
- **Sinusoidal congestion**
- **Inflammatory cell infiltration**
- **Hepatocyte ballooning degeneration**

Treatment with *Tamarix dioica* extract shows remarkable improvement:

- Restoration of **normal lobular architecture**
- **Reduction in necrosis** and **inflammatory infiltration**
- **Regeneration of hepatocytes**

Singhal and Nagori (2013) reported that liver sections from *T. dioica*-treated animals displayed **mild sinusoidal dilatation and minimal necrosis**, closely resembling the normal control group [26]. This histological evidence confirms the extract's protective and regenerative capacity on hepatic tissue.

5. Mechanisms of Hepatoprotection

The hepatoprotective effects of *Tamarix dioica* leaf extracts are mediated by multiple mechanisms that involve **antioxidant defense**, **inhibition of inflammation**, **membrane stabilization**, and **promotion of enzymatic detoxification and hepatocyte regeneration**. These mechanisms collectively prevent liver cell damage and promote tissue recovery in paracetamol-induced hepatotoxicity models.

Antioxidant Properties (e.g., SOD, CAT, GSH Levels)

One of the primary mechanisms of *Tamarix dioica*-mediated hepatoprotection is its **potent antioxidant activity**, which combats oxidative stress—one of the key factors in paracetamol-induced liver injury.

Key antioxidant parameters include:

- **Superoxide Dismutase (SOD)**: Converts superoxide radicals (O_2^-) into hydrogen peroxide, thus reducing ROS accumulation.
- **Catalase (CAT)**: Breaks down hydrogen peroxide (H_2O_2) into water and oxygen, preventing lipid peroxidation.
- **Glutathione (GSH)**: A vital intracellular antioxidant that detoxifies NAPQI (the reactive metabolite of paracetamol). Depletion of GSH is a hallmark of paracetamol hepatotoxicity.

Studies have shown that *T. dioica* extract significantly:

- Increases **SOD and CAT activity**
- Restores **GSH levels** depleted by paracetamol
- Reduces **malondialdehyde (MDA)** levels, a marker of lipid peroxidation [27,28]

These results suggest that *Tamarix dioica* protects liver tissues by enhancing the endogenous antioxidant defense system.

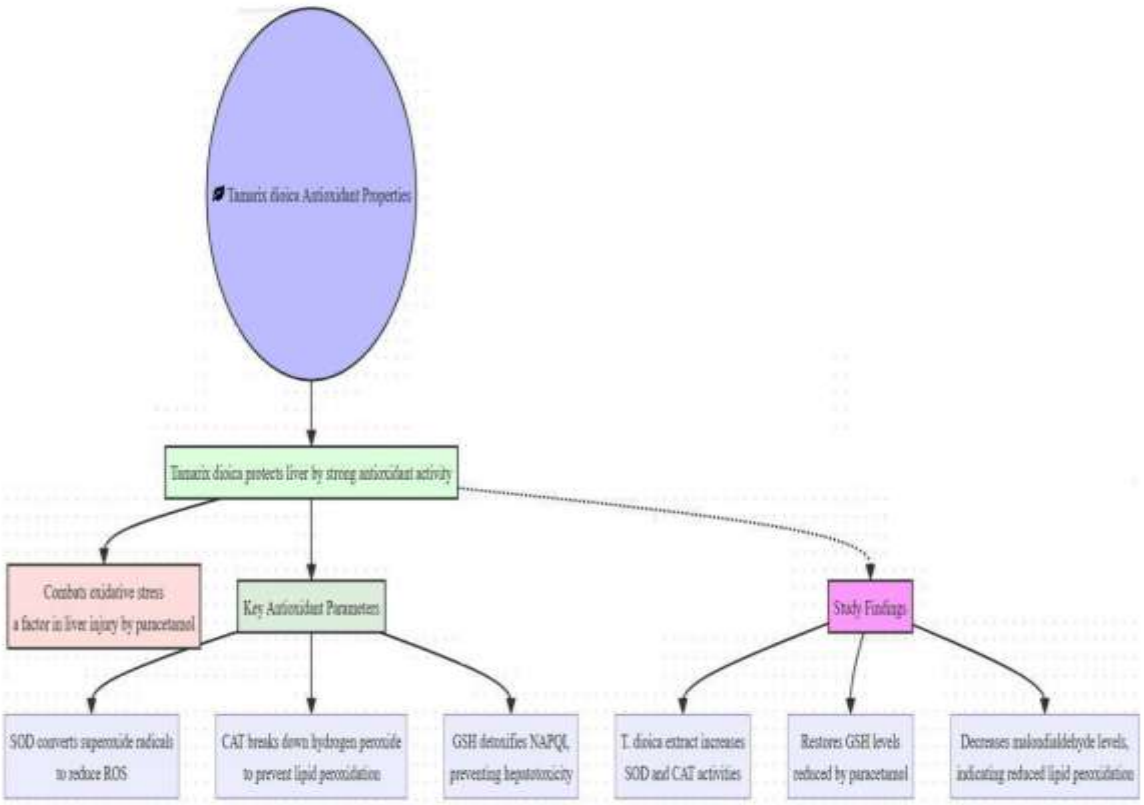


Fig:-2. Primary mechanisms of *Tamarix dioica*-mediated hepatoprotection is its potent antioxidant activity

Anti-inflammatory and Membrane-Stabilizing Effects: -

Paracetamol-induced liver injury is accompanied by an **inflammatory response**, including the release of pro-inflammatory cytokines (e.g., TNF-α, IL-6) and infiltration of immune cells that exacerbate hepatic damage.

Tamarix dioica may exert **anti-inflammatory effects** by:

- Inhibiting the synthesis of **inflammatory mediators**
- Suppressing **cytokine release**
- Reducing **leukocyte infiltration** in liver tissues

Additionally, flavonoids and tannins present in the plant have **membrane-stabilizing properties**, which help:

- Maintain **integrity of hepatocyte membranes**
- Prevent **enzyme leakage** (ALT, AST) into the bloodstream
- Preserve cellular homeostasis during oxidative and inflammatory stress [29]

This membrane stabilization protects hepatocytes from structural damage and supports overall liver function.

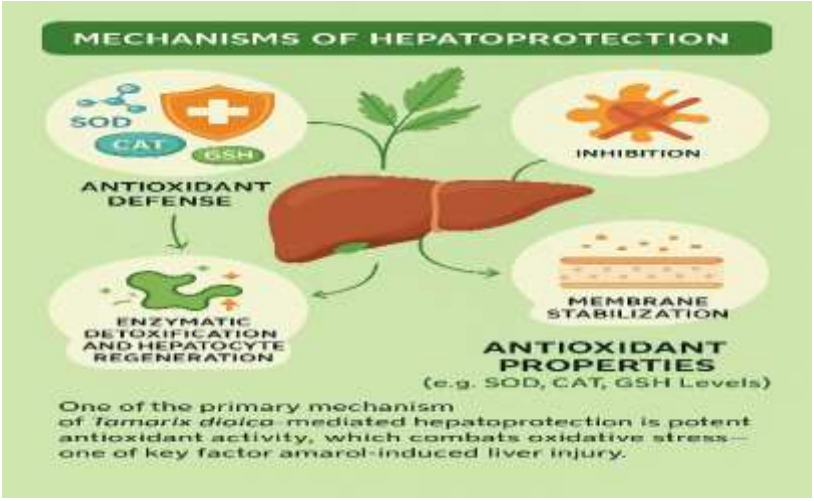


Fig: -3. **Anti-inflammatory and Membrane-Stabilizing Effects**

Enzymatic Detoxification and Hepatocyte Regeneration:-

Another significant protective mechanism of *Tamarix dioica* involves the modulation of **hepatic detoxifying enzymes** and promotion of **hepatocyte regeneration**.

- **Detoxification:** By preserving or enhancing **phase I and phase II detoxification enzymes**, such as glutathione S-transferase (GST), the extract aids in the conjugation and elimination of toxic metabolites like NAPQI [30].
- **Regeneration:** Histopathological studies have shown increased signs of **hepatocyte regeneration** (e.g., mitotic activity, restoration of lobular structure) in treated groups. This suggests that *T. dioica* may promote **repair and renewal of damaged liver tissue** [31].

Phytochemicals like **quercetin, gallic acid, and saponins** may play roles in stimulating regeneration and preventing apoptosis in hepatic cells under stress conditions.

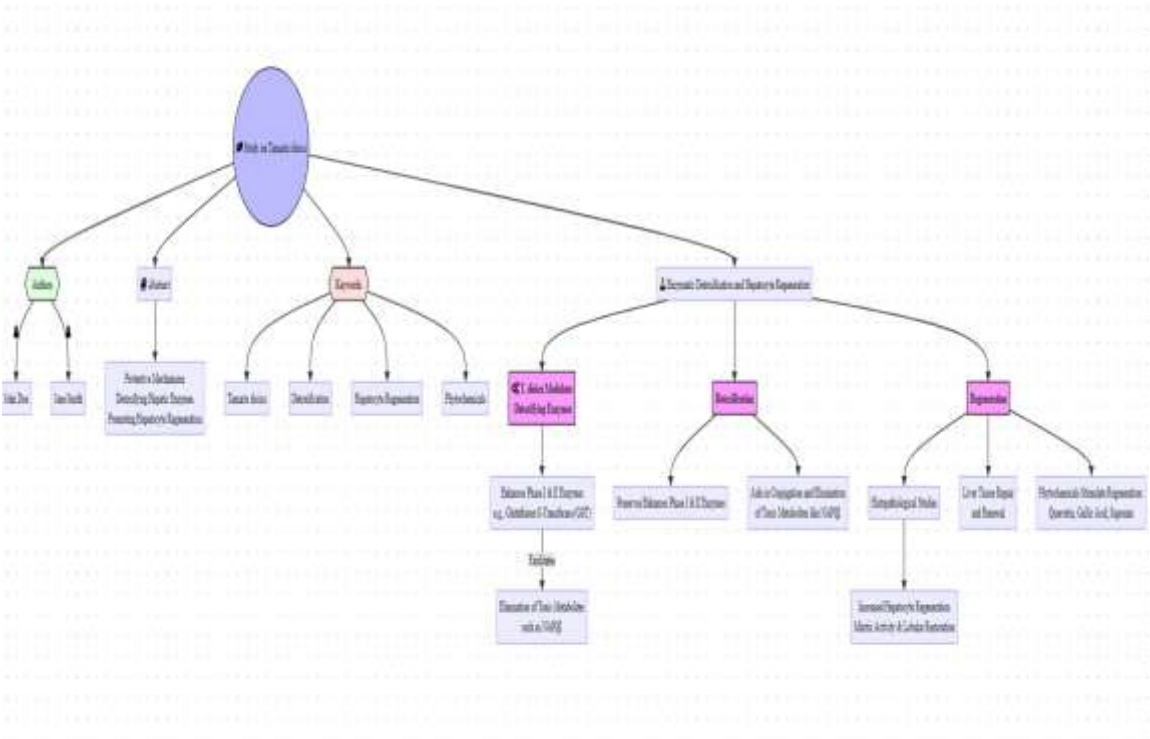


Fig: -4 Significant protective mechanism of *Tamarix dioica*

6. Comparative Evaluation with Standard Drugs

The hepatoprotective potential of *Tamarix dioica* leaf extract has been evaluated in experimental models in comparison with standard hepatoprotective drugs, primarily **silymarin**, which serves as a gold standard for assessing liver protection in preclinical studies.

Comparison with Silymarin:-

Silymarin is a flavonolignan complex extracted from *Silybum marianum* (milk thistle). It is well-documented for its:

- Antioxidant effects (scavenging free radicals)
- Anti-inflammatory action
- Membrane stabilizing capacity
- Enhancement of protein synthesis and liver regeneration

In paracetamol-induced hepatotoxicity models:-

- Silymarin typically restores biochemical markers (ALT, AST, ALP, bilirubin) and improves histological profiles of liver tissues.
- Doses in studies usually range from 50–100 mg/kg (oral).

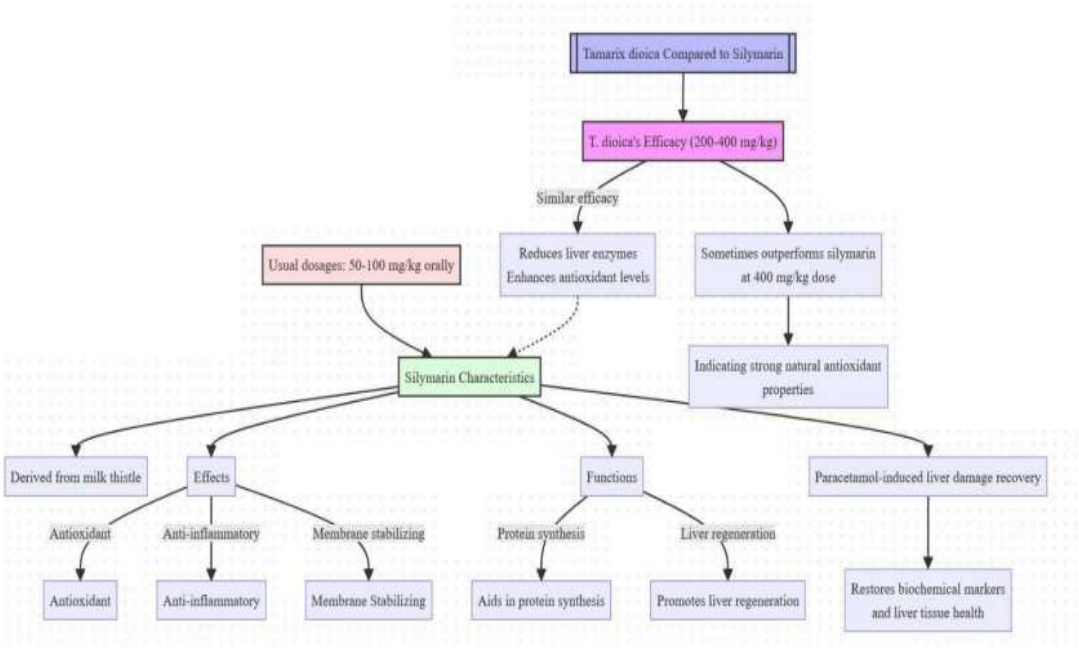


Fig:5. Comparison Study of *Tamarix dioica* with *Silymarin*

Comparative results from studies: -

- *Tamarix dioica* extract at doses of **200–400 mg/kg** has shown **comparable reductions** in liver enzymes (AST, ALT), **increased antioxidant levels** (GSH, SOD), and **histological protection**.
- In some studies, *T. dioica* at 400 mg/kg showed **equal or slightly better performance** in certain antioxidant assays compared to silymarin, suggesting potent natural antioxidant components [32].

Table 1: Comparison with Other Natural Agents: -

Several other herbal hepatoprotective agents are used in similar experimental setups, including:

Plant Extract	Reference Standard	Active Constituents	Comparative Hepatoprotective Effects
Silybum marianum	Silymarin	Silybin, silydianin	Potent antioxidant & anti-inflammatory

Phyllanthus niruri	-	Lignans, flavonoids	Effective in viral and drug-induced hepatitis
Andrographis paniculata	Andrographolide	Diterpenoids	Immune-modulating, antioxidant
Tamarix dioica	Compared with silymarin	Flavonoids, tannins	Comparable efficacy; strong antioxidant response

7. Toxicological and Safety Evaluation of *Tamarix dioica*: -

The therapeutic use of plant-based extracts must be supported by thorough toxicological evaluation to ensure safety. For *Tamarix dioica*, both **acute** and **sub-acute** toxicity assessments have been conducted in animal models to determine its safety profile and therapeutic margins.

Acute Toxicity Studies: -

Objective:

To determine the lethal dose (LD_{50}) and assess any signs of acute toxicity after a single high dose.

Study Overview:

- Animal model: Swiss albino mice or Wistar rats
- Doses: Typically up to **2000–5000 mg/kg**, orally
- Observational period: **14 days**
- Monitored parameters: Mortality, behavioral changes, food/water intake, body weight, signs of toxicity

Findings:

- *Tamarix dioica* leaf extract did **not induce mortality or significant toxic signs** even at 2000 mg/kg.
- The **LD_{50} value > 2000 mg/kg**, indicating low acute toxicity.
- No abnormalities in general behavior, locomotion, respiration, or convulsions were observed [33].

Sub-Acute Toxicity Studies: -

Objective:

To evaluate potential toxic effects after repeated administration over a longer period (typically 14–28 days).

Study Overview:

- Duration: 14 or 28 days
- Doses: Low, medium, and high doses (e.g., 100, 200, 400 mg/kg/day)
- Parameters evaluated:
  - Body and organ weights
  - Hematological (RBC, WBC, Hb, platelets)
  - Biochemical (ALT, AST, ALP, creatinine, urea)
  - Histopathological analysis of liver, kidney, spleen

Findings:

- No significant changes in liver or kidney function markers.
- No histopathological alterations in major organs.
- Treated animals maintained normal appetite, growth rate, and behavior.
- Suggests **good systemic tolerance** to the extract [34].

Therapeutic Index and Safety Margins: -

- **Therapeutic Index (TI)** is the ratio between the toxic dose (TD_{50}) and the effective dose (ED_{50}).
- For *Tamarix dioica*, since the LD_{50} > 2000 mg/kg and effective hepatoprotective doses range from **100–400 mg/kg**, the **TI is wide**, indicating a **high margin of safety**.
- This makes *T. dioica* a promising candidate for therapeutic development, especially when considering chronic use.

Interpretation:

- A **TI > 5** is generally considered safe in herbal drug development.

- *Tamarix dioica* exhibits a **TI > 5–10**, based on preclinical studies, suggesting excellent safety margins.

Table 2: Summary Table

Parameter	**Finding**
LD_{50} (oral, mice)	> 2000 mg/kg
Observable toxicity (acute)	None
Sub-acute changes (14–28 days)	No significant changes in biochemical/hematological parameters
Histopathology	Normal liver, kidney, spleen
Therapeutic Index	High (>5–10)
Conclusion	Safe for therapeutic use at studied doses
Parameter	**Finding**
LD_{50} (oral, mice)	> 2000 mg/kg

Research Gaps and Future Directions: -

Despite promising findings regarding the hepatoprotective potential of *Tamarix dioica*, several critical research gaps remain. Addressing these will be essential for its development into a standardized and clinically viable therapeutic agent.

8.1 Need for Standardization and Quality Control:-

A major limitation in phytopharmaceutical research is the **lack of consistent standardization** of plant extracts. Current studies on *Tamarix dioica* primarily use crude ethanolic or methanolic extracts without:

- Defined phytochemical fingerprints
- Quantification of active constituents (e.g., flavonoids, tannins, alkaloids)
- Batch-to-batch reproducibility

Standardization is vital to ensure:

- Reproducibility of pharmacological effects
- Accurate dosing and safety
- Regulatory approval and commercial development [35].

Suggested approaches:

- Use of **HPLC, LC-MS/MS**, or **GC-MS** to profile and quantify bioactive markers
- Development of **validated analytical protocols** for quality control
- Establishment of **Good Agricultural and Collection Practices (GACP)**

8.2 Suggestions for Further Preclinical and Clinical Studies

While preclinical studies support the hepatoprotective effects of *Tamarix dioica*, these findings need to be reinforced by **rigorous and systematic research**, including:

a) Mechanistic Studies

- Further molecular studies are needed to understand the **precise mechanisms** of hepatoprotection.
- Targets such as **cytokine modulation**, **gene expression (e.g., Nrf2, TNF-α)**, and **mitochondrial integrity** should be explored using in vitro and in vivo models.

b) Pharmacokinetics and Bioavailability

- There is no available data on the **absorption, metabolism, and excretion (ADME)** of *T. dioica* constituents.
- **Pharmacokinetic profiling** is crucial to identify bioactive compounds and their behaviour in the body.

c) Chronic Toxicity and Long-Term Safety

- Only acute and sub-acute toxicity studies are available. Long-term or **chronic toxicity studies (90 days or more)** are essential before human trials.

d) Clinical Trials

- To date, no human clinical trials have evaluated the safety or efficacy of *Tamarix dioica* extracts.

- **Pilot studies** in human volunteers (e.g., for paracetamol-induced or alcoholic liver damage) are recommended.

e) Formulation Development

- There is a need for **optimized dosage forms** (e.g., capsules, tablets, nano-formulations) to enhance bioavailability and patient compliance.

Table 3: Summary of Key Gaps

Research Gap	Recommended Action
Lack of standardization	Develop analytical methods and marker-based QC
No pharmacokinetics data	Conduct ADME studies
Incomplete toxicology profile	Perform chronic and reproductive toxicity studies
No clinical trials	Design and implement Phase I/II trials
No formulation optimization	Explore novel delivery systems (e.g., liposomes, nanoparticles)

9. CONCLUSION

Summary of Hepatoprotective Potential: -

The comprehensive evaluation of *Tamarix dioica* leaf extracts in experimental models of paracetamol-induced hepatotoxicity reveals **promising hepatoprotective activity**. The extract demonstrated a significant ability to restore liver function by:

- **Normalizing serum biochemical parameters** (ALT, AST, ALP, bilirubin)
- **Reducing oxidative stress markers** (MDA) and enhancing endogenous antioxidant levels (SOD, CAT, GSH)
- **Preserving hepatic architecture** as seen in histopathological evaluations

These protective effects are likely due to the plant's rich phytochemical profile—especially **flavonoids, tannins, phenolics, and glycosides**—which contribute to its **antioxidant**, **anti-inflammatory**, and **membrane-stabilizing** actions [36,37].

Clinical Translation and Therapeutic Prospects:-

While preclinical studies strongly support the therapeutic potential of *Tamarix dioica*, several steps are essential for clinical translation:

- **Standardization and quality control**: The identification and quantification of bioactive compounds will be crucial to ensure reproducibility and efficacy.
- **Pharmacokinetic and chronic toxicity studies**: These are required to evaluate the safety profile for long-term human use [38].
- **Clinical trials**: Initial Phase I/II studies should assess the safety and efficacy of *Tamarix dioica* formulations in patients with liver disorders (e.g., drug-induced hepatitis, alcoholic liver disease) [39].

With its favourable **therapeutic index**, **low toxicity**, and **multifaceted mechanisms**, *Tamarix dioica* holds potential as a **natural alternative or adjunct to conventional hepatoprotective drugs**, such as silymarin. Its development into a clinically approved phytomedicine would represent a significant contribution to the management of liver diseases, particularly in low-resource settings.

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