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PARACETAMOL-INDUCED HEPATOTOXICITY: A COMPREHENSIVE REVIEW OF MECHANISMS, BIOMARKERS, AND THERAPEUTIC ADVANCES

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ABSTRACT

Background: Paracetamol (acetaminophen) is one of the most frequently used drugs for relieving pain and fever. Although safe at therapeutic doses, an overdose can lead to serious liver damage and is a major contributor to drug-induced liver injury worldwide. **Objective**: This review presents an overview of paracetamol-induced liver toxicity, exploring mechanisms of injury, risk factors, diagnostic approaches, and both conventional and emerging treatments including natural hepatoprotective agents. **Methods**: Peer-reviewed studies were examined to summarize current understanding of paracetamol pharmacokinetics, liver toxicity mechanisms, diagnostic markers, and novel therapeutic strategies. **Results**: The primary toxic effect results from the formation of a reactive metabolite (NAPQI), which depletes glutathione and causes oxidative stress, mitochondrial dysfunction, and hepatocyte death. Factors like chronic alcohol intake, malnutrition, and genetics can worsen toxicity. While N-acetylcysteine remains the standard antidote, new therapies involving antioxidants and phytochemicals have shown promise in experimental studies. **Conclusion**: Paracetamol-induced hepatotoxicity is a preventable but potentially life-threatening condition. Early intervention is crucial, and recent advances in biomarkers and therapeutic agents offer hope for better management and outcomes.

KEYWORDS: Paracetamol, Acetaminophen, Hepatotoxicity, N-acetylcysteine, Oxidative stress, Glutathione, Mitochondrial dysfunction, Biomarkers, Necroptosis, Liver injury, Antioxidants

1. INTRODUCTION

Paracetamol (acetaminophen) is one of the most widely used over-the-counter medications for pain relief and fever reduction. Its popularity is due to its effectiveness, low cost, and relatively mild gastrointestinal side effects compared to nonsteroidal anti-inflammatory drugs (NSAIDs).[1] However, despite its perceived safety, paracetamol overdose remains a leading cause of acute liver failure (ALF) in many countries.[2,3]

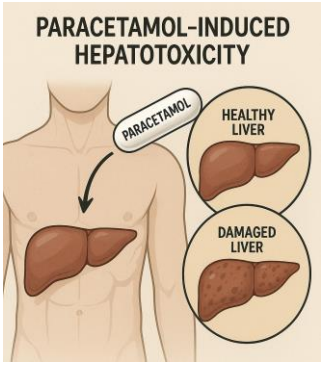

Figure 1: Paracetamol induced hepatotoxity.

Under normal therapeutic conditions, paracetamol is primarily metabolized in the liver through glucuronidation and sulfation. A small fraction is oxidized by cytochrome P450 enzymes to produce a highly reactive intermediate, N-acetyl-p-benzoquinone imine (NAPQI). This toxic metabolite is usually detoxified by conjugation with glutathione. In overdose situations, however, glutathione stores become depleted, allowing NAPQI to bind to cellular proteins, leading to oxidative stress, mitochondrial damage, and hepatocyte necrosis.[4,5]

Recent studies have expanded the understanding of paracetamol-induced liver injury beyond oxidative damage. New evidence highlights the role of sterile inflammation, immune system activation, and regulated cell death pathways such as necroptosis and apoptosis in amplifying hepatotoxicity.[6] These complex mechanisms help explain the variability in individual responses to overdose, which may also be influenced by genetic polymorphisms, nutritional status, alcohol consumption, and concurrent medication use.[7]

Timely administration of N-acetylcysteine (NAC) remains the most effective antidote, especially when given within 8–10 hours of overdose. However, delayed diagnosis and treatment can worsen outcomes, particularly in settings with limited access to healthcare. Consequently, research is increasingly focused on early diagnostic biomarkers and the development of novel hepatoprotective agents, including plant-based antioxidants and targeted molecular therapies.[8]

This review provides a comprehensive evaluation of the pharmacology, toxicokinetics, biomarkers, experimental models, and current as well as emerging therapeutic strategies related to paracetamol-induced hepatotoxicity. Understanding these mechanisms is crucial for advancing clinical management and minimizing the global burden of drug-induced liver injury.

2. PHARMACOLOGY OF PARACETAMOL: Mechanism of Action and ADME

Paracetamol (acetaminophen) is a widely used non-opioid analgesic and antipyretic, favored for its efficacy in treating mild to moderate pain and fever. Unlike NSAIDs, it has minimal peripheral anti-inflammatory activity and does not significantly inhibit cyclooxygenase (COX)-1 or COX-2 enzymes outside the central nervous system.[9]

2.1 Mechanism of Action

The analgesic and antipyretic effects of paracetamol are believed to arise mainly from central inhibition of prostaglandin synthesis, particularly prostaglandin E2 (PGE2) in the hypothalamus.[10] One proposed mechanism involves interaction with a COX isoform termed COX-3, although its functional relevance in humans remains debatable.[11]

Paracetamol also appears to inhibit the peroxidase function of COX enzymes in low-peroxide environments typical of the CNS.[12]

Additionally, its central analgesic activity may involve activation of descending serotonergic pathways, modulation of TRPV1 channels, and cannabinoid receptor interaction through its metabolite AM404.[13]

2.2 Absorption

Following oral administration, paracetamol is rapidly absorbed from the gastrointestinal tract, reaching peak plasma levels within 30–60 minutes. While food can delay this process, it does not significantly alter its high oral bioavailability (70–90%).[14]

2.3 Distribution

Paracetamol is widely distributed in body tissues, with low protein binding (10–25%) and effective cerebrospinal fluid penetration. Its volume of distribution is approximately 0.9–1.0 L/kg in adults.[15]

2.4 Metabolism

In the liver, paracetamol undergoes glucuronidation (40–67%) and sulfation (20–46%) to form non-toxic, water-soluble metabolites. A small fraction (<10%) is oxidized by CYP450 enzymes, especially CYP2E1, into the reactive metabolite N-acetyl-p-benzoquinone imine (NAPQI).[4] Normally, NAPQI is detoxified by glutathione conjugation, but in overdose or GSH-deficient states, it accumulates and binds to cellular proteins, triggering hepatocellular injury.[16]

2.5 Excretion

Paracetamol and its conjugated metabolites are mainly excreted via urine, with 90–100% cleared within 24 hours. Less than 5% of the parent drug is excreted unchanged. The elimination half-life is about 1.5 to 3 hours in healthy individuals but increases significantly in liver dysfunction or overdose.[17]

3. METABOLISM AND TOXIC MECHANISM OF PARACETAMOL

Paracetamol's hepatotoxicity is closely tied to its hepatic metabolism. While therapeutic doses are primarily cleared through conjugation pathways, a small but significant portion undergoes oxidative metabolism, producing a reactive intermediate that initiates liver injury.[15]

3.1 Normal Metabolic Pathways

Roughly 90% of an ingested paracetamol dose is metabolized in the liver via phase II conjugation—mainly glucuronidation (40–67%) and sulfation (20–46%)—catalyzed by uridine diphosphate-glucuronosyltransferase (UGT) and sulfotransferase (SULT) enzymes.

These pathways yield non-toxic, water-soluble metabolites that are excreted in the urine.[18] A minor fraction (2–5%) is excreted unchanged.[19]

3.2 Formation of Toxic Metabolite (NAPQI)

A small but critical portion of paracetamol undergoes cytochrome P450-mediated oxidation—primarily by CYP2E1 and, to a lesser extent, CYP1A2 and CYP3A4—leading to the formation of N-acetyl-p-benzoquinone imine (NAPQI), a highly reactive metabolite.[20]

Under normal conditions, NAPQI is neutralized through conjugation with reduced glutathione (GSH). However, during overdose or in glutathione-depleted individuals, NAPQI accumulates and forms covalent adducts with cellular proteins, triggering hepatotoxicity.[21]

3.3 Hepatotoxic Mechanisms

NAPQI-induced liver injury involves oxidative stress, lipid peroxidation, and mitochondrial dysfunction, leading to ATP depletion and impaired calcium homeostasis. These changes ultimately result in centrilobular hepatocyte necrosis—a hallmark of paracetamol-induced liver damage.[8]

The hepatocellular damage also triggers the release of damage-associated molecular patterns (DAMPs), which activate innate immune responses and intensify inflammation.[22] Recent evidence highlights the role of regulated cell death pathways—such as necroptosis, pyroptosis, and autophagy—in influencing injury severity. Additionally, interactions between hepatocytes and non-parenchymal cells (e.g., Kupffer cells and hepatic stellate cells) contribute to the propagation and resolution of hepatic injury.[23]

4. RISK FACTORS

Table No 1: Risk Factors Contributing to Paracetamol-Induced Hepatotoxicity.

Risk Factor	Mechanism	Impact	Reference
Dose-Dependent Toxicity	At high doses (>150 mg/kg), conjugation pathways are saturated, diverting metabolism to CYP-mediated NAPQI formation.	Sharp increase in hepatocyte necrosis and liver failure risk during overdose.	[24]
Glutathione Depletion	Conditions like fasting, malnutrition, and aging reduce GSH, impairing detoxification of NAPQI.	Enhanced oxidative stress and hepatocellular damage even at near-therapeutic doses.	[25]
Chronic Alcohol Use	Induces CYP2E1 (increasing NAPQI) and depletes GSH; alcohol liver disease worsens vulnerability.	Dual mechanism increases toxicity risk significantly, even at low-to-moderate doses.	[26]
Genetic Polymorphisms	Variants in CYP2E1, UGT, or SULT genes can alter metabolic efficiency and increase NAPQI formation.	Inter-individual differences in susceptibility; some patients develop toxicity at safe doses.	[27]
Drug Interactions	Enzyme inducers (rifampicin, phenytoin) increase CYP activity; some drugs also reduce antioxidant defense.	Synergistic toxicity; increased hepatic stress and NAPQI burden.	[28]
Pre-existing Liver Disease	Liver diseases impair drug clearance and detoxification pathways.	Reduced hepatic resilience; even normal doses may trigger significant injury.	[29]
Age-Related Differences	Infants have immature enzymes and low GSH; older children rely on sulfation, which may offer partial protection.	Neonates are highly vulnerable; dosing must be closely monitored in early life.	[30]

5. EXPERIMENTAL MODELS OF PARACETAMOL-INDUCED HEPATOTOXICITY

Experimental models are crucial for understanding the hepatotoxic mechanisms of paracetamol and for evaluating hepatoprotective interventions. Both in vivo and in vitro systems are widely used to mimic human liver injury and assess biochemical and histological changes.[31]

In vivo rodent models, particularly using mice and rats, are most commonly employed due to their metabolic similarities to humans. A dose of 250–500 mg/kg in mice reliably induces centrilobular necrosis, with rats requiring higher doses due to more efficient sulfation.[32]

These models allow evaluation of serum liver enzymes (ALT, AST), oxidative stress markers (GSH, MDA), inflammatory cytokines (TNF-α, IL-6), and therapeutic responses to interventions like N-acetylcysteine or herbal extracts.[4]

In vitro models provide mechanistic insights while reducing animal use. Primary hepatocytes offer accurate metabolic profiles but have limited viability. HepG2 cells are frequently used due to ease of culture, though they lack full enzymatic function. More advanced **3D liver spheroids and organoids** better mimic in vivo liver architecture and support chronic toxicity testing.[33,34]

Despite their utility, these models have limitations. Rodents do not always replicate human responses, and in vitro systems may lack immune interactions and spatial liver organization. Therefore, an integrated approach combining in vivo, in vitro, and computational models offers the most comprehensive evaluation of paracetamol-induced hepatotoxicity.[35]

6. CLINICAL MANIFESTATIONS AND DIAGNOSIS OF PARACETAMOL-INDUCED HEPATOTOXICITY

Paracetamol overdose presents with a characteristic progression of clinical symptoms and biochemical changes. Early identification is essential to prevent irreversible liver damage, particularly in delayed or intentional overdoses.[2]

6.1 Stages of Toxicity

Paracetamol poisoning unfolds in four overlapping stages:

- **Stage I (0–24 hrs):** Initial symptoms include nausea, vomiting, fatigue, and diaphoresis. Liver enzymes are often within normal limits.[26]
- **Stage II (24–72 hrs):** Symptoms may temporarily improve. However, hepatic injury becomes evident with elevated ALT, AST, and bilirubin levels. Right upper quadrant pain and hepatomegaly may appear.[36]

- **Stage III (72–96 hrs):** This is the peak of liver damage. Clinical features include jaundice, coagulopathy, hypoglycemia, encephalopathy, and possibly renal failure or metabolic acidosis. This phase has the highest mortality risk.[37]

- **Stage IV (4–14 days):** In survivors, liver function gradually returns to normal. Some may recover completely, while others progress to acute liver failure requiring transplantation.[38]

6.2 Diagnostic Tools

Diagnosis is based on clinical history and laboratory evaluation:

- **Paracetamol Levels:** The **Rumack-Matthew nomogram** helps assess hepatotoxic risk within 4–24 hours of ingestion and guides antidotal use of **N-acetylcysteine (NAC)**.[39]

- **Liver Function Tests (LFTs):** Dramatic elevations in ALT and AST (often >1,000 IU/L) are typical. Bilirubin, ALP, and INR help gauge severity.[40]

- **Renal Function Tests:** Acute kidney injury is a complication in severe cases and requires monitoring of creatinine and urea.[41]

- **Coagulation Profile:** An elevated INR and prolonged prothrombin time reflect hepatic synthetic dysfunction and serve as poor prognostic indicators.[42]

- **Arterial Blood Gas (ABG):** Metabolic acidosis and elevated lactate levels suggest tissue hypoxia and systemic involvement.

6.3 Emerging Biomarkers

In addition to standard liver panels, newer biomarkers offer earlier and more precise detection of liver injury:

- **Glutamate dehydrogenase (GLDH)** – Reflects mitochondrial damage
- **Keratin-18 (K18/M65)** – Indicates apoptotic and necrotic cell death
- **MicroRNA-122 (miR-122)** – Liver-specific marker of early injury
- **High mobility group box 1 (HMGB1)** – Marker of cell stress and immune activation[43]

7. BIOMARKERS OF LIVER INJURY IN PARACETAMOL TOXICITY

Timely detection of liver injury is crucial in paracetamol overdose, as early intervention can significantly reduce morbidity and mortality. While standard liver function tests are widely used, they often rise only after substantial hepatocellular damage has occurred, prompting the need for more sensitive and specific biomarkers.[44]

7.1 Traditional Biomarkers

- **ALT and AST** are the most common enzymes for assessing liver injury. In paracetamol toxicity, levels can exceed 1,000 IU/L, reflecting extensive hepatocyte necrosis. However, they lack specificity and may rise in other hepatic or muscular disorders.[45]

- **Bilirubin** serves as a marker of impaired hepatic excretion and becomes elevated during late stages of toxicity or in cases of severe cholestasis.[46]

- **Prothrombin Time (PT)/INR** indicates liver synthetic function. Prolonged PT or an INR >1.5 often signals worsening liver failure and correlates with poor outcomes.[47]

7.2 Emerging Biomarkers

Recent research has identified novel markers that detect liver damage earlier or offer better specificity:

- **Glutamate Dehydrogenase (GLDH):** A mitochondrial enzyme released during necrotic hepatocyte injury; it is more liver-specific than ALT and less affected by muscle breakdown.[48]

- **High Mobility Group Box 1 (HMGB1):** A nuclear protein released during cell necrosis and inflammation. Distinct acetylated forms may differentiate necrosis from apoptosis.[49]

- **Keratin-18 (K18):** Released during cell death; M65 reflects necrosis while M30 indicates apoptosis. These markers can help clarify the dominant mechanism of injury.[50]

- **MicroRNA-122 (miR-122):** A liver-specific microRNA that rises early in hepatotoxicity, even before ALT elevations. It offers high sensitivity and specificity for liver injury.[51]

- **Cytokines like IL-18 and M-CSF** are under investigation as indicators of immune-mediated liver damage, reflecting inflammation severity.

7.3 Prognostic Utility

Combining emerging biomarkers with traditional tests enhances diagnostic precision and prognostic assessment. For example, **miR-122** and **K18** may outperform existing tools like the **King's College Criteria**, which rely on INR, creatinine, and encephalopathy to predict liver transplant need.[52] Early integration of these markers into clinical settings and point-of-care platforms may facilitate timely and individualized treatment decisions.

8. HEPATOPROTECTIVE INTERVENTIONS IN PARACETAMOL-INDUCED HEPATOTOXICITY

Early intervention in paracetamol overdose is crucial to limit hepatocellular injury and prevent progression to acute liver failure. Current treatments target the reduction of NAPQI accumulation, enhancement of glutathione (GSH) reserves, and support of hepatic repair.

Alongside standard antidotal therapy, emerging experimental and natural compounds are being evaluated for their hepatoprotective effects.[15]

8.1 N-Acetylcysteine (NAC)

NAC remains the cornerstone of treatment for paracetamol toxicity. It restores hepatic GSH levels, detoxifies NAPQI, and improves microvascular perfusion. When administered within 8 hours of ingestion, NAC significantly reduces the risk of liver damage, though delayed use still offers benefit due to its antioxidant properties.[53]

- **Oral NAC:** Administered over 72 hours and generally used in mild-to-moderate overdose.
- **Intravenous NAC:** Delivered over 21 hours, preferred in patients with altered mental status, persistent vomiting, or fulminant hepatic failure.[54]

8.2 Adjunctive and Supportive Therapies

- **Activated Charcoal:** Limits drug absorption when given within 1–2 hours post-ingestion.
- **Antioxidants (Vitamin E, C):** May help reduce oxidative stress, though primarily used as adjuncts to NAC.[4]
- **S-Adenosylmethionine (SAMe):** Enhances GSH synthesis and supports mitochondrial integrity.
- **Cimetidine:** A CYP inhibitor proposed to reduce NAPQI formation, but clinical efficacy is unconfirmed.

8.3 Liver Transplantation

For patients with advanced hepatic failure unresponsive to medical therapy, **orthotopic liver transplantation (OLT)** remains the definitive intervention. Criteria for transplantation include INR > 6.5, severe encephalopathy, creatinine > 300 µmol/L, or metabolic acidosis with pH < 7.3.[44]

8.4 Phytochemicals and Herbal Agents

Many plant-derived compounds show hepatoprotective activity in experimental settings:

- **Silymarin (Milk Thistle):** Antioxidant and membrane-stabilizing effects.[55]
- **Curcumin (Turmeric):** Reduces oxidative injury and pro-inflammatory cytokine production.
- **Diosgenin and Trigonelline:** Studied in preclinical models for their antioxidant and anti-inflammatory roles.[56]
- **Flavonoids and Alkaloids:** From various medicinal plants, these show potential in mitigating hepatocellular stress.

8.5 Experimental Molecular Approaches

Cutting-edge therapies are targeting molecular pathways in paracetamol toxicity:

- **Inhibitors of JNK, RIPK1, and MLKL:** Suppress necroptosis and inflammation.
- **Mitochondria-targeted antioxidants (e.g., MitoQ):** Protect against oxidative mitochondrial injury.
- **MicroRNA-based therapies:** Exogenous miRNAs and siRNAs modulate stress, apoptosis, and inflammatory signaling.[43]

Although many of these agents are in preclinical or early clinical stages, they offer promising avenues for improving hepatoprotection beyond current standard care.

9. ROLE OF ANTIOXIDANTS AND PHYTOCHEMICALS IN HEPATOPROTECTION

Oxidative stress is a central mechanism in paracetamol-induced hepatotoxicity, making antioxidants a crucial focus in the search for hepatoprotective therapies. Natural products, particularly phytochemicals with antioxidant and anti-inflammatory properties, have gained attention for their potential to mitigate liver injury and support hepatic recovery. These agents act by enhancing endogenous defense systems, reducing free radical generation, and preventing cellular damage.[57,15]

9.1 Oxidative Stress in Paracetamol Toxicity

Excessive production of NAPQI in overdose conditions leads to the depletion of glutathione (GSH), the liver's primary antioxidant. The resulting redox imbalance promotes mitochondrial dysfunction, lipid peroxidation, protein oxidation, and ultimately hepatocyte necrosis. Interventions that counteract these processes can protect liver cells and improve outcomes.[4]

9.2 Endogenous and Synthetic Antioxidants

- **N-Acetylcysteine (NAC):** Functions as both a GSH precursor and a direct free radical scavenger. Its therapeutic success reinforces the importance of antioxidant defense in paracetamol toxicity.[57,15]
- **Vitamin E (α-tocopherol):** A lipid-soluble antioxidant that protects cell membranes from lipid peroxidation. Its co-administration has shown protective effects in experimental models.[58]
- **Vitamin C (ascorbic acid):** A water-soluble antioxidant that reduces oxidative damage and supports tissue regeneration.[59]
- **Melatonin:** Exhibits antioxidant, anti-inflammatory, and anti-apoptotic properties. It modulates nitric oxide production and supports mitochondrial function.[60]

9.3 Phytochemicals with Hepatoprotective Potential

Numerous plant-derived compounds have demonstrated efficacy against paracetamol-induced liver damage in experimental settings:

- **Silymarin (from Silybum marianum):** Stabilizes hepatocyte membranes, reduces lipid peroxidation, and increases SOD and CAT levels. It is one of the most studied herbal hepatoprotective agents.[4,61]
- **Curcumin (from *Curcuma longa*):** Inhibits NF-κB signaling, reduces pro-inflammatory cytokines, and enhances antioxidant enzyme activity.[62]
- **Trigonelline (from fenugreek):** Demonstrated dose-dependent hepatoprotection via enhancement of antioxidant enzymes (SOD, CAT) and reduction of

MDA in animal models.[58,63]

- **Diosgenin (from *Dioscorea* species):** A steroidal saponin with antioxidant, anti-inflammatory, and anti-apoptotic properties. It reduces liver enzyme elevation and restores histoarchitecture.[58,64]
- **Flavonoids (quercetin, kaempferol, apigenin):** Known to inhibit ROS generation and modulate inflammatory pathways.[65]
- **Resveratrol (from grapes):** Activates SIRT1, reduces mitochondrial oxidative damage, and prevents hepatocyte apoptosis.[66]

9.4 Limitations and Future Potential

Although many of these phytochemicals have shown promise in preclinical studies, challenges remain, including low bioavailability, variability in plant extract composition, and lack of clinical trials. Nanotechnology-based formulations and standardized extracts may enhance efficacy and reproducibility in future research.[67]

10. MOLECULAR TARGETS AND EMERGING THERAPIES IN PARACETAMOL-INDUCED HEPATOTOXICITY

Recent advancements in molecular pharmacology have expanded our understanding of paracetamol-induced liver injury, highlighting new therapeutic avenues beyond traditional detoxification and antioxidant strategies. These novel interventions aim to interrupt mitochondrial dysfunction, cell death signaling, and inflammatory cascades—key contributors to hepatocellular damage.[4,31]

10.1 Targeting Mitochondrial Dysfunction

Mitochondria are central to the progression of liver injury, where NAPQI-induced oxidative stress disrupts membrane potential and triggers ATP depletion and calcium overload.[68]

Mitochondria-targeted antioxidants such as MitoQ and SkQ1 have shown promise by scavenging reactive oxygen species at the source.[68] Cyclosporine A, which inhibits the mitochondrial permeability transition pore, has demonstrated hepatoprotective effects in preclinical studies, although its immunosuppressive properties limit clinical utility.[69]

10.2 Inhibition of Regulated Cell Death

Regulated forms of cell death, including necroptosis and apoptosis, are critical in paracetamol toxicity. Inhibitors targeting receptor-interacting protein kinases (RIPK1, RIPK3) and mixed lineage kinase domain-like protein (MLKL) have been shown to reduce necroinflammatory injury in animal models.[4,70] Additionally, c-Jun N-terminal kinase (JNK) inhibitors prevent mitochondrial dysfunction and hepatocyte apoptosis by blocking downstream signaling.[71]

10.3 Anti-inflammatory Strategies

Inflammation following hepatocyte necrosis exacerbates liver injury through cytokine release and immune activation. Inhibitors of tumor necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β), and toll-like receptor 4 (TLR4) have shown potential in dampening the inflammatory response and preventing further damage.[72,73]

10.4 RNA-Based and Gene Therapies

RNA-targeted therapies are emerging as precision tools in hepatoprotection. Small interfering RNAs (siRNAs) and antisense oligonucleotides targeting pro-apoptotic genes like TNF-α, Bax, and FasL have demonstrated efficacy in experimental settings.[74] MicroRNA-based interventions, especially miR-122 mimics, help stabilize hepatocytes and support regeneration after injury.[75]

10.5 Stem Cell and Regenerative Therapies

Stem cell-based strategies, particularly using mesenchymal stem cells (MSCs) and induced pluripotent stem cells (iPSCs), offer regenerative potential by replacing damaged hepatocytes and modulating immune responses. Though promising in preclinical studies, challenges remain in ensuring safety, immunogenicity, and ethical compliance before clinical translation.[76]

11. CONCLUSION AND FUTURE PERSPECTIVES

Paracetamol remains one of the most commonly used drugs worldwide for pain and fever relief due to its effectiveness and general safety at recommended doses. However, its potential to cause serious liver injury in overdose situations underscores the need for vigilance and deeper understanding of its toxic profile. The hepatotoxicity results primarily from excessive formation of the reactive metabolite NAPQI, leading to oxidative stress, glutathione depletion, mitochondrial injury, and regulated cell death.

Timely diagnosis and administration of N-acetylcysteine (NAC) are vital to reducing morbidity and mortality, but treatment options remain limited once severe liver injury has occurred. This has prompted intense research into new diagnostic biomarkers and targeted therapies. Promising directions include agents that modulate necroptosis and mitochondrial dysfunction, microRNA-based therapies, and regenerative approaches such as stem cell therapy.

Phytochemicals like silymarin, curcumin, diosgenin, and trigonelline have demonstrated protective effects in experimental models by targeting oxidative stress, inflammation, and apoptosis. While these compounds show potential, further clinical validation is necessary.

Similarly, novel biomarkers like miR-122 and HMGB1 may allow earlier detection and better risk stratification in clinical practice.

In summary, although paracetamol-induced liver injury is largely preventable, it remains a significant public health concern. A combination of early intervention, improved diagnostics, and the integration of conventional and emerging therapies may lead to more effective, personalized management strategies in the future.

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