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Review Article

Lamium Album–Derived Modulators of Tetanolysin: A Novel Hypothesis in Tetanus Pathogenesis

Mosab Nouraldein Mohammed Hamad[1*]
[1]Assistant Professor of Microbiology, Excellence Research Center, Elsheikh Abdallah Elbadri University, Berber, Sudan, email : musab.noor13@gmail.com

***Corresponding Author**
Mosab Nouraldein Mohammed Hamad
Assistant Professor of Microbiology, Excellence Research Center, Elsheikh Abdallah Elbadri University, Berber, Sudan

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Abstract: Tetanus is a life-threatening neurotoxic disease caused by *Clostridium tetani*, with clinical manifestations primarily attributed to tetanospasmin. However, the contribution of tetanolysin, a cholesterol-dependent cytolysin produced by *C. tetani*, remains poorly characterized. Here, we propose that tetanolysin plays a critical facilitating role in early tissue injury and toxin dissemination. Furthermore, we introduce a novel hypothesis that bioactive compounds derived from *Lamium album*, particularly phytoecdysteroids, may attenuate tetanolysin activity via antioxidant and lipid-modulating mechanisms. Given the cholesterol dependency of tetanolysin pore formation, modulation of membrane lipid dynamics represents a plausible therapeutic target. This perspective integrates bacterial toxin biology with phytochemical pharmacology and highlights tetanolysin as a potentially modifiable determinant of tetanus severity. Experimental validation of this hypothesis may open new avenues for adjunctive interventions in toxin-mediated bacterial diseases.

Keywords: Tetanus, Tetanolysin, *Clostridium Tetani*, *Lamium Album*, Cholesterol-Dependent Cytolysins, Phytoecdysteroids, Neurotoxicity.

INTRODUCTION

Tetanus remains a significant global health concern, particularly in low-resource settings, despite the availability of effective vaccination strategies. The disease is caused by *Clostridium tetani*, an anaerobic, spore-forming bacterium that produces potent exotoxins. While tetanospasmin is well established as the principal neurotoxin responsible for the clinical manifestations of tetanus, the role of tetanolysin has received comparatively little attention [1].

Tetanolysin belongs to the family of cholesterol-dependent cytolysins (CDCs), a group of pore-forming toxins that includes streptolysin O and perfringolysin O. These toxins are known to disrupt host cell membranes, contributing to tissue damage and immune modulation [2]. Understanding the role of tetanolysin in tetanus pathogenesis may reveal previously unrecognized mechanisms of disease progression.

Tetanolysin as a Facilitator of Toxin Dissemination

Cholesterol-dependent cytolysins exert their effects by binding to membrane cholesterol and forming large transmembrane pores. This process leads to:

- Cell lysis and hemolysis
- Disruption of tissue integrity
- Amplification of inflammatory responses

We hypothesize that tetanolysin enhances tetanospasmin neurotoxicity indirectly by

compromising local tissue barriers and facilitating toxin access to peripheral nerves. This mechanism may be particularly relevant in wounds located near neural structures, where reduced diffusion distance could accelerate toxin uptake.

Additionally, tetanolysin-mediated cytotoxicity may create a microenvironment conducive to bacterial survival and toxin persistence, further exacerbating disease severity.

Interaction with Complement and Peripheral Nerve Injury

The complement system plays a dual role in host defense and tissue injury. Complement receptor 1 (CR1), expressed on erythrocytes and Schwann cells, regulates complement activation and protects against excessive hemolysis [3, 4].

We propose that tetanolysin-induced membrane disruption may:

- Impair CR1 function
- Enhance complement-mediated cytotoxicity
- Increase susceptibility of peripheral nerves to inflammatory damage

This interaction suggests a convergence between bacterial toxin activity and host immune dysregulation in tetanus pathogenesis.

Lamium Album as a Source of Bioactive Modulators

Lamium album (white dead nettle) is a medicinal plant belonging to the Lamiaceae family, traditionally used for treating inflammatory and traumatic conditions. Contemporary studies have demonstrated its:

- Antioxidant properties
- Anti-inflammatory effects
- Antimicrobial activity
- Neuroprotective potential [5–7]

Notably, oil extracts of *L. album* have shown antianemic effects in hemolytic models, indicating potential protection against cytolysin-induced membrane damage [7]. These findings suggest that *L. album* may counteract key pathological processes relevant to tetanolysin activity.

Phytoecdysteroids and Cholesterol-Dependent Cytolysin Inhibition

Phytoecdysteroids are biologically active plant steroids present in *L. album*. These compounds exhibit:

- Antioxidant activity
- Neuroprotective effects
- Modulation of lipid metabolism [8, 9]

Given that tetanolysin requires membrane cholesterol for pore formation, phytoecdysteroids may interfere with toxin activity through:

1. Alteration of membrane lipid composition
2. Disruption of cholesterol–toxin interactions
3. Stabilization of cellular membranes

This provides a mechanistic framework linking phytochemistry with bacterial toxin inhibition.

Hypothesis and Testable Predictions

We propose that *Lamium album*-derived compounds attenuate tetanolysin-mediated cytotoxicity, thereby reducing tissue injury and limiting tetanospasmin dissemination.

Testable Predictions

- *L. album* extracts will reduce tetanolysin-induced hemolysis in vitro
- Phytoecdysteroids will disrupt cholesterol-dependent pore formation
- Treated models will show reduced tissue damage and improved neural integrity
- Lipidomic profiling will reveal altered membrane cholesterol dynamics.

Experimental Approaches: To validate this hypothesis, the following approaches are recommended:

In Vitro Studies:

- Hemolysis inhibition assays using purified tetanolysin
- Cell viability and membrane integrity assays
- Cholesterol-binding interference studies

Molecular and Biophysical Analysis:

- Lipidomics and membrane fluidity assays
- Structural modeling of toxin–membrane interactions

In Vivo Models:

- Animal models of tetanus to assess disease severity
- Histopathological evaluation of tissue injury
- Neurofunctional outcome measures

Clinical and Translational Implications:

While vaccination and passive immunization remain the cornerstone of tetanus management, adjunctive therapies targeting cytolysins may:

- Reduce early tissue destruction
- Limit toxin dissemination
- Improve clinical outcomes

Plant-derived compounds offer a promising, accessible, and potentially low-toxicity approach, particularly in resource-limited settings.

Limitations

This work is hypothesis-driven and based on indirect evidence. Key limitations include:

- Lack of direct experimental validation
- Uncertainty regarding bioavailability of active compounds
- Potential variability in plant extract composition

These limitations underscore the need for rigorous experimental investigation.

CONCLUSION

This study identifies tetanolysin as an underappreciated factor in tetanus pathogenesis and proposes *Lamium album* as a novel source of cytolysin-modulating compounds. By integrating microbial pathogenesis with phytochemical pharmacology, this work opens new perspectives for adjunctive therapeutic strategies in toxin-mediated infections.

DECLARATIONS

Funding: No external funding was received.

Conflicts of Interest: The author declares no conflict of interest.

Ethical Approval: Not applicable.

Data Availability: No datasets were generated or analyzed in this study.

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