Can Paracetamol be used for Dengue fever, and if so, what are the potential benefits and risks?

Paracetamol cannot be used as a preventive measure against dengue fever as no evidence supports its prophylactic use, and when used for symptomatic treatment it increases liver enzyme elevation risk from 10% to 22% without clear antipyretic benefit.

Abstract

Paracetamol is not supported as a preventive measure against dengue fever. All examined studies focused on its use for symptomatic relief rather than prophylaxis. In one multicentre randomized trial in adult dengue patients, paracetamol given at 500 mg every four hours (median daily dose 1.5 g) increased transaminase elevation from 10% in the placebo group to 22% (incidence rate ratio 3.77, p = 0.011) without clear antipyretic benefit. Narrative reviews and retrospective analyses similarly note that while paracetamol is frequently used to reduce fever, its benefits remain unquantified in dengue and it poses a risk of hepatic injury, especially when used at high or indiscriminate doses.

Key points from the studies are:

1. There is no evidence that paracetamol prevents dengue fever.
2. Its use for fever reduction in dengue has not consistently demonstrated improvement in clinical outcomes.
3. Hepatic risk is a significant concern, with one study reporting a notably higher rate of liver enzyme elevation compared to placebo.
4. Short-term, moderate dosing may result in a low incidence of worsening liver function, but the risk increases with heavier or prolonged use.

These findings indicate that paracetamol should be regarded solely as a symptomatic treatment in dengue, with careful attention paid to dosing to minimize hepatic complications.

Paper search

Using your research question "Can Paracetamol be used as a preventive measure against Dengue fever, and if so, what are the potential benefits and risks?", we searched across over 126 million academic papers from the Semantic Scholar corpus. We retrieved the 50 papers most relevant to the query.

Screening

We screened in sources that met these criteria:

- **Preventive Intervention**: Does the study involve paracetamol/acetaminophen administered as a preventive measure before dengue infection occurs (rather than as treatment for existing dengue fever)?
- **At-Risk Population**: Does the study population include individuals at risk of dengue fever exposure (such as those in endemic areas, outbreak settings, or other high-risk populations)?
- **Preventive Outcomes**: Does the study report on dengue fever incidence, prevention rates, or other related preventive outcomes?
- **Safety Outcomes**: Does the study document safety outcomes, adverse effects, or risk assessments related to paracetamol use?
- **Dengue Diagnosis Criteria**: Does the study use clearly defined dengue fever diagnosis criteria (clinical, serological, or molecular standards)?

- **Study Design**: Is the study design a randomized controlled trial, controlled clinical trial, cohort study, case-control study, systematic review, or meta-analysis (i.e., NOT a case report, case series, editorial, commentary, or conference abstract)?
- **Intervention Focus**: Does the study focus on preventive interventions rather than solely on paracetamol as treatment for existing dengue fever?
- **Isolatable Effects**: Can the effects of paracetamol be isolated in this study (i.e., is paracetamol studied alone OR in combination with other interventions where paracetamol's individual effects can be determined)?
- **Study Quality**: Is the study of sufficient methodological quality (i.e., NOT a case report, case series, editorial, commentary, or conference abstract)?

We considered all screening questions together and made a holistic judgement about whether to screen in each paper.

Data extraction

We asked a large language model to extract each data column below from each paper. We gave the model the extraction instructions shown below for each column.

- **Study Design**:

  Extract the study design type including:

- Study type (RCT, cohort, case-control, systematic review, etc.)
- Sample size
- Study duration/follow-up period
- Number of centers/sites involved

- **Population & Setting**:

  Extract details about participants and study context including:

- Age range and demographics
- Dengue status at enrollment (confirmed cases, suspected cases, at-risk population)
- Geographic location and healthcare setting
- Inclusion and exclusion criteria
- Baseline dengue severity if applicable

- **Paracetamol Use Type**:

  Clearly identify whether paracetamol was used as:

- Preventive measure (given before dengue infection/symptoms)
- Symptomatic treatment (given after dengue diagnosis/symptoms)
- Prophylactic use in high-risk populations
- Other specific indication Note timing relative to dengue exposure or symptom onset.

- **Paracetamol Regimen**:

  Extract complete details about paracetamol administration including:

- Dose per administration (mg)
- Frequency (times per day)
- Total daily dose
- Duration of treatment

- Route of administration
- Triggers for administration (e.g., fever >38℃)
- Any dose adjustments made

- **Comparator Group**:

  Extract what paracetamol was compared against including:

- Placebo
- Other medications (specify type, dose)
- No treatment/standard care
- Different paracetamol dosing regimens
- Sample size of each comparison group

- **Benefits Measured**:

  Extract all potential benefits or protective effects assessed including:

- Reduction in dengue incidence or severity
- Fever reduction (temperature changes, duration)
- Pain relief scores
- Reduction in hospitalization
- Prevention of complications
- Other symptom improvements Include measurement methods and time points.

- **Risks & Harms**:

  Extract all adverse effects and safety outcomes including:

- Hepatotoxicity (liver enzyme elevations, clinical significance)
- Bleeding complications
- Gastrointestinal effects
- Other adverse drug reactions
- Drug interactions
- Deaths or serious adverse events Include measurement methods, severity grading, and attribution to paracetamol.

- **Key Findings**:

  Extract the main results and conclusions including:

- Primary endpoint results with effect sizes and confidence intervals
- Statistical significance of key comparisons
- Clinical significance of findings
- Authors' conclusions about paracetamol's role in dengue
- Any recommendations made
- Limitations acknowledged by authors

Results

Characteristics of Included Studies

Study	Study Design	Population	Intervention	Primary Outcome	Key Findings	Full text retrieved
Pinheiro et al., 2023	Narrative review	No mention found	Paracetamol for symptomatic relief in dengue	Hepatic complications, symptom relief	Paracetamol is widely used for symptom relief in dengue but carries hepatic risk, especially at high doses; alternatives are lacking	Yes
Vasikasin et al., 2019	Multicentre randomized controlled trial (sample size 125)	Adults (age 18 or older) with confirmed dengue, Thailand, 3 hospitals	Paracetamol 500 mg every 4 hours as needed for fever above 38℃ versus placebo	Transaminase elevation (greater than 3 times upper limit of normal), antipyretic efficacy	Paracetamol increased transaminase elevation (22% versus 10% placebo, incidence rate ratio 3.77, p=0.011) without clear antipyretic benefit; some severe adverse events in paracetamol group	No

Study	Study Design	Population	Intervention	Primary Outcome	Key Findings	Full text retrieved
Kellstein and Fernandes, 2019	Systematic review/meta-analysis	No mention found	Acetaminophen versus non-steroidal anti-inflammatory drugs (especially ibuprofen)	Bleeding risk, hepatic safety	Non-steroidal anti-inflammatory drugs (except aspirin) may not increase bleeding risk in dengue; acetaminophen carries risk of hepatotoxicity, especially in hepatitis; recommends reconsidering guidelines	No
Syed et al., 2017	Retrospective study (sample size 113)	Severe dengue hepatitis inpatients, Karachi	Paracetamol for fever control (most common dose 2g, 1 day)	Worsening liver function (alanine aminotransferase)	Only 11.5% had worsening liver function after paracetamol; most improved; deaths not related to liver dysfunction	No
Mateus et al., 2022	Systematic literature review	No mention found	Paracetamol in dengue (focus on hepatic biomarkers)	Hepatic injury, thrombocytopenia	Paracetamol can exacerbate hepatic injury in dengue, especially with excessive use; highlights importance of monitoring hepatic biomarkers	Yes

Summary of study characteristics:

- Study design:Included studies comprised one narrative review, two systematic reviews/meta-analyses, one multicentre randomized controlled trial, and one retrospective study.
- Interventions:Three studies examined paracetamol alone for dengue symptom relief or hepatic safety. One study compared paracetamol to placebo. One study compared acetaminophen to non-steroidal anti-inflammatory drugs (especially ibuprofen).
- Primary outcomes:All five studies assessed hepatic complications, injury, or liver function. Three studies assessed symptom relief, fever control, or antipyretic efficacy. One study assessed bleeding risk. One study assessed thrombocytopenia.
- Key findings:
  - Four studies found evidence of hepatic risk or complications associated with paracetamol use in dengue.
  - One study (Syed et al.) found low hepatic risk, with most patients improving after paracetamol.
  - The randomized controlled trial (Vasikasin et al.) found paracetamol increased transaminase elevation compared to placebo, without clear antipyretic benefit.
  - One systematic review/meta-analysis (Kellstein and Fernandes) found non-steroidal anti-inflammatory drugs (except aspirin) may not increase bleeding risk in dengue, while acetaminophen carries hepatotoxicity risk, especially in patients with hepatitis.
  - One study (Pinheiro et al.) noted that alternatives to paracetamol are lacking for symptom relief in dengue.
  - One study (Mateus et al.) highlighted the importance of monitoring hepatic biomarkers when using paracetamol in dengue.
  - One study (Kellstein and Fernandes) recommended reconsidering current guidelines regarding antipyretic use in dengue.
- Comparators:Placebo was used as a comparator in two studies. Non-steroidal anti-inflammatory drugs (ibuprofen) were used as a comparator in two studies. Dipirona was used as a comparator in one study. Two studies did not include a comparator.

We did not find studies that evaluated non-paracetamol interventions for symptom relief in dengue, except for the comparison to non-steroidal anti-inflammatory drugs in one systematic review/meta-analysis.

Effects

Hepatic Safety Outcomes

Study	Transaminase Elevation Rate	Effect Size	Statistical Significance
Pinheiro et al., 2023	No direct measurement; narrative synthesis of risk	No mention found	No mention found
Vasikasin et al., 2019	Paracetamol: 22%; Placebo: 10%	Incidence rate ratio 3.77 (95% confidence interval 1.36–10.46)	p=0.011
Kellstein and Fernandes, 2019	No direct measurement; review of hepatotoxicity risk	No mention found	No mention found

Study	Transaminase Elevation Rate	Effect Size	Statistical Significance
Syed et al., 2017	11.5% had worsening alanine aminotransferase; 88.5% improved	No mention found	No mention found
Mateus et al., 2022	No direct measurement; review of risk, especially with excessive use	No mention found	No mention found

Summary of hepatic safety outcomes:

- Direct measurement:Two studies (Vasikasin et al., Syed et al.) directly measured transaminase elevation rates.
  - Vasikasin et al. reported a transaminase elevation rate of 22% in the paracetamol group and 10% in the placebo group, with an incidence rate ratio of 3.77 (95% confidence interval 1.36–10.46, p=0.011).
  - Syed et al. reported that 11.5% had worsening alanine aminotransferase and 88.5% improved; we did not find an effect size or statistical significance for this comparison.
- Narrative or review-based assessment:Three studies (Pinheiro et al., Kellstein and Fernandes, Mateus et al.) did not directly measure transaminase elevation rates but provided narrative or review-based assessments of risk.
- Effect size and statistical significance:Only Vasikasin et al. provided effect size and statistical significance for transaminase elevation.

Antipyretic Efficacy

Study	Antipyretic Efficacy Findings
Pinheiro et al., 2023	Paracetamol used for fever reduction; no quantitative efficacy data
Vasikasin et al., 2019	No reduction in fever or pain scores compared to placebo
Kellstein and Fernandes, 2019	Ibuprofen and acetaminophen have equivalent or superior antipyretic activity in general; no dengue-specific data
Syed et al., 2017	Paracetamol used for fever control; no efficacy data reported
Mateus et al., 2022	Paracetamol used for fever reduction; no quantitative efficacy data

Summary of antipyretic efficacy:

- Use for fever reduction:Paracetamol was used for fever reduction in three studies, but we did not find quantitative efficacy data in these studies.
- Randomized controlled trial findings:One study (Vasikasin et al.) reported no reduction in fever or pain scores compared to placebo.

- Comparative review:One study stated that ibuprofen and acetaminophen have equivalent or superior antipyretic activity in general, but we did not find dengue-specific efficacy data.
- No quantitative dengue-specific data:We did not find any studies that reported quantitative antipyretic efficacy data specific to dengue.

Dosage-Related Effects

Study	Paracetamol Regimen	Dose-Related Safety/Efficacy Findings
Pinheiro et al., 2023	No mention found; mentions risk with doses above 20g during viremia	Hepatic risk increases with higher or indiscriminate dosing
Vasikasin et al., 2019	500 mg every 4 hours as needed for fever above 38℃; median daily dose 1.5g	Increased transaminase elevation at standard dosing
Kellstein and Fernandes, 2019	No mention found; reviews over-the-counter dosing (up to 1,200 mg/day for ibuprofen)	Hepatic risk with acetaminophen, especially in hepatitis
Syed et al., 2017	Most common dose 2g, median duration 1 day	Low rate of worsening liver function at these doses
Mateus et al., 2022	No mention found; focus on excessive or indiscriminate use	Hepatic injury risk with excessive use

Summary of dosage-related effects:

- Standard dosing regimens:Two studies specified standard dosing regimens (500 mg every 4 hours as needed, median daily dose 1.5g; most common dose 2g for 1 day).
  - One study found increased transaminase elevation at standard dosing.
  - One study found a low rate of worsening liver function at these doses.
- Excessive or indiscriminate use:Three studies did not specify dosing but discussed excessive or indiscriminate use, all finding increased hepatic risk with high or indiscriminate dosing.
- Safety outcomes:All five studies reported safety outcomes related to hepatic risk or transaminase elevation; we did not find efficacy outcomes (such as fever reduction) in these studies.
- Lack of evidence for safety at high doses:We did not find studies that reported no hepatic risk at excessive dosing, nor did we find studies that specified both regimen and efficacy outcomes.

Comparative Safety Profile

Study	Comparator	Comparative Safety Findings
Pinheiro et al., 2023	Placebo, dipirona, ibuprofen (from cited studies)	Paracetamol preferred for symptom relief, but hepatic risk noted; ibuprofen and dipirona have their own risks
Vasikasin et al., 2019	Placebo	Paracetamol increased transaminase elevation versus placebo; some severe adverse events in paracetamol group
Kellstein and Fernandes, 2019	Ibuprofen (up to 1,200 mg/day)	Non-steroidal anti-inflammatory drugs (except aspirin) may not increase bleeding risk; acetaminophen has greater hepatic risk in hepatitis
Syed et al., 2017	No comparator	No comparator; low rate of hepatic worsening with paracetamol
Mateus et al., 2022	No comparator	No comparator; focus on paracetamol's hepatic risk

Summary of comparative safety findings:

- Comparators:Placebo was used as a comparator in two studies. Non-steroidal anti-inflammatory drugs (ibuprofen) were used as a comparator in two studies. Dipirona was used as a comparator in one study. Two studies did not include a comparator.
- Hepatic risk:All five studies reported on hepatic risk associated with paracetamol or acetaminophen.
- Other risks:Two studies also discussed other risks associated with non-steroidal anti-inflammatory drugs or dipirona.
- Direct comparative safety findings:Three studies provided direct comparative safety findings (paracetamol versus another agent or placebo); two studies focused only on paracetamol's hepatic risk.

Synthesis and Limitations

Key synthesis points:

- No evidence for prevention:Across all included studies, we did not find evidence to support the use of paracetamol as a preventive measure against dengue fever. All studies focused on symptomatic treatment, with hepatic safety as a recurring concern.
- Hepatic risk:The only randomized controlled trial demonstrated increased liver enzyme elevations with standard-dose paracetamol, without clear antipyretic benefit. Observational data suggest that short-term, moderate dosing may be relatively safe in most patients, but risk increases with higher or prolonged dosing, or in those with pre-existing hepatic injury.
- Comparative safety:Some included reviews suggest that non-steroidal anti-inflammatory drugs (except aspirin) may not increase bleeding risk as much as previously thought, and may be safer than acetaminophen in patients

with hepatic compromise, but this is based on limited evidence. The lack of randomized controlled trials directly comparing these agents in dengue limits the strength of this conclusion.

Limitations of the evidence base:

- Study design limitations:
  - Predominance of reviews and observational studies.
  - Only one moderate-sized randomized controlled trial and one retrospective cohort provided primary data.
- Generalizability:
  - Most studies were conducted in single-country settings.
  - Some studies had early termination.
  - Lack of pediatric or preventive studies.
- Data limitations:
  - Incomplete reporting of dosing regimens and efficacy outcomes.
  - Limited access to full texts for some studies, restricting detailed assessment.

References

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