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Hepatotoxicity associated with the irrational use of paracetamol as an over-the-counter medication: a systematic review.

Hepatotoxicity associated with the irrational use of paracetamol as an over-the-counter medicine: a systematic review

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Summary

Paracetamol is one of the most widely used over-the-counter medications in the world due to its effectiveness in treating pain and fever. Although considered safe when used in recommended doses, its irrational use, characterized by self-medication, administration of high doses, and combination with other medications containing the same active ingredient, can cause severe hepatotoxicity and acute liver failure. This study aimed to analyze the hepatotoxicity associated with the irrational use of paracetamol, highlighting the main risk factors, the mechanisms involved in liver injury, and prevention strategies. The methodology consisted of a systematic literature review, conducted through the analysis of scientific articles published in national and international databases. The studies showed that the excessive formation of the toxic metabolite N-acetyl-p-benzoquinone imine (NAPQI), resulting from overdose or prolonged use, is the main mechanism responsible for liver injury.

It is concluded that guidance from healthcare professionals, the rational use of medication, and public awareness are fundamental measures to prevent hepatotoxicity and promote patient safety.

Keywords: Paracetamol. Hepatotoxicity. Self-medication. Over-the-counter medications.

Abstract

Paracetamol is one of the most widely used over-the-counter medications worldwide because it effectively relieves pain and reduces fever. Although it is considered safe when used within the recommended dosage, its irrational use, characterized by self-medication, excessive doses, and the concomitant use of other products containing the same active ingredient, may result in severe hepatotoxicity and acute liver failure. This study aimed to analyze hepatotoxicity associated with the irrational use of paracetamol, highlighting the main risk factors, the mechanisms involved in liver injury, and preventive strategies. The methodology consisted of a systematic literature review based on scientific articles published in national and international databases. The findings demonstrated that the excessive formation of the toxic metabolite N-acetyl-p-benzoquinone imine (NAPQI), resulting from overdose or prolonged use, is the primary mechanism responsible for liver damage. It is concluded that guidance provided by healthcare professionals, the rational use of medications, and public awareness are essential measures to prevent hepatotoxicity and promote patient safety.
Keywords: Paracetamol. Hepatotoxicity. Self-medication. Nonprescription drugs.

Introduction

Self-medication is a widespread practice in Brazil and represents a

This is a significant challenge for public health. National epidemiological studies demonstrate that a

A significant portion of Brazilians use medications without a prescription, most notably...

Analgesics and antipyretics are among the most commonly used classes (ARRAIS *et al.,* 2016). This

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Behavior is related to the culture of self-care, ease of acquisition, and the influence of
advertising and the misconception that Over-the-Counter (OTC) Medicines
They present minimal risks (PONS *et al.,* 2017).

Among OTC (over-the-counter) medications, paracetamol (acetaminophen) stands out as one of the most widely used analgesics and antipyretics.
Consumed worldwide, used to treat mild to moderate pain and fever in children.
Adults, the elderly, and pregnant women. It is classified as an OTC (over-the-counter) medication by the National Health Surveillance Agency.
The Brazilian Health Surveillance Agency (ANVISA) allows the purchase of these drugs without a prescription, which expands access, but also...
It encourages repeated use, combination with other products containing the same active ingredient, and...
use without professional supervision (BRAZIL, 2024; CHIDIAC *et al.,* 2023).

Although safe at recommended doses, paracetamol has hepatotoxic potential in certain situations.
irrational use, such as ingesting doses higher than recommended, prolonged use, duplication
therapeutic factors and their association with risk factors, such as alcoholism, prolonged fasting, and liver disease.
(RAMACHANDRAN; JAESCHKE, 2019). Under these conditions, saturation of conjugation pathways
increases the formation of the reactive metabolite N-acetyl-p-benzoquinone imine (NAPQI) by CYP2E1,
which, by depleting hepatic glutathione, promotes oxidative stress, centrilobular necrosis and,
potentially acute liver failure (KANG *et al.,* 2020; RAMACHANDRAN;
JAESCHKE, 2019).

Drug-induced liver injury is among the leading causes of liver failure.
acute liver disease in Brazil (SANTOS *et al.,* 2021), which reinforces the importance of the pharmacist in
promoting rational use through guidance during dispensing and identifying risk factors.
risk and prevention of therapeutic duplication (BAILEY *et al.,* 2017).

Given this scenario, the present study aimed to analyze, through a systematic review...
From the literature, the pharmacological, toxicological, and clinical aspects of hepatotoxicity associated with
Irrational use of paracetamol as an OTC medication, addressing the mechanisms involved, the risk factors,
the clinical manifestations, therapeutic management with N-acetylcysteine (NAC), and the role of
Pharmacist in the prevention of these events.

Theoretical Framework

2.1 Pharmacological and regulatory aspects

Paracetamol differs from non-steroidal anti-inflammatory drugs (NSAIDs) in that it has little...
peripheral anti-inflammatory activity. Its effect stems mainly from the inhibition of the synthesis of
prostaglandins in the central nervous system, where the low concentration of peroxides allows the action

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Regarding cyclooxygenase; in inflamed tissues, excess peroxides inactivate the drug, which explains the absence of a relevant anti-inflammatory effect, the lesser gastrointestinal irritation, and the absence of antiplatelet effect. Its metabolite AM404 also participates in the activation of the cannabinoid system. endogenous and central serotonergic modulation, enhancing analgesia (MALLET *et al.,* 2023; OHASHI; KOHNO, 2020).

In Brazil, paracetamol is classified as an OTC (over-the-counter) medication according to RDC No. 98/2016, which requires a specific profile of... known safety, low toxicity potential, and clear information on labeling and package inserts regarding Maximum daily dose, contraindications and risks of concomitant use with alcohol (BRAZIL, 2016). In For adults, the recommended dose is 500 to 1,000 mg every 4 to 6 hours, not exceeding this amount. 4 g/day, or 3 g/day in at-risk groups, such as those with liver disease, alcoholics, and malnourished individuals (CHIDIAC). *et al.,* 2023).

2.2 Liver metabolism and risk factors

At therapeutic doses, approximately 85% to 90% of paracetamol is conjugated by glucuronidation and Sulfation occurs, producing inactive metabolites that are excreted by the kidneys, while 5% to 10% undergo oxidation by cytochrome P450, mainly by CYP2E1, forming NAPQI. Under conditions In physiological processes, this metabolite is rapidly neutralized by reduced glutathione (GSH). In case of overdose, saturation of the conjugation pathways diverts metabolism towards the oxidative pathway and depletes the body. GSH; free NAPQI then binds covalently to mitochondrial proteins of the hepatocytes of centrilobular zone, triggering mitochondrial dysfunction, oxidative stress, and necrosis. hepatocellular (RAMACHANDRAN; JAESCHKE, 2018, 2019).

The main risk factors for this process are summarized in Table 1.

Table 1 – Risk factors for paracetamol-induced hepatotoxicity.

Risk factor	**Pharmacological mechanism :**	**Risk level**
Dose above 4 g/day: Saturation of glucuronidation and sulfation ÿ (adults)	Shift to CYP2E1 ÿ excessive production of NAPQI	Very high
Alcohol use	Chronic induction of CYP2E1 and reduction of glutathione stores. Prolonged fasting	Very high
or reduction of GSH stores ÿ less malnutrition.	Neutralization of NAPQI **Risk**	High
factor	**Pharmacological mechanism** Isoniazid, rifampicin, and	**Risk level**
Enzyme inducers	phenytoin increase oxidative metabolism Reduced detoxification and glutathione	High
Pre-existing liver disease	synthesis capacity Alterations in hepatic enzyme activity and polypharmacy	High
Extreme age	in the elderly	Moderate

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CYP2E1 polymorphisms and UGT	Increased toxic bioactivation or reduction of safe conjugation pathways	Moderate
Polypharmacy, with hepatotoxic	Association with NSAIDs, statins, and antibiotics may cause additive injury.	Moderate

Source: Adapted from Ramachandran and Jaeschke (2018), Yoon *et al.* (2016) and Gerriets, Patel and Nappe (2024).

2.3 Clinical picture and diagnosis

Poisoning progresses in stages. In the first 24 hours (Phase I), the symptoms are nonspecific.
(nausea, vomiting, malaise) and transaminases may be normal, which makes it difficult to
Early recognition. Between 24 and 72 hours (Phase II), there is an elevation of alanine aminotransferase.
(ALT) and aspartate aminotransferase (AST), increased bilirubin and INR, and hypochondrium pain.
right, sometimes with apparent improvement of gastrointestinal symptoms. Between 72 and 96 hours (Phase III),
Transaminase levels can reach 10,000 to 50,000 IU/L, with a risk of jaundice and encephalopathy.
Hypoglycemia, metabolic acidosis, coagulopathy, and hepatorenal syndrome. Starting on day 4 (Phase IV),
Most treated patients recover, but severe cases can progress to liver failure.
transplant or death (SERPER *et al.,* 2016; SILVA JÚNIOR *et al.,* 2019; BATEMAN *et al.,* 2014).
The Rumack-Matthew nomogram guides the indication of NAC by relating the concentration
plasma paracetamol levels over time since ingestion, valid for single acute ingestions between
4 and 24 hours; values above the treatment threshold (from 150 µg/mL at 4 hours) make the
mandatory antidote (PRESCOTT, 2024). In cases of acute liver failure, the criteria of
King's College (arterial pH < 7.30, or INR > 6.5 associated with creatinine > 3.4 mg/dL and encephalopathy)
Grades III or IV) indicate urgent liver transplantation (SPEISER *et al.,* 2015).

2.4 Treatment with N-acetylcysteine

NAC is the antidote of choice, and its timely administration is the most critical factor in preventing the disease.
fulminant hepatic failure (BATEMAN *et al.,* 2014). It acts as a cysteine precursor for
the synthesis of glutathione, as a direct antioxidant through its sulfhydryl group and, in later stages,
improving microcirculation and oxygen supply to tissues (LUO; HUANG; ZHANG, 2023).
Its effectiveness is at its maximum when initiated within 8 to 10 hours after ingestion, and remains significant.
up to 24 hours, and even after that period, it reduces mortality and the need for transplantation in
patients with established lesions (DOWNS *et al.,* 2021). The administration protocols most
The methods used are described in Table 2.

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Table 2 – N-acetylcysteine administration protocols.

Parameter	protocol, UK (SNAP adapted) Oral	Intravenous route – Rumack route – Rumack protocol
Main indications	Conscious patients, without intractable vomiting, decreased level of consciousness, mild to moderate intoxication.	fulminant hepatic hemorrhagic fever or pregnant women
Loading dose	140 mg/kg	150 mg/kg in 15 to 60 minutes
Maintenance doses: 70 mg/kg every 4 hours.		50 mg/kg over 4 hours, followed by 100 mg/kg over 16 hours.
Total duration	72 hours (17 doses)	21 hours (extended if persistent toxicity occurs)
Disadvantages	Unpleasant odor, difficult adhesion, higher	risk of reactions, high rate of vomiting. anaphylactoids related to infusion rate

Source: Adapted from Chiew *et al.* (2016) and Bateman *et al.* (2014).

2.5 The pharmacist's role in prevention and management

When dispensing OTC medications, it is the pharmacist's responsibility to actively screen for liver disease. Alcoholism, malnutrition, and the use of enzyme inducers; provide guidance regarding the maximum daily dose and the... intervals between doses and warn about the presence of paracetamol in cold and flu combinations and analgesics, preventing accidental overdose due to therapeutic duplication (CHIDIAC *et al.,* 2023). This guidance is especially relevant given the limitations in understanding package inserts and packaging by individuals with low health literacy and the absence, in Brazil, of restrictions on packaging size, a measure that in the United Kingdom has been associated with a reduction of around 43% in deaths related to paracetamol (BERTOLDI *et al.,* 2018; HURWITZ *et al.,* 2014).

In a hospital setting, the pharmacist validates the prescription and calculates the NAC dose based on actual weight. It supervises its dilution and monitors anaphylactoid reactions — which occur in up to 15% of patients. and are usually managed by reducing the infusion rate or using antihistamines — and It monitors the evolution of INR and transaminases to support the decision to interrupt or prolong treatment. the treatment (BAILEY *et al.,* 2017; YAMAMOTO *et al.,* 2014). In addition to this, its role in pharmacovigilance, through the notification of adverse events and poisonings to NOTIVISA, contributing to the monitoring of the safety of this medicine (BRAZIL, 2024).

Methodology

This is a systematic literature review, using a qualitative and descriptive approach, conducted according to the PRISMA 2020 guidelines (PAGE *et al.,* 2021). The research question was structured by PICO strategy: P – adults and/or pediatric patients using paracetamol as an OTC medication in a

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irrational (excessive doses, prolonged self-medication, association with alcohol); I – irrational use,
Overdosage, chronic use without prescription, polypharmacy with hepatotoxic drugs, and concomitant ingestion.
of alcohol; C – use in therapeutic doses (500–1,000 mg/dose; maximum of 4 g/day in adults), without
Risk factors; O – occurrence of hepatotoxicity and its clinical and laboratory outcomes.
The search was conducted in the PubMed, SciELO, and LILACS databases, using MeSH descriptors.
(Medical Subject Headings), using the strategy ("Acetaminophen" OR "Paracetamol" OR
"APAP") AND ("Drug-Induced Liver Injury" OR "Hepatotoxicity" OR "Liver failure"), with filters
The articles were based on language (Portuguese, English, and Spanish) and restricted to publications between 2014 and 2024.
pre-selected based on titles and abstracts, and then evaluated in full.
Original studies, reviews, meta-analyses, case series, and studies were included.
Pharmacovigilance focusing on hepatotoxicity associated with paracetamol used as an OTC or
in self-medication, available in full and with documented liver laboratory parameters.
(ALT, AST, bilirubin, INR). Studies on prescribed and monitored paracetamol were excluded.
Clinically, case reports without clear toxicological relevance, studies exclusively in animals,
Opinion pieces and editorials, duplicates, and studies that did not differentiate between rational and irrational use.
Since this was a review of published data, there was no need for review by an ethics committee.
in research.

Results and discussion

The search identified 92 records (51 in PubMed, 37 in LILACS, and 4 in SciELO). After removing
7 duplicates, 85 studies were screened; 20 articles published before 2014 and 10 were excluded.
non-indexed monographs. Of the 55 studies evaluated for eligibility, 20 were excluded because
17 did not meet the thematic scope and 17 were pre-clinical studies in animals, resulting in 18
studies included (Figure 1; Table 3).

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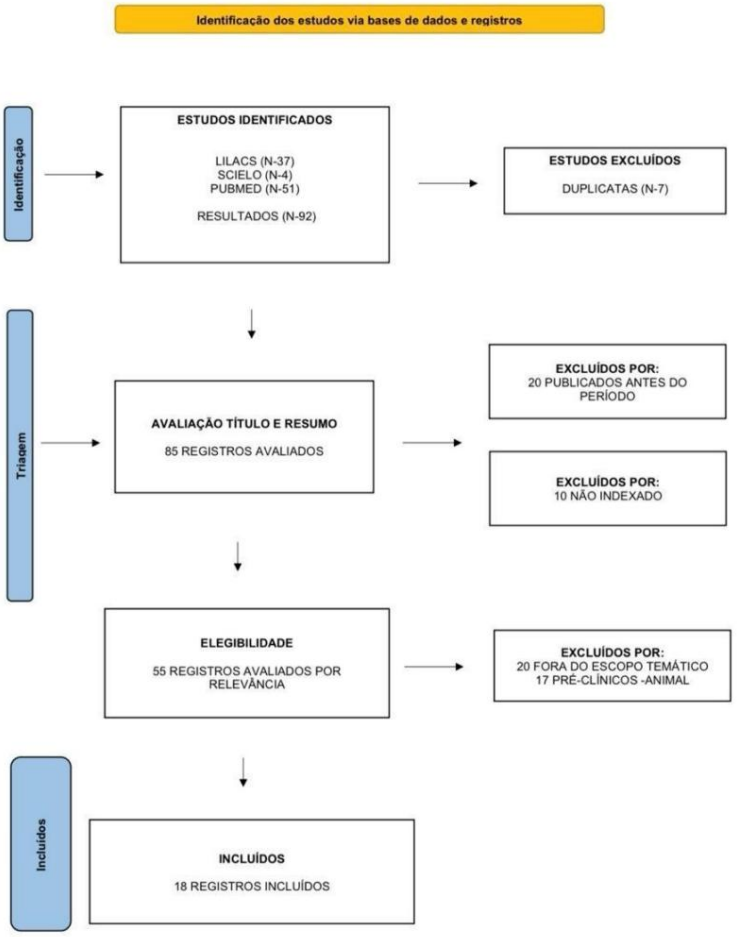
Figure 1 – Study selection flowchart (PRISMA 2020).



Source: The author (2026), based on the PRISMA 2020 model (PAGE *et al.,* 2021).

Table 3 – Characteristics of the included studies.

Number of Authors	Year	Type of study	Key findings
1 Marks *et al.*	2017	Retrospective observation	Massive paracetamol overdose and clinical outcomes
2 Egan *et al.*	2019	Retrospective	ALT < 50 U/L on admission does not rule out liver damage.
3 Heppell and Isbister	2017	Retrospective	Combined overdose with codeine did not increase respiratory depression.
4 Bucaretchi *et al.*	2014	Case Report	Acute liver failure in neonates after repeated doses.
5 Chiew *et al.*	2020	Prospective Cohort	Protein adducts predict hepatotoxicity.
6 Heard *et al.*	2017	Pediatric Cross-sectional Observational	Biomarkers in patients
7 Kang *et al.*	2020	Crossover Clinical Trial	4-methylpyrazole inhibits the oxidative pathway of paracetamol.
8 Van Rongen *et al.*	2016	Pharmacokinetic	Morbid obesity increases oxidation via CYP2E1.

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No.	Authors	Year	Type of study	Key findings
9	Wong *et al.*	2019	Clustered ECR multicenter procedure.	Early cessation of NAC is a safe under defined criteria
10	Shah and Beuhler	2022	Retrospective	Single-bag NAC is associated with lower hepatotoxicity.
11	Isbister *et al.*	2016	Prospective observation	Two-phase protocol reduces adverse reactions.
12	Santos *et al.*	2021	Multicenter observational	Drug-induced liver injury as a cause of acute liver failure
13	Chiew *et al.*	2023	Prospective observation	Metabolites predict hepatotoxicity after poisoning.
14	Mena *et al.*	2024	Case Series	Liver failure in adolescents
15	Porteous *et al.*	2019	Retrospective Cohort	Management of acute liver failure induced by paracetamol
16	Heard *et al.*	2016	Clinical Trial	Protein adducts at therapeutic doses
17	Amer *et al.*	2022	Retrospective observation	Paracetamol overdose combined with opioids
18	Pape *et al.*	2019	Observational	Unintentional overdose and toothache

Source: The author (2026).

Ingesting doses higher than recommended was the most frequent risk factor among the studies. included. Pape *et al.* (2019) observed high levels of unintentional overdose use by Patients with toothache, highlighting the role of self-medication and lack of knowledge about dosage. maximum daily intake. Egan *et al.* (2019) showed that repeated supratherapeutic intake can lead to hepatotoxicity even with initial ALT below 50 U/L, so that isolated tests in Admission does not exclude serious injury. Situations of vulnerability were also described, such as... acute liver failure in neonates after repeated administration (BUCARETCHI *et al.,* 2014) and cases of poisoning in adolescents, in which psychosocial factors should be investigated (MENA) *et al.,* 2024).

Regarding overdoses, Marks *et al.* (2017) associated massive ingestions with more severe outcomes. while Heppell and Isbister (2017) did not observe an increase in respiratory depression with co-ingestion with codeine and Amer *et al.* (2022) pointed out that the association with opioids may favor ingestion. inadvertent ingestion of hepatotoxic doses. These findings indicate the risk of combined intoxications. It depends on the co-ingested drug and the pattern of use. From a mechanistic point of view, Van Rongen *et al.* (2016) demonstrated increased oxidation via CYP2E1 in morbidly obese individuals, and Kang *et al.* (2020) Studies have shown that 4-methylpyrazole reduces this pathway, reinforcing its centrality in the pathophysiology of intoxication.

In diagnostics, paracetamol protein adducts have shown potential as biomarkers in therapeutic doses (HEARD *et al.,* 2016), in pediatric patients (HEARD *et al.,* 2017) and in

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early prediction of hepatotoxicity after overdose (CHIEW *et al.,* 2020), as well as the drug metabolites at admission (CHIEW *et al.,* 2023). Regarding treatment, NAC It remains the primary therapy: its early discontinuation is safe under defined criteria (WONG). *et al.,* 2019), the single-bag regimen was associated with less hepatotoxicity than the three-bag regimen. (SHAH; BEUHLER, 2022) and the two-phase protocol reduced adverse reactions (ISBISTER *et al.,* (2016). In cases of acute liver failure, appropriate clinical management allowed for positive outcomes. favorable even without transplantation in selected patients (PORTEOUS *et al.,* 2019), and the lesion Drug-induced liver disease has emerged as a significant cause of this outcome in Brazil. (SANTOS *et al.,* 2021).

As a limitation, the included studies presented heterogeneous designs, which prevents... direct comparisons and quantitative syntheses, and some of them focused on specific populations, For neonates and children, repeated supratherapeutic use and use above recommended doses is a an important risk factor for hepatotoxicity, mediated by the excessive formation of NAPQI. Biomarkers and early diagnostic strategies show promise for identifying High-risk patients, and N-acetylcysteine remains the primary choice for adolescents, limiting generalization. for adults. Still, the evidence converges in indicating that self-medication, the repeated use above of the recommended doses and the lack of awareness of the presence of paracetamol in different formulations as determinants of liver injury.

Final Considerations

This review highlighted the irrational use of paracetamol, especially through self-medication and ingestion. as a treatment of choice, with better results when administered early.

Despite its wide availability as an OTC medication, inappropriate use of paracetamol can result in Acute liver failure. Therefore, health education and pharmaceutical guidance in dispensing are crucial. Strengthening pharmacovigilance is essential to promoting the rational use of medicines. and reduce the occurrence of hepatotoxic events.

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