



ISSN : 2347 - 2243

Indo - American Journal of Life Sciences and Biotechnology



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Hepatoprotective Effect of *Phyllanthus amarus* Leaf Extract Against Paracetamol-Induced Liver Injury in Wistar Rats

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Received: March 24, 2025 Accepted: July 15, 2025 Published: November 16, 2025

DOI: [10.62644/iajlb.2025.v22.i4.pp1-8](https://doi.org/10.62644/iajlb.2025.v22.i4.pp1-8)

ABSTRACT

Paracetamol (acetaminophen) is safe at therapeutic doses yet remains a leading cause of acute liver failure after overdose, and it is the toxicant most often used to test whether a plant extract protects the liver. *Phyllanthus amarus*, a small herb used in several traditional medicine systems, is among the plants most often tested this way. This narrative review asks what the published literature actually supports about its hepatoprotective activity, with attention to rodent paracetamol models such as the Wistar rat. It reports no new experiments and no local data. We first outline how paracetamol injures the liver, then describe the phytochemistry of the plant and the evidence from cell, rodent and human studies, and finally appraise how far that evidence can be trusted. Protective signals are consistent across several toxicants and several *Phyllanthus* species, and plausible mechanisms centre on antioxidant defence and preservation of glutathione. The weaknesses are equally consistent: crude and poorly characterised extracts, uncertain plant identity, few studies among those we reviewed that use paracetamol itself in the rat, little comparison of timing with the standard antidote, and, as in animal research generally, incomplete reporting of methods. The review concludes that protection in rodents is credible but that its size, mechanism and relevance to people remain unproven, and it lists what a decisive study would need.

Keywords: *Phyllanthus amarus*; Paracetamol; Hepatoprotection; Oxidative stress; Wistar rat; Herbal medicine; Narrative review

Citation: McAllister, Gruber and Vermeulen [2025]. Hepatoprotective Effect of *Phyllanthus amarus* Leaf Extract Against Paracetamol-Induced Liver Injury in Wistar Rats. *Indo-Am. J. Life Sci. Biotechnol.* 22(4):1-8. DOI: [10.62644/iajlb.2025.v22.i4.pp1-8](https://doi.org/10.62644/iajlb.2025.v22.i4.pp1-8)

Article Class: Narrative Review

1. Introduction

Paracetamol is one of the most widely used medicines in the world and, at the doses recommended on the label, one of the safest. Taken in excess, it becomes a

common cause of acute liver failure in many countries (1, 2). The same toxicity that worries clinicians has made the drug a convenient tool for experimenters, because a single large dose produces reproducible



centrilobular liver injury in rodents within hours (3, 4). A great many plant extracts have been tested against it.

Phyllanthus amarus is a small annual herb of tropical regions that features in several traditional medicine systems, often for jaundice and liver complaints (5, 6). Its leaves contain lignans, tannins and flavonoids, and extracts have been reported to protect the liver in a number of experimental settings (7, 8). The title of this article names a Wistar rat model, which is a common choice for such tests.

This is, however, a narrative review of the published literature and not a report of an experiment. The authors did not treat animals, collect samples or analyse data, and no local findings are reported. The question is a reviewer's one: what do the published studies actually establish about the liver-protective effect of this herb against paracetamol injury, and what would a convincing study of it, in the rat, need to show? The aim is a fair account of what has been shown and what has only been repeated.

2. Literature Review

2.1 How Paracetamol Injures the Liver

At ordinary doses paracetamol is mostly conjugated and excreted. A small fraction is oxidised by cytochrome P450 enzymes to a reactive quinone-imine (9, 10), which is normally neutralised by glutathione. After an overdose the conjugation routes saturate, glutathione is consumed, and the reactive metabolite binds to cellular proteins, especially in mitochondria (3, 11). Figure 1 sketches this sequence and the places where a protective agent might act.

What follows the protein binding is a chain of events inside the cell. Oxidant stress rises in mitochondria, stress kinases are activated and the organelle's function fails, which leads to necrosis (12, 13, 14). The

injury is then amplified by sterile inflammation, which also contributes to repair (15, 16). Table 1 lines these stages up against the places where an extract might intervene.

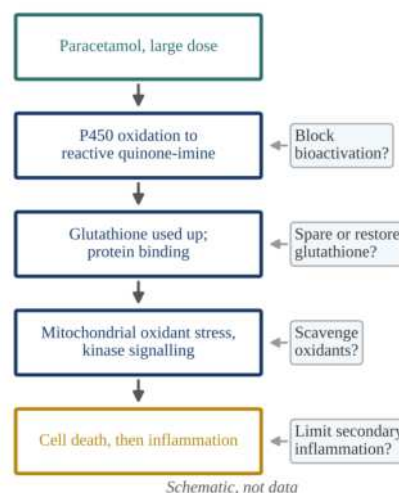


Figure 1. Paracetamol bioactivation and the points at which a plant extract could act (schematic, not data).

Table 1. Stages of paracetamol injury and where a protective extract might act.

Stage	Key event	Possible point of action
Bioactivation	Oxidation to a reactive quinone-imine (9, 10)	Reduced enzyme activity (untested for most extracts)
Detoxification	Conjugation; glutathione consumed (11)	Spare or restore glutathione
Mitochondrial stress	Oxidant stress and kinase signalling (13, 14)	Scavenge oxidants
Cell death	Mitochondrial damage, DNA fragmentation (17)	Late; little scope for prevention
Inflammation	Sterile inflammation and repair (15, 16)	Dampen secondary injury
Adaptive defence	Nrf2-driven genes (18, 19)	Enhance antioxidant genes

Note: Qualitative summary of the cited mechanistic literature; the right-hand column lists hypotheses, not demonstrated actions of any extract.



2.2 Endogenous Defences and the Antidote

The liver does not simply wait for damage. The transcription factor Nrf2 drives genes that support glutathione synthesis and detoxification, and mice lacking it are more sensitive to paracetamol (18, 19). A plant that raises these defences might therefore protect without ever touching the drug's metabolism, and that is one reason antioxidant explanations are so popular.

The established antidote, N-acetylcysteine, works largely by restoring glutathione and is most effective when given early (20). Any herbal claim has to be read against it. An extract that protects when given before the toxicant tells us little about an extract given after it, which is the situation in which a patient would present.

2.3 The Plant and Its Constituents

Reviews of the genus describe phyllanthin and hypophyllanthin among the lignans, together with gallic acid derivatives, ellagitannins and flavonoids such as quercetin and rutin (5, 7). These classes are plausible antioxidants, but their amounts vary with the plant part, the solvent and the source. The genus also has taxonomic problems: several *Phyllanthus* species look alike and are traded together, and molecular work on market samples has shown admixture (21). Even correctly identified material can differ a great deal from one market or season to the next. A study that does not authenticate its plant is a study of an unknown mixture.

2.4 Evidence in Cells, Rodents and People

In cultured cells, phyllanthin protected against carbon tetrachloride injury in a human liver line (22) and against ethanol injury in rat hepatocytes (23). In rodents, extracts of *P. amarus* have been reported to protect against ethanol (24, 25) and aflatoxin B1 (26). For paracetamol itself

the closest studies concern the related *P. niruri*, in rats and in mice (27, 28). The overall pattern is encouraging, but it rests on neighbouring species and neighbouring toxicants.

The human literature concerns hepatitis B, not drug injury. An early report of benefit in chronic carriers (29) was followed by a systematic review that found the trials small, varied and of limited quality (30). That history shows how a promising first signal can fail to mature. This is the reason a trial of the herb in hepatitis B cannot be used to support protection against a drug overdose.

3. Materials and Methods

3.1 Scope

The review asks whether published work supports a hepatoprotective effect of *P. amarus* leaf extract against paracetamol-induced injury, particularly in the Wistar rat, and how strong that support is. It is limited to the biology of the injury, the plant, the experimental evidence and the quality of that evidence. None of these limits is unusual, but each shapes what the conclusions can mean.

3.2 Literature Assembly

Sources are peer-reviewed articles and reviews on paracetamol toxicity, on *Phyllanthus* phytochemistry and pharmacology, on hepatic biomarkers and assays, and on the design and reporting of animal studies. No formal systematic search was carried out and none is claimed; this is a narrative synthesis, and the selection reflects judgement.

3.3 Appraisal Framework

Each body of work was read against six questions, summarised in Table 2. They follow general guidance on risk of bias and reporting in animal research (31, 32), and the concerns about preclinical reproducibility that prompted it (33). The



framework is qualitative, no scores were calculated, and no study was excluded on the basis of it.

Table 2. Questions used to appraise each study.

Domain	Question asked
Material	Is the plant authenticated, and is the extract characterised (21)?
Model	Is the species, fasting state and paracetamol dose stated (4)?
Timing	Was the extract given before, with or after the toxicant?
Comparator	Is there a positive control and a vehicle control?
Outcomes	Are blood enzymes backed by histology (34, 35)?
Bias	Were allocation, blinding and numbers reported (31, 32)?

Note: The framework is a narrative-review aid adapted from published reporting and risk-of-bias guidance, not a validated scoring tool.

4. Results

4.1 What the Mechanistic Literature Predicts

Paracetamol injury in rodents is well characterised, which makes it a good test of a hepatoprotective claim and also an unforgiving one. Mice are the usual model and rats are generally regarded as less susceptible, so a protective effect in the Wistar rat depends on the dose and on the fasting state of the animals (3, 4). Studies that omit these details cannot be compared with one another. A protective effect found in one set of conditions is a hypothesis for the next, not a finding about all of them.

The commonly measured outcomes are blood enzymes, liver glutathione, lipid peroxidation, and histology. The enzymes ALT and AST rise with hepatocyte injury but are not perfectly specific, and their interpretation depends on timing (34, 35). Lipid peroxidation is often measured with a thiobarbituric acid assay (36), glutathione with a thiol reagent (37), and catalase by a spectrophotometric method

(38). Antioxidant capacity of an extract in a test tube is commonly assessed with a stable radical (39), and it says little about what happens in the animal. An enzyme value read without its timing and histology is a starting point, not a result.

4.2 Strength of the Evidence for *Phyllanthus*

Figure 2 maps each evidence type against four questions. The cell and rodent studies give a consistent signal of protection and plausible antioxidant mechanisms (22, 24, 26). They say much less about paracetamol in the rat, about dose that is relevant to people, or about a protective effect when the extract is given after the toxicant. Table 3 summarises the evidence types and their main weaknesses.

Table 3. Types of evidence on *Phyllanthus* and the liver, with the main weakness of each.

Evidence type	What it shows	Main weakness
Cell culture	Protection from oxidant or toxicant injury (22, 23)	Concentrations may not be reachable in vivo
Rodent, other toxicants	Protection against ethanol or aflatoxin (24, 25, 26)	Different mechanism from paracetamol
Rodent, paracetamol	Protection by related species (27, 28)	Few studies; mostly <i>P. niruri</i> and mice
Human, hepatitis B	Early report of benefit (29)	Later reviews found weak trials (30)

Note: Summary of the studies cited in the text; it is not a count of studies or a measure of effect.

The pattern across studies is of related findings, not repeated ones. The studies differ in species, toxicant, extract type and dose, so they do not replicate one another in the usual sense. A reader should therefore treat the quantity of positive reports as weaker evidence than it first appears.

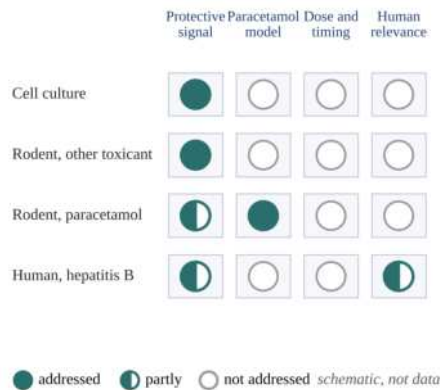


Figure 2. Qualitative map of how well each evidence type addresses each question (authors' reading; schematic, not data).

4.3 Reporting Quality

Across animal research generally, reports often omit randomisation, blinding, sample size justification and the handling of exclusions (31, 32). We did not audit individual *Phyllanthus* papers for these omissions and make no claim about any specific report; the point is that the questions in Table 2 are rarely answerable from the text alone.

Dose is a related problem. Extracts are given in milligrams per kilogram of body weight, but the equivalent exposure in a person is not obtained by simple scaling, and conversion between species follows body surface area rather than weight (40). Treatment effects in animals have also been found to differ from those later seen in human trials (41), which is a reminder that a rat result is a prompt for further work and not a recommendation. It is a modest reading, and it is the one the evidence will currently bear.

5. Discussion

5.1 Interpretation

Taken at face value, the literature suggests that *Phyllanthus* preparations protect rodent liver against several chemical injuries, and that a similar effect against paracetamol is credible. The most likely

explanation is support for antioxidant defences rather than blocking of the drug's bioactivation (42, 43), though this has seldom been tested directly. Nothing here argues against studying the plant; it argues for studying it with the care the question deserves.

The timeline in Figure 3 shows why timing matters. Protection from an agent given before the toxicant is a very different claim from protection when the agent follows it, and the antidote works in the second setting (20). Few herbal studies compare against it. Without that comparison, the clinical meaning of any positive result is unclear.

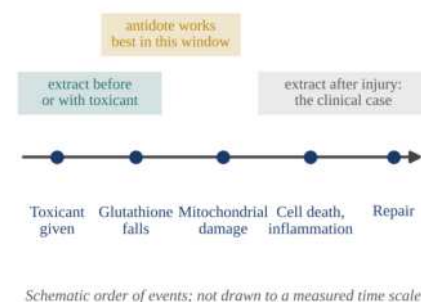


Figure 3. Schematic timeline of paracetamol injury and the window in which a protective agent can act (not drawn to a measured scale).

Herbal origin is also not a safety argument. Herbal and dietary supplements are a recognised cause of liver injury (44), and an extract that protects in one model may carry its own risks at other doses. A herb may be gentler than a drug, but gentler is not the same as harmless. Safety data on repeated high dosing are, by comparison with the protective claims, sparse.

5.2 Limitations

The review is narrative and shares the limits of that form. Selection of sources reflects the authors' choices, no systematic search or quality scoring was done, and individual effect sizes are deliberately not quoted because they could not be checked against the primary papers for this article.



Much of the evidence discussed comes from related species, other toxicants and cell lines, which are imperfect proxies for *P. amarus* in paracetamol-treated rats. Reviews of this kind are more useful when they say where the evidence stops than when they smooth it over.

5.3 Future Work

A decisive study would authenticate the plant and characterise the extract, state the strain, fasting state and paracetamol dose, and include vehicle and positive controls (21, 32). It would test several doses and several time points, including treatment after the toxicant, measure glutathione and histology alongside enzymes (34), and report allocation and blinding (31). None of this is expensive when set against another underpowered rodent study. A formal systematic review of the existing *Phyllanthus* studies, with risk-of-bias assessment, would show how much of the current signal survives scrutiny. These points apply with equal force to any herb tested against any hepatotoxin, not only to this one.

6. Conclusion

Phyllanthus amarus is a credible candidate for hepatoprotection, and the published work gives reasons to take it seriously: consistent protective signals, plausible antioxidant mechanisms and a long history of traditional use. It does not, at present, establish how large the protective effect against paracetamol is in the rat, by what mechanism it acts, or whether it would matter for people. The work most needed is careful and unglamorous: authenticated material, defined extracts, relevant timing and complete reporting.

7. Acknowledgements

The authors thank colleagues who commented on earlier drafts of this review.

8. Funding

This work received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

9. Conflict of Interest

The authors declare no conflict of interest.

10. Author Contributions

B.M. conceived the review and wrote the sections on paracetamol toxicity and experimental models. M.G. wrote the sections on the plant and its constituents. S.V. wrote the sections on formulation, dose and study appraisal. All authors revised the manuscript and approved the final version.

11. Ethics Statement

This is a review of published literature. No animals were used and no ethical approval was required.

12. Data Availability

No new data were generated. All sources are cited in the reference list.

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