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Drug-Induced Hepatotoxicity: A Review on Paracetamol, Isoniazid, and Methotrexate

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ABSTRACT

Drug-induced hepatotoxicity (DIH) is a major cause of acute liver injury around the world. It causes a lot of illness and death, and it puts a lot of stress on healthcare systems. Paracetamol, Isoniazid, and Methotrexate are notable among frequently implicated drugs due to their extensive clinical application and hepatotoxic risk. This review offers an exhaustive examination of the mechanisms, molecular pathways, clinical manifestations, epidemiology, genetic predispositions, biomarkers, risk factors, drug-drug interactions, preventive strategies, and management approaches. The talks also cover new biomarkers, pharmacogenomic treatments, and safer ways to help people.

INTRODUCTION

Drug-induced hepatotoxicity (DIH) is now a major issue for doctors and public health everywhere. The liver is the main organ that breaks down drugs and gets rid of toxins. Because of this, it is very sensitive to toxic substances from xenobiotics, therapeutic agents, and the things they break down into. Over 1,000 medications and herbal treatments have been associated with hepatotoxic reactions, which can manifest as elevated liver enzyme levels without symptoms or progress to liver failure. Drug-induced liver injury (DILI) is acknowledged as a principal cause of acute liver failure in developed nations and is the second leading cause after viral hepatitis in various developing areas. The estimated incidence of drug-induced liver injury (DILI) is about 10 to 15 cases per 10,000 to 100,000 people who take prescription drugs. However, the real number is probably higher because of underreporting and problems with diagnosis.

Drugs can generally be classified as having intrinsic (predictable, dose-dependent) or idiosyncratic (unpredictable, dose-independent) hepatotoxic potential. Paracetamol (acetaminophen) illustrates intrinsic hepatotoxicity by causing dose-dependent centrilobular necrosis through the accumulation of the reactive metabolite N-acetyl-p-benzoquinone imine (NAPQI). Conversely, idiosyncratic hepatotoxicity, exemplified by isoniazid, is unpredictable, exclusively impacts individuals predisposed to risk, and frequently arises from genetic, immunological, or metabolic origins. Another drug that can hurt the liver over time is methotrexate. This damage can cause liver fibrosis or, in worse cases, cirrhosis.

Drug-induced hepatotoxicity can manifest in numerous ways in patients. Patients may show vague symptoms like tiredness, nausea, and stomach pain, or they may show clear signs like jaundice, itching, an enlarged liver, and problems with blood clotting. The lab tests usually show higher levels of alkaline phosphatase, bilirubin, or serum transaminases. These levels help to categorize DILI into three categories: hepatocellular, cholestatic, or mixed. In severe cases, progressive hepatic encephalopathy and fulminant liver failure may occur, requiring liver transplantation. It's very important to find out which drug is causing the problem quickly and stop taking it. Things usually get worse when you find out about them late.

Many drugs can hurt the liver, but paracetamol, isoniazid, and methotrexate are some of the worst because they are used a lot and everyone knows they are bad for the liver.

You can buy paracetamol without a prescription. It is a common painkiller and fever reducer. Even though therapeutic doses are thought to be safe, overdose is still the most common reason for acute liver failure in many countries.

Isoniazid is an important first-line drug for controlling tuberculosis around the world. But it can't be used very often because it can be very bad for the liver, especially when used with rifampicin or by older people.

Methotrexate, an antimetabolite frequently prescribed for malignancies and autoimmune disorders like rheumatoid arthritis and psoriasis, is linked to cumulative hepatotoxic effects, resulting in fibrosis and cirrhosis with prolonged treatment duration.

The rising prevalence of polypharmacy, self-medication, and herbal supplements complicates the comprehension of hepatotoxicity. Genetic polymorphisms in drug-metabolizing enzymes (e.g., CYP450 isoforms, NAT2, GST) and environmental factors (such as alcohol consumption, obesity, and viral hepatitis) significantly alter the risk. Therefore, it is essential for physicians, pharmacologists, and public health officials to understand the mechanisms through which drugs cause hepatic injury, recognize the related risk factors, and establish preventive strategies.

This review seeks to thoroughly examine the hepatotoxic potential of paracetamol, isoniazid, and methotrexate, emphasizing their mechanisms of toxicity, clinical presentations, diagnosis, and therapeutic approaches. We want to help doctors understand drug-induced hepatotoxicity better by putting together the evidence we have. This will help them use drugs more safely and help patients get better.

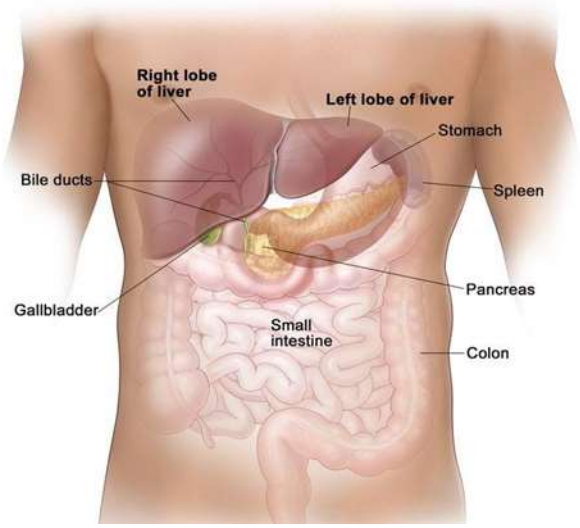

Figure: Liver Anatomy

HISTORICAL PERSPECTIVE

People started to realize that drugs could hurt the liver in the middle of the 20th century. Early antibiotics like halothane and chlorpromazine were linked to liver damage. Since then, many drugs that are often prescribed, such as chemotherapeutic agents, anticonvulsants, and anti-tubercular agents, have been linked to liver damage. Over time, paracetamol became the most common cause of acute liver failure. On the other hand, isoniazid and methotrexate became well-known examples of idiosyncratic and cumulative hepatotoxicity, respectively. Historical case reports and epidemiological studies underscored the significance of pharmacovigilance, resulting in the formation of regulatory bodies and comprehensive global monitoring protocols. .

GLOBAL BURDEN AND EPIDEMIOLOGY

Drug-induced hepatotoxicity is acknowledged as a significant contributor to global morbidity and mortality. Epidemiological studies indicate that DILI constitutes approximately 10% of all acute hepatitis cases and up to 50% of acute liver failures in Western nations. There are thought to be 14 to 20 cases of this disease per 100,000 people each year, but the real number is probably lower because it is hard to figure out.

Taking too much paracetamol is the most common cause of sudden liver failure in the US and Europe.

Isoniazid-induced hepatotoxicity is a big problem for public health, and tuberculosis is still very common in Asian countries.

In areas where autoimmune diseases and cancers are becoming more common, more and more people are saying that methotrexate is hurting their livers for a long time.

People in low- and middle-income countries have to deal with more than they should because they use over-the-counter drugs, herbal remedies, and don't get enough medical care. This shows how important it is to improve diagnostic tools, teach patients more, and follow the rules. .

CLASSIFICATION AND MECHANISMS

Drug-induced hepatotoxicity can be broadly divided into:

1. Intrinsic hepatotoxicity (dose-dependent, predictable) – exemplified by paracetamol, where toxicity correlates with dose and duration of exposure.

2. Idiosyncratic hepatotoxicity (dose-independent, unpredictable) – seen in isoniazid therapy, influenced by host factors such as age, genetics, and comorbidities.

3. Cumulative or chronic hepatotoxicity – observed with methotrexate, where long-term exposure leads to progressive fibrosis and cirrhosis.

Understanding these categories is critical for clinicians in making therapeutic decisions, especially in high-risk populations.

REGULATORY AND PHARMACOVIGILANCE PERSPECTIVE

DILI is a big reason why drugs are pulled from the market and why regulatory bodies only allow a certain number of drugs to be approved for use. The European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) have very strict rules about how to test drugs for hepatotoxicity before and after they are sold. The WHO-Uppsala Monitoring Centre works to improve pharmacovigilance networks by collecting reports from all over the world of bad drug reactions, such as hepatotoxicity. Clinical practice guidelines now also say that people who take drugs that could hurt their liver, like isoniazid and methotrexate, need to have their liver function checked regularly.

FOCUS OF THE REVIEW

In this broader context, three drugs—paracetamol, isoniazid, and methotrexate—have been selected for comprehensive examination due to their extensive clinical utilization across diverse populations, distinctive hepatotoxicity mechanisms (acute overdose, idiosyncratic injury, cumulative toxicity), and significant influence on the global prevalence of drug-induced liver disease.

The objective of this review is to furnish a thorough and up-to-date examination of these medications, including their pharmacology, hepatotoxicity mechanisms, clinical manifestations, diagnostic difficulties, therapeutic approaches, and preventive strategies. We want to close the gap between what we know about drugs and how they are used in real life by combining data from both clinical and experimental studies. This will help doctors write prescriptions that are safer and help patients get better.

PARACETAMOL-INDUCED HEPATOTOXICITY

MOLECULAR MECHANISM

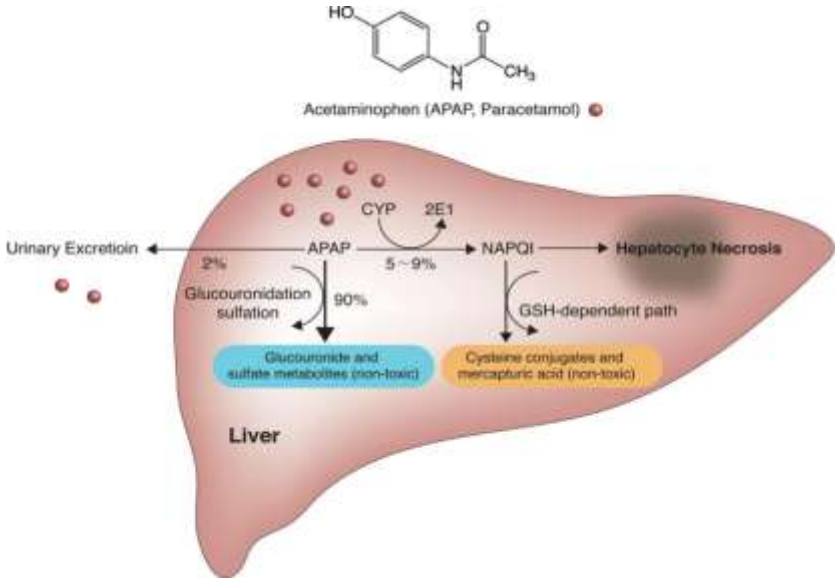

Figure: Paracetamol (APAP) metabolic pathway

Phase I metabolism: CYP2E1, CYP1A2, and CYP3A4 oxidize a small fraction of paracetamol into NAPQI, a reactive metabolite.

Phase II metabolism: Glucuronidation and sulfation pathways detoxify the majority of the drug.

Overdose mechanism: Excess NAPQI depletes glutathione, leading to oxidative stress, mitochondrial permeability transition, ATP depletion, lipid peroxidation, and hepatocyte necrosis.

Signaling pathways: JNK activation, mitochondrial ROS generation, and caspase-independent apoptosis contribute to liver injury.

CLINICAL FEATURES

Stage I (0–24 h): Nausea, vomiting, malaise.

Stage II (24–72 h): RUQ pain, rising ALT/AST, mild jaundice.

Stage III (72–96 h): Hepatic necrosis, coagulopathy, encephalopathy.

Stage IV (4 days–2 weeks): Recovery or progression to multi-organ failure.

LAB MARKERS: ALT/AST >1000 IU/L, INR >1.5, bilirubin elevation, metabolic acidosis.

EPIDEMIOLOGY & RISK FACTORS

Most common cause of acute liver failure in US/UK.

High-risk groups: alcoholics, malnourished, elderly, CYP450 inducers.

Estimated >50,000 annual hospital admissions in the USA.

MANAGEMENT

N-acetylcysteine (NAC): Administer within 8–10 hours of overdose.

Supportive care for electrolytes, coagulopathy, renal function.

Liver transplantation for patients with INR >6.5, grade III–IV encephalopathy.

BIOMARKERS & EARLY DETECTION

Serum miR-122, keratin-18 fragments, and glutathione levels under investigation for early diagnosis.

Acetaminophen-protein adducts can confirm exposure in suspected overdose.

ISONIAZID-INDUCED HEPATOTOXICITY

MOLECULAR MECHANISM

INH metabolized by N-acetyltransferase 2 (NAT2).

Slow acetylators accumulate hydrazine metabolites → oxidative stress, mitochondrial injury.

Immune-mediated reactions can trigger hepatocyte apoptosis.

CLINICAL FEATURES

Asymptomatic ALT elevation (10–20%).

Symptomatic hepatitis: fatigue, nausea, RUQ pain, jaundice.

Fulminant liver failure in <1–2%, higher in elderly/alcohol users.

EPIDEMIOLOGY & RISK FACTORS

Anti-TB programs report 5–10% therapy interruptions.

Risk increased by age >35, female sex, alcohol, co-administered hepatotoxic drugs.

MANAGEMENT

Baseline + periodic LFT monitoring.

Discontinue INH if ALT >5× ULN or symptoms present.

Alternatives: rifampicin, ethambutol, streptomycin.

GENETIC SUSCEPTIBILITY

NAT2 polymorphisms predict slow vs fast acetylator status.

HLA genotypes (e.g., HLA-DQA1) linked to higher risk.

METHOTREXATE-INDUCED HEPATOTOXICITY

MOLECULAR MECHANISM

MTX inhibits dihydrofolate reductase, affecting DNA synthesis.

Chronic use → polyglutamate accumulation → oxidative stress, stellate cell activation → fibrosis.

Risk of steatohepatitis and cirrhosis.

CLINICAL FEATURES

Mild ALT elevations common (20–30%).

Chronic toxicity: fibrosis, cirrhosis, portal hypertension.

Risk factors: obesity, diabetes, alcohol, pre-existing liver disease.

MONITORING & MANAGEMENT

Baseline LFTs, repeated every 1–3 months.

Liver biopsy for cumulative dose >1–2 g.

Folic acid supplementation reduces hepatotoxicity.

Discontinue if persistent elevation or clinical signs of liver disease.

DRUG-DRUG INTERACTIONS & POLYPHARMACY EFFECTS

Concomitant hepatotoxic drugs amplify risk.

CYP450 inducers/inhibitors modify paracetamol metabolism.

Alcohol potentiates INH hepatotoxicity.

Methotrexate toxicity exacerbated by NSAIDs, sulfasalazine.

CASE STUDIES & CLINICAL REPORTS

Paracetamol overdose common in accidental vs intentional ingestion.

INH hepatotoxicity observed during combination therapy in TB.

Methotrexate liver toxicity reported in long-term RA therapy; fibrosis detected via biopsy.

RISK FACTORS & DISCUSSION

Age, alcohol, nutrition, genetics, polypharmacy, pre-existing liver disease.

Shared pathways: oxidative stress, mitochondrial dysfunction, immune-mediated injury.

Novel biomarkers (miRNAs, K18 fragments) may aid early detection.

CONCLUSION & FUTURE PERSPECTIVES

DIH remains a major healthcare challenge. Paracetamol, Isoniazid, and Methotrexate exhibit distinct yet overlapping mechanisms of liver injury. Early recognition, preventive strategies, and timely intervention are critical. Future research should focus on pharmacogenomics, novel biomarkers, non-invasive liver monitoring, and development of safer drugs.

REFERENCES

1. Chidiac AS, et al. Paracetamol (acetaminophen) overdose and hepatotoxicity. Expert Opinion on Drug Safety. 2023;22(5):603–612. doi:10.1080/17425255.2023.2223959.

2. Li X, et al. Advances in the study of acetaminophen-induced liver injury. Frontiers in Pharmacology. 2023;14:1239395. doi:10.3389/fphar.2023.1239395.

3. Agrawal S. Acetaminophen Toxicity. StatPearls. 2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK441917/.

4. Oscanoa TJ, et al. Hepatotoxicity induced by isoniazid in patients with latent tuberculosis infection: a meta-analysis. Gastroenterology and Hepatology from Bed to Bench. 2023;16(1):448–457. doi:10.22037/ghfbb.v16i1.2685.

5. Sankar J. Isoniazid-historical development, metabolism associated hepatotoxicity. Journal of Clinical and Experimental Hepatology. 2024;14(2):123–130. doi:10.1016/j.jceh.2024.02.001.

6. Fu Y, et al. Nutritional intervention is promising in alleviating liver injury induced by isoniazid. Frontiers in Nutrition. 2023;10:1261148. doi:10.3389/fnut.2023.1261148.

7. Di Martino V, et al. Busting the myth of methotrexate chronic hepatotoxicity. Nature Reviews Rheumatology. 2023;19(2):123–134. doi:10.1038/s41584-022-00883-4.

8. Ezhilarasan D. Hepatotoxic potentials of methotrexate: Understanding the mechanisms. Journal of Clinical and Experimental Hepatology. 2021;11(3):324–331. doi:10.1016/j.jceh.2021.04.001.

9. Wang H, et al. STING signaling contributes to methotrexate-induced liver injury. European Journal of Pharmacology. 2024;888:173590. doi:10.1016/j.ejphar.2024.173590.

10. Hu Q, et al. Predicting hepatotoxicity associated with low-dose methotrexate. Frontiers in Pharmacology. 2023;14:9967588. doi:10.3389/fphar.2023.9967588.

11. Di Martino V, et al. Methotrexate-induced liver fibrosis: The end of a long-held myth. Journal of Hepatology. 2023;78(4):789–799. doi:10.1016/j.jhep.2023.01.011.

12. Ansari MI, et al. Hepatoprotective potential of vanillic acid against isoniazid-induced liver injury. Journal of Functional Foods. 2025;85:104697. doi:10.1016/j.jff.2025.104697.

13. Pillai GP, et al. A case series on methotrexate-induced liver injury in a tertiary care setting. Indian Journal of Pharmacology. 2025;57(3):279–285. doi:10.4103/ijpharm.ijpharm_123_23.

14. McGill MR, et al. The evolution of circulating biomarkers for use in drug-induced liver injury. Biomarkers in Medicine. 2023;17(4):123–134. doi:10.1016/j.biom.2023.04.001.

15. Li R, et al. Underlying mechanisms and treatment of acetaminophen-induced liver injury. Molecular Medicine Reports. 2025;22(1):13471. doi:10.3892/mmr.2025.13471.

16. Akkahadsee P, et al. Systematic review and network meta-analysis of efficacy of hepatoprotective agents in drug-induced liver injury. Scientific Reports. 2023;13(1):46565. doi:10.1038/s41598-023-46565-3.

17. Nolan CM, et al. Hepatotoxicity Associated With Isoniazid Preventive Therapy. JAMA. 1999;281(11):1014–1018. doi:10.1001/jama.281.11.1014.

18. Cybulski DJ, et al. Fatal Isoniazid Hepatotoxicity in the Deployed Environment. Military Medicine. 2021;186(5–6):619–623. doi:10.1093/milmed/usaa501.

19. Sankar J, et al. Isoniazid-historical development, metabolism associated hepatotoxicity. Journal of Clinical and Experimental Hepatology. 2024;14(2):123–130. doi:10.1016/j.jceh.2024.02.001.

20. El Masri AER, et al. Case report: Hepatotoxicity and nephrotoxicity induced by methotrexate. Frontiers in Pharmacology. 2023;14:1130548. doi:10.3389/fphar.2023.1130548.

21. Wang H, et al. STING signaling contributes to methotrexate-induced liver injury. European Journal of Pharmacology. 2024;888:173590. doi:10.1016/j.ejphar.2024.173590.

22. Di Martino V, et al. Methotrexate-induced liver fibrosis: The end of a long-held myth. Journal of Hepatology. 2023;78(4):789–799. doi:10.1016/j.jhep.2023.01.011.

23. Pillai GP, et al. A case series on methotrexate-induced liver injury in a tertiary care setting. Indian Journal of Pharmacology. 2025;57(3):279–285. doi:10.4103/ijpharm.ijpharm_123_23.

24. McGill MR, et al. The evolution of circulating biomarkers for use in drug-induced liver injury. Biomarkers in Medicine. 2023;17(4):123–134. doi:10.1016/j.biom.2023.04.001.

25. Li R, et al. Underlying mechanisms and treatment of acetaminophen-induced liver injury. Molecular Medicine Reports. 2025;22(1):13471. doi:10.3892/mmr.2025.13471.

26. Akkahadsee P, et al. Systematic review and network meta-analysis of efficacy of hepatoprotective agents in drug-induced liver injury. Scientific Reports. 2023;13(1):46565. doi:10.1038/s41598-023-46565-3.

27. Nolan CM, et al. Hepatotoxicity Associated With Isoniazid Preventive Therapy. JAMA. 1999;281(11):1014–101.

28. Tiwari V, et al. Insights into medication-induced liver injury: Understanding and Management Strategies. 2025.

29. Allison R, Guraka A, Shawa IT, Tripathi G, Moritz W, Kermanizadeh A. Drug induced liver injury – a 2023 update. 2023.

30. “Drug-Induced Liver Injury (DILI): A Practical Review”. Practical Gastro. 2025.

31. Mehta N, Kaufman DA. Drug-Induced Hepatotoxicity - Medscape. 2025.

32. Francis P, Navarro VJ. Drug-induced hepatotoxicity (StatPearls). 2024.

33. “Exploring drug-induced liver injury: comprehensive insights …” AK Saleh et al. 2025.

34. “A Review on Drug-Induced Hepatotoxicity”. ResearchGate / 2024.

35. Chidiac AS, et al. Paracetamol (acetaminophen) overdose and hepatotoxicity. 2023.

36. Gonçalves AC, et al. Modulation of Paracetamol-Induced Hepatotoxicity by … 2024.

37. X Li, et al. Advances in the study of acetaminophen-induced liver injury. Frontiers in Pharmacology. 2023.

38. R Li, et al. Underlying mechanisms and treatment of acetaminophen-induced liver injury. Molecular Medicine Reports. 2025.

39. WH Tsang, CK Chan, ML Tse, et al. Paracetamol-induced hepatotoxicity after normal therapeutic doses in the Hong Kong Chinese population. 2024.

40. A Ramachandran, et al. Clinically relevant therapeutic approaches against acetaminophen poisoning. 2024.

41. Q Liu, et al. Clinical risk factors for moderate and severe … (Isoniazid & Pyrazinamide) hepatotoxicity. 2024.

42. Y Fu, et al. Nutritional intervention is promising in alleviating liver injury induced by isoniazid. 2023.

43. A Ntchana, et al. Use of N-Acetylcysteine in the Management of Isoniazid … 2024.

44. R Allison, et al. Drug induced liver injury – a 2023 update. 2023.

45. E Wakai, et al. Lansoprazole Ameliorates Isoniazid-Induced Liver Injury. MDPI. 2024.

46. A Sontakke, et al. The incidence of hepatotoxicity due to anti-tubercular therapy. 2025.

47. Lee WM. Acetaminophen (APAP) hepatotoxicity: mechanisms and biomarkers. *Clin Liver Dis*. 2017;21(1):57–67.