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# Acetaminophen Liver Toxicity (Review)

**Kalpana Ramachandran[1], Pushpalatha tanneeru[2], Leena Dennis Joseph[3]**
[1]Professor and Head, Department of Anatomy, SRIHER Porur, Chennai, Tamil Nadu, India
[2]PhD scholar, Dept. Of Anatomy, SRIHER Porur, Chennai.
[3]Professor and HOD, Department of pathology, SRIHER,Porur,Chennai.

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**ABSTRACT**
**Acetaminophen, also known as paracetamol, is among the most commonly used over-the-counter analgesics and antipyretics globally. While generally safe when taken at therapeutic doses, overdose frequently results in hepatotoxicity, leading to acute liver failure. Acetaminophen-induced hepatotoxicity is now the most common cause of acute liver failure in both the United States and the United Kingdom. The underlying mechanism involves the metabolism of acetaminophen into the highly reactive toxic metabolite, N-acetyl-p-benzoquinoneimine , which depletes hepatic glutathione stores and binds covalently to mitochondrial proteins, causing hepatocellular necrosis. Effective intervention relies on early diagnosis and treatment with N-acetylcysteine . Liver transplantation remains the definitive therapy for advanced acute liver failure, offering the best survival rate when recovery is unlikely. However, widespread availability and misconceptions about its safety contribute to high rates of unintentional overdose and significant associated healthcare costs.**



## INTRODUCTION:

Acetaminophen (APAP), known internationally as paracetamol, is one of the most popular and most commonly used analgesic and antipyretic drugs around the world. It is widely available over-the-counter (OTC), often in both single and multi-component preparations. (1)

Acetaminophen/paracetamol has a long history, with the chemical compound first synthesized in 1878. (2) Despite being discovered earlier, APAP gained prominence when it was determined in 1948 to be the active metabolite responsible for the analgesic effects of acetanilide and phenacetin. It was first sold in 1955 by McNeil Laboratories as a prescribed analgesic and antipyretic drug for children under the brand name Tylenol Children's Elixir. One year later, 500-mg tablets were available OTC in Great Britain under the trade name Panadol (3)

When administered in therapeutic doses, APAP is considered relatively nontoxic and produces few side effects, particularly relating to the gastrointestinal tract, making it the **drug of choice** for patients in whom non-steroidal anti-inflammatory drugs (NSAIDs) are contraindicated (e.g., those with gastric ulcers, aspirin hypersensitivity, or coagulation impairments). The usual adult dosing is 325–650 mg every 4–6 hours or 1 g every 4–6 hours, not exceeding **4 g per day (4)**.in this study aim to review on acetaminophen toxicity in organ damage.

**Pathophysiology of Hepatotoxicity:**

The hepatotoxicity caused by acetaminophen (APAP), also known as paracetamol, is a critical consequence of overdose that can lead to acute liver failure (ALF). APAP is classified as a predictable hepatotoxin, meaning that the ensuing liver damage is dose-related, typically resulting in

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centrilobular necrosis within 24 to 48 hours after the time of overdose.

The underlying pathophysiology is complex and involves three primary mechanisms: the generation of a toxic metabolite, mitochondrial dysfunction, and the alteration of innate immunity (5).

Acetaminophen metabolism normally follows detoxification pathways, but these pathways become saturated during an overdose, redirecting the drug toward the production of a highly reactive, toxic intermediate (6)

In therapeutic doses, the majority of APAP is metabolized by the liver through conjugation pathways:1. Greater than 90% of APAP is metabolized to nontoxic phenolic glucuronide and sulfate conjugates by glucuronyltransferases and sulfotransferases, which are subsequently excreted in the urine.2. A small fraction, approximately 5% to 10%, of APAP is metabolized by the cytochrome P450 enzyme system, primarily the enzyme CYP2E1, into the highly reactive, electrophilic molecule known as N-acetyl-p-benzoquinoneimine (NAPQI) .(7)

:Normally, NAPQI is swiftly detoxified by conjugating with the antioxidant glutathione (GSH) to produce a harmless metabolite of mercapturic acid that is eliminated. Non-toxic sulfotransferases and glucuronyltransferases become saturated when APAP is overdosed. This redirects surplus APAP to the P450 system, resulting in the production of NAPQI in quantities that exhaust the hepatic GSH reserves. NAPQI starts to build up in the hepatocytes if GSH is not promptly restored. Subsequently, the accumulating NAPQI damages cells by establishing covalent connections with proteins, particularly the sulfhydryl groups on the cysteine and lysine residues of the mitochondrial proteins of hepatocytes.(7)

NAPQI's attachment to mitochondrial and cellular macromolecules starts a series of actions that immediately cause irreversible cell damage: NAPQI alters the structure and function of cellular proteins by creating covalent connections with them. Calcium ATPase activities decline as a result of this disruption, raising cytosolic calcium levels. The production of blebs in the cell membrane and subsequent loss of membrane integrity are caused by abnormal cellular calcium homeostasis, which also changes cell permeability (8&9). High levels of cytosolic calcium, along with the alteration of mitochondrial proteins caused by NAPQI binding, suppress adenosine triphosphate (ATP) synthesis and mitochondrial respiration. This results in the generation of peroxynitrite, a strong oxidant and nitrating agent, as well as mitochondrial oxidant stress.The breakdown of the mitochondrial membrane potential and the leakage of mitochondrial proteins into the cytoplasm of the cell are the results of this extensive disruption. Hepatocytes eventually experience oncotic necrosis as a result of the ATP production stopping and the changes that follow. (8 and 9)

The liver's native immune response significantly contributes to the progression of liver injury. The Cell death caused by the toxic APAP metabolites first activates Kupffer cells (KCs)—the phagocytic macrophages of the liver.(10)Tumor necrosis factor-$\alpha$ (TNF-$), interleukin-12, and interleukin-18 are among the proinflammatory mediators and cytokines released by activated KCs\alpha$).(11) These cytokines worsen hepatic damage by encouraging the recruitment and accumulation of neutrophils in the liver, a process known as the "inflammatory cascade." The hepatic pathophysiological response is changed when either TNF-$\alpha$ or interleukin-1$\alpha$ (IL-1$\alpha$) is selectively neutralized. These cytokines are produced in response to APAP injury. Pretreatment with antibodies against TNF-$\alpha$ or IL-1$\alpha$ reduced the increase in liver enzymes linked to damage at the 4-hour and 8-hour time points in mouse models, but only partially. (12). In contrast, the administration of antibodies against the naturally occurring IL-1 receptor antagonist (anti-IL-1ra) increased the degree of hepatic necrosis and serum enzyme concentrations, worsening the liver damage caused by APAP.(13).

The epidemiology of acetaminophen (APAP), or paracetamol, toxicity highlights its substantial role as a critical public health concern globally, particularly due to its capacity to cause acute liver failure (ALF).

Paracetamol is one of the most commonly used analgesic and antipyretic drugs worldwide. Despite being considered relatively nontoxic in therapeutic doses, paracetamol toxicity is one of the most common causes of poisoning worldwide. APAP is currently the most common cause of ALF in both the United States and the United Kingdom. Paracetamol overdose is the leading cause of acute poisoning in the United States.(14)

• In the United States, APAP toxicity accounts for a significant portion of acute hepatic injury cases. Studies have shown APAP toxicity accounting for 39% to 42% of all ALF cases. One report showed an increase in incidence of APAP-induced ALF from 28% in 1998 to 52% in 2003 .(15) It remains the almost exclusive cause of liver transplantation related to an acute drug overdose. National

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estimates for APAP toxicity include 26,000 hospitalizations and more than 450 deaths annually During the period 1990–1998, estimated national numbers included 56,000 emergency room visits, 26,000 hospitalizations, and 458 deaths annually related to acetaminophen-associated overdoses(16) . A 2009 annual report found 401 deaths caused by paracetamol or a paracetamol combination product reported to the American Association of Poison Control Centers' National Poison Data System (17).

In the United Kingdom (UK), paracetamol accounts for about 50% of self-poisoning cases every year. Paracetamol overdose causes around 200 deaths every year in the UK (18). Between 1993 and 1997, approximately 500 deaths annually in England and Wales were attributed to drugs containing paracetamol(19). Despite the high rate of overdose, a study in the UK reported that fewer than 10% of patients develop severe liver damage, and only 1% to 2% develop ALF following an acetaminophen overdose (20).The rate of paracetamol overdose in Scotland increased almost 400% between 1981–83 and 1991–93, with higher rates observed in more deprived areas(21).European countries show large variations, with Ireland having a six-times higher risk and the UK having a two-fold higher risk of liver transplant associated with paracetamol overdose compared with the average of other surveyed European countries(22)

Acetaminophen overdose results from three main types of ingestion: intentional, unintentional, and chronic supratherapeutic misuse.Dose Limitation in FDA in the United States mandated that the total amount of APAP in any prescription drug should not be more than 325 mg per tablet. When combining over-the-counter APAP with prescription opioids that contain it, this was done to avoid unintentional overdose. Pack Size Limitation Under UK law, pharmacists are only allowed to sell 32 tablets (16 g) of OTC APAP packs, whereas other retailers are only allowed to sell 16 tablets (8 g).

In patients with acetaminophen-induced ALF, 74% to 79% were women, 88% to 90% were of white ethnicity, and the median age was 36 to 37 years (27). Patients over the age of 40 have an increased risk of ALF, death, and need for liver transplantation after APAP overdose. In children under 5 years old, ingestion of toxic substances is almost invariably unintentional (28). In children, 53% of overdose presentations were due to unintentional ingestion and 3% due to dosage error. Intentional overdose was seen primarily in teenagers, most of whom were female.(29)

Paracetamol is one of the top ten most frequently involved exposure substances received at the Poison Control Center, Ain Shams University Hospitals, Egypt, during 2019. A survey revealed that only 24.4% of participants had good knowledge about paracetamol and its potential toxicities. (30)Paracetamol was among the most prevalent exposures in hospitalizations and poison information center consultations in a survey conducted at Tygerberg Academic Hospita in South Africa.(31)Paracetamol was the most often overdosed analgesic drug ( 57% of all analgesic poisoning) in calls received by the Ministry of Health Saudi Poisons Control Centers during 2017(32). Low rates of hepatotoxicity were observed among Asian patients with paracetamol overdose, even in cases of high doses and delayed hospitalization(33).

**Results and Findings on Acetaminophen Toxicity:**
Acetaminophen is one of the most widely used analgesics and antipyretics globally. Although it is considered relatively nontoxic when administered in therapeutic doses, toxicity is a common consequence of overdose, which can lead to acute liver failure (ALF).(34)

APAP is currently the most common cause of ALF in both the United States and the United Kingdom.( 35-38). In the US, studies have shown that APAP toxicity accounts for 39% to 42% of all ALF cases.(39). APAP remains the leading cause of liver transplantation related to acute drug overdose(40). National estimates for APAP toxicity in the United States include 26,000 hospitalizations and more than 450 deaths annually. In the UK, APAP accounts for about 50% of self-poisoning cases, resulting in around 200 deaths every year ◦ Morbidity and mortality are often greater with unintentional overdose due to delayed presentation and treatment.(41).

According to an Egyptian poll, only 24.4% of respondents knew enough about paracetamol and any possible toxicities associated with it. During the COVID-19 epidemic, the practice of giving more paracetamol than is permitted per day became much more common. Many participants believed that paracetamol was safer than other drugs and could recommend its use to others without a prescription (42).

**Pathophysiology and Mechanism of Toxicity:**
As a known hepatotoxin, acetaminophen causes dose-related centrilobular necrosis. The main causes of hepatotoxicity are changes in innate immunity, mitochondrial malfunction, and its toxic metabolite.When the hazardous metabolite N-

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acetyl-p-benzoquinoneimine (NAPQI) damages the liver directly, it is known as hepatotoxicity.(43).At therapeutic dosages, more than 90% of APAP is converted to safe glucuronide and sulfate conjugates. Only 5–10% of it is converted to NAPQI by cytochrome P450, primarily CYP2E1.Normally, NAPQI undergoes conjugation with glutathione (GSH) for detoxification. With overdose, the non-toxic metabolic pathways are saturated, diverting APAP to the P450 system, generating NAPQI in amounts that deplete glutathione stores.(44) Accumulated NAPQI forms covalent bonds with cellular proteins, leading to decreased calcium ATPase activity and loss of membrane integrity.(45)

ATP production and mitochondrial respiration are suppressed by NAPQI binding to mitochondrial proteins and elevated cytosolic calcium levels. This results in peroxynitrite generation and mitochondrial oxidant stress, which ultimately cause the collapse of the mitochondrial membrane potential and hepatocyte oncotic necrosis.46

The course of liver injury is significantly influenced by the activation of the liver's innate immune system, particularly Kupffer cells (hepatic macrophages). Cytokines such as IL-12, IL-18, TNF-$\alpha$, and IL-1$\alpha$ are released by activated Kupffer cells, activating natural killer cells, attracting neutrophils, and worsening hepatic damage. (47)

**Clinical Course and Diagnosis(48);**

**Table: 1 The signs and symptoms of untreated APAP overdose are generally divided into four phases:**

| Phase | Time Interval | Symptoms/Findings |
|---|---|---|
| **Phase 1** | First 24 hours | Anorexia, abdominal pain, nausea, vomiting, lethargy, malaise, diaphoresis. |
| **Phase 2** | 24 to 72 hours | Symptoms may improve or disappear, but biochemical abnormalities (elevated transaminases, bilirubin, prolonged PT) become evident. Right upper quadrant abdominal pain may occur. |
| **Phase 3** | 72 to 96 hours | Worsening nausea and vomiting, malaise, jaundice , and central nervous system symptoms (confusion, coma). Hepatocellular injury peaks, and oliguria/acute tubular necrosis may develop. |
| **Phase 4** | 4 to 14 days | Resolution of liver damage and return to normal hepatic architecture within 3 months. |

**Key Diagnostic Indicators:**

• A significant increase in transaminases (AST > 10,000 IU/L; ALT > 1000 IU/L) is possible. Prothrombin Time (PT) and International Normalized Ratio (INR) can both be significantly elevated in cases of severe coagulation abnormalities. The best sign of liver damage is thought to be the PT.

• Hypophosphatemia, hypoglycemia (indicating poor hepatic gluconeogenesis), and metabolic acidosis—which affects as many as 50% of patients—are examples of metabolic abnormalities (48).

**Risk Factors•** A number of factors are suggested to enhance vulnerability to APAP hepatotoxicity:

• Individuals over 40 are at higher risk for ALF, mortality, and liver transplantation.

• Long-term usage of antituberculous medication (isoniazid) or anticonvulsants.

• Chronic alcohol use increases toxicity, inhibits glutathione synthesis, and raises CYP2E1 activity, while fasting depletes glutathione storage and increases CYP2E1 activity, which worsens hepatotoxicity. Nonetheless, there is debate in certain research on the therapeutic significance of long-term alcohol use and fasting.(49)

**Management and Treatment:**

Interventions for acetaminophen overdose aim to inhibit absorption, remove the drug, or detoxify the metabolite.(50)

The best treatment for stopping more liver damage is NAC. In individuals with ALF, NAC lowers the risk of hepatotoxicity and death. It functions by improving nontoxic sulfate conjugation, binding directly to NAPQI, and restoring glutathione reserves.

If given within 8 to 10 hours of intake, NAC is very effective at preventing serious harm and death. With the administration of NAC, the overall fatality rate for acetaminophen overdose decreased from as high as 5% to 0.7%. NAC can be given intravenously or orally. The Rumack-Matthew nomogram serves as a guide for determining whether patients need NAC treatment for a single acute overdose. Even when liver damage has been proven, NAC therapy may still be helpful for up to 24 hours or more (51)

The multisystem illness known as ALF includes cerebral edema, coagulopathy, sepsis, and acute renal failure. Patients need urgent support in critical care. Prothrombin Time (PT), which measures a significant reduction in hepatic synthetic function, is the best indicator of liver injury.Metabolic acidosis is recognized as the most significant single predictor of likely death and transplant requirement. Patients with worsening coagulopathy (INR >5 at any time, or fulfilling specified INR thresholds at 24, 48, or 72 hours), renal impairment (creatinine >2.3 mg/dL), or metabolic acidosis (pH <7.35) should be evaluated for early transfer to a transplant facility (52).

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For patients with permanent ALF, liver transplantation is the only option that will considerably improve their odds of survival and is considered the gold standard of care. Drug-induced liver failure that necessitates a transplant is most commonly caused by acetaminophen (53). Since the death rate for patients who do not receive a liver transplant is higher than 90%, the King's College Hospital (KCH) criteria are the most often used technique for choosing patients for liver transplantation. But compared to ALF from other causes, acetaminophen-induced ALF has the highest chance of spontaneous recovery, and only 6–8% of people with this illness end up getting a liver transplant (54).

## DISCUSSON:

Acetaminophen is the international name used in the USA, while Paracetamol is the name used in Europe; both refer to the same chemical compound. APAP was synthesized in 1878, but its use in medical treatment began later. Its widespread use started in the 1960s, replacing more toxic analgesics available at the time. Hepatotoxicity resulting from APAP overdose was first reported in humans in 1966 **(55)**.

Today, APAP is available over-the-counter (OTC) as a single formulation or in combination with other substances. It is positioned on all three steps of the WHO analgesic ladder and is the drug of choice for patients who cannot take non-steroidal anti-inflammatory drugs (NSAIDs), such as those with peptic ulcers or coagulation impairments. Epidemiology of Acetaminophen-Induced Acute Liver Failure (ALF) Acetaminophen overdose is the most common cause of ALF in both the United States and the United Kingdom.

Based on national estimates, APAP poisoning is responsible for about 450 fatalities and 26,000 hospitalizations in the US each year. The most common cause of acute poisoning in the United States is APAP overdose. Between 39% and 42% of all ALF cases in the US are caused by APAP poisoning. 20% of instances of ALF were found to be caused by APAP poisoning in the late 1990s; according to one investigation, this prevalence rose from 28% in 1998 to 52% in 2003. In the United States, APAP continues to be the primary cause of liver transplants associated with acute drug overdose.

A considerable portion of overdoses are inadvertent (48% to 61% of ALF cases), even if many are purposeful (suicidal intent: 27% to 44% of ALF cases). Unintentional overdosage may result in higher morbidity and mortality, possibly as a result of delayed presentation and treatment. Inadvertent overdose frequently occurs when patients consume more over-the-counter APAP because they are unaware that their prescription painkillers (such as hydrocodone combinations) also include APAP.

Acetaminophen is categorized as a predictable hepatotoxin which means that dose-related centrilobular necrosis is produced when biochemical indicators of liver damage appear 24 to 48 hours after an overdose. The threshold dose for hepatotoxicity is 150 mg/kg for children or 10 to 15 g for adults; the toxicity is dose-dependent.

Normal Metabolism more than 90% of APAP is converted by the liver into harmless phenolic glucuronide and sulfate conjugates when administered in therapeutic dosages. These conjugates are then eliminated in the urine.NAPQI is an electrophilic, extremely reactive chemical. It is typically quickly conjugated with glutathione (GSH) and eliminated. The glucuronyltransferases and sulfotransferases become saturated in the event of an overdose, which causes more drug to be diverted to the P450 pathway and increased NAPQI synthesis. GSH reserves are depleted as a result. NAPQI builds up in hepatocytes and creates covalent connections with mitochondrial and cellular proteins if GSH is not restored. (56)

Early diagnosis is essential because rapid deterioration is common, and current treatments are highly effective in preventing morbidity and mortality.N-Acetylcysteine (NAC) is the most effective treatment to prevent the progression to liver failure and reduce mortality in APAP hepatotoxicity.NAC functions by boosting nontoxic sulfate conjugation, binding directly to NAPQI, and restoring glutathione reserves.It is quite successful in preventing mortality, serious liver damage, and renal failure if given within {8 to 10 hours} of the drug being used. If administered within 16 hours, the damage can still be lessened.Giving NAC up to 24 hours after an overdose is safe and helpful. In comparison to those who did not get NAC, those who received therapy after 48 hours after ingestion exhibited reduced incidence of cerebral edema and higher survival rates. Serum APAP concentration plotted against time post-ingestion is utilized in the drug {Rumack-Matthew nomogram} to predict hepatotoxicity in single acute overdoses, directing the need for NAC treatment.(57)

The best long-term survival for APAP overdose patients who develop ALF is liver transplantation, which is still the gold standard of care. Selection Criteria Prognostic indicator-based criteria are employed because of the severity and irreversible nature of LT. The most commonly used criteria for

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patient selection is the drug{King's College Hospital (KCH) criteria}. Without a transplant, the mortality rate for patients who fit KCH criteria is more than 90% (54). Results Compared to ALF from other causes, APAP-induced ALF has the highest percentage of spontaneous recovery, which means that fewer patients (only 6% to 8%) eventually need transplantation. After LT, overall survival is around to 70%.

**Other Toxicities and Regulatory Considerations**
While hepatotoxicity is the main side effect, an APAP overdose can also cause cardiovascular problems and renal tubular necrosis.

• Renal Toxicity: One to two percent of APAP overdose patients experience renal insufficiency. Cytochrome P450 is partially responsible for the pathogenesis, although glutathione conjugates that create nephrotoxic chemicals are also implicated.

• Cardiovascular Effects: Peripheral inhibition of COX-2 by APAP has been demonstrated. Patients with coronary artery disease who get APAP on a regular basis over an extended period of time may experience elevated blood pressure.

The high rate of unintentional and deliberate overdoses has prompted regulatory agencies to take action to reduce toxicity.

• Dose Limitation: The FDA in the United States mandated that the total amount of APAP in any prescription drug should not be more than $\textbf{325 mg}$ per tablet. When combining over-the-counter APAP with prescription opioids that contain it, this was done to avoid unintentional overdose.

• Pack Size Limitation: Under UK law, pharmacists are only allowed to sell 32 tablets (16 g) of OTC APAP packs, whereas other retailers are only allowed to sell 16 tablets (8 g).

## CONCLUSION:

In conclusion, the efficacy and wide accessibility of acetaminophen/paracetamol are balanced by the profound toxicity risks associated with overdose, necessitating continuous efforts in awareness promotion, education, and regulatory oversight to mitigate this critical public health problem.

## CONFLICT OF INTEREST:

The authors declare that they have no conflict of interest

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