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Bacterial Protein Toxins with Emphasizing on Bacterial Enterotoxins

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Authors
Ala Amiri, *MSc*[1]
Parisa Nouriyeh, *MSc*[2]
Mohammad Zibaei, *PhD*[3,4]
Sepeta Zibaei, *MD*[5]
Farzaneh Firoozeh, *PhD*[6,7*]

[1] Department of Biotechnology, Faculty of Biological Sciences, Alzahra University, Tehran, Iran
[2] Razi Vaccine and Serum Research Institute, Education and Extension Organization (AREEO), Karaj, Iran
[3] Department of Parasitology and Mycology, Alborz University of Medical Sciences, Karaj, Iran
[4] Kosar Clinical Research Development Unit, Alborz University of Medical Sciences, Karaj, Iran
[5] Student Research Committee, Alborz University of Medical Sciences, Karaj, Iran
[6] Department of Microbiology, School of Medicine, Alborz University of Medical Sciences, Karaj, Iran;
[7] Evidence-Based Phytotherapy and Complementary Medicine Research Center, Alborz University of Medical Sciences, Karaj, Iran

** Correspondence*
Department of Microbiology, School of Medicine, Alborz University of Medical Sciences, Karaj, Iran.
E-mail: ffiroozeh@ut.ac.ir

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ABSTRACT

Background: Bacterial toxins are virulence factors that manipulate the functions of host cells and take over the control of main processes of living organisms. Importantly, they are non-curable, non-contagious, and non-infectious by chemotherapeutic agents and/or antibiotics. The multifactorial nature of the toxicity of bacterial toxins has made their investigation more complicated.
Materials & Methods: In this review, we investigated some biological activities, structure, and action mechanism of several bacterial toxins using data from studies published in major international databases.
Conclusion: Bacterial protein toxins are very diverse based on size, structure and mode of action. Based on the structure and the type of cell surface receptors, the mentioned toxins have activity on the cell surface (signal transmission, pore formation) or have intracellular activity. Many bacterial protein toxins have the ability to enter the cell by the endocytosis mechanism, and according to their intracellular targets, they can induce different intracellular effects, which in many cases lead to the death of the target cell. A large and interesting group of bacterial toxins are enterotoxins. The majority of toxigenic bacteria are environmental, and the digestive system is one of the most common ways of entering or encountering environmental bacteria or their toxic products through eating food. Many enteropathogenic bacteria produce enterotoxins in food, in the intestinal lumen or on the surface of the intestinal mucosa. Also, some entero-invasive bacteria penetrate the cells by inoculating some toxins into the intestinal cells. The challenge of studying bacterial toxins and enterotoxins lies in their complex nature and the need for comprehensive characterization, but the future holds promise with advancements in technology and interdisciplinary approaches to further our understanding and develop effective strategies for prevention and treatment.

Keywords: Bacteria, Toxins, Enterotoxins, Exotoxins; Review

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Introduction

Toxigenesis, or the capability to generate a variety of toxins, is an underlying process by which pathogenic bacteria can lead to various disease and conditions [1]. At chemical levels, there are two major kinds of bacterial toxins, proteins, which are secreted from bacteria and may operate at sites removed from bacterial growth, and lipopolysaccharides, which are related to the cell wall of Gram-negative bacteria [2, 3]. The diffusible extracellular toxins are pointed out as exotoxins, while cell-related toxins are considered as endotoxins [3]. Exotoxins are often released by various bacteria and operate at tissue sites removed from the site of bacterial growth. However, some exotoxins are only secreted through cell lysis in bacteria; these types of toxins usually have a protein (polypeptide) nature, whose mechanism of action is direct impact on the target cell, and/or enzymatic, which can lead to the stimulation of several immune responses of the host [2]. Most exotoxins take action at tissue points remote from the native site of bacterial growth/invasion. Of course, some of these toxins operate at the point of bacterial colonization and might take part in the invasion process [4]. Endotoxins are cell-related materials that are observed as structural components in bacteria [2]. The soluble endotoxins might be secreted from an intact bacterium or from a cell that is lysed as an output of the activity of antibiotics or by a host defense mechanism [4].

Bacterial protein enterotoxins are an important class of toxins produced by various pathogenic bacteria. Extensive research has provided insights into the diverse characteristics and mechanisms of this kind of toxins [5]. Bacterial protein enterotoxins are typically synthesized as precursor proteins that undergo post-translational modifications to become biologically active toxins [5]. These toxins can target specific host cell receptors, leading to their internalization and subsequent interference with essential cellular processes. The effects of protein enterotoxins can vary widely, ranging from cytotoxicity and disruption of host cell signaling pathways to modulation of immune responses and induction of inflammation [6]. The activity of protein enterotoxins can have significant implications for the pathogenesis of infectious diseases, including diarrhea, food poisoning, and systemic infections. Understanding the properties and mechanisms of bacterial protein enterotoxins is crucial for elucidating the molecular basis of bacterial pathogenesis and for the development of effective preventive and therapeutic strategies to combat toxin-mediated diseases [6].

Given the increasing importance of bacterial protein toxins like bacterial enterotoxins, in the present review, we investigated some biological activities, structures, and mechanisms of action of several bacterial toxins using data from studies published in major international databases. We discussed the different types of protein toxins, the mode of action, and the mechanism involved in toxin synthesis, release, attachment, and cell entry.

Protein Toxins in Bacteria: Bacterial protein toxins are generally secreted by living bacteria within the exponential stage of the growth process [7]. The ability for toxin production is usually specific to a special bacterial species that can produce disease conditions related to the toxin (e.g., only *Corynebacterium diphtheriae* generates diphtheria and/ or only *Clostridium tetani* generates tetanus toxin)[8, 9]. Normally, virulent strains of the bacteria give rise to toxins, whereas non-virulent strain does not. Indeed, the toxin is the main determiner of virulence (e.g. tetanus and diphtheria). Formerly, it was speculated that toxin generation was restricted largely to Gram-positive bacte-

ria, but obviously, both Gram-negative and Gram-positive bacteria can generate soluble protein toxins [3]. This category of toxins is the most powerful poison in humans and retains high activity at much higher dilution. In Table 1, the lethality of endotoxin, snake venom, and strychnine is compared to the lethality of the most potent exotoxins [8-10].

Normally the location of damage derived from exotoxins demonstrates the site for the activity of those toxins [11]. Descriptive terms such as hemolysin, leukocidin, neurotoxin, or enterotoxin illustrate the target location of some well-known protein toxins [9, 11-14]. A couple of bacterial toxins that give rise to the death of cells are named lethal toxins. Although the tissue influenced and the target substrate/location may be recognized, the accurate mechanisms by which cellular deaths occur are not obvious [2]. Several bacterial toxins operate locally to enhance bacterial invasions, called invasins. Examples are extracellular enzymes–such as streptokinase, collagenase, and hyaluronidase– that decompose fibrin or tissue matrices, permitting the bacterial cells to outspread[15]. Some invasin toxins degrade membrane components, like lecithinases and phospholipases. As well, the pore-forming toxin that inserts pores into the cell membrane is categorized as invasion[15].

Some exotoxins possess special cytotoxic activities (i.e., they attack special kinds of cells). For instance, tetanus and botulinum toxins invade only nerve cells[16]. However, some toxins (as generated through clostridia, streptococci, staphylococci, etc.) possess broad cytotoxic function and result in non-specific death of different kinds of cells, ultimately leading to the death of body tissues [17].

It was found that bacterial exotoxins are strongly antigenic. Special antibodies neutralize the toxicity of these toxins in vivo. However, particular antitoxins may not completely prevent their activity in vitro [18]. The level of neutralization of the active sites might rely on the interval from the antigenic sites on the intended protein [16]. Because the toxins are completely neutralized in vivo, this proposes that the other host factors may participate in an important function in toxins neutralization [19].

Tables 2 and 3 describes some bacterial toxins with known biological activities of the toxins in humans [14, 20-39].

Bacterial protein enterotoxins: Bacterial protein enterotoxins have been the subject of extensive research and exploration throughout history [43]. The investigation into these toxins dates back to the mid-20th century, with researchers aiming to understand their role in infectious diseases [44]. Early studies involved the identification and characterization of well-known bacterial protein enterotoxins, such as staphylococcal enterotoxins and shiga toxins [44]. These seminal discov-

Table 1) Lethal toxicity of protein toxins from bacteria

Toxins	Toxic Doses (mg)	Hosts	Lethality compared with		
			Strychnine	Endotoxin (LPS)	Snake Venom
Diphtheria toxin	$6x10^{-5}$	Guinea pig	$2x10^{3}$	$2x10^{4}$	$2x10^{2}$
Shiga toxin	$2.3x10^{-6}$	Rabbit	$1x10^{6}$	$1x10^{7}$	$1x10^{5}$
Tetanus toxin	$4x10^{-8}$	Mouse	$1x10^{6}$	$1x10^{7}$	$1x10^{5}$
Botulinum toxin	$0.8x10^{-8}$	Mouse	$3x10^{6}$	$3x10^{7}$	$3x10^{5}$

Table 2) Biological activities of several bacterial protein toxins

Exotoxins	Biological efficacies	Enzymatic activities
Exfoliatin B from *Staphylococcus aureus*	Separation of the stratum granulosum of the epidermis, between the living and superficial dead layers.	Cleaves desmoglein I, a cadherin detected in the epidermis desmosomes
AC toxin (A/B) from *Bordetella pertussis* and EF (A1+B) from *Bacillus anthracis*	Enhances cAMP in phagocytes resulting in suppression of phagocytosis via macrophages and neutrophils; also leads to leukolysis and hemolysis	Calmodulin-regulated adenylate cyclases that catalyze the production of cAMP from ATP in the sensitive cell, and the production of the ion-permeable pore in the cell membrane
Anthrax LF (A2+B)	Along with the B subunit (PA), LF can induce cytokine release and death of experimental animals or host cells	Metallo protease that can cleave MAPKK enzymes
Tetanus (A/B)	Prohibits neurotransmitter release from inhibitory neurons in the central nervous system leading to spastic paralysis	Zn^{++} dependent protease operates on synaptobrevin in central nervous system
Botulinum (A/B)	Prevents presynaptic acetylcholine release from peripheral cholinergic neurons leading to flaccid paralysis	Zn^{++} dependent protease operates on synaptobrevin at motor neuron ganglioside
Exotoxin A (A/B) from *Pseudomonas*	Impedes protein synthesis in sensitive cell, leading to cell death of the	ADP ribosylates elongation factor-II similar to diphtheria toxin
Shiga (A/5B)	Inactivates the 60S ribosomal subunits and results in inhibition of proteins synthesis and sensitive cell death; pathology is hemolytic uremic syndrome (HUS), hemorrhagic colitis (HC), and/or diarrhea.	Glycosidase cleavage of s a single Adenine base from the 28SrRNA)
Heat-labile toxin LT (A-5B) from *E. coli*	Identical or similar to cholera toxin	ADP ribosylates adenylyl cyclase Gs regulatory proteins
Pertussis (A-5B)	Impedes inhibition of adenylate cyclase; enhanced level of cAMP reduces phagocytic activity and influences hormone activity	ADP ribosylates adenylyl cyclase Gi regulatory proteins
Diphtheria (A/B)	Prohibits proteins synthesis in the animal cell, leading to cell death	ADP ribosylates elongation factor II
Cholera (A-5B)	Activates adenylate cyclase; enhanced levels of intracellular cAMP promote secretion of electrolytes and fluid in the intestinal epithelium, resulting in diarrhea	ADP ribosylates eucaryotic adenylate cyclase Gs regulatory protein

eries provided a foundation for subsequent investigations into the diversity and mechanisms of protein enterotoxins [43].

The explanation of bacterial protein enterotoxins lies in their complex structure and function. These toxins are typically produced by pathogenic bacteria and can target specific host cells and tissues [5]. They are synthesized as precursor proteins that undergo various post-translational modifications, such as proteolytic cleavage, to become biologically active toxins [5]. Bacterial protein enterotoxins often exert their effects by binding to specific receptors on the surface of host cells, leading to internalization and interference with cellular processes [45]. The mechanisms of action can vary, with some toxins disrupting intracellular signaling pathways, while others modulate immune responses or induce inflammation [45].

Table 3) Common bacterial protein toxins, name of producing bacteria and mechanism of action

Bacteria	Toxin	Activity
Streptococcus pyogenes	Erythrogenic toxin (streptococcal pyrogenic exotoxin (SPE))*	Super antigen same as TSST – shock, fever, and inflammation; causes scarlet fever (localized erythematous reactions)
Staphylococcus aureus	Toxic shock syndrome toxin (TSST-1)*	Super antigen operates on the vascular system leading to fever, shock, and inflammation
Staphylococcus aureus	Staphylococcus enterotoxins*	Super antigen provokes the activation of the immune system, including macrophages and lymphocytes; precise function in emesis not acknowledged
Staphylococcus aureus	Exfoliatin *	Cleavage within epidermal cells; also operates as a super antigen
Bordetella pertussis	Pertussis (Ptx)	ADP ribosylation of G protein inhibits suppression of adenylyl cyclase in sensitive cell
Bacillus anthracis	Anthrax (LF)	Lethal Factors (LFs) are Zinc dependent proteases inducing cytokine secretion and are toxic to host cell by unknown mechanisms
Pseudomonas aeruginosa	Exotoxin A	Similar to diphtheria exotoxin, blocks protein synthesis
Corynebacterium diphtheriae	Diphtheria (Dtx)	ADP ribosylation of elongation factor II results in suppression of protein synthesis in the host cell
Clostridium tetani	Tetanus	Zinc dependent proteases that block neurotransmission at inhibitory synapse leading to spastic paralysis
Clostridium botulinum	Botulinum	Zinc dependent proteases that block neurotransmission at neuromuscular synapse leading to flaccid paralysis
Clostridium difficile	ToxinA/ToxinB	Modifies Rho, a category of small G-proteins that regulate the actin cytoskeletons. Deamidation of the Gln at position 63 of Rho to a Glu generates a dominant active Rho protein incapable to hydrolyze bound guanosine-5'-triphosphate. Pathological output is bloody diarrhea and cell necrosis
Clostridium perfringens	Perfringens enterotoxin	Stimulates adenylate cyclase resulting in enhanced cAMP in epithelial cells
Shigella dysenteriae *E. coli* O157: H7	Shiga	Enzymatically cleaves 28S rRNA leading to suppression of proteins synthesis in sensitive cells. Leads in hemolytic uremic syndrome (HUS), hemorrhagic colitis (HC), and diarrhea
Escherichia coli	*E. coli* ST toxin	Binding of the heat-stable toxins to guanylate cyclase receptors leads to an enhancement in cyclic guanosine monophosphate that negatively affects electrolyte flux. Increases release of electrolytes and water from intestinal epithelium resulting in diarrhea.
Escherichia coli	*E. coli* LT toxin	Leading to ADP-ribosylation of G protein, and activation of AC, giving rise to increase cyclic AMP

Bacteria	Toxin	Activity
Vibrio cholerae	Cholera enterotoxin (Ctx)	ADP ribosylations of G proteins stimulate adenylyl cyclase and enhances cyclic adenosine monophosphate in GI tract cells, leading to release of electrolytes and water causing diarrhea
Staphylococcus aureus	Alpha toxin	Protein subunits assemble into an oligomeric structure that produces an ion channel in the plasma membrane of the cell
Bordetella pertussis	Adenylate cyclase toxin (pertussis AC)	Operates locally to enhance the level of cAMP in phagocytes and production of ion-permeable pores in host cellular membranes
Bacillus anthracis	Anthrax (EF)	An adenylate cyclase enzyme that enhances intracellular cAMP level in phagocytes and induces of ion-permeable pores in cellular membranes. Causing declined phagocytic response and edema

*The pyrogenic exotoxins generated by *Streptococcus pyogenes* and *Staphylococcus aureus* have been designated as superantigens[40]. Pyrogenic exotoxins present a category of toxins with the capability to induce large activation of the immune system. Superantigens share the capability to provoke T-lymphocyte propagation through interaction with the major histocompatibility complex II on specific V beta chains of the T- lymphocyte receptors[41]. The highlight property of this interaction is the generation of lymphokine which seems to be the basic mediator of diseases related to the exotoxins[42].

The importance of bacterial protein enterotoxins stems from their significant role in bacterial pathogenesis and the development of enterotoxin-mediated diseases. These toxins can cause severe gastrointestinal symptoms, such as diarrhea, vomiting, and abdominal pain, which can lead to dehydration and life-threatening complications [44]. Bacterial protein enterotoxins are implicated in various foodborne illnesses, including those caused by *Escherichia coli*, *Salmonella*, and *Clostridium perfringens* [44]. Understanding the diversity, mechanisms, and importance of bacterial protein enterotoxins is crucial for developing effective preventive measures, diagnostic tools, and therapeutic interventions to mitigate the impact of these toxins on human health [46].

The structure of bacterial toxins : Most protein toxins, especially those that operate in the cells, have two components: subunits A and B. The subunit B is responsible for binding to a specific receptor on the recipient cell membrane and transmitting the enzyme segment across the membrane. The subunit A is responsible for the enzymatic activities of the exotoxin [2]. The A subunits are not active until they are removed from the primary toxins [15]. Detached enzymatic components are enzymatically active, but are deficient in binding ability and penetration into the target cell [2]. Detached B subunit binds to the host cell and even impedes the binding of primary toxins, but it cannot be toxic [15]. Exotoxin subunits can be synthesized and assembled by several mechanisms: A/B indicates that the toxin is synthesized as a single polypeptide, which can be broken via proteolytic cleavage into A and B domains; A-5B exhibiting that the binding domain of the toxin includes 5 identical subunits; A-B displays that the B and A subunits are individually synthesized, but linked via non-covalent bond within secretion and binding to the cells; A+B exhibits that the toxin is synthesized and released as two distinct subunits interacting at the cell surface [2, 3].

The structure of bacterial enterotoxins: The structure of bacterial protein enterotoxins is a key aspect of understanding their function and mechanisms of action [47].

Table 4) Common bacterial protein enterotoxins, name of producing bacteria, targets and mechanism of action

Bacterial Protein Enterotoxin	Bacterial Species	Target Cells/Tissues	Activities
Cholera Toxin	*Vibrio cholerae*	Intestinal epithelial cells	Activates adenylate cyclase, increases cAMP levels, causes electrolyte and water secretion, leading to severe diarrhea
Staphylococcal Enterotoxins	*Staphylococcus aureus*	Various tissues (e.g., gastrointestinal tract)	Superantigens, stimulate massive T-cell activation, release of pro-inflammatory cytokines, and contribute to food poisoning
Shiga Toxins	*Escherichia coli (EHEC strains)*	Renal endothelial cells, intestinal epithelial cells	Inhibit protein synthesis, cause damage to endothelial cells, leading to hemolytic uremic syndrome and bloody diarrhea
Heat-Labile Toxin	*Enterotoxigenic Escherichia coli (ETEC)*	Intestinal epithelial cells	Activates adenylate cyclase, increases cAMP levels, disrupts ion transport, leading to watery diarrhea
Cytotoxic Necrotizing Factor	*Escherichia coli*	Various cell types	Induces cytoskeletal rearrangements, disrupts cellular architecture, causes cell rounding and detachment, implicated in urinary tract infections
Vacuolating Cytotoxin A	*Helicobacter pylori*	Gastric epithelial cells	Induces vacuole formation, disrupts cellular processes, implicated in the development of gastric ulcers and gastric cancer

Through the examination of numerous scholarly papers, it is evident that these toxins exhibit diverse structural characteristics[3]. Bacterial protein enterotoxins often consist of multiple subunits arranged in distinct architectures [47]. For example, toxins like cholera toxin have an A-B subunit structure, where the A subunit carries the toxic activity and the B subunit facilitates receptor binding and internalization [5]. These toxins can also feature complex folded domains, disulfide bridges, and enzymatic domains responsible for their specific activities [2]. Moreover, bacterial protein enterotoxins may possess additional structural elements such as helices, beta-sheets, and loops that contribute to their stability and interactions with target cells [2]. Understanding the structure of bacterial protein enterotoxins is crucial for unraveling their molecular mechanisms and aids in the development of targeted interventions and therapeutics [5].

Functions and Mechanisms of Action of Bacterial Toxins and Enterotoxins: The function and mechanism of action of bacterial enterotoxins are critical aspects of understanding their role in pathogenicity and the development of enterotoxin-mediated diseases. Extensive research, based on studies from various scholars, has shed light on the diverse functions and intricate mechanisms of these toxins [48]. Bacterial enterotoxins pri-

marily target and disrupt the normal functioning of host cells, particularly intestinal epithelial cells [49]. They achieve this through a variety of mechanisms, including binding to specific receptors on the host cell surface, internalization via endocytosis, and subsequent modulation of intracellular signaling pathways. These toxins can interfere with essential cellular processes involved in ion transport, tight junction integrity, and water homeostasis, leading to disturbances in fluid and electrolyte balance, resulting in diarrhea [50]. Moreover, certain enterotoxins exhibit immunomodulatory properties by stimulating immune responses and promoting inflammation [50]. They can activate immune cells and trigger the release of pro-inflammatory cytokines, amplifying tissue damage and inflammatory responses [2]. Uncovering the intricate function and mechanism of enterotoxins is crucial for developing targeted interventions and preventive strategies to mitigate the impact of enterotoxin-mediated diseases on health [48].

Attachment and Cell Entry of Bacterial Toxins: Researchers suggested two mechanisms for toxins to be entered into the target cell. In one mechanism called direct entrance, the subunits B of the primary toxins bind to special receptors on the host cell surface and induce the formation of pores in membranes through which the subunits A are transmitted into the cellular cytoplasm [15]. In another mechanism, the primary toxins bind to host cells, and the B+A structure is taken into cells through the receptor-mediated endocytosis process. These toxins are internalized in the cellular membrane-surrounded vesicles, and endosomes. H+ ions get into the endosomes reducing the interior pH, and hence causing the B+A subunits to detach. The subunit B affects the release of the A subunits from endosomes so that they reach their targets in the cytoplasm of the cells. The subunit B remains in the endosomes and recycles to cell surfaces [3]. The special receptor for the subunits B on host tissues/cells is generally glycoprotein, called G-protein, on the lipid bilayer [3].

In both cases, relatively big proteins must insert into and cross endosome membranes, cell membranes, and/or membrane lipid bilayer [2]. This function revealed the capability of B/A toxins, B+A toxins, and/or their B components, to incorporate into artificial membranes and produce ions permeable paths. In some cases, the subunits B contain hydrophobic regions that incorporate into the membranes (as in the case of diphtheria), referred to as the T (translocation) domains [2]. Diphtheria is found to use both receptor-mediated endocytosis and direct entry to get into the recipient cells, which is not unexpected because both processes are variants on a theme [51]. Exotoxins with resembling mechanisms of enzymatic activity might get into the host cell through various mechanisms. For instance, diphtheria toxin A, which possesses the same enzymatic mechanism, enters its target cell in various manners [52]. The adenylate cyclase toxin produced by *Bordetella pertussis* and anthrax EF from *Bacillus anthracis*, similarly operates to catalyze the formation of cyclic adenosine monophosphate from intracellular adenosine monophosphate supplies in target cells [29, 51, 53, 54]. However, the pertussis adenylate cyclase enters the membrane directly, while the anthrax toxin comes into the cell through receptor-mediated endocytosis[54].

Attachment and Cell Entry of bacterial enterotoxins: The attachment and cell entry of bacterial protein enterotoxins are complex processes that involve specific interactions between the toxins and host cells [55]. Extensive research has provided valuable insights into these mechanisms [29]. Bacterial protein enterotoxins typically utilize various strategies to attach to the surface of target cells [54]. This attachment

often involves specific recognition and binding to cell surface receptors. The binding of enterotoxins to their receptors initiates a cascade of events that facilitate their internalization into host cells [55].

Once attached, bacterial protein enterotoxins employ different mechanisms to enter the host cells. Some toxins are internalized by receptor-mediated endocytosis, where the toxin-receptor complex is engulfed into clathrin-coated pits and internalized into endosomes [56]. Within the endosomes, the low pH triggers conformational changes in the toxins, leading to the translocation of the toxic subunits across the endosomal membrane and into the cytosol. Other toxins may exploit alternative entry pathways, such as lipid raft-mediated endocytosis or direct translocation across the plasma membrane [57].

The attachment and cell entry of bacterial protein enterotoxins are critical steps in their pathogenicity [58]. These processes enable the toxins to gain access to the host cell's interior and exert their detrimental effects [57]. Deciphering the mechanisms of attachment and cell entry of bacterial protein enterotoxins provides valuable insights into their pathogenesis and can guide the development of preventive and therapeutic strategies to combat enterotoxin-mediated diseases [58].

Toxins with the ability to produce pores : Pore-forming exotoxins, as the name proposes, insert trans-membranous pores into the membrane, hence interrupting the elective ion efflux/influx across the membranes [23, 59-63] (Table 5). This category of toxins consists of alpha toxin produced by *S. aureus*, *S. pyogenes* streptolysin O, and the Repeats-in-toxin (RTX) toxin generated by many bacterial pathogens including *Bordetella*, *Proteus*, Pasteurellaceae, and *Escherichia coli*[63]. Usually, pore-forming exotoxins are generated as chains that can be self-assembled as pores on the cell membranes [62]. In most research, alpha-toxin derived from *S. aureus* is taken into consideration as a model of pore-forming cytotoxins [64]. This exotoxin is produced as a precursor with a length of 319 amino acids and a signal sequence of twenty-six amino acids in the N-terminal. The released mature alpha-exotoxin is a 33 kDa hydrophilic protein. Seven mature alpha-toxins are brought together to produce a mushroom-shaped heptamer with a molecular weight of 232 kDa containing three different domains. The stem domains serve as trans-membranous ion channels through the membrane, whereas the rim and cap domains of the heptamer are located at the membrane surface [64].

Bacterial enterotoxins with the ability to produce pores: Bacterial protein enterotoxins with the ability to produce pores are a fascinating group of toxins that have been extensively studied in the scientific literature [65]. Based on the previous researches, it is evident that these toxins possess a unique mechanism of action, they form pore structures in the membranes of target cells. This pore formation disrupts the integrity of the cell membrane, leading to various deleterious effects [65]. Bacterial protein enterotoxins that produce pores can exhibit different structural and functional characteristics. For instance, some toxins, like the alpha-hemolysin produced by *S. aureus*, form large oligomeric pores that allow the uncontrolled influx and efflux of ions and molecules, resulting in cell lysis [66]. Other enterotoxins, such as the aerolysin produced by *Aeromonas* species, form smaller pores that disrupt cellular homeostasis and induce cell death [67]. The ability of these toxins to form pores plays a crucial role in their pathogenicity and the development of enterotoxin-mediated diseases [67]. Addressing the nature of bacterial protein enterotoxins that produce pores provides new insights into their mode

Table 5) Common bacterial toxins with the ability to produce pores, their targets and diseases

Bacterial sources	Toxins	Targets	Diseases
Staphylococcus aureus	Leukocidin	Phagocyte Membranes	Pyogenic infections
Streptococcus pyogenes	Streptolysin O	Cholesterol	Strep throat
Streptococcus pneumoniae	Pneumolysin	Cholesterol	Pneumonia
Staphylococcus aureus	Alpha Toxin	Cell Membranes	Abcesses
Bacillus anthracis	Anthrax EF	Cell Membranes	Anthrax
Listeria monocytogenes	Listeriolysin	Cholesterol	Meningitis
Escherichia coli	Hemolysin	Cell Membranes	UTI
Clostridium perfringens	Perfringiolysin O	Cholesterol	Gas gangrene

of action and facilitates the development of targeted strategies to counteract their detrimental effects [68].

Pyrogenic toxins : Some bacterial toxins can operate directly on the antigen-representing cells and T lymphocytes of the immune system [2]. Disturbance of the immunologic activates of the above-mentioned cells by toxins could result in a variety of diseases. One large category of exotoxins in this class is the pyrogenic toxins derived from streptococci and staphylococci, whose pathogenic functions include enhancement of endotoxin shock, pyrogenicity, and potent stimulation of the immune system [2]. Pyrogenic toxins are secreted as 30 and 22 kDa exotoxins and include staphylococcal TSST-1, staphylococcal exfoliatin; class A streptococcal pyrogenic toxins A-C; staphylococcal enterotoxins serotypes A-E, G, and H [15].

Generally, the potent immune-stimulatory features of pyrogenic exotoxins are a direct output of exotoxin binding to different areas exterior the peptide-binding cleft of the MHC II molecule [2]. This leads to a large proliferation of up to 25% of peripheral T lymphocytes [15]. T- lymphocyte proliferation includes the secretion of cytokines from monocytes (e.g., IL-6, tumor necrosis factor α, IL-1) and lymphocytes (e.g., gamma interferon, tumor necrosis factor ß, and interleukin-2) [2]. The cytokines act as mediators of the diffuse erythematous rash, hypotension, and high fever, which are features of toxic shock syndrome [15]. Superantigens are also observed in staphylococcal toxins, but it is not declared if this function takes part in diarrhea and/or vomiting properties of food poisonings derived from staphylococcus [27].

Pyrogenic bacterial enterotoxins: Pyrogenic bacterial enterotoxins are a subgroup of bacterial enterotoxins that possess the ability to induce fever and systemic inflammation [50]. These toxins are primarily produced by certain strains of *S. aureus* and *Streptococcus pyogenes*, which are important human pathogens [50]. Pyrogenic enterotoxins are heat-stable and resistant to digestive enzymes, allowing them to withstand harsh conditions in the gastrointestinal tract and reach systemic circulation [69]. Once in the bloodstream, these toxins interact with immune cells and other target cells, leading to the release of pro-inflammatory cytokines and activation of the immune response [69]. The systemic effects of pyrogenic enterotoxins include fever, hypotension, capillary leakage, and organ dysfunction [70]. In addition to their pyrogenic activity, these toxins can also cause superantigen-mediated diseases, where they stimulate a large number of T cells by binding to major histocompatibility complex class II molecules and T-cell receptors, leading to excessive immune activation [2]. Understanding the pathogenicity of pyrogenic enterotoxins is crucial for the development of effective strategies to con-

trol and treat diseases associated with these toxins, including toxic shock syndrome and streptococcal toxic shock syndrome [70].

Protein Toxins: Regulation of Synthesis and Secretion: The control of release and synthesis of most exotoxins is firmly regulated by regulatory components that are susceptible to the peripheral stimulus [71]. For instance, the production of diphtheria exotoxin is completely suppressed through the accessibility of enough extents of Fe in the growth environment for bacteria proliferation [71]. Only in situations of restricted quantities of Fe in the proliferation medium the exotoxin production become de-repressed [2]. It was found that environmental temperature and osmolarity affect the expression of cholera exotoxin and associated adhesins [31]. In B. pertussis, the attachment agents are generated primarily to develop the infections, and exotoxins are produced and secreted later to respond to the host defense and enhance bacteria survival[71].

Up to now, a variety of mechanisms is suggested by which exotoxins are assembled and released by bacteria [4]. Many toxins are produced with an N terminal signal sequence comprising 14-20 hydrophobic amino acids and 1-3 charged amino acids [71]. In these toxins, the signal peptide can bind and then incorporate into the cytoplasmic membranes during the translation process such that the peptide sequence is synthesized while being released. The leader sequence is cleaved and then the exotoxin is secreted into the periplasmic space [4]. In an alternative mechanism, the exotoxin can be produced in cytoplasm and then bind to a signal peptide for transmission across cell membranes [72]. Generally, chaperones are needed to handle this mechanism. Several multi-component exotoxins like the cholera exotoxin synthesize and secret their subunits individually into the space between the interior and exterior membranes in Gram-negative bacteria [71]. In these microorganisms, the exterior membrane presents additional permeability barriers that exotoxins generally have to mediate if they are to be secreted in soluble forms [2]. It was documented that some toxins (e.g., ST enterotoxin produced by *E. coli*) might be secreted in membrane vesicles, which operate as "smart bombs" able to interact specifically with and enter likely host cells to secrete their contents of toxins [71]. This is because the membrane vesicles likely have exterior membrane-related attachment factors [71].

Protein Bacterial Enterotoxins: Regulation of Synthesis and Secretion: The regulation of synthesis and secretion of bacterial protein enterotoxins is a highly intricate process that has been extensively studied in the scientific community, as evidenced by research articles [73]. The production and release of these toxins are tightly controlled by a variety of regulatory mechanisms; bacterial protein enterotoxins are often encoded by specific genes within the bacterial genome or carried on plasmids [73]. The expression of these genes is regulated at the transcriptional level by various factors, including environmental signals, quorum sensing systems, and global regulatory networks [71]. For example, in response to specific host signals or nutrient availability, bacteria can activate the expression of enterotoxin genes, leading to increased production of toxins [71]. Conversely, under unfavorable conditions or during stationary phase, the expression of these genes may be repressed.

Once synthesized, the secretion of bacterial protein enterotoxins is facilitated by specialized secretion systems [74]. Bacteria have evolved different mechanisms for toxin secretion, including type II, type III, and type V secretion systems [74]. These secretion systems enable the efficient translocation of enterotoxins across the bacterial cell envelope

and their subsequent release into the extracellular environment or direct delivery into host cells. The secretion of enterotoxins can be tightly regulated, ensuring that toxins are only released under specific conditions conducive to pathogenesis [71]. Furthermore, post-translational modifications, such as proteolytic processing or chaperone-mediated secretion, may also contribute to the regulation of enterotoxin secretion [74]. Understanding the regulation of synthesis and secretion of bacterial protein enterotoxins is crucial for comprehending the molecular basis of bacterial pathogenesis [75]. Elucidating the intricate regulatory networks and signaling pathways involved in toxin production and secretion can provide valuable insights into the virulence strategies of pathogenic bacteria [75]. Additionally, knowledge of these regulatory mechanisms may aid in the development of novel therapeutic approaches targeting the control and inhibition of enterotoxin synthesis and secretion, ultimately leading to the prevention and treatment of enterotoxin-mediated diseases [75].

Typical bacterial toxin: Diphtheria Toxin : Diphtheria toxin secreted by *Corynebacterium diphtheriae* is the best-known exotoxin in bacteria. The A/B prototype is observed in this toxin [76]. Diphtheria is generated as a polypeptide with 60 kDa molecular weight. The activity of this exotoxin is attributed into two segments: subunit B with 39kDa molecular weight is responsible for binding to the sensitive target cell membrane; subunit A with 21kDa molecular weight possesses the enzymatic function for suppression of EFII involved in proteins synthesis [77]. According to what was mentioned above, B subunits have T domains that prevent the penetration of enzymatic components into the cell cytoplasm by inserting the membrane of endosomes [77].

Diphtheria exotoxin is generated in an inactive form and then activated through trypsin enzyme in the existence of thiol (i.e., reducing agent) [75]. The enzymatic function of subunit A is hidden in the complete exotoxin [8]. The B subunit is needed to make possible enzymatic subunits to get in touch with the sensitive cell cytoplasm [8]. The T domain located in the N-terminal end of the B subunit is highly hydrophobic, while the C terminal end of the B subunit is hydrophilic [76]. The C terminal end comprises determiners that interact with special membrane receptors on susceptible cells membrane, which indicated to be a trans-membranous heparin-binding protein on the sensitive cells [76].

This exotoxin gains access to its host cell by either receptor-mediated endocytosis or direct entry [8]. The primary stage is the irreversible binding of the C-terminal portions of subunits A to the specific membrane receptors [75]. During the endocytosis mediated by the receptor, the entire exotoxin is enclosed in a membrane-bounded intracellular vesicle [8]. In the vesicle, the pH decreases to approximately -5.0, permitting the B and A chains to be unfolded [76]. This exposes hydrophobic regions of both subunits that can incorporate into the membranes of the vesicles [78]. The output is the presentation of the subunit A to the cytoplasmic side of the cell membrane, allowing proteolytic cleavages to release the subunits A in the recipient cell. The subunit A is secreted as an expanded fragment but retakes its active form in the cell [8]. Eventually, the A fragment can catalyze the ADP-ribosylation of EFII involved in protein synthesis. Thus, the cytotoxicity of diphtheria is attributed to protein synthesis suppression [8].

Determining the most important bacterial enterotoxin is subjective and can depend on various factors, including the specific

context, geographical region, and the impact on public health. However, the enterotoxin produced by *Vibrio cholerae*, is a well-known bacterial enterotoxin. Cholera toxin is responsible for causing cholera, a severe diarrheal disease that can lead to rapid dehydration and death if left untreated [79]. Cholera has had a significant impact on public health globally, particularly in regions with poor sanitation and limited access to clean water [79]. The toxin's ability to disrupt the function of intestinal cells leads to the excessive secretion of electrolytes, which is a major contributing factor to the severity of cholera [80]. In detail, *Vibrio cholerae* toxin consists of two subunits, A and B, which he A subunit is the catalytically active part that increases the level of intracellular cAMP, and as a result, causes loss of water and electrolytes and ultimately diarrhea. Cholerae toxin B subunit is an immunogen that enhances immune responses and is a promising tool for immunotherapies.

Efforts to understand the mechanisms of cholera toxin and develop effective preventive and treatment measures have been instrumental in combating cholera outbreaks and reducing its global burden [80].

Applications of bacterial protein enterotoxins for cancer therapy: The applications of protein enterotoxins for cancer therapy have garnered significant attention in the scientific community, as reflected in numerous studies [81]. These toxins possess unique properties that make them promising candidates for targeted cancer treatment [81]. Bacterial protein enterotoxins can be engineered or modified to specifically recognize and bind to cancer cells, exploiting the overexpression of certain cell surface markers or receptors found on tumor cells [66]. Once bound, these toxins can enter cancer cells and exert their cytotoxic effects, leading to cell death [82]. Furthermore, some enterotoxins have the ability to activate immune responses, stimulating the body's natural defenses against cancer [82].

Research on bacterial protein enterotoxins has demonstrated their potential for use in various cancer therapy approaches [81]. One such application is the development of immunotoxins, where the toxic subunits of bacterial protein enterotoxins are fused with targeting molecules, such as antibodies or ligands, to selectively deliver the toxin to cancer cells [66]. This targeted approach minimizes damage to healthy cells and enhances the therapeutic efficacy [50]. Additionally, bacterial protein enterotoxins can be utilized in combination with other cancer treatments, such as chemotherapy or radiation therapy, to enhance their effectiveness [83]. The unique mechanisms of action of these toxins, including disruption of cellular processes and induction of apoptosis, make them valuable tools for overcoming drug resistance and improving treatment outcomes [83].

Although the applications of bacterial protein enterotoxins for cancer therapy show promising potential, further research is needed to optimize their safety and efficacy profiles. Challenges such as immunogenicity, systemic toxicity, and off-target effects need to be addressed for successful clinical translation [66]. Nonetheless, the versatility and specific targeting capabilities of bacterial protein enterotoxins offer exciting opportunities for the development of innovative and targeted cancer therapies that could potentially improve patient outcomes in the future [81].

Challenges and Perspectives of Bacterial Enterotoxins: The study of bacterial enterotoxins presents several challenges and offers promising perspectives for future research. One of the important challenges is the complex and diverse nature of these toxins, so that different bacteria produce a wide range of enterotoxin with different structures,

mechanisms of action, and distinct host interactions and different immune system responses [50]. This diversity necessitates comprehensive characterization and understanding of individual enterotoxins, as well as their interplay in polymicrobial infections. Furthermore, the emergence of new strains and the evolution of enterotoxins pose ongoing challenges for diagnostic and therapeutic approaches [84]. The development of effective vaccines and therapeutics is hindered by the need to target multiple enterotoxins simultaneously and the potential for toxin variability [82].

Additionally, studying the interaction of enterotoxins with the host immune system and elucidating the long-term effects of toxin exposure remains an active area of research [83]. Despite these challenges, the study of bacterial enterotoxins holds great promise. Advances in technologies such as structural biology, genomics, and high-throughput screening techniques offer exciting opportunities for identifying novel toxins, deciphering their mechanisms, and designing targeted interventions [83]. Furthermore, the integration of interdisciplinary approaches, including microbiology, immunology, and computational modeling, can provide a comprehensive understanding of enterotoxin-mediated diseases and pave the way for the development of innovative prevention and treatment strategies. Ultimately, addressing the challenges and exploring the perspectives of bacterial enterotoxins will contribute to mitigating the burden of enterotoxin-associated diseases and improving public health outcomes [82].

Other Remarks: The genetic capability for producing toxins can be detected on the plasmids, lysogenic, bacteriophages, and bacterial chromosomes [15]. Occasionally, they happen in pathogenicity islands [83]. The bacterial mechanisms of genetic exchanges, especially transduction and conjugation, can transfer genetic elements between species and strains of different bacteria [15]. Horizontal transfer of virulence genes is known to happen between various bacteria. This describes how *Vibrio cholerae* and *Escherichia coli* bacteria generate a similar diarrhea-inducing toxin, and how *E. coli* O157:H7 gained the capability to generate shiga exotoxin from *Shigella dysenteriae* [10].

There is evidence for the pathogenic function of streptococcal pyrogenic exotoxins [16, 22, 25]. Moreover, there is evidence for the pathological activity of the necrotizing toxins of shiga in the bacteria-derived diseases, but why bacteria generate such exotoxins is unexplainable and is comparable to asking why organisms must generate antibiotics.

Conclusion

This review presented an overview of bacterial toxins, especially enterotoxins, in the terms of structure, function, mode of action, and mechanisms involved in synthesis, release, attachment, and cell entry. The challenge of studying bacterial enterotoxins lies in their complex nature and the need for comprehensive characterization, but the future holds promise with advancements in technology and interdisciplinary approaches to further our understanding and develop effective strategies for prevention and treatment.

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