Bacteriocins synthesized by *Bacillus thuringiensis*: generalities and potential applications

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The members of the *Bacillus thuringiensis* group, commonly known as Bt, produce a huge number of metabolites, which show biocidal and antagonistic activity. *B. thuringiensis* is widely known for synthesizing Cry, Vip and Cyt proteins, active against insects and other parasporins with biocidal activity against certain types of cancerous cells. Nevertheless, *B. thuringiensis* also synthesizes compounds with antimicrobial activity, especially bacteriocins. Some *B. thuringiensis* bacteriocins resemble lantibiotics and other small linear peptides (class IIa) from the lactic acid bacteria bacteriocins classification system. Although many bacteriocins produced by Bt have been reported, there is no proper classification for them. In this work, we have grouped these based on molecular weight and functionality. Bacteriocins are small peptides synthesized by bacteria, presenting inhibitory activity against Gram-positive and Gram-negative bacteria and to a lesser extent against fungi. These molecules represent a good study model in the search for microbial control alternatives. Lactic acid bacteria produces a huge number of these types of molecules with great potential. Nonetheless, members of the *Bacillus, cereus* group, especially *B. thuringiensis,* emerge as an attractive alternative for obtaining bacteriocins showing novel activities. This review describes the potential applications of *B. thuringiensis* bacteriocins in the control of foodborne pathogens, environment and medical area.

Introduction

The steadily increasing use of antibiotics with the aim of controlling microorganisms which may damage food or infective agents for human, plants or animals led to the emergence of resistant microorganisms to a wide range of antimicrobial agents [1]. It is estimated that in Europe, approximately 25 000 persons are deceased on an annual basis because of infections caused by bacteria which are antibiotic resistant [2]. The emergence of drug–resistant bacteria requires us to search for and develop new antimicrobial agents. One viable alternative could be the use of bacteriocins [3–5]. Bacteriocins are small peptides (approximately between 12 and 70 amino acids) with antimicrobial activity, synthesized by prokaryotes. These peptides originally emerged as adaptation mechanisms [6], which allow them to compete for nutrients and space in their habitat, inhibiting growth within the members of the same producer species or members of different bacterial genera [4,7]. Lactic acid bacteria have been widely studied as bacteriocin producers [8]. For example, nisin, the most–commonly studied lantibiotic, has been approved as a food preservative in more than 50 countries [9]. In food, the addition of bacteriocins represents an

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excellent strategy to control pathogenic bacteria and/or food spoilers, such as *Listeria monocytogenes, Clostridium botulinum, Yersinia enterocolitica, Staphylococcus aureus, Escherichia coli, Salmonella enterica* subsp. *enterica* and *Bacillus cereus*, among others [10]. Dissemination of multidrug-resistant bacteria as *S. aureus, Pseudomonas aeruginosa* and *Enterococcus* sp. represents a matter of great concern through an important increase in the hospital costs and morbimortality [11]. During the 1970s another bacterium, *Clostridium difficile*, was found to be responsible for nosocomial diarrhoea [12]. Since then, the cases have increased in number and severity in many parts of the world. The main predisposing factor is broad-spectrum antibiotics, which eradicate beneficial bacteria, leading to *C. difficile* overgrowth [13].

The emergence of its resistance to certain conventional antibiotics leads to research with a view to discovering novel therapeutic strategies. In addition to lactic acid bacteria, different members of the *Bacillus* sp. genus, particularly from the *cereus* group, such as *Bacillus thuringiensis,* have been studied because of their capability of producing bacteriocins. *B. thuringiensis* is a Gram-positive bacterium, which produces endospores and is well known for synthesizing an enormous 'battery' of compounds with biological activity, specially Cry, Cyt and Vip proteins, possessing biocidal activity against certain kinds of insects. Although *B. thuringiensis* also synthesizes proteins with antimicrobial activity [14]. In this regard, the knowledge relating to the mode of action of several *B. thuringiensis* antimicrobials is still limited. The application of *B. thuringiensis* antimicrobials is very important within different areas such as food biopreservation, medicine and environmental care. This review describes some of the most important aspects of bacteriocins synthesized by different strains of *B. thuringiensis*, such as activity spectrum, molecular mass and biological activity.

Bacteriocins synthesized by *B. thuringiensis*

In the last few years, there has been a resurgence in interest with respect to the discovery of new treatments including the use of microorganisms as natural products. *B. thuringiensis* is considered a model organism for production of metabolites, which is currently employed in the biological control of plagues and agricultural crops. In 1989, Favret and Younsten [15] reported the detection of a peptide synthesized by a *B. thuringiensis*, which was subsequently named thuricin. So far, there is a report of 18 bacteriocins synthesized by different *B. thuringiensis* strains. Among these 18 bacteriocins are five inhibitory substances, which resemble bacteriocins known as bacteriocin-like inhibitory substance (BLIS) [16] (Table 1). Bacteriocins are peptides with a different molecular weight, varying from almost 1 kDa (thuricin, 0.950 kDa) to 12.4 kDa (entomocin 9). In terms of molecular weight, we propose to divide these bacteriocins, into groups A and B. Group A is composed of the bacteriocins weighing less than 5 kDa and group B which weigh more than 5 kDa. Although from a functional point of view, within group A, we can find two types: single peptide and two-component peptide. Almost all of them belong to type I and only thuricin CD and thuricin 439 belong to type II (Table 1). Another important aspect is that members of the serological subsp. *entomocidus*

Table 1. Bacteriocins synthesized by different strains of *Bacillus thuringiensis*.

	Bacteriocin	Molecular mass (kDa)	Producer strain (subsp.)	Reference
AI	Thuricin	0.950	HD2 (*thuringiensis*)	Favret and Younsten 1989 [15]
	Thuricin S	3.137	HD198 (*entomocidus*)	Chehimi *et al.* 2007 [29]
			9 (*entomocidus*)	Chehimi *et al.* 2012 [30]
			HD110 (*entomocidus*)	Chehimi *et al.* 2012 [30]
			HD125 (*tolworthy*)	Chehimi *et al.* 2012 [30]
	Thuricin Bn1	3.139	Bn1 (*kurstaki*)	Ugras *et al.* 2013 [27]
	Thurincin H	3.140	SF361	Lee *et al.* 2009 [37]
	Bacthuricin F4	3.160	BUPM4 (*kurstaki*)	Kamoun *et al.* 2005 [22]
	Thuricin 17	3.172	Bt non-*Bradyrhizobium*	Gray *et al.* 2006 [36]
	Entomocin 110	4.800	HD110 (*entomocidus*)	Cherif *et al.* 2008 [31]
AII	Thuricin CD	Trn-α 2.760	DPC 6431	Rea *et al.* 2010 [13]
		Trn-β 2.860		
	Thuricin 439	(A) 2.919	B439	Ahern *et al.* 2003 [40]
		(B) 2.803		
BI	Morricin 269	~10.000	LBIT269 (*morrisoni*)	Barboza-Corona *et al.* 2007 [16]
	Kurstacin 287	~10.000	LBIT287 (*kurstaki*)	Barboza-Corona *et al.* 2007 [16]
	Kenyacin 404	~10.000	LBIT404 (*kenyae*)	Barboza-Corona *et al.* 2007 [16]
	Entomocin 420	~10.000	LBIT420(*entomocidus*)	Barboza-Corona *et al.* 2007 [16]
	Tolworthcin 524	~10.000	LBIT524 (*tolworthi*)	Barboza-Corona *et al.* 2007 [16]
	Tochicin	10.500	HD868 (*tochigiensis*)	Paik *et al.* 1997 [39]
	BacthuricinF103	~11.000	BUMP103	Kamoun *et al.* 2011 [35]
	Thuricin 7	11.600	BMG1.7	Cherif *et al.* 2001 [21]
	Entomocin 9	12.400	HD9 (*entomocidus*)	Cherif *et al.* 2003 [26]

Table 2. *Bacillus thuringiensis* bacteriocins with biological activity against Gram-positive bacteria.

	Sensitive strain	Reference
Thuricin	*Bacillus megaterium, B. cereus, Bacillus polymyxa, Bacillus sphaericus, Corynebacterium xerosis, S. aureus, E. epidermidis, L. monocytogenes*	Favret and Younsten 1989 [15]
Thuricin S	*L. monocytogenes, B. cereus,* Bt, *B. subtilis, B. megaterium, Pediococcus acidolacticis, Streptococcus thermophilus*	Chehimi *et al.* 2007 [29]
Thuricin Bn1	*B. cereus, Lactococcus lactis, L. monocytogenes*	Ugras *et al.* 2013 [27]
Thurincin H	*B. cereus, B. subtilis, B. megaterium, L. monocytogenes, L. innocua, L. ivanovii, S. aureus, Carnobacterim psicola, Geobacillus stearothermophillus*	Lee *et al.* 2009 [37]
Bacthuricin F4	*B. cereus, B. subtilis, Bacillus licheniformis, S. aureus, Brevibacterium flavum*	Kamoun *et al.* 2005 [22]
Thuricin 17	*B. cereus*	Gray *et al.* 2006 [36]
Entomocin 110	*B. cereus, Bacillus coagulans, B. megaterium, Bacillus mycoides, Bacillus pseudomycoides, Lactococcus lactics, L. monocytogenes, Paenibacillus larvae Paenibacillus polymyxa*	Cherif *et al.* 2008 [31]
Tochicin	*B. cereus, Leuconostoc mesenteroides*	Paik *et al.* 1997 [39]
Bacthuricin F103	*B. cereus, B. subtilis, B. licheniformis, L. monocytogenes*	Kamoun *et al.* 2011 [35]
Thuricin 7	*B. cereus, B. subtilis, B. pseudomycoides B. mycoides, Staphylococcus pyogenes, L. monocytogenes, B. weihenstephanensis*	Cherif *et al.* 2001 [21]
Entomocin 9	*B. cereus, B. pseudomycoides, B. mycoides, B. weihenstephanensis, Lactobacillus sp. Lactococcus lactics, L. monocytogenes*	Cherif *et al.* 2003 [26]
Morricin 269	*B. cereus, B. weihenstephanensis, C. difficile, Listeria innocua, S. aureus, Staphylococcus, S. pyogenes, Enterococcus faecium*	Barboza-Corona *et al.* 2007 [16]
Kurstacin 287 Kenyacin 404 Entomocin 420 Tolworthcin 524		
Thuricin CD	*B. cereus, Bacillus firmus, B. mycoides, C. difficile, C. tyrobutyricum, Clostridium lithuseburense, Clostridium indolis, Clostridium perfringens, Listeria monocytogenes, Li. innocua, Lactobacillus fermentum, La. johnsonii, La. crispatus, Lactococcus lactis*	Rea *et al.* 2010 [13]
Thuricin 439	*B. cereus, Li. innocua 4202*	Ahern *et al.* 2003 [40]

produce three different peptides, thuricin S, entomocin 110 and entomocin 9 (Table 1). On the other hand, the same peptide can be produced by different sub-species such as thuricin S, which is produced by the serological subsp. *entomocidus* and subsp. *tolworthy* (Table 1).

Gram-positive bacteria inhibited by *B. thuringiensis* bacteriocins

Most bacteriocins synthesized by *B. thuringiensis* are broad-spectrum, inhibiting several bacterial species. Some *B. cereus* strains synthesize toxins, which induce diarrhoea, whereas others may be responsible for causing nausea and vomiting [17]. Another important pathogen is *L. monocytogenes*, which may be inhibited by different bacteriocins, amongst which include: thuricin, thuricin S, thuricni Bn1, thurincin H, entomocin 110, bacthuricin F103, thuricin 7, entomocin 9 and thuricn CD. Listeriosis is a zoonotic disease, which is rare in humans but is still extremely serious, presenting low morbidity and high mortality. Generally, contamination takes place while consuming food containing *L. monocytogenes*, which are responsible of causing the disease [18]. Another bacterium, methicillin-resistant *Staphylococcus aureus*, has become immensely important in intrahospital as a causative agent of wound infections [19,20]. Bacteriocins such as thuricin, thurincin H, bacthuricin F4 and BLIS reported by Barboza-Corona *et al.* [16], morricin 269, kurstacin 287, kenyacin 404, entomocin 420 and tolworthcin 524 may represent the best option to control this problematic bacterium (Table 2).

Gram-negative bacteria inhibited by *B. thuringiensis* bacteriocins

Bacteriocins including bacthuricin F4, thuricin 7, morricin 269, kurstacin 287, kenyacin 404, entomocin 420 and tolworthcin 524 have the potential to control *Klebsiella pneumoniae*; a Gram-negative bacillus, which lives in the human intestine as part of its microbiota [16,21,22], considered one of the most important agents in relation to nosocomial infections, producing septicaemia and urinary and respiratory tract infections [23]. Another important microorganism is *P. aeruginosa*, which may be found in hospitals. This opportunistic pathogen is frequently present in extra intestinal infections, mainly in inmmunocompromised and malnourished patients [24]. This microorganism shows resistance to almost all conventional antimicrobials [25], even though it is susceptible to entomocin 110 and entomocin 9 (Table 3).

Some members of the BLIS group showed inhibitory activity against *Vibrio cholerae*. Since ancient times, cholera has been the cause of deadly epidemics; however, nowadays its morbimortality has diminished. Nonetheless, there are certain endemic zones presenting with a high percentage of this disease, which causes acute

Table 3. *Bacillus thuringiensis* bacteriocins with biological activity against Gram-negative bacteria.

	Sensitive strain	Reference
Thuricin S	*Enterobacter cloacae, Pseudomona srynigae. S. enterica* ser. *Cholerae*	Chehimi *et al.* 2007 [29]
Thuricin Bn1	*Paucimonas lemoignei, Pseudomonas savastanoi*	Ugras *et al.* 2013 [27]
Bacthuricin F4	*K. pneumoniae*	Kamoun *et al.* 2005 [22]
Thuricin 17	*E. coli* MM294	Gray *et al.* 2006 [36]
Entomocin 110	*P. aeruginosa*	Cherif *et al.* 2008 [31]
Bacthuricin F103	*A. tumefaciens*	Kamoun *et al.* 2011 [35]
Entomocin 9	*P. aeruginosa*	Cherif *et al.* 2003 [26]
Morricin 269	*V. cholerae,* Shigella flexneri, Salmonella sp., *E. coli, K. pneumoniae,* Enterobacter cloacae, Proteus vulgaris	Barboza-Corona *et al.* 2007 [16]
Kurstacin 287		
Kenyacin 404		
Entomocin 420		
Tolworthcin 524		

gastroenteritis. If the disease is not correctly treated, it may even cause death [19] (Table 4).

Fungi inhibited by *B. thuringiensis* bacteriocins

Fungi may also be targeted by some bacteriocins. For instance, Bn1 bacteriocin and entomocin nine inhibit *Aspergillus* growth [26,27]. Food containing starch (as in the case of potatoes and bread) may stimulate its growth. In addition, it may grow within dirty air conditioning units located in buildings and houses, representing a serious problem, including in hospitals. Frequently, *Aspergillus niger* is present in human ear infections and in certain instances it can even infect the lungs of people who present with a weak immune system. *A. niger* may be toxic if ingested through infected fruits, vegetables or grains; it can produce food poisoning (single ingestion) or cancer (chronic consumption) [28].

Potential applications of *B. thuringiensis* bacteriocins

Thuricin S: This bacteriocin is heat resistant and stable in a wide range of pH conditions and inhibits not only the pathogens that are transmitted through food causing poisoning such as *L. monocytogenes* and *B. cereus*, but also a great number of Gram-negative pathogens such as *S. enterica* subsp. *enterica* and *P. aeruginosa*. The use of *B. thuringiensis* as a biological insecticide, as well as the information about the bacteriocins, like thuricin S, empower its practical use as an antagonistic agent towards phytopatogenic bacteria such as *Pseudomonas syringae* [29,30]. **Thuricin Bn1:** This peptide is synthesized by *B. thuringiensis* subsp. *kurstaki* Bn1, which presents bifunctional properties in agriculture. This strain is active against insects through a crystalline protein [31] and active against plant pathogenic bacteria through a bacteriocin. On the other hand, the *Bacillus* genus includes a great variety of species that may be safely used within industry. Example, *B. thuringiensis* Bn1 produces Bacteriocin Bn1, which as proteinaceous nature, can be used as a natural food preservative [32]. Besides, bacteriocins have gained importance as natural biopreservatives for degradation control and against pathogenic bacteria transmitted by food [6]. **Thurincin H:** This bacteriocin inhibits the growth of *B. cereus, L. monocytogenes, Listeria innocua* and *Listeria ivanovii* [33]. All of these bacteria seem to affect both animals and humans [18]. An example includes the fatal case where *L. innocua* was found on a hemoculture. In this situation, the patient died because of septic shock caused by cholangitis [34]. **Bacthuricin F4:** This bacteriocin is stable at a wide pH range and heat treatment, which indicates that the bactericidal function can be preserved even in extreme conditions. This presents an extremely interesting characteristic for its use in the agro-industry. The study of the bacteriocin

Table 4. *Bacillus thuringiensis* bacteriocins with biological activity against fungi.

	Sensitive strain	Reference
Entomocin 9	*Aspergillus nidulans, Fusarium graminis*	Cherif *et al.* 2003 [26]
Morricin 269	*Rizophus* sp., *Fusarium oxysporum, Mucor rouxii IM80, Trichoderma* sp. *SH1, Trichoderma* sp. *SD3.*	De la Fuente-Salcido *et al.* 2008 [10]
Kurstacin 287		
Kenyacin 404		
Entomocin 420		
Tolworthcin 524		

inhibition spectrum against indicator strains revealed that this bacteriocin presents a bactericidal effect against bacterial strains highly linked to *B. thuringiensis* and other Gram-positive bacteria. Importantly, it is highly active against *B. cereus,* which is one of the most virulent bacteria that may be found in agro-industrial products [22]. Although this bacteriocin is less active against Gram-negative bacteria [35]. It is the only bacteriocin produced by *B. thuringiensis,* which displays activity against *K. pneumoniae.* **Thuricin 17:** This peptide was isolated from a bacterium, which promotes plant growth [36], and has been demonstrated to increase plant growth [37]. This peptide is stable in a wide range of temperatures and is biologically active between pH 1.00 and 9.25. In addition, thuricin 17 is the only *B. thuringiensis* bacteriocin which shows activity against *E. coli* [36]. **Entomocin 110**: This bacteriocin has been demonstrated to be inhibitory to several Gram-positive bacteria, including *L. monocytogenes, Paenibacillus larvae* and other *Bacillus* species [31]. *P. larvae* are extremely important bacteria within the apiculture sector, as they produce the American foulbrood disease, which affects bee larvae [38]. **Tochicin:** This bacteriocin exhibits activity against *B. cereus* and certain *B. thuringiensis* subspecies [39]. Although its spectrum of activity is unclear as it has not been tested against *L. monocytogenes,* as is the case of bacthuricin F4 it has not been tested in *L. monocytogenes* or *S. aureus,* as it happens in the case of thuricin S. For this reason, its application and potential use in biomedical treatments has not been completely defined. **Thuricin F103**: This bacteriocin presents a wide spectrum of inhibition against the related bacteria and different pathogens transmitted through food such as *L. monocytogenes, B. cereus* and the phytopatogenic bacterium *Agrobacterium tumefaciens.* Subsequently, Kaumon and his colleagues [35] demonstrated that bacthuricin F103 may be applied to raw beef meat with the purpose of avoiding contamination by *L. monocytogenes* [35]. **Thuricin 7**: The action and inhibitory spectrum of this bacteriocin includes *B. cereus* and *Bacillus weihenstephanensis* strains (commonly associated with the deterioration of dairy products and raw milk). Such properties make thuricin 7 the perfect candidate to be used as a food antimicrobial agent in order to control Gram-positive bacterial contaminants, without interfering with lactic acid bacteria growth [21]. **Entomocin 9:** This bacteriocin displays antimicrobial activity against *L. monocytogenes, P. aeruginosa* and several fungi. Entomocin 9 is a new bacteriocin produced by *B. thuringiensis* HD9 characterized as being heat stable. Lack of toxicity against Vero cells renders strain HD9 as being suitable for a safe application in antimicrobial treatments. The importance and impact of entomocin 9 makes *B. thuringiensis* strain HD9 an attractive microorganism in biotechnological applications as an antimicrobial agent in the food and agricultural industry [26]. **Thuricin CD:** The effectiveness of thuricin CD against the clinical *C. difficile* isolates, especially hypervirulent PCR R027 strains, makes it

extremely interesting because of its structural characteristics and potential as a therapeutic agent. The isolation and characterization of thuricin CD may represent a structural class of bacteriocins as well as potentially providing a treatment for *C. difficile*-associated disease [13]. **Thuricin 439:** *B. thuringiensis* strain B439 produces thuricin 439, a small substance like bacteriocin produced as two active peptides with different molecular mass. Thuricin 439 is active against *B. cereus* and *B. thuringiensis* strains, while at the same time showing activity against *L. innocua* 4202 [40]. This bacteriocin could be used to control *B. cereus*, which can cause diarrhoea and vomiting. **Bt-BLIS:** The *B. thuringiensis* BLIS include morricin 269, kurstacin 287, kenyacin 404, entomocin 420 and tolworthcin 524, produced by *B. thuringiensis* strains isolated in Mexico. These BLIS have been shown effective against Gram-positive and Gram-negative bacteria, including a etiologic agents of human diseases such as throat infections, scarlet fever, septicaemia, pneumonia, urinary tract infections, emetic and gastrointestinal syndromes and different types of fungal infections. Furthermore, activity of the five BLIS mentioned earlier was tested against isolates of *S. aureus* associated with bovine mastitis. All the *S. aureus* isolates were shown to be susceptible to the five bacteriocins synthesized by *B. thuringiensis*, mainly to morricin 269 and kurstacin 287, followed by kenyacin 404, entomocin 420 and tolworthcin 524 [16].

Conclusion

In this report, we propose a classification of Bt based on molecular weight, and functionality in single peptide and two-component peptide bacteriocins.

Because of the broad-spectrum nature of some *B. thuringiensis* bacteriocins, some may be included in antimicrobial strategies against virus, fungi, parasitic diseases and cancer, as well as in the immune system modulation [41]. The potential applications of these peptides reinforce the importance of studying their biological properties.

As previously mentioned, nisin, a bacteriocin approved by the Food and Drug Administration, is employed to inhibit bacterial growth in processed food. Although the potential application can be quite diverse and requires greater knowledge and tests that may be used in different health sectors as pathogen control in hospitals, environment and new antibiotics for controlling human and animal diseases.

For decades, *B. thuringiensis* has been one of the best options, as it has been safely employed as a bioinsecticide and applied in different human consumption crops without showing adverse effects. In particular, thuricin CD is a good example as it displays specific activity against

C. difficile and it has no effect on the good flora living in the intestine, as is the case with most traditional antibiotics [42].

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Conflicts of interest

There are no conflicts of interest.

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