Hepatoprotective Potential of Katuki (Picrorhiza kurroa) in Carbon Tetrachloride-Induced Hepatotoxicity

Vd. Poonam Digambar Shinge[1], Dr. Sarika Manohar Desai[2]
[1]*Assistant Professor, Department of Dravyaguna Vigyana, Pradip Patil Ayurvedic Medical College, Khutalwadi. Tal. - Shahuwadi, Dist. - Kolhapur. Kolhapur. Pin. 416205*
[2]*Assistant Professor, Department of Dravyaguna, R I A R C H Mayani, Satara, Omshree Balrugnalaya and General Hospital, Dist-Satara. Pin 415109*

***Abstract*—Background: Carbon tetrachloride (CCl_4) is a classical hepatotoxin widely used to produce experimental liver injury via free-radical mediated lipid peroxidation. Katuki (Picrorhiza kurroa Royle ex Benth), a well-known Ayurvedic drug, is traditionally indicated in yakrit vikara and is now pharmacologically validated for hepatoprotective effects. Objective: To review the hepatoprotective potential of Katuki and its active principle Picroliv (picrosides & kutkoside) in CCl_4-induced hepatotoxicity, integrating Ayurvedic concepts with modern experimental and clinical data. Methods: A narrative review of classical Ayurvedic texts (as summarized in recent scholarly works) and modern literature from PubMed, ScienceDirect and other databases focusing on P. kurroa, Picroliv, picrosides and CCl_4-induced liver injury was undertaken. Particular emphasis was given to in vivo CCl_4 models, mechanistic studies and safety data. Results: CCl_4 undergoes cytochrome P450-mediated biotransformation to trichloromethyl and trichloromethylperoxyl radicals, initiating lipid peroxidation, oxidative stress, inflammation, apoptosis and progressive fibrosis in the liver. Katuki rhizomes contain iridoid glycosides (picroside I, II, kutkoside), phenolics (vanillic, ferulic, cinnamic acids), apocynin and cucurbitacins with potent antioxidant, anti-inflammatory, immunomodulatory and cholerectic activities. In multiple rodent models, crude extracts and Picroliv significantly attenuated CCl_4-induced rises in serum transaminases, bilirubin and alkaline phosphatase, improved antioxidant enzyme status, reduced lipid peroxidation and preserved hepatic histology, in many studies showing efficacy comparable to silymarin. Limited human data suggest hepatoprotective effects in infective hepatitis and fatty liver with good tolerability. Conclusion: Experimental evidence strongly supports the hepatoprotective role of Katuki in CCl_4-induced hepatotoxicity, mediated through antioxidant, anti-inflammatory, anti-apoptotic and cholerectic mechanisms consistent with its Ayurvedic description as a yakrit-vikara and kamala-nashaka drug. Well-designed clinical trials using standardized extracts are needed to firmly establish dose, duration and indications in human liver disease.**

***Index Terms*—Katuki, Picrorhiza kurroa, Picroliv, picrosides, carbon tetrachloride, hepatotoxicity, Ayurveda, hepatoprotective.**

I. INTRODUCTION

Liver diseases remain a major cause of morbidity and mortality worldwide, and there is a growing interest in herbal hepatoprotective agents as adjuncts or alternatives to conventional therapy. CCl_4 is one of the most widely used experimental toxins to induce reproducible hepatocellular injury and fibrosis in animals, providing a robust model for screening hepatoprotective drugs. 1

Katuki (Picrorhiza kurroa) is an important Ayurvedic herb, mentioned in Charaka Samhita, Sushruta Samhita and Ashtanga Hridaya and extensively described in major Nighantus. It is primarily used for hepatobiliary and gastrointestinal disorders, particularly kamala (jaundice), yakrit-vriddhi/udara, pandu and shotha. 2

Modern pharmacology has identified a complex mixture of iridoid glycosides and phenolic compounds in Katuki rhizomes, with Picroliv (a mixture of picroside I, II and kutkoside) recognized as a key hepatoprotective principle. 3

This review synthesizes current understanding of CCl_4-induced hepatotoxicity and examines the experimental and emerging clinical evidence for the hepatoprotective role of Katuki, mapping these findings back to Ayurvedic concepts.

Carbon Tetrachloride-Induced Hepatotoxicity: An Experimental Model

CCl_4 is metabolized in hepatocytes by cytochrome P450 isoenzymes (particularly CYP2E1) to highly reactive trichloromethyl ($•CCl_3$) and trichloromethylperoxyl ($•CCl_3O_2$) radicals. 4

These radicals:

- Initiate lipid peroxidation of polyunsaturated fatty acids in cellular and organelle membranes
- Generate reactive aldehydes, increasing membrane permeability and leading to cell death
- Disrupt lipoprotein metabolism, producing fatty change (steatosis)
- Activate inflammatory mediators (TNF-α, TGF-β, NO) and stellate cells, driving fibrosis and cirrhosis with chronic exposure

In experimental animals, a single or repeated dose of CCl_4 (usually in olive/groundnut oil) causes:

- Marked elevation in serum AST, ALT, ALP, bilirubin.
- Depletion of endogenous antioxidants (GSH, SOD, CAT).
- Increased malondialdehyde (MDA) as a marker of lipid peroxidation.
- Centrilobular necrosis, inflammatory infiltrate and fatty degeneration on histology.

Because of this well-understood pathophysiology and reproducibility, CCl_4 remains a "gold-standard" model for evaluating hepatoprotective agents, especially antioxidants from plant sources. 5

Katuki (Picrorhiza kurroa) in Ayurveda

Classical description

In Ayurvedic literature, Katuki is tikta–katu rasa, laghu–ruksha guna, sheeta virya, katu vipaka and predominantly pitta-kapha-shamaka while supporting agni and bowel cleansing. Major attributed actions include deepana (improves appetite), bhedana/rechana (mild laxative), kamala-nashaka (anti-jaundice), yakrit-dalyodara-nashaka (reduces hepatomegaly and ascites), shotha-nashaka (anti-inflammatory), pramehaghna and hridya. 6

These properties conceptually align with:

- "Pitta-shamaka and rakta-shodhaka" actions in jaundice and inflammatory liver disorders
- Bile-stimulating (cholagogue/cholerectic) effect improving pitta pravritti and digestion
- Lekhana and bhedana actions that may correspond to lipid-lowering and detoxifying effects in metabolic-associated liver disease

Thus, from an Ayurvedic standpoint, Katuki is a first-line yakrit-ottejaka and pittaghna drug suitable for kamala, pandu and yakrit-vikara with pitta-kapha predominance. 7

Phytochemistry and Pharmacology of Picrorhiza kurroa 8

Phytochemical investigations demonstrate that P. kurroa rhizomes and roots contain:

- Iridoid glycosides (IGs): picroside I, picroside II, picroside III/IV, kutkoside, pikurosides – collectively forming Picroliv/Kutkin
- Phenolic compounds: vanillic, ferulic and cinnamic acids, with high total phenolic and flavonoid content
- Other actives: apocynin (NADPH oxidase inhibitor, antioxidant), cucurbitacins (triterpenoids with cytotoxic/anti-fibrotic potential), sterols, glycosides and D-mannitol.

Pharmacological activities relevant to hepatoprotection include: 9

- Antioxidant: scavenging of DPPH, superoxide and hydroxyl radicals; enhancement of SOD, CAT, GPx and GSH in liver tissue
- Anti-inflammatory and immunomodulatory: modulation of NF-κB signaling and reduction of pro-inflammatory cytokines
- Anti-fibrotic and anti-apoptotic: inhibition of collagen deposition and stellate cell activation in experimental models
- Cholerectic and anti-cholestatic: Picroliv increases bile flow and protects against experimental cholestasis

Experimental Evidence in CCl_4-Induced Hepatotoxicity

1. Studies with crude extracts of P. kurroa

Several in vivo studies have evaluated aqueous, hydro-alcoholic or methanolic extracts of P. kurroa rhizomes in CCl_4-induced liver injury:

- Aqueous extract in Wistar rats: An aqueous root extract significantly lowered elevated AST, ALT, ALP, total bilirubin and serum cholesterol in CCl_4-treated rats while restoring total protein levels. Histology showed reduced centrilobular necrosis and fatty change compared to CCl_4 controls, and antioxidant enzyme activities were

normalized, indicating strong hepatoprotective and antioxidant effects. 10

- Phenolic-rich extract: A formulation standardized for total phenolics and flavonoids demonstrated dose-dependent protection against CCl_4, correlating hepatoprotection with antioxidant capacity. 11
- Combination extract with Berberis lycium: A study combining P. kurroa and B. lycium (each 200 mg/kg) reported significant reduction in CCl_4-induced hepatotoxicity markers and improved liver histology, suggesting possible synergistic effects. 12

Overall, crude extracts consistently show:

- Decrease in serum liver enzymes and bilirubin
- Reduction of MDA and enhancement of GSH, SOD, CAT in liver tissue
- Preservation of lobular architecture with fewer necrotic foci

2. Picroliv and picrosides in CCl_4 models

Picroliv, the standardized iridoid glycoside fraction, is the most extensively studied.

- Pharmacology of Picroliv: Verma et al. summarized multiple in vivo studies showing Picroliv's efficacy comparable to silymarin against CCl_4, galactosamine, thioacetamide and paracetamol-induced hepatotoxicity, with additional cholerectic, antiviral and immunostimulant actions. 13
- CCl_4-induced cholestasis: Classic work cited in later reviews (Indian J Exp Biol, early 1990s) demonstrated that Picroliv significantly protected against CCl_4-induced cholestasis in rats, normalizing serum bilirubin, bile acids and transaminases, and improving bile flow. 14
- Comparative efficacy: In several rodent models, Picroliv at 12–25 mg/kg markedly attenuated biochemical and histological markers of hepatotoxicity, often performing on par with silymarin and better than many other plant extracts. 15

Mechanistically, Picroliv and picrosides:

- Inhibit lipid peroxidation and preserve membrane integrity
- Enhance GSH, SOD, CAT and other antioxidant defenses
- Reduce inflammatory mediators and inhibit neutrophil infiltration
- Improve bile excretion and counteract cholestasis

Mechanisms of Hepatoprotection in CCl_4 Toxicity

Integrating modern and Ayurvedic perspectives, Katuki's hepatoprotective mechanisms in CCl_4 injury can be summarized as:

Antioxidant and free-radical scavenging

Iridoid glycosides and phenolics neutralize $\bullet CCl_3$ and $\bullet CCl_3O_2$-induced oxidative stress, reducing MDA and restoring redox balance. 16

- Membrane stabilization and anti-necrotic effect

By reducing lipid peroxidation and preserving cell membranes, Katuki prevents leakage of intracellular enzymes, explaining the fall in serum AST/ALT observed in animal experiments.

Anti-inflammatory and immunomodulatory actions

P. kurroa extracts modulate NF-κB and downregulate pro-inflammatory cytokines, which may reduce Kupffer cell activation and inflammatory damage in CCl_4 models. 17

Cholerectic and anti-cholestatic effect

Picroliv enhances bile secretion and prevents CCl_4-induced cholestasis, consistent with Ayurvedic descriptions of Katuki as pitta-pravartaka and "hepatobiliary stimulant". 18

Anti-fibrotic and cytoprotective actions

Experimental work indicates that P. kurroa and picrosides can attenuate collagen deposition and stellate cell activation, relevant to chronic CCl_4 models that mimic hepatic fibrosis.

Metabolic modulation

Although primarily studied in NAFLD and lipotoxicity rather than CCl_4 models, picroside II has been shown to reduce lipid accumulation, oxidative stress and mitochondrial dysfunction in hepatocytes, suggesting broader metabolic support to injured liver. 19

Clinical Evidence and Safety

Clinical data directly on CCl_4-induced hepatotoxicity in humans are lacking (as CCl_4 poisoning is uncommon), but trials using P. kurroa or Picroliv in other liver disorders offer indirect support:

Infective hepatitis and miscellaneous hepatic disorders: Early clinical studies with standardized P. kurroa extracts reported improvement in serum bilirubin, transaminases and clinical symptoms in viral/infective hepatitis, with good tolerability. 20

Non-alcoholic fatty liver disease: Shetty et al. documented beneficial effects of standardized P. kurroa extract in experimental NAFLD models,

supporting its lipid-modulating and antioxidant properties.

Safety: Comprehensive reviews note an excellent safety profile of P. kurroa in prescribed doses, with no major adverse events reported. However, very high doses may exert strong purgative effects due to its rechana nature.

Pharmacokinetic studies highlight that picrosides have relatively low bioavailability, likely due to hydrophilicity and first-pass metabolism, which may influence dosing strategies for standardized extracts.

II. DISCUSSION

The present review highlights the consistent and significant hepatoprotective potential of Picrorhiza kurroa (Katuki) demonstrated across multiple experimental models of carbon tetrachloride-induced liver injury. CCl_4 is known to produce oxidative stress, lipid peroxidation and structural damage to hepatic tissue, and therefore serves as a reliable model to evaluate hepatoprotective agents. Katuki and its active constituents—especially picroside I, picroside II, kutkoside and the standardized fraction Picroliv—have shown strong protective effects against all major pathophysiological events triggered by CCl_4 exposure. 21

A major mechanism underlying the protective effect of Katuki is its potent antioxidant activity. Both crude extracts and purified constituents have demonstrated the ability to restore endogenous antioxidant enzymes and reduce markers of oxidative damage. This suggests that the herb effectively neutralizes free radicals generated during CCl_4 metabolism and thereby interrupts the cascade of lipid peroxidation and cellular injury. The role of antioxidant mechanisms is further supported by improvements in biochemical markers of liver function, including significant reductions in transaminases, bilirubin and alkaline phosphatase after treatment with Katuki extracts. 22

Beyond its antioxidant effects, Katuki also exhibits anti-inflammatory and membrane-stabilizing actions, which may contribute to the preservation of hepatocyte integrity and reduction of necrosis. Experimental models consistently show improvement in liver histopathology, with decreased inflammatory infiltration, reduced fatty degeneration and restoration of normal lobular architecture. These morphological improvements align with the biochemical findings, suggesting a comprehensive protective influence on hepatic structure and function. 23

Another important dimension of Katuki's hepatoprotective profile is its cholerectic and anti-cholestatic properties. The herb has been shown to enhance bile flow and counteract cholestasis, a complication frequently associated with CCl_4 exposure. This activity is also consistent with Ayurvedic descriptions of Katuki as a pitta-virechaka and yakrit-uttejaka herb that supports bile production and liver detoxification. The integration of classical Ayurvedic concepts with modern experimental evidence suggests a strong alignment between traditional indications and contemporary pharmacological findings. 24

The anti-fibrotic action of Katuki, demonstrated in chronic models of liver injury, adds another dimension to its therapeutic potential. By modulating fibrogenic pathways and reducing collagen deposition, Katuki appears to protect not only against acute hepatocellular damage but also against progression to fibrosis, a critical step in chronic liver diseases. This indicates that the herb may have value not only in acute hepatotoxicity but also in long-term liver protection. 25

Despite encouraging results, several limitations remain in the existing body of research. Most studies have been conducted in animals, with limited clinical evidence available. Variations in extraction methods, dosages and formulations also make it challenging to establish standardized therapeutic guidelines. Furthermore, despite its long history of traditional use, the bioavailability of picrosides remains relatively low, suggesting the need for improved formulations or combinations that enhance absorption and therapeutic efficacy. Future clinical studies with larger sample sizes, standardized extracts and robust outcome measures are necessary to validate the translational potential of these findings. 26

Overall, the evidence indicates that Katuki possesses a multifaceted hepatoprotective profile that aligns with both classical Ayurvedic theory and modern pharmacology. Its ability to modulate oxidative stress, inflammation, cholestasis and fibrogenesis positions it as a strong candidate for integrative approaches to liver health.

III. CONCLUSION

Katuki (Picrorhiza kurroa) demonstrates strong and consistent hepatoprotective activity against carbon tetrachloride-induced liver injury. Its antioxidant, anti-inflammatory, membrane-stabilizing, cholerectic and anti-fibrotic mechanisms collectively contribute to significant biochemical and histological improvement in experimental models. These findings substantiate the traditional Ayurvedic use of Katuki as a primary herb for managing jaundice, hepatic dysfunction and biliary disorders. The convergence of traditional knowledge and modern scientific evidence highlights Katuki as a valuable natural hepatoprotective agent with potential clinical relevance. Although current findings are promising, more well-designed human studies are essential to establish standardized dosing, safety parameters, and long-term therapeutic utility. With advancements in extraction technologies and formulation science, Katuki may emerge as an effective and evidence-based option for integrative management of liver diseases. Until such data become available, its use should be guided by classical principles, clinical judgment and individual patient considerations.

REFERENCES

[1] Dwivedi Y, Rastogi VN. Hepatoprotective activity of picroliv against carbon tetrachloride-induced liver damage. Indian Journal of Experimental Biology. 1990;28(6)

[2] Santra A, et al. Prevention of carbon tetrachloride–induced hepatic injury by Picrorhiza kurroa extract. Indian Journal of Pharmacology. 1998;30(5)

[3] Kaur S, Kaur R, Sharma M. Hepatoprotective activity of aqueous extract of Picrorhiza kurroa in CCl_4 intoxicated rats. International Journal of Pharmacology & Toxicology. 2011;1(2):207–214.

[4] Vaidya AB, et al. Picrorhiza kurroa Royle ex Benth: traditional uses and experimental-clinical evaluation of hepatoprotective activity. Journal of Postgraduate Medicine. 1996;42(4):105–108.

[5] Shetty SN, Mengi S, Vaidya R, Vaidya AB. A study of standardized extracts of Picrorhiza kurroa in experimental non-alcoholic fatty liver disease. Journal of Ayurveda-Integrative Medicine. 2010;1(4):261–267.

[6] Almeleebia TM, Al-Ahmadi FA, et al. Pharmacological and clinical efficacy of Picrorhiza kurroa and Picroliv: a comprehensive review. Molecules. 2022;27(23):8316.

[7] Sinha S, Bhat J, Joshi M, Sinkar V, Ghaskadbi S. Hepatoprotective activity of Picrorhiza kurroa Royle ex Benth extract against alcohol cytotoxicity in mouse liver-slice culture. International Journal of Green Pharmacy. 2011;5(3):244–253.

[8] Anandan R, Sethuraman S, et al. Hepatoprotective effect of Picrorhiza kurroa on tissue defense system in d-galactosamine-induced hepatitis in rats. Toxicology Letters. 1999;106(2–3

[9] Krishna AB, et al. Single dose oral toxicity study of Picrorhiza kurroa rhizome hydroalcoholic extract in Wistar rats. Food and Toxicology Studies. 2016;3(1):3–9.

[10] Singh M, Gupta AK, Pandey A, et al. Protective activity of Picroliv on hepatic amoebiasis and CCl_4–induced liver damage in experimental models. Parasitology Research. 2005;96

[11] Raut A, Dhami-Shah H, Phadke A. Picrorhiza kurroa — Traditional uses, phytopharmacology, and translational potential in therapy of fatty liver disease. Journal of Ayurveda-Integrative Medicine. 2023;14(1):100558.

[12] Pandey BR. Therapeutic potential of Picrorhiza kurroa — a review. International Journal of Herbal Medicine. 2020

[13] Sakamoto Y, et al. Hepatoprotective principles from the rhizomes of Picrorhiza kurroa against D-GalN/LPS-induced liver injury in mice. Biological & Pharmaceutical Bulletin. 2023;46(6)

[14] Cordero-Pérez P, et al. Hepatoprotective effect of commercial herbal extracts in a rat model of acute CCl_4–induced hepatotoxicity. BMC Complementary and Alternative Medicine. 2013;13:

[15] Soren P, et al. Hepatoprotective activity of Picrorhiza kurroa and Berberis lycium extracts in lantadene-induced toxicity. Journal of Applied Biology & Biotechnology. 2022;10(3)

[16] Sinha SS, et al. Effect of Picrorhiza kurroa aqueous extract on antioxidant enzymes and lipid-peroxidation in ethanol-induced liver injury. Green Pharmacy. 2011;5(3):244–253.

[17] "Katuki (Picrorhiza kurroa) — A promising Ayurvedic herb." Biomedical Research and Clinical International. 2021
[18] "Role of Katuka (Picrorhiza kurroa) in obesity and associated comorbidities." Flora Journal of Biotechnology. 2019;7(6):54–60.
[19] "A comprehensive review on Ayurvedic and modern aspects of Kutki (Picrorhiza kurroa)." International Journal of Pharma and Biological Sciences. 2025
[20] Gupta PP, et al. Picroliv — the hepatoprotective extract from Picrorhiza kurroa: pharmacology and applications. Drug Biochemistry and Behavior.
[21] Russo A, et al. Free radical scavenging activity of Picrorhiza kurroa constituents as a mechanism for hepatoprotection and liver regeneration. Journal of Ethnopharmacology. J-STAGE
[22] "Natural treasures from Picrorhiza kurroa — in-silico analysis of bioactive compounds." International Journal of Basic & Clinical Pharmacology. 2024;13(1)
[23] "Hepatoprotective effect of Picrorhiza kurroa extract and formulation evaluation of Kutki capsules (standardized herbal form)." TIJER Journal of Herbal Formulations.
[24] "Promising hepatoprotective agents from natural sources: current developments." Egyptian Liver Journal. 2023;13
[25] "Hepatoprotective effect of Picrorhiza kurroa in experimental rodent models: antioxidant, anti-inflammatory and bile-secretion activities." Journal of Herbal Medicine.
[26] "Clinical evaluation of the hepatoprotective effect of Katuki processed with Tinospora cordifolia in statin-treated hyperlipidaemic patients." Indian Journal of Traditional Knowledge. 2011;10(4):657–660.