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Microbial Toxins: Types, Mechanisms of Action, and Pathogenic Significance

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Abstract

General Background: Microbial toxins are critical virulence factors that contribute to disease by directly damaging host cells or modulating immune responses. **Specific Background:** Existing classifications, including exotoxins and endotoxins, often fail to integrate structural characteristics with mechanisms of entry, activation, and signaling pathways, particularly in relation to lipopolysaccharide recognition and mycotoxin-related public health concerns. **Knowledge Gap:** A cohesive framework linking toxin structure, delivery mechanisms, and immunopathological outcomes remains insufficiently developed in current literature. **Aims:** This review aims to establish an integrated classification of microbial toxins and to elucidate their mechanisms of action across molecular, cellular, and immunological levels. **Results:** The study identifies key toxin categories, including A–B toxins, membrane-disrupting toxins, superantigens, lipopolysaccharides, and mycotoxins, and outlines core mechanistic principles such as delivery, cellular selectivity, post-entry activation, and signal amplification, leading to inflammation and cell death. It also highlights the role of host variability and microbiota interactions in shaping toxic responses. **Novelty:** The review proposes a multidimensional framework combining structural, functional, and immunological perspectives to better interpret toxin behavior and disease patterns. **Implications:** These findings support the development of targeted interventions, including toxin-neutralizing therapies, improved vaccine design, and standardized research approaches for clinical and laboratory applications.

Highlights:
- Integrated framework links toxin structure with delivery and activation processes
- Functional classification connects mechanisms to specific pathological outcomes
- Host variability and microbiota interactions shape toxin-related disease patterns

Keywords: Microbial Toxins, Exotoxins, Endotoxin, Lipopolysaccharide, Mycotoxins

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1. Introduction

Microbial toxins are among the most influential virulence factors in pathological microbiology because they can cause direct cellular and tissue damage or reprogram the immune response, increasing disease severity and accelerating clinical deterioration even when the microbial load is relatively low. Microbial toxins are often defined as compounds produced by microbes, especially bacteria and fungi, that cause disease by disrupting essential cellular functions, eroding epithelial barriers, or generating excessive inflammatory signals ([1]).

In many diseases, pathogen toxicity is a major explanatory element linking the features of the microbial isolate to certain clinical presentations such secretory diarrhea, toxic shock, or multi-organ damage ([2]; [1]). Recent reviews have verified this.

Traditionally, bacterial toxins have been classified into two groups: exotoxins, which are secreted or released proteins with highly specific mechanisms, and endotoxins, which usually refer to the lipopolysaccharide LPS in Gram-negative bacteria and act as a potent inducer of innate immunity ([3]; [4]). This categorization is actually important since protein toxins often exhibit unique cellular/tissue selectivity and operate via structural-functional models such as AB/AB5. On the other hand, LPS is a membrane-bound structural molecule that, when stereotype recognition pathways are activated, starts a systemic inflammatory cascade ([1]; [4]). However, mycotoxins—common food/feed by-products—are becoming more important from the perspective of public health and food safety since they are associated with long-term repercussions such oxidative stress and hepatotoxicity/renal toxicity. Some may also be carcinogenic or immunosuppressive ([5]; [6]).

Bacterial exotoxins are associated with mechanisms of action that typically include: (1) binding to surface receptors that identify the toxin's target to specific cells; and (2) causing damage intracellularly through enzymatic activity that targets central pathways like protein synthesis or cell transport signaling, or at the membrane level (such as pore-forming toxins) ([1]). Recent studies suggest that understanding these pathways helps to explain why certain bacteria create "distinctive" clinical patterns. As shown in instances associated with Staphylococcus aureus and Streptococcus pyogenes, superantigens, for example, produce wide, nonspecific T-cell activation and a cytokine storm that may result in organ failure and toxic shock syndromes ([2]; [7]). In Gram-negative infections or even in non-infectious inflammatory models, the LPS–TLR4 axis plays a significant role in the release of inflammatory mediators and may help maintain inflammatory homeostasis. Likewise, LPS remains a traditional paradigm of innate immunity-mediated toxicity ([3]; [4]).

Additionally, contemporary research stresses that toxins are not merely deadly "products," but rather a component of a nuanced evolutionary connection between diseases and hosts. Toxins facilitate colonization and dissemination by destroying epithelial barriers, weakening immunity, or creating an inflammatory environment that facilitates the utilization of resources and damaged tissues by pathogens ([1]). Because toxin transport and secretion often rely on specialized protein secretion systems that allow the delivery of virulence factors to the extracellular space or into host cells, microbial toxicology is connected to the biology of host-pathogen interactions at the molecular and systemic levels [8]. Reviews from 2025 state that chronic mycotoxin exposure is a global issue that requires a mix of toxicity reduction techniques, contamination monitoring, and preventative actions throughout the whole food supply chain [5]; [6].

Based on the above, this review aims to provide an updated conceptual framework for classifying microbial toxins and interpreting their mechanisms of action at the molecular, cellular, and immunological levels, highlighting their pathogenic importance in bacterial diseases and mycotoxins, and linking this to diagnostic and preventive implications in microbiology and life sciences ([1]; [4]; [5]).

Methodology

This review is written on the basis of an exhaustive and integrative search of the current scientific literature in order to detail the classification, mechanisms of action, and significance of microbial toxins. We conducted a systematic review of studies that are relevant to this relationship and that have appeared in the peer-reviewed literature (molecular, clinical, and experimental) to find a common conceptual framework for linking structure of a toxin to functional output. This process starts by dividing microbial toxins into broad classes of toxins, such as exotoxins, endotoxins (lipopolysaccharides), and mycotoxins, with exotic toxins further refined into functional classes (A–B toxins, membrane-disrupting toxins, superantigens) [3]. Three groups were categorized based on molecular design, delivery method, and target. The methodology also delves into fundamental mechanistic principles of toxicity such as delivery via specialized secretion systems, receptor-mediated attachment and entry pathways, post-entry activation, and signal amplification processes that promote pathophysiologic effects. Lastly, it was shown that host factors, including the modulation of the immune response, signaling pathways responsible for inflammation (for example TLR4 activation), and mechanisms for cell death were also involved in how toxins contribute to the progression of disease. Immunopathological responses, such as cytokine storm and systemic inflammation, are included here as they represent an interesting balance of microbial and host factors involved in defense. In addition, therapeutic and preventive strategies were surveyed, such as toxin neutralization, inhibition of mechanisms of entry, other types of vaccine development, and methods to decrease exposure, with an emphasis on foodborne mycotoxins. Using these multidimensional perspectives, the methodology creates an integrated context of microbial toxin biology and clinical relevance [33].

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Result and Discussion

2. Microbial Toxins Classification

Microbial toxin classification is a crucial conceptual and methodological step in microbiology and the life sciences. It links the toxin's source, its chemical/protein structure, its mechanism of action, and its expected pathogenic outcomes. It also helps standardize research terminology when comparing toxins from different pathogens or when translating knowledge into diagnosis, treatment, and prevention ([1]). Modern classifications tend to combine three axes: (1) location and structure (e.g., secreted protein versus membrane component), (2) function/mechanism of action (e.g., AB toxins or pore-forming toxins), and (3) biological-genetic context (e.g., phage-borne or island-borne toxin) ([1]).

2.1 Classical Classification

The distinction between exotoxins and endotoxins is one of the most well-established classifications in the literature because it differentiates between protein toxins that are often secreted (exotoxins) and a membrane-bound structural component in Gram-negative bacteria that induces inflammation (endotoxin/LPS) ([1]). Recent reviews confirm that LPS is considered an “endotoxin” due to its ability to induce strong inflammatory responses in the host via innate immune recognition pathways, and that this axis forms the basis for linking classification to systemic pathogenesis ([3]; [4]).

According to this framework, LPS typically causes systemic inflammatory effects by activating pattern recognition systems like TLR4 and its related helper molecules and signaling pathways, whereas exotoxins are thought to be highly functionally specific because they are proteins that interact with particular cellular receptors or targets ([4]). According to the 2025 studies, LPS may activate non-immune cells as well, causing a range of inflammatory reactions that can be dangerous if they are severe or persistent ([3]).

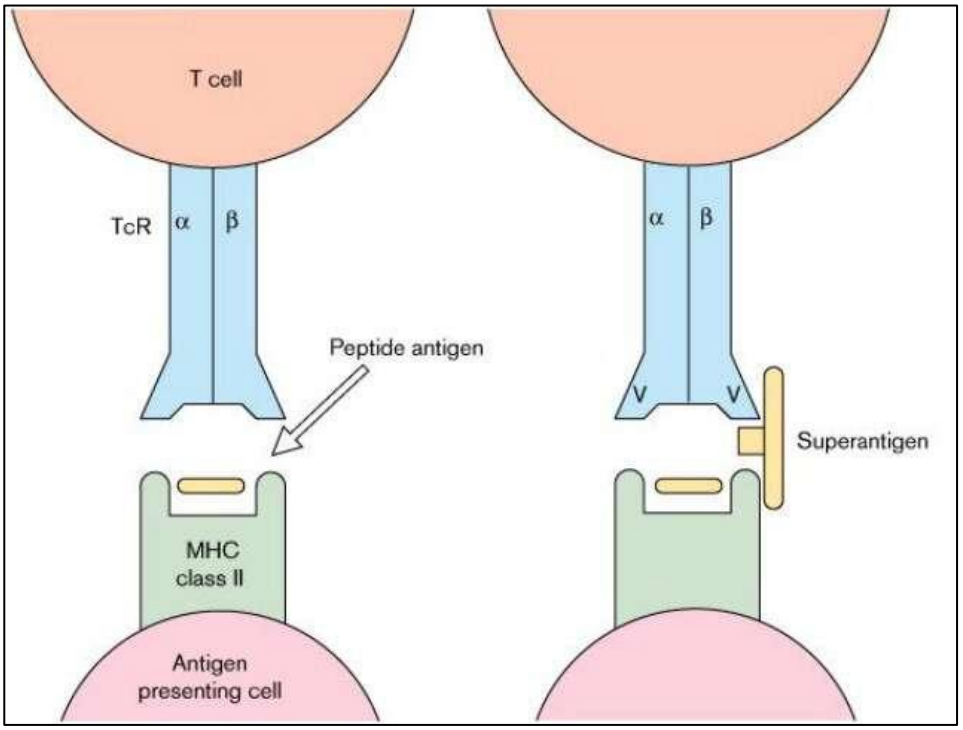
2.2 Classification of Exotoxins

According to recent assessments, exotoxins may be divided into three operational groups based on "structure and function": (a) superantigens, (b) membrane-disrupting toxins, and (c) A–B toxins. Because it explicitly connects the category to the predicted kind of harm (cytokine storm, membrane damage, intracellular disruption), this categorization improves its application ([9]).

2.2.1 Superantigens

Because their mode of action is so different from that of enzyme toxins, superantigens are categorized separately. Unlike traditional antigenic presentation, which can result in massive cytokine release and severe syndromes like toxic shock, superantigens cause broad and nonspecific T-cell activation ([2]). According to recent assessments of TSST-1, the clinical picture, which is mostly systemic hyperinflammation rather than only localized injury, may be explained by classifying these toxins separately ([7]).

Figure 1. Comparison between T cell activation with a conventional peptide antigen and with a superantigen (Deacy, et al., 2021).



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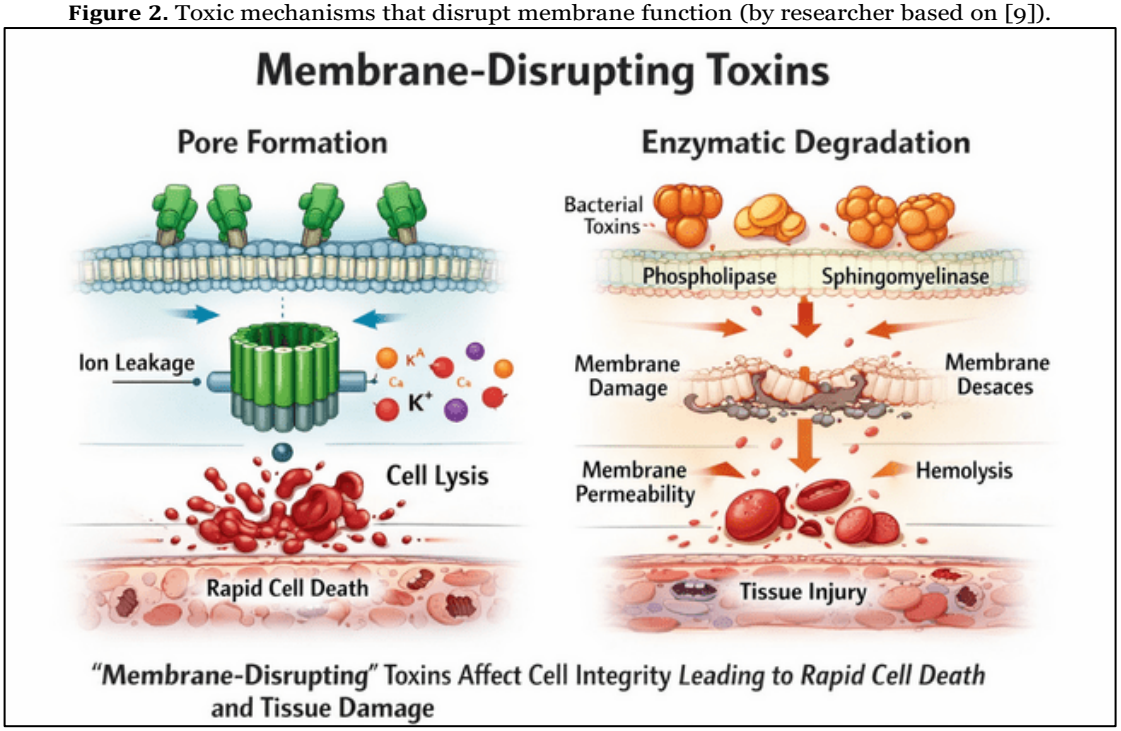
In the traditional response, the TCR selectively recognizes the peptide antigen once it attaches within the MHC class II binding groove. Bypassing traditional antigen processing, the superantigen attaches as a "complete protein" outside the MHC class II binding groove and cross-links the T cell receptor via the Vβ region of the TCR, causing extensive T cell activation and a significant release of cytokines.

2.2.2 Membrane-disrupting toxins

This category includes toxins that cause damage primarily by affecting cell membrane integrity, either through pore formation or enzymatic degradation of membrane components ([9]). Recent literature (within a “structural-functional classification”) shows that including pore-forming toxins in this category explains the rapid cell death or acute ionosomal imbalance and subsequent inflammation and tissue damage ([1]). In practice, considering these toxins as “membrane-disrupting” makes it easier for researchers to correlate laboratory measurements (such as hemolysis or membrane permeability) with pathogenesis predictions ([9]).

Figure 2. Toxic mechanisms that disrupt membrane function (by researcher based on [9]).

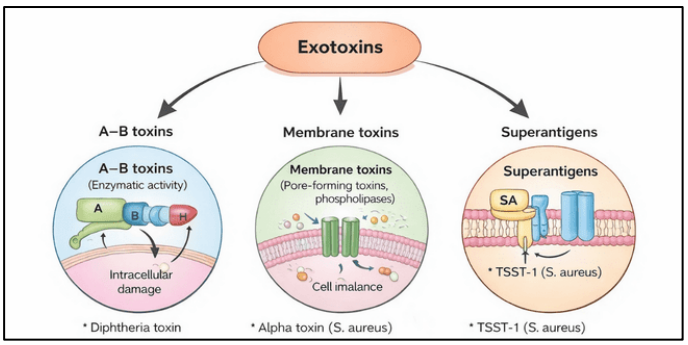


This diagram illustrates the two main mechanisms by which membrane-disrupting toxins damage host cells: pore formation and enzymatic membrane degradation. Pore-forming toxins create transmembrane channels that disrupt ionic balance and induce rapid cell lysis, while enzymatic toxins degrade membrane phospholipids and other structural components, leading to increased membrane permeability, hemolysis, tissue damage, and acute inflammatory responses. Adapted from the structural-functional concept of membrane-active bacterial toxins described in recent literature ([1]; [9]).

2.2.3 A–B Toxins

A–B toxins are among the best-documented exotoxins because they rely on a clear functional separation: The B component binds/enters, while the A component has enzymatic activity that directs intracellular damage. Specialized summaries have indicated that exotoxins can be grouped into three broad categories, including intracellular target modulators (intracellular exotoxins) within the A–B logic, along with membrane toxins and superantigens. Because it explains cellular selectivity (tropism) and differentiates between the "entry phase" and the "enzymatic modification phase" when creating entrance inhibitors or neutralizing drugs, this categorization is very useful in pathogenic microbiology ([1]).

Figure 3. Exotoxin classification (by researcher based on [1]).



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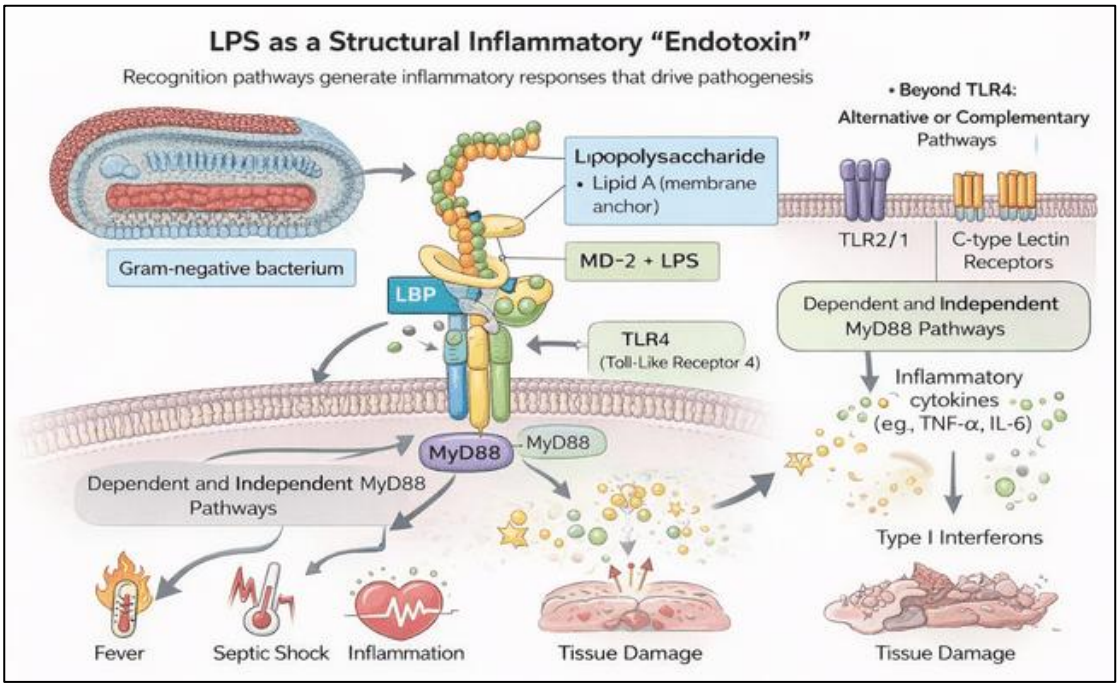
As illustrated in Figure 3, exotoxins are divided into three main functional categories: membrane toxins (such as phospholipases and pore-forming toxins), which impair membrane integrity; superantigens, which activate T cells widely through an unusual mechanism; and A–B toxins, which are identified by a distinct functional separation where component A has enzymatic activity that causes intracellular damage and component B is in charge of binding and entering the cell. This classification highlights how important it is to distinguish between the "enzymatic modification phase" and the "entry phase" when assessing cellular selectivity and developing entrance inhibitors or neutralizing agents.

2.3 Classification of Endotoxins (LPS)

New study suggests that LPS should be classified as a structural inflammatory toxin since its source is an outer membrane component rather than a protein release, despite the fact that it is often classified as an endotoxin. A 2025 review of the LPS–TLR4 pathway states that the classification of LPS should be read in conjunction with the classification of "recognition routes," such as the roles of LBP, CD14, MD-2, TLR4, and the dependent and dependent MyD88 pathways, since this cascade generates the inflammatory outputs that explain the pathogenic effect ([4]).

Additionally, recent studies indicate that TLR4 is not the only route that may recognize LPS, and that the existence of additional or alternative pathways adds levels to the categorization of LPS from both functional and immunological perspectives ([10]). In this way, the Endotoxin categorization becomes a framework that connects structure to the immune response and to inflammatory disease settings, rather than just a "name of a substance" ([3]; [4]).

Figure 4. A structural inflammatory agent and involves multilayered immune recognition pathways (by researcher based on [3]; [4]; [10]).



Because lipopolysaccharide (LPS) is produced from the outer membrane of Gram-negative bacteria, as shown in Figure 4, it is recognized in contemporary literature as a structural inflammatory toxin rather than a protein-secreted product. LPS binds to LBP to initiate immunological recognition, which is then transferred to CD14 and the LPS–MD-2 complex is formed. Fever, inflammation, septic shock, tissue damage, and inflammatory cytokines including TNF-α and IL-6 are produced as a result of this complex's activation of TLR4 and MyD88-dependent and non-dependent signaling pathways. The image also indicates the availability of alternative/complementary routes for identifying LPS components/signals (such as TLR2/1 and certain lectin receptors), providing functional and immunological "layers" to the categorization of LPS within inflammatory disease situations ([3]; [4]; [10]).

2.4 Mycotoxins

Aflatoxins, ochratoxins, zearalenone, fumonisins, and the dioxynevalinol/nivalenol (DON/NIV) group are examples of "major groups" of secondary chemicals that are often found in food, according to the 2025 reviews ([6]). Due to their ubiquity and correlation with global health and economic hazards, comprehensive evaluations conducted in 2025 also show a recurrent emphasis on these same groups when investigating main cereal grains (rice, wheat, and corn) [11].

From an eco-epidemiological standpoint, fungi that produce toxins are classified as either storage fungi, which contaminate items after harvest, or field fungi, which infect crops before to harvest. This section improves knowledge of how and when contamination occurs, which informs food chain safety and control measures ([6]).

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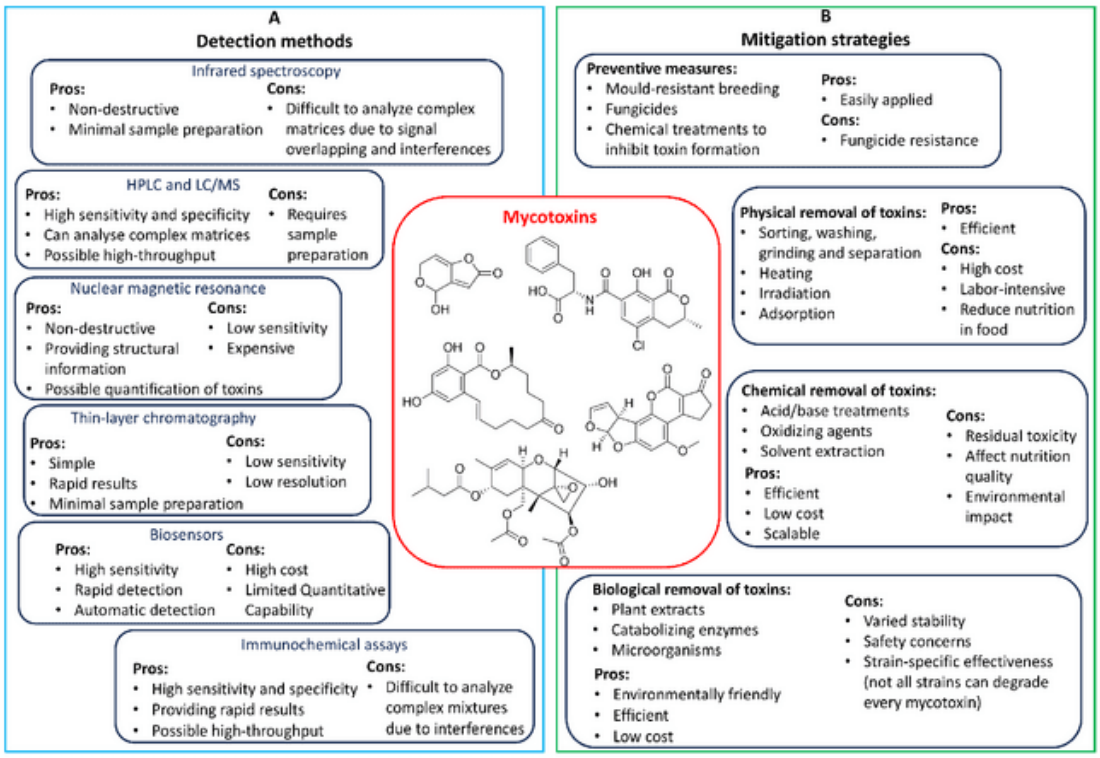
Recent reviews also focus on two prominent toxins, aflatoxins and OTA, in terms of prevalence, health effects, regulatory approaches, and prevention strategies. This makes the classification of mycotoxins practical from a regulatory and health priority perspective as well [12].

This scientific classification overlaps with regulatory classification; regulatory frameworks (such as recent EU regulations) set maximum limits for a number of mycotoxins in food, leading many recent studies to focus on "regulated" mycotoxins when presenting applied classifications (International Journal of Food Studies, 2025).

Figure 5. Chemical structures of representative mycotoxins (Pławińska-Czarnak, et al., 2024)



2.5 Toxin–Antitoxin Systems

Within the broad category of "microbial toxins," toxin–antitoxin systems (TA systems) stand out as a distinct classification from classical secreted toxins. They are genetic units within bacteria that often regulate stress response, genetic stability, or tolerance/latency phenomena, and may also be involved in phage defense ([13]; [14]). Therefore, they are sometimes referred to as "endotoxins," affecting bacterial physiology rather than being direct host toxicants ([15]).

A 2025 review of the classification of TA units clarifies that systems are divided into types based on the nature of the antitoxin and the mechanism of toxin inactivation. One of the most common types is:

Type I, in which the antitoxin is a little RNA that either decreases the stability of the harmful mRNA or prevents its translation ([15]).

Type II: The antitoxin is a protein that attaches itself to the protein toxin and inhibits it directly ([15]).

Type III: RNA-protein interactions are the main way that the structured RNA antitoxin interacts with the protein toxin ([15]).

Type IV: The antitoxin shields the cellular target from harm while not binding directly to the toxin ([15]).

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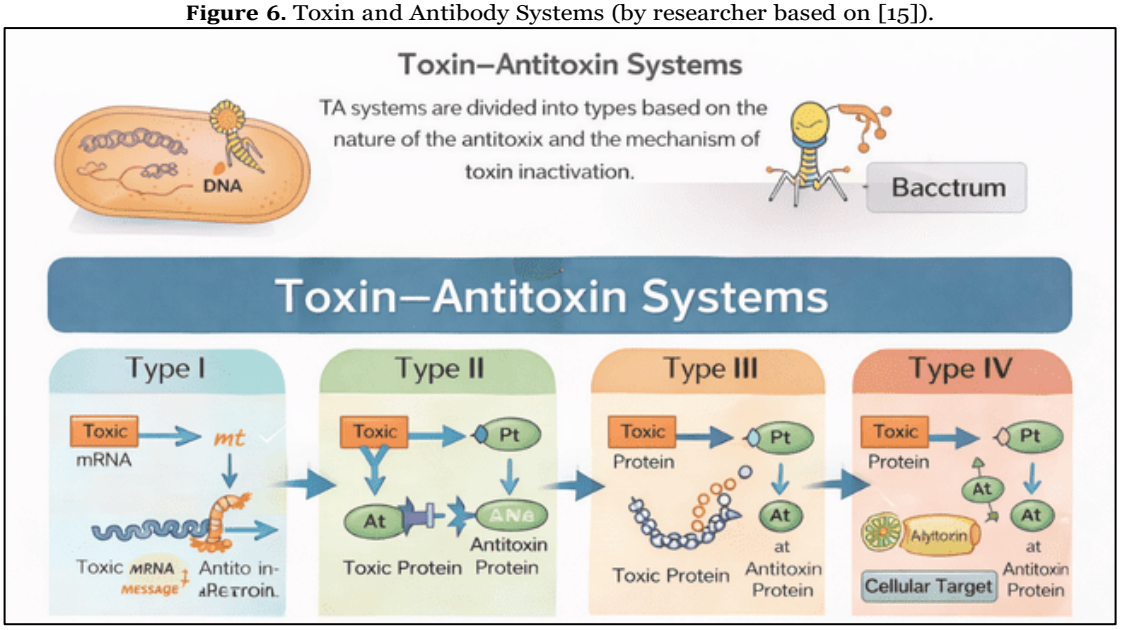
Figure 6. Toxin and Antibody Systems (by researcher based on [15]).



Additionally, certain TA subunits are involved in defense phenomena against phages via processes similar to abortive infection, in which the infected cell loses its existence to stop phage propagation, according to recent research and reviews. The inclusion of TAs in a particular functional categorization (defensive/regulatory toxins) is supported by this context ([14]). This supports the trend toward classifying toxins not only according to "what they do to the host" but also according to "what they do to the microbial system itself" (e.g., genetic stability or defense) ([13]).

Recent reviews suggest that relying on a single dimension (e.g., Exo/Endo) may be insufficient when dealing with a broad spectrum of toxins, as some toxins may be better understood if simultaneously classified according to (a) mechanism of action (AB vs. PFTs), (b) target (neurological/gastrointestinal/immune), (c) genetic context (phages/islands of pathogens), and (d) public health context (food-regulated mycotoxins) ([1]; [6]). For this reason, 2025 reviews discussing exotoxins in medicine adopt a functional framework (superantigens/membrane-disrupting/A–B) because it is more "translatable" to clinical manifestations and therapeutic approaches than a crude structural classification ([9]). Similarly, recent LPS reviews adopt a perspective that links classification to recognition and signaling pathways (TLR4 and others) because the ultimate effect is strongly determined by these networks ([4]; [10]).

3. General Principles of Toxic Mechanisms

The mechanisms of toxicity in microbial toxins are based on a set of common principles, regardless of whether the toxin is an exotoxin, a structural inflammatory factor, or even a fungal byproduct.

The first of these principles is that toxicity is not an inherent property of the toxin alone, but rather the result of a three-way interaction between (1) the toxin's properties (dose, stability, structure), (2) the route of delivery from the microbe to the host, and (3) the host's state (epithelial barrier/immunity/basal inflammation) ([16]).

Toxicity requires delivery; many virulence factors don't start working until they get to the right place at the right time. Specialized secretion systems of Gram-negative bacteria, especially the Type III secretion system (T3SS), provide a clear picture of how genetic information is converted into pathogenicity via an apparatus that delivers chemicals straight into the host cell, much like a molecular injector. This direct delivery demonstrates that the toxicity mechanism basically starts at the transport/injection stage prior to intracellular activity and explains how a small number of active chemicals may effectively modify cellular pathways ([16]).

Binding to receptors and entry routes determines cellular selectivity, or tropism. Toxins' capacity to connect to receptors or surface elements that dictate which cell will be impacted contributes significantly to their specificity, in addition to their enzymatic nature. Many pathogens use entrance mechanisms, such as caveolin-mediated endocytosis or clathrin-dependent entry, to help them enter, survive, and evade the immune system. According to a recent analysis, bacterial manipulation of the caffeoin system may affect the severity of the illness by changing the dynamics of inflammatory signaling and intracellular molecular mobility in addition to facilitating entrance ([17]).

The impact is enhanced by post-entry activation. Before they start to really injure people, many toxins go through internal activation stages (such pH changes in vesicles, protein breakage, or refolding). This idea explains why "toxin inhibitors" are designed with two stages in mind: either blocking entrance or blocking conversion to the active form ([18]).

Small doses become deadly due to signal amplification. Because a single active molecule may alter a large number of target molecules (such as regulatory proteins or parts of the neurosecretory system), enzymatic poisons demonstrate the concept of amplification. Neurotoxins such as botulinum neurotoxin, for instance, have a structural division of labor consisting of

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receptor recognition and entry domains and an enzyme domain (zinc-metalprotease) that cleaves important targets in the neurovesicular excretion pathway, causing significant dysfunction even at relatively low doses ([18]).

Membrane toxins may not merely induce lysis; they may also initiate controlled cell death systems. Instead of only causing osmotic lysis, it is now believed that membrane rupture or perforation may serve as a signal to initiate controlled cell death pathways. According to the 2025 review, membrane toxins can cause systemic damage or persistent tissue inflammation rather than just quick localized cell death because pore-forming proteins and factors (both immune and microbial) can control cell fate by alternating between various death modes ([19]).

Immunopathological toxicity is common. An excessive inflammatory response (such as a cytokine storm) that results in multiple organ failure may worsen the clinical prognosis even in cases when direct damage is minimal. Recent analyses of cytokine storms in sepsis show that, when they overpower regulatory systems, the products of acute inflammation (TNF, IL-6, etc.) may be important drivers of pathogenesis rather than just markers. This puts the processes of toxicity in a more comprehensive context: a toxin may cause an adverse immune response or directly destroy cells ([20]).

The end result is determined by the dose-time-context factor. Depending on the immune system, the integrity of the epithelial barrier, and the mode of exposure (gastrointestinal, cutaneous, or inhalation), the same toxin may have varying effects. As a result, it is crucial to stress that the process is not linear but rather a network that depends on the dynamics of entrance, activation, amplification, and inflammatory homeostasis while outlining the "general principles" in your review ([17]; [20]).

By connecting delivery, selectivity, activation, amplification, cell death processes, and immunity, these seven principles enable us to understand the majority of microbial toxins, whether they are membrane toxins, A–B toxins, or pro-inflammatory agents. This immediately relates to our review's goal of elucidating the "Mechanisms of Action" and how they relate to "Pathogenic Significance."

4. Pathogenic Significance

Through two primary mechanisms—direct damage to cells and tissues and amplification of the inflammatory/immune response to the point where immunity itself becomes part of the disease (immunopathology)—microbial toxins acquire their pathogenic significance by transforming a microbe's presence from mere colonization/infection into a clinically defined disease of specific severity and pattern. This is especially true in cases of sepsis and septic shock, when the damage is caused by "toxic inputs" that activate immune recognition networks and reroute the response toward an excessive or dysfunctional pattern in addition to pathogen multiplication ([21]; [22]).

One of the clearest examples of the “importance of toxins in shaping disease” is LPS in Gram-negative bacteria. It is now viewed not only as a “defining” component but also as a pathogen driver that can create an identifiable clinical pattern within sepsis called the “endotoxemic septic shock endotype.” This means that the presence/burden of toxins may explain the severity of infection and organ failure in a specific subset of patients, and treatment can be targeted accordingly ([23]). Recent mechanistic studies support this perspective by showing that the efficacy of the TLR4 pathway is not determined by LPS binding alone but is also influenced by post-translational modifications within the “signaling complex.” Recent work has shown that acetylation of TIR domains within the TLR4–Mal–MyD88 complex enhances NF-κB signaling and binds to inflammatory polarity markers (M1) in monocytes of septic patients, providing a molecular explanation for how a single microbial stimulus translates into a severe inflammatory pattern ([22]). Thus, the “importance of LPS” lies not only in its ability to activate the immune system, but also in the susceptibility of this activation to amplification via cellular regulation that may transform it into systemic pathogenesis ([21]; [22]).

In contrast, superantigens exhibit a different kind of pathogenic importance because they directly reshape adaptive immunity through broad and atypical T-cell activation. Toxic shock syndrome is associated with an overactive immune response that can lead to shock and organ failure, with recent evidence suggesting that certain superantigens selectively target specific TRBV subsets within memory T cells, resulting in a disruption of the homeostasis (including the subsequent development of non-response/functional fatigue). Therefore, the pathogenic significance of superantigens lies not only in their release of cytokines but also in their qualitative/long-term reprogramming of the adaptive response, which can promote colonization or exacerbate infection outcomes ([24]).

Membrane-damaging toxins (particularly pore-forming toxins) highlight a third dimension of pathogenic significance: the generation of tissue damage via indirect mechanisms (mediators/vesicles/cell communication). For example, recent research in iScience showed that pneumolysin toxin (from Streptococcus pneumoniae) can promote the release of extracellular vesicles from host cells during infection, and that these vesicles contribute to the transmission of inflammatory effects and pathogenesis beyond the “direct contact site” between the bacteria and the cell. This type of finding supports the idea that toxins may act as “network pumps” of inflammation via media produced by the host, which explains why the damage can be extensive even when the bacteria are relatively localized ([25]).

Mycotoxin exposure is often low-dose and persistent, yet it may have a significant impact on gut health via three interrelated pathways: microbiome dysbiosis, mucosal immune dysfunction, and alteration of the epithelial barrier ([26]; [27]). A recent review in Current Opinion in Food Science suggests that mycotoxin exposure may be associated with functional features that resemble or overlap with indicators of inflammatory bowel disease, by affecting gut homeostasis and triggering low-grade or chronic inflammation ([27]). A 2025 review in Toxics also summarizes that common toxins such as DON, ZEN, FUMs, AFB1, and T-2/HT-2 can induce intestinal damage via pathways that include inflammation, oxidative stress, disruption of tight junctions, and alterations in the gut microbiota ([26]). This makes the pathogenic significance of

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mycotoxins a public-health burden, as they are linked to the food chain and have associated health and productivity implications ([27]; [26]).

Therefore, the “pathogenic significance” of microbial toxins as an applied framework is useful in two ways: First, it explains clinical heterogeneity (why some patients develop shock/organ failure while others do not with the same infection) through concepts such as “endotype” and signaling alterations in TLR4 ([23]; [22]). Second, it directs interventions toward the toxin or its pathway (e.g., removing/neutralizing the toxin, targeting immune signaling nodes, or controlling food safety and reducing mycotoxin exposure), which enhances the translatability of knowledge from mechanistic review to preventive/therapeutic recommendations ([21]; [23]; [27]).

5. Therapeutic and Preventive Implications

The practical value of reviewing microbial toxins stems from the fact that “toxicity” is not merely a mechanistic description, but an actionable target on three levels: (1) neutralizing the toxin or directly inactivating its activity, (2) interrupting the “binding-entry-activation-amplification” chain before harm reaches the point of no return, and (3) reducing the burden of exposure or preventing infection through vaccines and preventive interventions, especially in the context of foodborne toxins such as mycotoxins ([28]; [29]; [30]). Therefore, therapeutic and preventative approaches to toxins should be based on a map of the stages of action: pre-cellular (binding/entry), post-cellular (activation/enzymatic action), and systemic (inflammation/end-organ dysfunction), as each stage opens a window for different interventions ([31]; [32]; [33]).

5.1 Therapeutic Implications

A. Passive Immunotherapy Against Toxins or Virulence Agents

Monoclonal antibodies (mAbs) have become an increasingly popular option in combating antibiotic-resistant infections because they can neutralize toxins, prevent their binding to receptors, or enhance immune clearance, with less selective pressure on the microbiome compared to broad-spectrum antibodies ([34];). Because toxins cause rapid damage that can become irreversible if intervention is delayed, recent reviews confirm that the success of mAbs is linked to precise target identification (toxin/adhesin/capsule) and the selection of an appropriate clinical context (pre-exposure prophylaxis, early treatment, or adjuvant therapy with an antibiotic) ( ). Additionally, recent advancements go beyond conventional mAbs to include hybrid formulations such antibody-antibiotic conjugates, which combine targeted medication delivery or bacterial killing with highly selective targeting. This method is thought to be a potential defense against severe or limited intracellular or tissue infections ([35]).

B. Inhibitors of Toxic Structure Binding/Entry

For poisons that depend on receptor binding or membrane complex formation, stopping the entry phase makes sense. The creation of small-molecule inhibitors that stop pneumolysin toxin from forming pores by blocking the pore formation step and eliminating hemolysis and cytotoxicity in in vitro models is a recent, significant example that shows the possibility of a "pore-forming toxin countermeasure" ([31]). Similarly, aptamers have been suggested as selective binding molecules capable of suppressing toxins such as Shiga toxin by interrupting their contact with the target/function. Because aptamers can be created really fast and altered to enhance stability and pharmacokinetics, this is a crucial therapeutic approach ([32]). In actuality, these methods convert the "entry-phase" concept into therapeutic instruments that focus on the biomechanics of toxicity (such as assembly/oligomerization or structural stability) as opposed to just enzymatic activity. ([31]; [32]).

C. Adjunctive Endotoxin-Targeted Strategies for Sepsis

Because LPS is associated with systemic inflammatory pathology, “hemodialysis” interventions aimed at reducing the toxin burden in the blood have emerged as adjunctive therapy in sepsis/septic shock. The most prominent of these is Polymyxin-B hemoperfusion (PMX-HP), which relies on the absorption of LPS outside the body ([33]). Recent reviews/analyses indicate that the results of PMX-HP in previous trials have been inconsistent, and one of the most important keys to efficacy is patient selection using indicators such as the Endotoxin Activity Assay to identify those with “endotoxin-driven physiology.” This transforms the intervention from a general application to one targeted to a population with a high toxin burden ([33]). Recent meta-analyses have also supported the possibility of improved short-term outcomes (such as hemodynamics or survival indicators), but more rigorous studies are needed due to the variability in clinical designs ([22]). Thus, targeting LPS exemplifies how understanding toxins opens the door to precision medicine within sepsis by identifying the endotoxin-endotype and then selecting the appropriate intervention ([33]; [22]).

D. Developing Safer and More Effective Toxoids

A 2025 review in Toxicon confirms that “detoxification while preserving immunity” is the cornerstone of toxoid vaccines, and that inactivation/detoxification techniques must be carefully evaluated because they may reduce immunity or leave toxic residues if misapplied. This directly links the mechanisms of toxicity to a therapeutic/preventive decision: understanding the structure-function determines which sites should be preserved to create neutralizing antibodies, and which parts should be inactivated to ensure safety ([28]).

5.2 Protective Implications

A. Vaccines Against Toxins or Toxin-Producing Bacteria

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Modern vaccines against bacteria are no longer limited to traditional toxoids; they are moving toward mRNA and DNA/saRNA platforms, viral vectors, and nanoparticles, with particular attention to multidrug-resistant bacteria. Reviews from 2024–2025 indicate that mRNA platforms allow for the rapid selection of multiple antigens (e.g., toxins/adhesion factors) and easy updating with changing strains, but their challenges include selecting the protective antigen, eliciting a mucosal response when needed, and fine-tuning the deliverability/supports ([29]; [36]). From a toxicology perspective, the benefit of these platforms is that they allow for the design of vaccines targeting toxins, binding/entry fragments (B domains), or neutralizing peptides, thus supporting the prevention of "toxin-driven disease" even in cases of limited colonization ([36]).

B. Dietary prevention of mycotoxins

Mycotoxins present a preventive challenge because control is not only clinical but also agricultural/supply chain-related. Therefore, interventions are expanding toward "bioneuthesis" within the digestive tract or through functional food components that reduce absorption or convert toxins into less toxic metabolites. Recent reviews support the idea that the microbiome can contribute to the neutralization/decomposition of some toxins, and that employing beneficial bacteria or microbial enzymes represents a promising preventive avenue, provided efficacy is demonstrated in real-world models and safety is controlled ([37][38][39]).

Furthermore, a 2024 systematic review in Food & Function discussed the role of probiotics/prebiotics/synbiotics/postbiotics in mitigating the effects of mycotoxins or modifying their interaction with the microbiome, supporting the inclusion of food-microbial interventions in prevention strategies, particularly in cases of chronic, low-dose exposure ([30][40][41]).

C. Clinical Prevention

At the clinical microbiological level, prevention is not limited to vaccination. Reducing the chances of infection or the microbial load in the early stages necessarily reduces toxin loading and the resulting irreversible harm. Reviews of mAbs application indicate that their use may be prophylactic in high-risk groups (such as critically ill or immunocompromised patients) when the risk of a specific infection is high, similar to the logic of passive prophylaxis against specific toxins or virulence factors ( ). Likewise, combining antitoxic interventions with antibiotics may reduce inflammatory damage and limit the progression of organ failure—a principle recalled in reviews of mAb therapies and antibody-antibiotic combinations as a "therapeutic complementarity" rather than a replacement ([34]; [35]).

6. Conclusions

This review confirms that microbial toxins are a central explanatory axis in pathomicrobial medicine because they link pathogen characteristics to specific clinical manifestations through pathways that include direct cellular/tissue damage or reprogramming of the immune response, thus increasing disease severity even at a limited microbial load.

It is also evident that the classical (exotoxin/endotoxin) classification remains useful as a starting point, but becomes more explanatory when combined with a functional classification that distinguishes between superantigens (immune hyperactivation), membrane toxins (membrane dysfunction/inflammation), and A–B toxins (inclusion/binding from intracellular enzymatic activity), in addition to considering LPS as a "structural inflammatory factor" associated with multiple recognition and signaling layers.

The general principles of toxicity mechanisms show that delivery, cellular selectivity, post-entry activation, and signal amplification all interact intricately to determine a toxin's final effect. Immune/inflammatory programs and controlled cell death play a critical role in converting toxicity into systemic pathology.

Mycotoxins stand out as a persistent burden associated with the food supply chain in public health and food science, making prevention (control, contamination reduction, and detoxification/reduction approaches) a crucial component of comprehending their pathogenicity.

The review concludes by confirming that, within the framework of the "entry phase – enzymatic/membrane action phase – inflammatory output phase," the most promising contemporary therapeutic and preventive approaches treat toxins as targetable objectives (neutralization/entry inhibition/endotoxin-targeted strategies/vaccines). This calls for filling up research gaps in the areas of finding treatable endotypes, standardizing multidimensional categorization, and converting lab results into repeatable clinical effectiveness.

References

1. M. R. Popoff, "Overview of bacterial protein toxins from pathogenic bacteria: Mode of action and insights into evolution," Toxins, vol. 16, no. 4, p. 182, 2024, doi: 10.3390/toxins16040182.
2. E. Atchade, C. De Tymowski, N. Grall, S. Tanaka, and P. Montravers, "Toxic shock syndrome: A literature review," Antibiotics, vol. 13, no. 1, p. 96, 2024, doi: 10.3390/antibiotics13010096.
3. P. Arya, V. Sharma, P. Singh, S. Thapliyal, and M. Sharma, "Bacterial endotoxin-lipopolysaccharide role in inflammatory diseases: An overview," Iran. J. Basic Med. Sci., vol. 28, no. 5, pp. 553–564, 2025, doi: 10.22038/ijbms.2025.82302.17799.
4. R. Luo et al., "An examination of the LPS–TLR4 immune response through the analysis of molecular structures and protein–protein interactions," Cell Commun. Signal., vol. 23, p. 142, 2025, doi: 10.1186/s12964-025-02149-4.
5. R. Shekhar et al., "A comprehensive review of mycotoxins, their toxicity, and innovative detoxification methods,"

Toxicol. Rep., vol. 14, p. 101952, 2025, doi: 10.1016/j.toxrep.2025.101952.
6. Y. Syraji et al., "Comprehensive review of aflatoxin contamination, its occurrence, effects, management, and future perspectives," Discover Food, vol. 5, p. 377, 2025, doi: 10.1007/s44187-025-00680-4.
7. R. Touaitia et al., "Toxic shock syndrome toxin-1 (TSST-1) in Staphylococcus aureus: Prevalence, molecular mechanisms, and public health implications," Toxins, vol. 17, no. 7, p. 323, 2025, doi: 10.3390/toxins17070323.
8. H. Jamali, F. Akrami, H. Layeghkhavidaki, and S. Bouakkaz, "Bacterial protein secretion systems: Mechanisms, functions, and roles in virulence," Microb. Pathog., vol. 206, p. 107790, 2025, doi: 10.1016/j.micpath.2025.107790.
9. Y. Xiao, Z. Yan, F. Ren, and Y. Tan, "Bacterial exotoxins in medicine: Potential value and perspectives," Int. J. Med. Sci., vol. 22, no. 9, pp. 2010–2019, 2025, doi: 10.7150/ijms.110104.
10. D. V. Grebennikova, U. K. Shandilya, and N. A. Karrow, "Beyond TLR4 and its alternative lipopolysaccharide (LPS) sensing pathways in zebrafish," Genes, vol. 16, no. 9, p. 1014, 2025, doi: 10.3390/genes16091014.
11. W. Niaz et al., "Mycotoxins: A comprehensive review of global trends in major cereals, advancements in chromatographic detections and future prospects," Food Chem. X, vol. 27, p. 102350, 2025, doi: 10.1016/j.fochx.2025.102350.
12. T. M. Nazareth et al., "Comprehensive review of aflatoxin and ochratoxin A dynamics: Emergence, toxicological impact, and advanced control strategies," Foods, vol. 13, no. 12, p. 1920, 2024, doi: 10.3390/foods13121920.
13. B. Mendoza-Guido and K. Rojas-Jimenez, "Beyond plasmid addiction: The role of toxin-antitoxin systems in mobile genetic elements," J. Bacteriol., vol. 207, no. 10, p. e00232-25, 2025, doi: 10.1128/jb.00232-25.
14. H. Pu et al., "A toxin-antitoxin system provides phage defense via DNA damage and repair," Nat. Commun., vol. 16, p. 3141, 2025, doi: 10.1038/s41467-025-58540-9.
15. A. Bahl et al., "Toxin–antitoxin modules: Genetic elements with many faces and functions," Bacteria, vol. 4, no. 4, p. 61, 2025, doi: 10.3390/bacteria4040061.
16. L. Jia and L. Zhu, "The bacterial type III secretion system as a broadly applied protein delivery tool in biological sciences," Microorganisms, vol. 13, no. 1, p. 75, 2025, doi: 10.3390/microorganisms13010075.
17. D. Barman and R. Drolia, "Caveolin-mediated endocytosis: Bacterial pathogen exploitation and host–pathogen interaction," Cells, vol. 14, no. 1, p. 2, 2024, doi: 10.3390/cells14010002.
18. R. Kumar and B. R. Singh, "Botulinum toxin: A comprehensive review of its molecular architecture and mechanistic action," Int. J. Mol. Sci., vol. 26, no. 2, p. 777, 2025, doi: 10.3390/ijms26020777.
19. S. Iranpour, M. Arif, and E. Szegezdi, "Disrupting membranes, controlling cell fate: The role of pore-forming proteins in cell death and therapy," Apoptosis, vol. 30, pp. 1961–1988, 2025, doi: 10.1007/s10495-025-02133-w.
20. J. B. Fan et al., "The 'cytokine storm' in infection and sepsis: Win the battle but lose the war," Mil. Med. Res., vol. 12, p. 95, 2026, doi: 10.1186/s40779-025-00678-0.
21. K. Roszak et al., "Endotoxin's impact on organism: From immune activation to tolerance and beyond," J. Clin. Med., vol. 14, no. 18, p. 6478, 2025, doi: 10.3390/jcm14186478.
22. C. Li et al., "The role of polymyxin B-immobilized hemoperfusion in sepsis and septic shock: A meta-analysis," Heliyon, vol. 10, no. 24, p. e33245, 2024, doi: 10.1016/j.heliyon.2024.e33245.
23. H. Gómez, "Endotoxin: A bona fide treatable sepsis endotype?," Blood Purif., early access, 2025, doi: 10.1159/000546294.
24. F. R. Shepherd et al., "The superantigens SpeC and TSST-1 specifically activate TRBV12-3/12-4+ memory T cells," Commun. Biol., vol. 6, 2023, doi: 10.1038/s42003-023-04420-1.
25. S. Parveen et al., "Bacterial pore-forming toxin pneumolysin drives pathogenicity through host extracellular vesicles," iScience, vol. 27, no. 8, p. 110589, 2024, doi: 10.1016/j.isci.2024.110589.
26. T. Li et al., "Mycotoxin-caused intestinal toxicity: Underlying molecular mechanisms and future directions," Toxics, vol. 13, no. 8, p. 625, 2025, doi: 10.3390/toxics13080625.
27. A. M. Gasperini, D. Faccenda, and E. García-Cela, "Unravelling the impact of mycotoxins on gut health: Implications for inflammatory bowel disease," Curr. Opin. Food Sci., vol. 64, p. 101316, 2025, doi: 10.1016/j.cofs.2025.101316.
28. P. Esmaeilnejad-Ahranjani et al., "Detoxification techniques for bacterial toxins: A pathway to effective toxoid vaccines," Toxicon, vol. 260, p. 108365, 2025, doi: 10.1016/j.toxicon.2025.108365.
29. A. Khlebnikova et al., "Current progress in the development of mRNA vaccines against bacterial infections," Int. J. Mol. Sci., vol. 25, no. 23, p. 13139, 2024, doi: 10.3390/ijms252313139.
30. Á. Lázaro et al., "Probiotics, prebiotics, synbiotics, and postbiotics in the context of emerging mycotoxins and gut microbiota: A systematic review," Food Funct., vol. 15, no. 19, pp. 8950–8974, 2024, doi: 10.1039/D4FO01705F.
31. U. B. A. Aziz et al., "Targeted small molecule inhibitors blocking the cytolytic activity of pneumolysin," Nat. Commun., vol. 15, p. 3738, 2024, doi: 10.1038/s41467-024-47741-3.
32. M. Duan et al., "Discovery and design of an aptamer that inhibits Shiga toxin: Toward nucleic-acid-based antitoxin strategies," Int. J. Biol. Macromol., vol. 260, p. 129826, 2024, doi: 10.1016/j.ijbiomac.2024.129826.
33. T. Iba et al., "Endotoxin activity assay-guided patient selection for polymyxin B hemoperfusion in sepsis and septic shock," Healthcare, vol. 13, no. 20, p. 2603, 2025, doi: 10.3390/healthcare13202603.
34. H.-C. Chen, "Monoclonal antibodies as a therapeutic strategy against bacterial infections: Current status and future perspectives," Life, vol. 14, no. 2, p. 246, 2024, doi: 10.3390/life14020246.
35. A. Darbandi et al., "Antibody–antibiotic conjugates: A comprehensive review of design strategies and clinical prospects," J. Clin. Lab. Anal., vol. 38, no. 5, p. e25071, 2024, doi: 10.1002/jcla.25071.
36. H. Chen, Y. Gu, L. Song, and L. Si, "Next-generation vaccines against bacterial pathogens: mRNA and beyond," Front. Immunol., vol. 16, p. 1709794, 2025, doi: 10.3389/fimmu.2025.1709794.
37. M. M. Islam et al., "Gut microorganism-mediated neutralization of mycotoxins: Advances in biological detoxification," Biomed Res. Int., vol. 2024, p. 8448547, 2024, doi: 10.1155/2024/8448547.
38. A. M. Deacy, S. K. Gan, and J. P. Derrick, "Superantigen recognition and interactions: Functions, mechanisms and applications," Front. Immunol., vol. 12, p. 731845, 2021, doi: 10.3389/fimmu.2021.731845.
39. X. Li et al., "Acetylation of TIR domains in the TLR4-Mal-MyD88 complex regulates immune responses in sepsis," EMBO J., vol. 43, pp. 4954–4983, 2024, doi: 10.1038/s44318-024-00237-8.
40. J. Pławińska-Czarnak, M. Zawadzki, and B. Wróblewska, "Mycotoxin biodegradation by Bacillus bacteria—A review,"

Vol. 3 No. 1 (2026): July
DOI: 10.21070/ijhsm.v3i1.443

Toxins, vol. 16, no. 11, p. 478, 2024, doi: 10.3390/toxins16110478.
41. S. Vitalini, M. Iriti, and L. Vallone, “Mycotoxins in European Union regulations (2023–2025),” Ital. J. Food Saf., vol. 15, no. 1, p. 14096, 2025, doi: 10.4081/ijfs.2025.14096.