Zhu et al. One Health Advances (2023) 1:21
https://doi.org/10.1186/s44280-023-00020-0

One Health Advances

REVIEW

Open Access

Mechanisms of probiotic *Bacillus* against enteric bacterial infections

Jiajia Zhu[1†], Yunsheng Chen[1†], Kálmán Imre[2], Damla Arslan-Acaroz[3,4], Fatih Ramazan Istanbullugil[5], Yuwen Fang[1], Gaspar Ros[6], Kui Zhu[1*] and Ulas Acaroz[5,7*]

Abstract

Gastrointestinal infection is a leading cause of gut diseases attracting global health concerns. The emerging antimicrobial resistance in enteric pathogens drives the search of viable and renewable alternatives to antibiotics for the health of both human beings and animals. Spore-forming probiotic *Bacillus* have received extensively interests for their multiple health benefits, including the restoration of microbiota dysbiosis and the reduction of drug-resistant pathogens. These promising benefits are mainly attributed to the activity of structurally diverse *Bacillus*-derived metabolites, such as antibacterial compounds, short-chain fatty acids, and other small molecules. Such metabolites show the capacity to directly target either the individual or community of bacterial pathogens, and to potentiate both host cells and gut microbiota. The better understanding of the mechanisms by which probiotic *Bacillus* and the metabolites modulate the metabolism of hosts and microbiota will advance the screening and development of probiotic *Bacillus*. In this review, we discuss the interaction among probiotic *Bacillus*, microbiota and host, and summarize the *Bacillus*-derived metabolites that act as key players in such interactions, shedding light on the mechanistic understanding of probiotic *Bacillus* against enteric bacterial infections.

Keywords Probiotics, *Bacillus*, Metabolites, Microbial interaction

† Jiajia Zhu and Yunsheng Chen contributed equally to this work.

*Correspondence:
Kui Zhu
zhuk@cau.edu.cn
Ulas Acaroz
ulasacaroz@hotmail.com
[1] National Key Laboratory of Veterinary Public Health and Safety, College of Veterinary Medicine, China Agricultural University, Beijing 100193, China
[2] Department of Animal Production and Veterinary Public Health, Faculty of Veterinary Medicine, University of Life Sciences "King Mihai I" from Timişoara, 300645 Timisoara, Romania
[3] Department of Biochemistry, Faculty of Veterinary Medicine, Afyon Kocatepe University, Afyonkarahisar 03200, Turkey
[4] Department of Biochemistry, Faculty of Veterinary Medicine, Kyrgyz-Turkish Manas University, Bishkek KG-720038, Kyrgyzstan
[5] Department of Food Hygiene and Technology, Faculty of Veterinary Medicine, Kyrgyz-Turkish Manas University, Bishkek KG-720038, Kyrgyzstan
[6] Department of Human Nutrition, Food Science and Technology, Faculty of Veterinary Medicine, University of Murcia, Campus de Espinardo, 30071 Murcia, Spain
[7] Department of Food Hygiene and Technology, Faculty of Veterinary Medicine, Afyon Kocatepe University, Afyonkarahisar 03200, Turkey

Introduction

Gut microbiota is a huge community of microbes engaged in multiple interaction that is vital for ensuring gastrointestinal (GI) system health. It is estimated that the number of microbial cells within gut lumen, containing a density of up to 10^{11}—10^{12} bacteria per gram, is ten times more than somatic and germ cells in mammals [1]. Most of gut microbes enrich in the caecum and proximal colon and build up as microbial barrier adjacent to physical (epithelial cells) and chemical (mucus, etc.) barriers. The maintenance of gut microbiota is well-known associated with the health of host, not only affect physiological processes such as appetite and digestion but also shape psychological state [2]. Many factors drive the change to composition and function of microbiota, including host genetics, dietary and lifestyle habits, and microbial infections. Notably, pathogenic invasion has been regarded as the critical factor that contributes to the alteration of microbiota [3]. Diverse pathogenic microbes are competitively competed with resident bacteria and decrease a plethora of 'good' bacteria, which compromise the gut barrier leading to metabolic disorder. Antibiotics are usually used as an effective approach to reduce the load of pathogenic microbes in intestinal infection. However, the therapy with antibiotic frequently leads to gut microbial dysbiosis and polymicrobial infection [4]. In some cases, antibiotics can cause the development of MDR mutants. In particular, sublethal levels of antibiotics improve the production of virulence factors to enhance the persistence of bacteria in epithelial cells [5]. Although the emergence of antimicrobial resistance (AMR) is a natural phenomenon no matter of antibiotic use, it can be promoted by the wasteful and uncritical use of antibiotics without adequate consideration. To conquer the AMR emerges and spreads globally, several novel antibacterial approaches are in development, including anti-virulence agents, engineered phages, and probiotics.

Probiotics have been used for long time historically and are generally recognized as safe (GRAS) and effective that can confer a range of benefits to its host. Additionally, probiotics have received increasing interests both in human healthcare and animal husbandry because they rarely induce the AMR and even reverse it [6]. Among numerous microorganisms, spore-forming *Bacillus* strains, with the ability of sporulation to survive in harsh environment of gut lumen, exhibit a wide range of activities in manipulating host immunity and eliminating invasive pathogens. Normally, probiotic *Bacillus* via oral administration can temporarily remain in intestinal tract, reaching from 10^5 to 10^8 CFUs/g in different intestinal section [7]. This colonization allows *Bacillus* to continuously employ multiple mechanisms to provide protection against infections [8]. Thus, probiotic *Bacillus* are increasingly selected and used as dietary supplements or live biotherapeutic products (LBPs) for the probiotic potential [9]. Nowadays, more than 40 species of probiotic *Bacillus* have been used in treating enteric diseases and other diseases for their antibacterial bioactivity and relatively strong stability [10]. It's noticeable that diverse *Bacillus*-derived metabolites can be diffused into the gut lumen and modify the collective community, resulting in elimination of enteric pathogens such as pathogenic *E. coli*, *Salmonella*, or other drug-resistant bacteria [11]. Some unique proteins exposed on the surface of spore show colonization resistance and host immunomodulatory effect in gut [12]. Metabolites produced by *Bacillus* is the key mediator in interaction with gut microbiota or host, such as antimicrobial compounds that directly inhibit the growth of pathogen and secondary metabolites like vitamins promote the health of host.

Reviews about the metabolites derived from the *Bacillus* genus and their structure classes and activities have been published elsewhere [13–15]. In this review, we focus on elucidating the mechanisms underlying the interaction between probiotic *Bacillus* and both the microbial community and host system. By shedding light on the prominent classes of *Bacillus*-derived metabolites with probiotic potential properties, we aim to gain deeper insights into the ecological role of probiotic *Bacillus* mediated through metabolites, which advance our understanding of the beneficial mechanism on the host.

Bacteria to bacteria interaction

Numerous of intestinal microbes colonized in nutrient limited intestinal lumen, namely gut microbiota, tend to find a suitable niche for survive and replication. These microbes densely colonize the mucous surface and are in close proximity to each other engaging in multiple interactions. Microbial interactions are associated with the homeostasis of gut microenvironment especially when foreign species introduce. Colonization of probiotic *Bacillus* has been reported to reduce pathogen adaptability in gut [16] and confer a range of benefits on the host, such as increased production of short chain fatty acids (SCFAs) [17]. So far, probiotic *Bacillus* mediate colonization resistance against enteropathogenic bacteria through bacterial interactions can be summarized as niche occupation, nutrient and oxygen competition, and metabolites mediated exploitation (Fig. 1).

Niche occupation

Dynamic ecological interactions are dominated by two opposite relationships: competition and cooperation

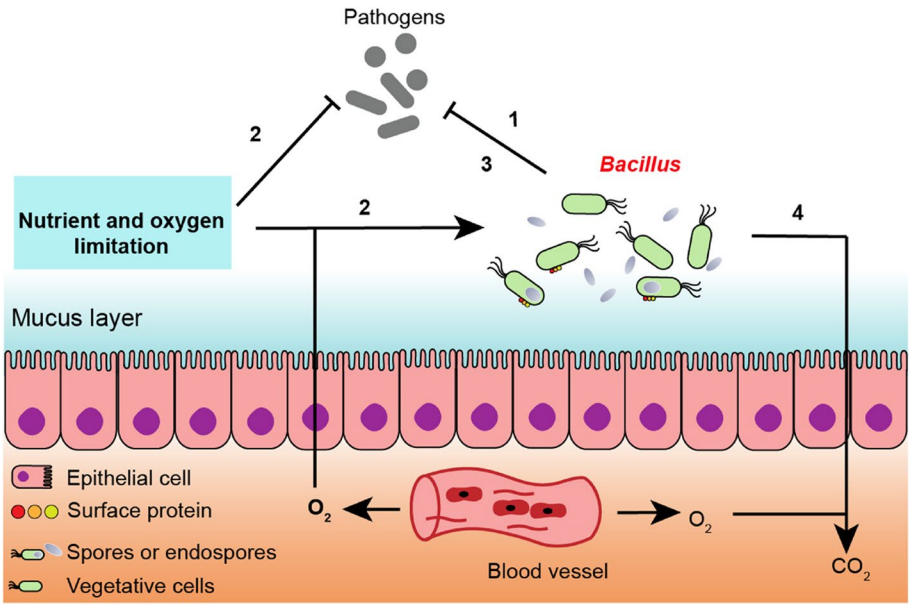

Fig. 1 Probiotic *Bacillus* employ multifactorial competition mechanism to restrict the expansion of pathogens through four pathways. **(1)** *Bacillus* adapt itself in suitable niche against niche-occupying competitors. It approaches the intestinal mucous layer and competitively binds to intestinal epithelial cells and mucous layer components via surface proteins. Thus, the effect of niche occupation by *Bacillus* expels harmful bacteria from the host intestinal epithelial barrier and reduces pathogen invasion. **(2)** Competitive utilization of nutrients for *Bacillus* growth. *Bacillus* secrete various enzymes to rapidly exploit both the macronutrients and micronutrients in gut environment, resulting in limited availability of nutrition to pathogenic bacteria. **(3)** *Bacillus* produce an arsenal of antibacterial metabolites that directly inhibit the growth of pathogens. The metabolites included lipopeptides, bacteriocins, polyketides, and SCFAs are effective against the expansion and invasion of pathogens. **(4)** *Bacillus* can consume excess oxygen from gut lumen and host circulation for maintaining the intestinal environment in a state of hypoxia, which drive a dominance of bacteria such as lactate acid bacteria that use fermentation for energy production

[18]. In these relationships, positive cooperation is common in gut microbiota [19]. Commensal microbes employ a myriad of mechanisms to keep a certain elastic fluctuation in community and exclude alien species. As for probiotic *Bacillus*, these species can transit unimpeded and occupy a niche in the nutrient-limited gastrointestinal tract (GIT) mostly attributed to the particularity of cell structure (spore). Spores are the dormant form of life in *Bacillus*, characterized by thick proteinaceous coat, peptidoglycan cortex, and a dehydrated core abundant in dipicolinic acid (DPA), divalent metal ions, and acid-soluble proteins (SASPs). These components collectively contribute to the exceptional resistance against heat, radiation, reactive chemicals, and extreme physical processing [20]. Besides, the outer sporular layer is responsible for environmental sensing [21], adhesion [22], host protection [23], host cell uptake [24] and immune inhibition [25]. Mutation in exosporium layer, an outer layer of spore, showed less hydrophobic than the wild-type strains [26], while hydrophobicity of the bacterial surface is correlated with the adhesion [27] suggested that the adhesion of spore depend on exosporium proteins. In vegetative form, specific components in cell membrane, such as surface layer (S-layer) proteins, pilus, and mucus-binding protein, exhibit a strong affinity for intestinal epithelial cells [28]. In addition, flagellins are relevant to strengthen the adhesion between bacteria and epithelial cells [29]. The presence of certain carbohydrate like sucrose, enhanced the length of flagellum so as to promote the colonization of *Bacillus* [30]. Collectively, diverse surface protein in dormant and vegetative cells promote the colonization of *Bacillus* in gut. Recent research demonstrated that *B. subtilis* employ an interesting strategy to compete with phylogenetically distinct pathogens by the increased production of antibiotics when encountering the peptidoglycan from pathogens in the same niche [31]. Therefore, *Bacillus* utilize multiple mechanism for outcompeting other gut bacteria in space competition.

Nutrient and oxygen competition

Microbial communities are commonly shaped by biotic and abiotic factors under the nutrient scarcity [32]. In normal, microbes with multiple metabolic pathways have a competitive advantage in auxotrophic environments. Probiotic *Bacillus* have the ability to utilize a wide range

of sugars, organic acids and other organic compounds as sources of cell structure and energy regeneration [33]. An intriguing phenomenon is *Bacillus* has secondary growth phase during the entire life cycle. This growth capability contributes to the survive under nutrient scarcity through selective nutrients utilization. In the context of limited nutrient condition such as gut lumen, *Bacillus* are prone to use glucose and enable themselves to rapidly capture the niche [34, 35]. Although the major source of energy generation is derived from carbohydrate, nitrates and nitrites can also be directly used as electron acceptors to maintain the energy balance in *Bacillus* [36]. In addition to the competition of carbohydrate and nitrogenous compounds, the sequestration of the essential nutrient metal is a powerful mean in combating the invasion of bacterial pathogens [37]. For instances, *Bacillus* product high affinity siderophore bacillibactin to create iron limited environment and restrain the expansion of pathogen due to iron starvation [38]. Additionally, *Bacillus* probiotics produce a range of nutrients, including extracellular polysaccharides, vitamins, and exoenzymes, that promote the growth of beneficial microbiota. For instance, the extracellular polysaccharides produced by *Bacillus* can serve as a carbon source for lactobacilli and enhance their capacity of adhesion and acetate production [39]; the organic acids produced by *Bacillus* and the hyporedox state mediated by *Bacillus* acidify the gut environment, thereby promoting an enrichment of beneficial SCFA-producing bacteria. Therefore, there are several metabolic features for *Bacillus* to outcompete enteropathogens and maintain the growth of beneficial microorganisms in the limited nutrients environment.

Oxygen availability is extreme limited (below 1 mmHg) in a healthy intestine [40]. Once the gut barriers disruption, the level of intestinal oxygen will be increased and contribute to the growth of invasive bacteria [41]. The maintenance of hypoxic environment in gut lumen is attributed by intestinal epithelium metabolism mainly directing toward oxidative phosphorylation [42] and oxygen consumption by microbiota such as the phyla of *Firmicutes* and *Bacteroidetes* [43]. *Bacillus* as facultative anaerobicity bacteria can ferment in hypoxic environment and consume excessive oxygen to maintain low oxidation state in the lumen. Although there is no direct research supporting the modulation of gut microbiota is due to the oxygen-capturing capability of *Bacillus*, the metabolites from *Bacillus* may contribute to the biological oxygen capturing capability resulting in microbiota regulation. The fermentation product surfactin enhance oxygen diffusion in the growth of early stationary phase and maintain viability during oxygen depletion by shift in metabolic profile and membrane depolarization [44], which acquire the advantage in interspecies bacterial competition under hypoxia. When oxygen complete depletion, *Bacillus* turn to dormant and form resistant spore to keep viability for germination in nutrient rich condition. Thus, probiotic *Bacillus* exhibit the extraordinary capability in depleting gut pathogens by competitively consuming limited nutrients and oxygens in distinct section of intestinal.

Metabolites mediated exploitation

Antagonistic microorganisms often have an advantage in a limited microbial environment due to their arsenal of antimicrobial compounds. The driving force and intricate pattern of microbial competition mainly attribute to the activities of antimicrobials. *Bacillus* are generally considered with strong capability in producing structurally diverse antimicrobial peptide (AMPs) for competitor inhibition [45, 46]. Although there are no evidences verified that antimicrobials from *Bacillus* directly mediate the exclusion of pathogenic bacteria *in vivo*, the production of antimicrobial metabolites, such as AMPs and bacteriocins, possibly dominate the bacterial interference between *Bacillus* and enteropathogenic bacteria in GI tract [47, 48]. Notably, *Bacillus* can regulate antibiotic production in response to the component from competitors [31]. We do know that *Bacillus* employ multiple distinct compounds that have been proven with antimicrobial activity to maintain viability while interact with other microbes, but no literature is available for summarizing the structural classification and corresponding biosynthetic gene clusters (BGCs) of these compounds in probiotic *Bacillus*. Thus, we summarized the information about antimicrobial metabolites produced by probiotic *Bacillus*, including the biosynthesis mechanisms, molecular targets within bacterial cells or communities, and antimicrobial spectrum.

Distribution of biosynthetic gene clusters in probiotic Bacillus

Bacterial metabonomic profile can be pre-identified by gene function prediction [49]. Regardless of the bacterial gene expressions being silent or unknown, this strategy expedites the discovery of active compounds with the ability to control the microbiota [50, 51]. BGCs are responsible for the synthesis of secondary metabolites involved in microbial exploitation. Previous research has revealed the positive association between BGCs and antagonistic activity in *Bacillus* [52]. This relevance provides a simple and efficacious way to find the important antibacterial compounds that dominate the interaction between *Bacillus* and other bacteria. Thus, to search most abundant BGCs in *Bacillus*, we first search the NCBI database for establishing genome assemblage of *Bacillus* with probiotic potential. A total of 452 isolates

are selected and used for further bioinformatics analysis. Prediction using antiSMASH database and in-house database showed that three major classes of biosynthetic gene cluster (BGCs) were predominated in probiotic *Bacillus* as: ribosomally synthesized and post-translationally modified peptides (RiPPs), polyketide synthases (PKS), and non-ribosomal peptide synthetases (NRPS), which have similar distribution as previous study [53]. Among these, probiotic *Bacillus* accommodates a high abundance of NRPS and RiPPs reaching up to 100% in *B. subtilis* group (the group including *B. subtilis*, *B. licheniformis*, *B. velezensis*, etc.). The peptide antibiotic such as lipopeptide synthesized by NRPS showed broad spectrum antibacterial activity, while ribosomally synthesized peptides selectively inhibit certain pathogens. *Bacillus*-derived antibiotics can contribute to enhance niche adaptation and spatially outcompete between different microbes [32].

In the analysis, the diversity and concrete distribution of the BGCs and functional genes were relevant to the phylogenetic relatedness. Probiotic *B. cereus* strains were all in the presence of the genes or BGCs responsible for synthesizing bacteriocins, quorum sensing molecules, terpenes, and vitamins, but in absence of PKS gene cluster and phosphonates synthesized genes (Table 1). In *B. subtilis* group, high abundance of PKS, NRPS, and NRPS/PKS hybrid BGCs were detected, many of which were involved in growth interference. Additionally, RiPPs were distributed in wide range of *Bacillus* species. The RiPPs products are documented that play a role in bacterial physiology and niche competition [54]. The antibacterial metabolites related to above BGCs were predicted by antiSMASH and listed in Table 2. As probiotic *Bacillus* can product diverse metabolites with antimicrobial activities that mediate the beneficial interaction between host and microbiota, we further highlight the notable example of bacteriocin, lipopeptide, and polyketide antibiotics for their modes of action and antimicrobial spectrum (Table 3 and Fig. 2).

Table 1 Distribution of BGCs and functional genes in probiotic *Bacillus*

Type of BGCs[a]	*B. cereus* group	*B. subtilis* group	*Bacillus* spp.
NRPS	100% (84/84)	99% (300/302)	50% (33/66)
NRPS-PKS	26% (22/84)	81% (244/302)	15% (10/66)
Bacteriocin	100% (84/84)	70% (210/302)	62% (41/66)
Lanthipeptide	44% (37/84)	55% (167/302)	20% (13/66)
Lassopeptide	17% (14/84)	12% (37/302)	18% (12/66)
Thiopeptide	1% (1/84)	21% (63/302)	2% (1/66)
Sactipeptide	17% (14/84)	31% (95/302)	6% (4/66)
PKS	-	97% (293/302)	77% (51/66)
Phosphonate	-	9% (26/302)	11% (7/66)
QSM	100% (84/84)	34% (104/302)	2% (1/66)
Immunomodulatory molecule	46% (39/84)	99% (300/302)	61% (40/66)
Siderophore	82% (69/84)	13% (40/302)	30% (20/66)
Terpene	100% (84/84)	98% (297/302)	76% (50/66)
Vitamin	100% (84/84)	88% (266/302)	38% (25/66)
other	73% (61/84)	96% (290/302)	41% (27/66)

[a] The abbreviations were listed after the main context

Bacteriocins and lipopetides

Bacterial cell membrane, cell wall synthesis, DNA synthesis, transcription, as well as folate synthesis are traditional targets by most of available antibiotic [120]. Bacteriocins or antimicrobial peptides employ multiple mechanisms to directly show antibacterial function by targeting cell membrane or cell wall leading to collapse of bacterial metabolism. Bacteriocins are ribosomally synthesized (poly)peptides produced by almost prokaryotic lineages [121], and non-ribosomal peptides is an indispensable part for bacterial adaptation [44]. Due to the flexible biosynthetic mechanism of NRPS, these compounds are structural diversity and exhibit relatively wide range of activity [17, 122]. In this section, we introduced the mode of action of bacteriocin and lipopeptide antibiotic and their function in microsystem regulation.

Bacteriocins As presented in Table 3, members of the *B. subtilis* group stands out for its abundance of BGCs responsible for antimicrobial compound production. With this group, notable species such as *B. amyloliquefaciens*, *B. subtilis*, *B. licheniformis*, and *B. velezensis* synthesize diverse lantibiotics. Strains belonging to the *B. cereus* group also produce diverse bacteriocin, such as *B. cereus* and *B. thuringiensis*. Based on the biosynthesis mechanism and chemical structure, probiotic *Bacillus*-derived bacteriocins can be classified into post-translationally modified peptides, nonmodified peptides, and other linear bacteriocin-like inhibitory substances (BLIS).

As for post-translationally modified peptides, the characteristic feature is containing intramolecular ring that form by thioether bonds between amino acids. Most of these lantibiotics targets cell membrane and disrupt the balance of energy metabolism, such as subtilin, subtilosin A, sublichenin, sublancin 168, lichenicidin, and cerecidins. Subtilin [74], entianin [60], and sublichenin [73] have strong structural similarities to each other with identical organization of lanthionine-bridging structure. Subtilin-like lantibiotics show potent MIC as low as 0.25 μg/mL against extended spectrum of foodborne Gram-positive (G^+) pathogens via cell wall biosynthesis interference and pores formation to cause leakage of the cytoplasmic

Table 2 Antimicrobial secondary metabolites in probiotic *Bacillus* predicted by antiSMASH

Species	Predicted antibacterial metabolites													
	Bacillaene	**Bacilysin**	**Bacitracin**	**Cerecidin**	**Difficidin**	**Fengycin**	**Lichenysin**	**Macrolactin**	**Mersacidin**	**Plantazolicin**	**Sublancin**	**Subtilin**	**Subtilosin**	**Surfactin**
***B. cereus* group (*n* = 84)**				94% (3)[a]		40% (33)								
B. cereus				94% (1)		40% (11)								
B. thuringiensis				94% (1)		40% (20)								
B. cereus group strains				94% (1)		40% (2)								
***B. subtilis* group (*n* = 302)**	99% (205)	100% (192)	79% (23)		94% (128)	88% (274)	81% (22)	99% (132)	100% (6)		100% (8)	100% (7)	100% (67)	72% (264)
B. amyloliquefaciene	100% (33)	100% (35)	44% (1)		87% (29)	87% (34)	57% (1)	99% (33)	100% (5)					67% (43)
B. licheniformis						46% (9)	100% (8)							48% (8)
B. paralicheniformis			79% (22)			73% (22)	100% (8)	100% (3)						70% (14)
B. subtilis	100% (50)	100% (56)			73% (2)	90% (75)	19% (3)		100% (1)		100% (8)	100% (7)	100% (50)	68% (73)
B. velezensis	100% (94)	100% (91)			98% (93)	97% (107)		100% (93)						81% (101)
B. subtilis group strains	99% (28)	100% (10)			70% (4)	80% (27)	32% (2)	73% (3)					98% (17)	69% (25)
***Bacillus* spp. (*n* = 66)**										100% (4)				
B. altitudinis														
B. coagulans														
B. megaterium														
B. pumilus										100% (2)				
B. safensis										100% (2)				
Other *Bacillus* spp.														

[a] The percentage represent the average identity with the reference sequence. And numbers in the parentheses indicate numbers of the BGCs-carrying *Bacillus* isolates

Table 3 Antimicrobial metabolites in probiotic *Bacillus*

Classification	Compounds	Producer species[a]	Type of BGCs[b]	Spectrum[c]	Targets[d]	References
Compounds synthesized by ribosome and post-translationally modified						
Lantibiotics	Amylolysin	*B. amyloliquefaciens*	RiPP	G^+	Cell membrane, lipid II	[55]
	Cerecidins	*B. cereus*	Lanthipeptide	G^+	Cell membrane	[56]
	Clausin	*B. clausii*	RiPP	G^+	Cell wall	[57, 58]
	Coagulin	*B. coagulans*	RiPP-like	G^+	-	[59]
	Entianin	*B. subtilis*	Lanthipeptide	G^+	Cell wall, membrane	[60]
	Formicin	*B. paralicheniformis*	RiPP	G^+	Cell membrane	[61]
	Haloduracin	*B. halodurans*	RiPP	G^+	Cell wall, membrane	[62, 63]
	Lichenicidin	*B. licheniformis*	Lanthipeptide	G^+	Cell membrane	[64, 65]
	Megacin	*B. megaterium*	RiPP	G^+	Cell membrane	[66, 67]
	Mersacidin	*Bacillus* sp.	Lanthipeptide	G^+	Cell wall, membrane	[68, 69]
	Pseudomycoicidin	*B. pseudomycoides*	RiPP	G^+	-	[70]
	Plantazolicin A, B	*B. velezensis*	RiPP	G^+	Cell membrane	[71]
	Sublancin 168	*B. subtilis*	Lanthipeptide	G^+	PTS	[72]
	Sublichenin	*B. licheniformis*	RiPP	G^+, G^-	-	[73]
	Subtilin	*B. subtilis*	Lanthipeptide	G^+	Cell wall	[74]
	Subtilomycin	*B. subtilis*	Lanthipeptide	G^+, G^-	-	[75]
	Subtilosin A	*B. subtilis*	Thiopeptide	G^+	Cell membrane, Quorum sensing	[76, 77]
	Thuricins	*B. thuringiensis*	RiPP	G^+	Cell membrane	[78, 79]
	Thurincin H	*B. thuringiensis*	RiPP	G^+, G^-	Cell membrane or cell wall	[80]
	Thiocillins	*B. cereus*	Thiopeptide	G^+	Protein synthesis	[81]
Peptide compounds synthesized by non-ribosomal peptide synthetase						
Cyclic Cationic Lipopeptides	Bacitracin	*B. subtilis*	NRPS	G^+	Cell wall	[82]
	Circulin group:					
	Circulin	*B. circulans*	NRPS	G^+, G^-, fungus	-	[83]
	Polypeptin A-B	*B. circulans*	NRPS	G^+, G^-	-	[84]
	Polymyxin analogues:					
	Polymyxin A-E	*B. polymyxa* (namely *Paenibacillus polymyxa*)	NRPS	G^+, G^-	Cell membrane	[85]
	Octapeptin analogues:					
	Octapeptin A-D	*Bacillus* sp. and *Paenibacillus* sp.	NRPS	G^+, G^-	Cell membrane	[86, 87]

Table 3 (continued)

Classification	Compounds	Producer species[a]	Type of BGCs[b]	Spectrum[c]	Targets[d]	References
Cyclic Noncationic Lipopeptides	Bacilotetrins A, B	*B. subtilis*	NRPS	G^+	-	[88]
	Locillomycin	*B. subtilis*	PKS/NRPS	G^+, virus	-	[89]
	Iturin analogues:					
	Bacillomycin	*B. velezensis*	PKS/NRPS	Fungus, G^+	Cell membrane	[90–92]
	Iturins	*B. subtilis*	PKS/NRPS	Fungus, G^+	Cell membrane	[45, 93]
	Mycosubtilin	*B. subtilis*	PKS/NRPS	Fungus, G^+	Cell membrane	[92, 94]
	Surfactin analogues:					
	Bacaucin	*B. subtilis*	NRPS	G^+	Cell membrane	[95]
	Lichenysins	*B. licheniformis*	NRPS	G^+	Cell membrane, biofilm formation	[96, 97]
	Pumilacidin	*B. pumilus*	NRPS	G^+, virus	-	[98, 99]
	Surfactins	*B. subtilis*	NRPS	Fungus, virus, G^+	Cell membrane, quorum sensing, protein synthesis, cell metabolism	[100, 101]
	Fengycin analogues:					
	Fengycins	*B. subtilis*	NRPS	Fungus, G^+	Cell membrane, quorum sensing	[16, 102]
	Plipastatin	*B. subtilis*	NRPS	Fungus, G^+	Cell membrane, wall	[31, 103]
	Fusaricidin analogues					
	Fusaricidins	*Paenibacillus* sp.	PKS/NRPS	G^+, Fungus	Cell membrane, cell metabolism	[104, 105]
Liner Cationic Lipopeptides	Bogorol A	*Bacillus* sp.	NRPS	G^+	-	[106]
	Cerexin A-D	*B. cereus*	NRPS	G^+	-	[107]
	Gageopeptides	*B. subtilis*	NRPS	G^-, G^+, fungus	-	[108]
	Gageostatins	*B. subtilis*	NRPS	G^-, G^+, fungus	-	[109]
	Gageotetrins	*B. subtilis*	NRPS	G^-, G^+, fungus	Cell membrane	[110]
	Tridecaptin A-C	*B. polymyxa* (namely *Paenibacillus polymyxa*)	NRPS	G^-	lipid II	[111]
	Zwittermicin A	*B. cereus*	PKS/NRPS	Fungus, G^+, G^-	-	[112]
Liner Lipopeptides	Bacillin	*B. subtilis*	NRPS	G^-, G^+	Cell membrane	[113]
	Bacilysin	*B. subtilis*	Other	G^-, G^+, fungus	Cell wall, membrane	[114]
Polyketide compounds synthesized by polyketide synthetase or polyketide synthetase/non-ribosomal peptide synthetase						
	Amicoumacin	*B. pumilus*	PKS/NRPS	G^-, G^+	Protein synthesis	[48, 115]
	Bacillaene	*B. subtilis*	PKS/NRPS	Fungus, G^-, G^+	Biofilm formation, Protein synthesis	[116, 117]
	Difficidin	*B. velezensis*	PKS/NRPS	Fungus, G^+, G^-	Cell wall, Protein synthesis	[114]
	Macrolactin	*B. velezensis*	PKS	G^-, G^+	Protein synthesis	[118, 119]

[a] Antimicrobial metabolites listed in the table are commonly produced by producer species but not limited in these species

[b] The type of BGCs is categorized according to the published researches and MIBiG database

[c] Their activities are shown in the way of whether exhibit the inhibition of the growth of pathogenic bacteria (Gram-positive G^+ and Gram-negative G^-), fungus or virus

[d] It represents unknown antibacterial targets. The abbreviations in the table can be found in the abbreviation list

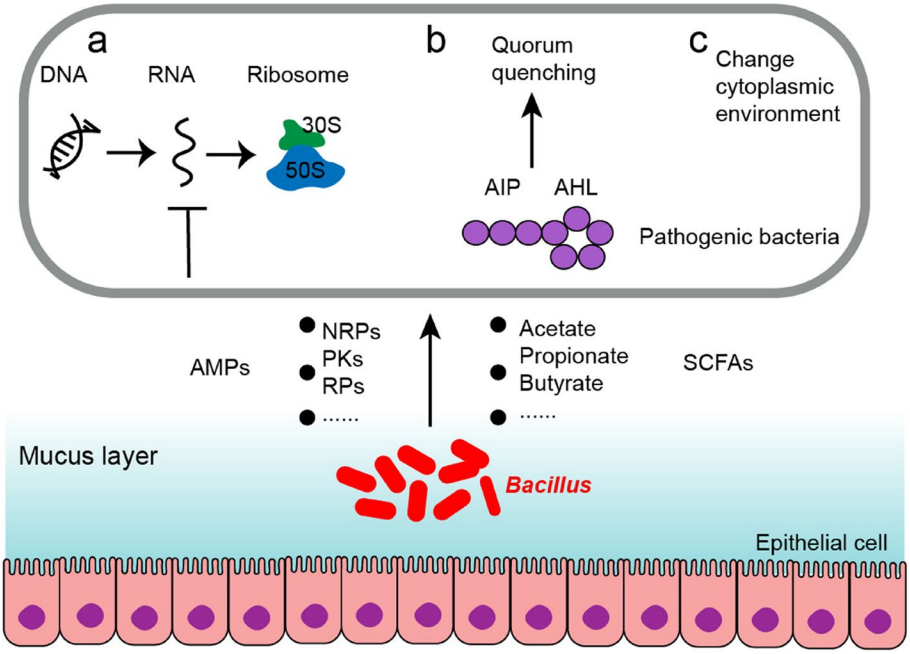

Fig. 2 The mode of action of AMPs and SCFAs derived from probiotic *Bacillus*. The antibacterial activity exhibited by *Bacillus* is mainly attributed to the production of AMPs and SCFAs. AMPs and SCFAs produced by probiotic *Bacillus* can directly **(a)** kill/inhibit pathogenic bacteria or antagonize the colonization of pathogenic bacteria by destroying bacterial cell membrane, genetic material and **(b)** interfere with bacterial quorum sensing system. Additionally, **(c)** the produced SCFAs can easily penetrate into the lipid membrane of the bacterial cell and cause the acidification of cytoplasm or require excess energy consumption to export the dissociated protons from SCFAs. These effects result in inhibition of pathogen's growth

small molecules. Subtilosin A, a cyclic lantibiotic protein, can interact with the lipid head group region of bilayer membranes in a concentration dependent manner [76] and act as a autoinducer-2 inhibitor to inhibit quorum sensing [77]. Sublancin 168 is a glycosylated bacteriocin with unique antibacterial mechanism to against G^+ bacteria. This compound affects the bacterial glucose uptake system rather than the integrity of cell wall or membrane to exert its activity. The deletion of the *ptsGHI*, the major glucose transporter components, results in resistance of sublancin [72]. Subtilomycin was identified from marine sponge associated *B. subtilis*. It exhibits a wide range of antibacterial activity towards important enteric pathogens including *L. monocytogenes*, MRSA and *P. aeruginosa* and resistance to certain extent of heat, acidic, enzymatic treatments [75]. Amylolysin, a type-B lantibiotic produced by *B. amyloliquefaciens*, also has the similar stability and antimicrobial activity as subtilomycin with pore-forming ability by depolarizing the cell membrane leads to cell leaking [55]. Lichenicidin is the first lanthipeptide showed antimicrobial activity on G^+ bacteria, that also targets bacterial membrane [64, 65]. Cerecidins is novel lanthipeptide from *B. cereus* against G^+ bacteria, its variants cerecidins A7 showed inhibition activity on MDRSA and VRE [56], which may also target the cell membrane. Formicin is a novel member in two-peptide lantibiotic with reduced hydrophobic α peptide and unusual negative charge β peptide, displaying a broad spectrum of foodborne G^+ pathogens inhibition such as *C. difficile* and *S. aureus* [61]. Mersacidin, an efficacious bactericidal lantibiotic specifically targeting G^+ bacteria, serves as a potent inducer of the cell wall stress response and a peptidoglycan synthesis inhibitor [68]. Furthermore, it exhibits superior activity compared to vancomycin in a mouse infection model [69]. Clausin displays high antimicrobial activity against G^+ bacteria by binding to lipid precursors of the bacterial cell wall to inhibit bacterial cell integrity [57, 58]. Haloduracin [62, 63] and pseudomycoicidin [70] are effective anti-G^+ lantibiotics originally found in *B. halodurans* and *B. pseudomycoides*, respectively. Thiocillins are members of the thiazolyl peptide class of natural product antibiotics not only known act as target G^+ bacteria [81], but also as a biofilm matrix inducer to modulate bacterial cellular physiology [123]. However, not all of bacteriocins secreted from *Bacillus* are effective to suppress multiple pathogenic bacteria. Plantazolicin is the highly post-translationally modified lanthipeptide with narrow-spectrum antibacterial activity toward the causative agent of anthrax. This antimicrobial compound exerts its action by penetrating

the outer layer of bacteria and subsequently disrupting the integrity of the plasma membrane through the formation of pores, leading to complete depolarization of the membrane [71].

As for nonmodified peptides, thuricin and thurincin are the representative nonmodified bacteriocins produced by *B. thuringiensis* exhibit inhibitory activity against Gram-positive pathogens. However, there are different mode of action among them. Thuricin binds to the membrane of target cell membrane leading to membrane permeabilization while thurincin causes loss of cell integrity without affecting membrane permeability and the detailed mechanisms is still unclear [78–80]. Coagulin is the first report of a pediocin-like peptide appearing naturally in a non-lactic acid bacterium genus with the specific characteristics of genetic environment that its structural gene harbor in plasmid I_4 [59]. It exhibits both bactericidal and bacteriolytic activity against multiple pathogenic bacteria, including *Listeria*, *Pediococcus* and *Enterococcus* [124]. Other BLIS such as megacin [66, 67] is a single polypeptides with approximately 2000 amino acids displaying antibacterial activity in close related species by inhibition of protein synthesis.

Antimicrobial lipopeptides Bacterial lipopeptides are non-ribosomal natural product biosynthesized by NRPSs or PKS-NRPS [125], with the majority of these compounds originating from species belonging to the *B. subtilis* group. *Bacillus*-derived lipopeptides can be can be categorized into three groups based on their chemical structures: cyclic cationic lipopeptides, non-cyclic cationic lipopeptides, and linear lipopeptides.

1) Cyclic cationic lipopeptides

Cyclic cationic lipopeptides are composed of a cyclic oligopeptide interlinked with feasible fatty acid chain, such as the antimicrobial compounds like circulin [83], polymyxins [85], polypeptins [84], and octapeptins [86]. Cationic peptides generally involve in formation of the channels through ions passing the channels and disrupting bacterial cytoplasmic membranes. Circulin group, polymyxin analogues and octapeptin analogues show potent activity against Gram-negative (G^-) bacteria by permeabilizing cell membrane. Circulin group cover broader spectrum antibacterial activity than Bacitracin and the other two group analogues. Octapeptin exhibits selective antibacterial activity by binding to lipid A and inducing membrane depolarization [87]. The cationic sugars, when combined with lipid A, reduce its efficacy; however, this occurs through distinct mechanisms compared to polymyxins [126]. Bacitracin from *Bacillus* strains inhibits G^+ bacteria via interference with the dephosphorylation of C55-undecaprenyl pyrophosphate (bactoprenol) resulting in block of cell wall synthesis [82].

2) Cyclic noncationic lipopeptides

Non-cationic peptides may bind to bacterial surface bilayer and change the linkage of negatively charged lipid tissue resulting in lipid bilayer restructure. The cyclic noncationic lipopeptides are iturin group, surfactin analogues, fengycin analogues, and fusaricidin analogues. Iturin group contain a β-hydroxy fatty acid with a 14-carbon chain, including iturins (variants A, C, D, and E), bacillomycins [90–92] (variants D, F, L, and Lc), and mycosubtilin [92, 94]. Iturns shows antibacterial activity by targeting cytoplasmic membrane resulting in formation of ion-conducting pores and increased K^+ permeability [93], but recent studies found that fungal DNA and biofilm matrix are also the target of some iturins. Surfactin is one of the most powerful known biosurfactants secreted by *Bacillus*. It is reported that surfactin exert multiple activities to impact the colonization and adherence of pathogens and acts not only as an antibiotic but also a competition factor to pathogen and contributor to its fitness in bacterial community [100, 127]. Lichenysin produced by *B. licheniformis* show similar structural and physiochemical properties with surfactin. This compound can not only cause permeabilization of phospholipid membrane but also decrease the load of pathogens through reduction of bacterial biofilm [96, 97, 128]. A novel lipopeptide, bacaucin, identified from *B. subtilis*, shows broad antibacterial activity against MDR G^+ pathogens by membrane-disruptive mechanism without induction of bacterial resistance [95]. Fengycin and Plipastatin have a strong antifungal activity and a restricted antibacterial activity against certain species. Their targets are the specific membrane component such as glycerol-3-phosphate transporter to affect membrane homeostasis [102]. Notably, fengycin can block *S. aureus* quorum sensing for colonization resistance acted as the analogue of autoinducer AIP [16]. Differ from the antimicrobial spectrum of fengycin group, fusaricidin analogues are more effective to against G^+ bacteria and included the activity to disrupt the balance of cellular metabolism [104, 105]. The natural

product Bogorol A, derived from *Bacillus* sp., was first discovered in 2001. It exhibits inhibitory activity against MRSA and VRE, but the precise target of its action remains unknown [106]. Bacilotetrins A and B [88] are two new cyclic-lipotetrapeptides produced by *B. subtilis* exhibit anti-MRSA activity with minimum inhibitory concentration (MIC) values of 8–32 μg/mL and show no cytotoxicity. Similarly, locillomycin is a novel family of cyclic lipopeptides produced by *B. subtilis* with low cytotoxicity, characterized by a unique nonapeptide sequence and macrocyclization. It has inhibitory activity against both bacteria and virus [89].

3) Linear lipopeptides

Although cyclic lipopeptide tend to be more stable than linear lipopeptide for its circular structure, linear lipopeptide has several advantages as follow: (1) reduced toxicity; (2) easier to synthesize; (3) multiple target within the target cells and microbiota modulation [129]. Linear noncationic lipopeptide such as bacillin [113] and bacilysin are both produced from *B. subtilis* possessing antimicrobial activity toward G^+ and negative bacteria, among which bacilysin act as an important factor in microcosm to shape interaction between species [130]. Gageopeptides [108], gageostatins [109], gageotetrins [110] were Leu-rich linear lipopeptide discovered from *B. subtilis* share the similar physicochemical and bioactive properties such as a broad spectrum antimicrobial activity on both bacteria and fungus, among which gageopeptides displays noncytotoxic character and extraordinary antimicrobial activity with MIC values of 0.02–0.09 μM. Tridecaptins are a re-emerging class of non-ribosomal antibacterial peptides (NRAPs) with potent activity against G^- bacteria [111]. Zwittermicin was initially discovered for its role in the competitive interactions between different bacterial species. It acts as a potent inhibitor against the growth of other microorganisms, giving the producing strain a competitive advantage in its ecological niche [131]. The compound is effective against a wide range of bacteria, including both G^+ and G^- species [112].

Polyketides and PKs/NRPs hybrids

Polyketides (PKs) are structurally diverse compounds with numerous biological activities particularly as antibacterial activity in *Bacillus*. The PKs machinery are linear assembly and minimally comprises three core domains: ketosynthase (KS), an acyltransferase (AT), and an acyl-carrier protein (ACP) domain, to orderly synthesis variable compounds. Unlike lipopeptide antibiotics often target cell membrane or cell wall to exert their activities, polyketide commonly interfere with the process of protein synthesis. Three main polyketides are found in *Bacillus*, including bacillaene, difficidin, and macrolactin, which play a crucial role in microbiota modulation. Bacillaene is an instable polyene antibiotic that inhibit bacteria by hindering prokaryotic protein synthesis [116]. It is reported that the competition between *B. subtilis* and *Salmonella typhimurium* in vitro is mediated by bacillaene through interrupt the growth of *S. typhimurium* under nutrient-rich condition [117]. Likewise, macrocyclic polyene difficidin regulate rhizosphere microbiota by suppressing the metabolism and virulence of phytopathogenic bacteria, which might exhibit same mechanistically action in gut microbiota regulation [114]. Macrolactin with both antifungal activity and broad antibacterial spectrum exerts the antagonistic activity by means of disturbance of bacterial cell wall synthesis. This compound could effectively suppress the colonization of multi-drug resistance bacteria in intestine [118], and in some cases, reduced the diversity of bacterial community and changed the collective metabolic pathways [119]. Amicoumacin is a ribosome-targeting antibiotic and vital for the negative interaction with anti-*Helicobacter pylori* and anti-*vibrio* activity [48, 115]. Along with the repeated discoveries of the genomic biosynthetic clusters and natural derivatives of amicoumacins in *Bacillus* species, the ecological role of amicoumacin was found to function as major antibacterial metabolite driving the reduce of competitor population [132].

Bacteria-host interactions

Metabolic crosstalk among commensals, host, and invaders contributes to a state of dynamic balance. Administration of probiotic *Bacillus* has been associated with a range of benefits to host. These include enhancement of pathogenic resistance [133], alteration of inflammation response [134], activation of innate immunity [135], and amelioration of intestinal damage [136, 137]. The benefits are likely mediated by the *Bacillus*-derived metabolites such as lactate secreted by *B. coagulans* that helps maintain an acidic environment in the gut and exoenzymes produced by *B. subtilis* that promote host digestibility. Although metabolomics studies reveal the diverse array of *Bacillus*-derived metabolites [138, 139], many of their functional role in host remain unclear. In this section, we summarize the reported metabolites that exert effects on the host, primarily through two mechanisms: (1) Involvement in intestinal cell metabolism to enhance the intestinal physical barrier; (2) Activation of innate immune responses to drive host's clearance of pathogens (Fig. 3).

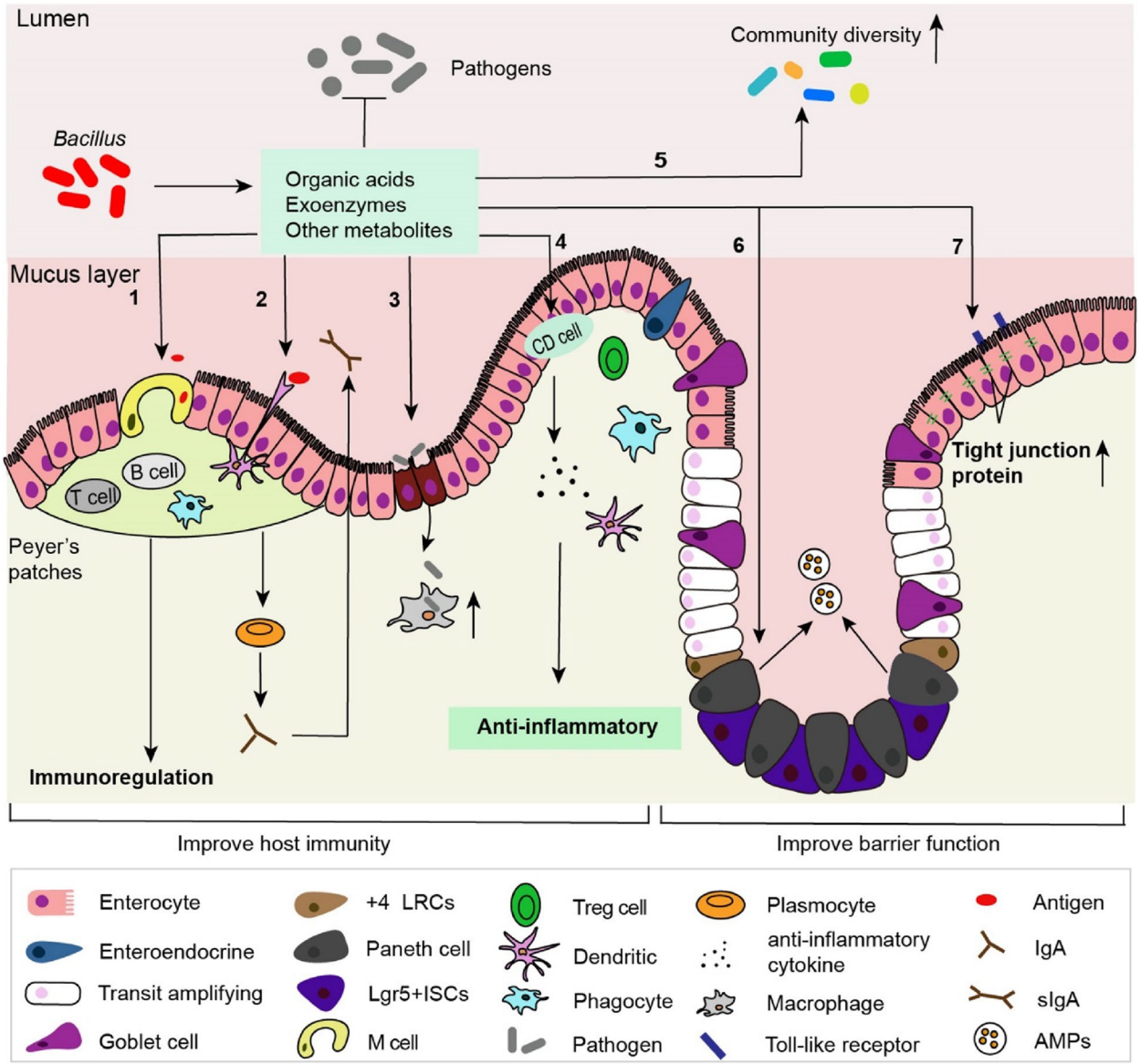

Fig. 3 Probiotic *Bacillus* produces various metabolites to activate intestinal immune. Metabolites trigger B cells and T cells through M cell **(1)** and dendritic cell **(2)**, as well as improve the phagocytosis ability of macrophages **(3)** resulting in enhanced clearance of pathogens; and stimulate the intestinal associated lymphoid tissue to produce $CD8^+$ and T cell **(4)**, alleviate some kinds of inflammation. In another aspect, the metabolites improve the diversity of commensal microbiota **(5)**, induce paneth cell producing AMPs (**6**) as well as enhance the expression of tight junction protein in epithelial cell (**7**), to strengthen the local barriers configuration

Organic acids

Bacteria have the capability of biosynthesis in organic acids, such as SCFAs, secondary bile acids (BAs), amino acids, and their derivatives [140], that deeply affect host metabolism [141]. *Bacillus* spp. employ these abundant secondary metabolites to participate in host circulation. We summarized the organic acids produced by *Bacillus* that have reportedly metabolic function in host (Table 4), many of which serve as important factors to regulate host homeostasis by immunity modulation. SCFAs are most studied metabolites that derive from the fermentation of dietary fibre. In the context of normal GI environment in mice and humans, acetate, propionate, and butyrate with a molar ratio of 60: 20: 20 comprise the majority of SCFAs pool in gut [142]. These compounds not only have the role in regulation of immunity system but also exert their antibacterial activities by directly inhibiting the growth of pathogenic bacteria [143], or act as adjuvants by enhancing the potency of antibiotic [144]. Mechanically, SCFAs mediate intracellular acidification that disrupt the respiration [145]

Table 4 *Bacillus*-derived organic acids, exoenzymes and other metabolites that involved in bacteria to host interaction

Substances	Producer species[a]	Functions	References
Organic acids			
Acetate	*B. subtilis* *B. coagulans* *B. clausii*	Pathogens inhibition and coordinate the formation of biofilm	[154–156]
Butyrate	*B. clausii* *B. subtilis*	Host metabolic improvement	[157]
Indoleacetic acid	*B. amyloliquefaciens*	Growth promotion	[158]
Lactate	*B. coagulans* *B. subtilis*	Intestinal barrier recovery and microbiota modulation	[137, 159]
Propionate	*B. thermoamylovorans* *B. clausii*	Enhance the efficacy of antibiotic and host immunity modulation	[154, 160, 161]
Tryptophan	*B. subtilis*	Host immunity modulation	[162]
Exoenzymes			
Amylases	*B. lichenformis* *B. cereus*	Bacterial adaption, nutrient digestibility and intestinal health improvement	[163, 164]
Cellulases	*Bacillus* sp.	Improving digestive of cellulose-like nutrients	[165]
Chitinase, Chitosanase	*B. subtilis*	Antifungal activity and chitin degradation	[166]
Fibrinolytic enzymes	*B. subtilis*	Treatment of cardiovascular	[167]
Lipase	*B. flexus*	Inhibit pathogen's biofilm formation	[168]
Lysozyme	*B. pumilus*	Antibacterial activity	[169]
Nattokinase	*B. subtilis*	Cardiovascular health improvement	[170, 171]
Phytase	*B. licheniformis*	Enhance nutrient availability	[172, 173]
Protease	*B. licheniformis* *B. proteolyticus* *B. clausii*	Nutrient digestibility improvement, antimicrobial activity, and toxin degradation	[174–176]
Other metabolites			
CSF	*B. megaterium*	Controls competence and spore formation	[177]
ComX pheromone	*B. licheniformis*	Antifungal activity	[178]
ESP	*B. subtilis*	Suppress inflammatory response, maintain intestinal barrier, and reduce pathogen's adhesion	[179, 180]
NAD	*B. subtilis*	Microbiota modulation and boost host NAD metabolism	[181, 182]
Spermidine	*B. subtilis*	Improve gut barrier integrity and gut microbiota function	[183, 184]
Vitamin B6	*B. subtilis*	Accelerate pathogen's clearance	[185]
Vitamin B12	*B. megaterium*	Affecting DNA synthesis and regulation, fatty acid synthesis and energy production	[186, 187]
Vitamin K	*B. subtilis*	Prevention of osteoporosis and cardiovascular disease	[188–190]

[a] The producer species listed in the table are representative of the producers of the corresponding metabolites; however, it should be noted that these strains are not the exclusive producers of these metabolites within the genus of *Bacillus*

and perturb the accumulation of anion [146]. The antibacterial activity or synergistic effect of SCFAs promote the recovery of gut microbiota through upregulation of lactic acid bacteria and other commensal flora [147]. However, the function of SCFAs mostly exhibit in intracellular processes involving in cell proliferation, differentiation and gene expression. For example, SCFAs can target G-protein coupled receptors (GPCRs) to activate host immune signaling cascades against IBD [148, 149], as well as regulate T cells to increase anti-inflammatory factors [150] and reduce pro-inflammatory factors [151]. Lactate and pyruvate can enhance immune responses by inducing GPCRs-mediated dendrite protrusion of intestinal C-X3-C motif chemokine receptor 1^+ cells [152]. The other secondary bile acid metabolized by *Bacillus*, can improve the permeability of the intestines and avoid the unnecessary increase of BAs production [153].

Exoenzymes

Various enzymes excreted by probiotic *Bacillus* have multiple functions, including inhibition of pathogenic microbes, decrease of virulence in enteric pathogens, and rebalance of intestinal homeostasis by regulating host immunity. Antimicrobial enzymes produced by probiotic

Bacillus significantly against pathogenic growth [191]. For example, two kinds of chitinases (ChiS and ChiL) [192] degrade butyrin and the peptidoglycan component of the fungal cell wall [193] or catalase and serine protease that reduce the pH and decrease the oxygen concentration of the intestinal tract [194]. Similarly, 1–3-glucanase is also reported with directly antimicrobial activity [195]. Others enzymes, like amylases, cellulases, lipase phytase or protease, are closely related to degradation of foods. Since quorum-sensing is important in regulating bacterial population, *Bacillus* is reported to use quorum-sensing molecules (QSMs)-pentapeptides-competence inducing cytoprotective heat shock proteins to protect intestinal epithelial cell from oxidative stress and loss of barrier function [196]. Additionally, they collectively regulate production of surfactin in *B. subtilis* [197] and enhances digestive enzyme activity to promotes host growth performance [198]. Pheromone produced by *B. subtilis* involved in bacterial quorum sensing that regulate bacterial competence and surfactant production [199]. Interestingly, a kind of serine protease secreted by *B. clausii* could inhibit hemolytic and cytotoxic effects of *Clostridium difficile* and toxic *B. cereus* [174]. Another intriguing function attributed to probiotic *Bacillus* is its potential in treating allergies. This effect is mediated by a specific sporular protein, which hinders the development of eosinophilia and goblet cell hyperplasia that are typically associated with allergic responses [200].

Other metabolites

In addition to the organic acids and exoenzymes, other metabolites such as vitamins also enhance the survival or growth fitness of commensal bacteria and serve as public goods in maintenance of host homeostasis. Given that about 45–60% of gut bacteria are genomic active in producing certain or all of the B-vitamins [201], some *Bacillus* strains show potential to biosynthesize vitamin B_1, B_2, B_3, B_5, B_6, B_7, B_9 and B_{12} [202], many of which contribute the absorption of food proteins in host [203], regulation of fatty acid synthesis, regeneration of energy production, as well as promoting the elimination of pathogens to maintain the microbiota homeostasis [204]. K-vitamin is emerged as fitness determinant for host to fight against cancer owing to that vitamin K_2 is both vital to cell respiration both in host and bacteria as well as participating in bone formation and absorption [188, 189]. Recently, researchers found that *Bacillus* could excrete vitamin B_3 to nourish the surrounding colonies [181, 205]. Vitamin B_3 is a vitamin family containing nicotinamide adenine dinucleotide (NAD) and the related precursors. These substances are vital for both host cell and bacterial growth that involved in many enzymatic processes [206]. *Bacillus* spp. is reported to produce these factors for boosting host energy metabolism as effective antiaging intervention [182]. Besides, most of *Bacillus* are biofilm-forming strains, which implies that they secrete numerous extracellular products such as exopolysaccharides (EPS) during their growth. EPS can not only act as prebiotics to provide nourishment for beneficial bacteria, but also inhibit enterotoxigenic *Escherichia* adherence via binding to colonization factor fimbriae on the cell surface [39]. Mucosal integrity and inflammatory responses are also regulated by *Bacillus* EPS. These extracellular components have been shown to enhance the expression of tight junction-related proteins (claudin-1, claudin-2 and occluding) and inhibit the secretion of the pro-inflammatory cytokine IL-6 and the activation of nuclear factor-κB pathway in macrophage, thereby alleviate gut inflammation [179, 207].

Concluding remarks and future perspectives

Collectively, probiotic *Bacillus* can perform probiotic benefit through directly interact with pathogenic bacteria or mediate by structurally diverse metabolites, which contribute to the stability and homeostasis of intestinal flora. However, the probiotic properties of *Bacillus* are strain-specific and activity-dependent [47]. This suggested that the qualification of *Bacillus* required to be determine before application. The probiotic activities are not only associated with their inherent species properties, but more importantly, are determined by the metabolites they secrete. Given that the intricate nature of microbial communities and host environment, the advantages of *Bacillus* in niche and resource competition against enteropathogens are conditional upon specific metabolites. Thus, determining the profiles of metabolites secreted from *Bacillus* under different culture conditions is a prerequisite for probiotic selection.

The transition between dormant spore and vegetative cell in *Bacillus* contribute to more resistance than other gut bacteria, which not only protects cell from harsh environment but also promotes self-colonization and growth in gut. Compared to most of bacteria (like some strictly anaerobic or aerobic), *Bacillus* species exhibit the ability to thrive in extreme environment by regulating cellular physiology through the overlapping regulatory systems of key metabolites to maintain viability [35]. Notably, the flexible metabolic regulatory network of *Bacillus* would be advantageous for causing nutrients stress to competitors, because nutrient intervention is new target for treating pathogens infections [208]. As the intestinal microbiota establishes itself within the resource-limited niches, the properties of *Bacillus* make it more suitable for self-survival and predisposed to outcompete invasive species.

Probiotic *Bacillus* harbors remarkable ability to directly mediate colonization resistance of pathogens

by various antibacterial compounds [51, 209]. Some of the compounds are promising agents, such as amicoumacin and surfactin, with potent antimicrobial activity and exert multiple function in host-microbiota system awaiting for further application. Besides, it is noteworthy that antimicrobial substances in *Bacillus* are predominantly synthesized by BGCs. Thus, we can selectively screen the *Bacillus* strains that possess abundant secondary metabolite gene clusters, particularly NRPS, for the development of probiotics [210]. In addition to exploring traditional antimicrobial compound, SCFAs have also garnered attention from antibacterial developers due to their synergistic effects when combined with antibiotics. Small molecular organic acid and vitamin derived from probiotic *Bacillus* can be developed as prebiotics and postbiotics for enhancing the host resistance to environment changes and pathogenic infections. Therefore, the ability to produce metabolites that mediate the interaction between *Bacillus* and host system are attracting direction to develop a novel probiotic *Bacillus* preparation. Furthermore, understanding the mechanisms that mediated by *Bacillus* metabolites in the intestine, could advance the development of stratagem of enteric infections. However, most studies demonstrated the positive result when probiotic *Bacillus* applied in disease model, but partial of them elaborated the underlying mechanisms of probiotic *Bacillus*, leaving ample scope for further mechanistic research. Currently, some studies unraveled the underlying beneficial mechanism between probiotic and host [211–213], but the metabolites that dominated the interaction remained unclear.

The use of *Bacillus* for probiotic and feed additive have been last for at least 50 years since the well-known Italian product (Enterogermina®) used for OTC medicinal supplement in 1958. Currently, probiotic *Bacillus* are widely used as a nutrient supplement and for the treatment enteric infection, such as the product NutriCommit®, Lactopure®, and Biosubtyl®. As the fast expansion of *Bacillus* probiotic in multiple field, increasing researches have demonstrated that the safety assessment of *Bacillus* probiotic is insufficient and should be laid more emphasis [214, 215]. In some specific species like *B. cereus*, they were found to secrete the enterotoxin Nhe, hemolysin Hly, and emetic cereulide causing severe foodborne disease. Around the year 2000, two commercial *B. cereus*-containing product Paciflor® and Esporafeed Plus® have been withdrawn by SCAN in Europe for the toxigenic potential and antimicrobial resistance found in probiotic *B. cereus*. Thus, to avoid the side effect and maximum the benefit bringing by probiotic *Bacillus*, selected strains should be comprehensively evaluated for their safety through *in vitro* and *in vivo* experiments.

Conclusively, our work provides advanced insight into the host interaction mechanism of probiotic *Bacillus*, particularly in relation to metabolites and strain properties.

Abbreviations

AMPs	Antimicrobial peptide. AMPs are oligopeptides with a varying number (from five to over a hundred) of amino acids, showing potent biological activity to inhibit diverse pathogenic bacteria
AMR	Antimicrobial resistance. Certain antibiotic that cannot inhibit the growth of the bacteria
Bas	Secondary bile acids. The secondary bile acids are derived from primary bile acids produced by the liver and are more hydrophobic than primary bile acids. The major secondary bile acids are deoxycholic acid (DCA) and lithocholic acid (LCA)
BGCs	Biosynthetic gene clusters. The BGCs are a locally clustered group of two or more genes that together encode a biosynthetic pathway for the production of a secondary metabolite
BLIS	Bacteriocin-like inhibitory substances. The BLIS has similar chemical struture with bacteriocin and not entirely characterized as bacteriocin
CSF	Competence and sporulation factor. A regulatory protein involved in the regulation of bacterial competence and sporulation processes plays a critical role in the regulation of competence development
DPA	Dipicolinic acid. DPA is a major component of Bacillus spore and functions as protective molecules to increase the stability of DNA
EPS	Exopolysaccharide. EPS are complex carbohydrate molecules produced and secreted by bacteria. These polysaccharides are synthesized and released into the surrounding environment, forming a protective matrix or biofilm
GI	Gastrointestinal. The part of the digestive system that consists of the stomach and intestines
GPCRs	G-protein coupled receptors. G protein-coupled receptor (GPCR), also called seven-transmembrane receptor or heptahelical receptor, locate in the cell membrane that binds extracellular substances and transmits signals from these substances to an intracellular molecule
LBPs	Live biotherapeutic products. LBPs are defined as live organisms designed and developed to treat, cure, or prevent a disease or condition, excluding vaccines, filterable viruses and so on
MDR	Multidrug resistance. The bacteria show resistance to a wide range of structurally unrelated antibiotics
MIC	Minimum inhibitory concentration. MIC defines in vitro levels of susceptibility or resistance of specific bacterial strains to applied antibiotic
NAD	Nicotinamide adenine dinucleotide. NAD is a molecule that participate in multiple cellular processes such as redox reactions and energy generations, to maintain the homestasis of metabolism
NRPS	Non-ribosomal peptide synthetases. The NRPS are large multienzyme machineries that assemble numerous peptides with large structural and functional diversity
NRPS-PKS	NRPS-PKS hybrids. They are responsible for the production of complex natural products that possess both peptide and polyketide components
PKS	Polyketide synthases. The PKS are multifunctional enzyme that use primary metabolites (acetyl-CoA and malonyl-CoA) to biosynthesize numerous natural product, many of which are antibiotics
PTS	Phosphoenolpyruvate: sugar phosphotransferase system. A bacterial transport system that facilitates the uptake and phosphorylation of sugars
QSMs	Quorum-sensing molecules. It also called autoinducer that acts as a cell-to-cell communication intermediator in response to fluctuations in cell-population density
RiPPs	Ribosomally synthesized and post-translationally modified peptides. The synthesis of RiPPs is ribosomal-dependent that produce polypeptide with modification by various dedicated enzymes

SASPs Acid-soluble proteins. SASPs stabilise the DNA in an A-helix configuration and confer a protection benefit from cleavage by enzymes or UV light

SCFAs Short chain fatty acids. A type of fatty acid with less than six carbon atoms mainly comprises acetate, propionate, and butyrate

Acknowledgements
Not applicable.

Authors' contributions
J.J.Z. and Y.S.C. performed literature search, confirmed and analyzed the information in the manuscript, and wrote the original draft. K.I., D.A.A., F.R.I., G.R. and Y.W.F., provided conceptualization and revised the manuscript. K.Z., wrote and finalized the manuscript, provided methodology, funding acquisition, and project administration. U.A. revised the manuscript and validated information. All authors have read and approved the final manuscript.

Funding
This study is supported by the National Key Research and Development Program of China (2022YFD1801600).

Availability of data and materials
Data are available upon reasonable request.

Declarations

Ethics approval and consent to participate
Not applicable.

Competing interest
Author Kui Zhu is a member of the Editorial Board for One Health Advances, he was not involved in the journal's review of this manuscript.

Received: 18 April 2023 Revised: 27 June 2023 Accepted: 19 July 2023
Published online: 15 August 2023

References

1. Guarner F, Malagelada JR. Gut flora in health and disease. Lancet. 2003;361(9356):512–9. https://doi.org/10.1016/S0140-6736(03)12489-0.
2. Jiang HY, Zhang X, Yu ZH, Zhang Z, Deng M, Zhao JH, et al. Altered gut microbiota profile in patients with generalized anxiety disorder. J Psychiatr Res. 2018;104:130–6. https://doi.org/10.1016/j.jpsychires.2018.07.007.
3. Baumler AJ, Sperandio V. Interactions between the microbiota and pathogenic bacteria in the gut. Nature. 2016;535(7610):85–93. https://doi.org/10.1038/nature18849.
4. Ghuneim LJ, Raghuvanshi R, Neugebauer KA, Guzior DV, Christian MH, Schena B, et al. Complex and unexpected outcomes of antibiotic therapy against a polymicrobial infection. ISME J. 2022;16(9):2065–75. https://doi.org/10.1038/s41396-022-01252-5.
5. Liu X, Liu F, Ding S, Shen J, Zhu K. Sublethal levels of antibiotics promote bacterial persistence in epithelial cells. Adv Sci (Weinh). 2020;7(18):1900840. https://doi.org/10.1002/advs.201900840.
6. Kim SG, Becattini S, Moody TU, Shliaha PV, Littmann ER, Seok R, et al. Microbiota-derived lantibiotic restores resistance against vancomycin-resistant *Enterococcus*. Nature. 2019;572(7771):665–9. https://doi.org/10.1038/s41586-019-1501-z.
7. Tam NK, Uyen NQ, Hong HA, le Duc H, Hoa TT, Serra CR, et al. The intestinal life cycle of *Bacillus* subtilis and close relatives. J Bacteriol. 2006;188(7):2692–700. https://doi.org/10.1128/JB.188.7.2692-2700.2006.
8. Lu S, Na K, Li Y, Zhang L, Fang Y, Guo X. *Bacillus*-derived probiotics: metabolites and mechanisms involved in bacteria-host interactions. Crit Rev Food Sci Nutr. 2022:1–14. https://doi.org/10.1080/10408398.2022.2118659.
9. Peng M, Liu J, Liang Z. Probiotic *Bacillus* subtilis CW14 reduces disruption of the epithelial barrier and toxicity of ochratoxin A to Caco-2 cells. Food Chem Toxicol. 2019;126:25–33. https://doi.org/10.1016/j.fct.2019.02.009.
10. Santacroce L, Charitos IA, Bottalico L. A successful history: probiotics and their potential as antimicrobials. Expert Rev Anti Infect Ther. 2019;17(8):635–45. https://doi.org/10.1080/14787210.2019.1645597.
11. Sumi CD, Yang BW, Yeo IC, Hahm YT. Antimicrobial peptides of the genus *Bacillus*: a new era for antibiotics. Can J Microbiol. 2015;61(2):93–103. https://doi.org/10.1139/cjm-2014-0613.
12. van Baarlen P, Wells JM, Kleerebezem M. Regulation of intestinal homeostasis and immunity with probiotic lactobacilli. Trends Immunol. 2013;34(5):208–15. https://doi.org/10.1016/j.it.2013.01.005.
13. Tran C, Cock IE, Chen X, Feng Y. Antimicrobial *Bacillus*: metabolites and their mode of action. Antibiotics. 2022;11(1):88. https://doi.org/10.3390/antibiotics11010088.
14. Ortiz A, Sansinenea E. Chemical compounds produced by *Bacillus* sp. factories and their role in nature. Mini Rev Med Chem. 2019;19(5):373–80. https://doi.org/10.2174/1389557518666180829113612.
15. Fazle Rabbee M, Baek KH. Antimicrobial activities of lipopeptides and polyketides of *Bacillus* velezensis for agricultural applications. Molecules. 2020;25(21):4973. https://doi.org/10.3390/molecules25214973.
16. Piewngam P, Zheng Y, Nguyen TH, Dickey SW, Joo HS, Villaruz AE, et al. Pathogen elimination by probiotic *Bacillus* via signalling interference. Nature. 2018;562(7728):532–7. https://doi.org/10.1038/s41586-018-0616-y.
17. Neijat M, Habtewold J, Shirley RB, Welsher A, Barton J, Thiery P, et al. *Bacillus* subtilis strain DSM 29784 modulates the cecal microbiome, concentration of short-chain gatty acids, and apparent retention of dietary components in shaver white chickens during grower, developer, and laying phases. Appl Environ Microbiol. 2019;85(14):e00402-19 . https://doi.org/10.1128/AEM.00402-19.
18. Microbiology MH. Microbial cooperative warfare. Science. 2012;337(6099):1184–5. https://doi.org/10.1126/science.1227512.
19. Cordero O, Wildschutte H, Kirkup B, Proehl S, Ngo L, Hussain F, et al. Ecological populations of bacteria act as socially cohesive units of antibiotic production and resistance. Science. 2012;337(6099):1228–31. https://doi.org/10.1126/science.1219385.
20. Cho WI, Chung MS. *Bacillus* spores: a review of their properties and inactivation processing technologies. Food Sci Biotechnol. 2020;29(11):1447–61. https://doi.org/10.1007/s10068-020-00809-4.
21. Moir A, Cooper G. Spore Germination. Microbiol Spectr. 2015;3(6):550–56. https://doi.org/10.1128/microbiolspec.TBS-0014-2012.
22. Lablaine A, Serrano M, Bressuire-Isoard C, Chamot S, Bornard I, Carlin F, et al. The morphogenetic protein CotE positions exosporium proteins CotY and ExsY during sporulation of *Bacillus* cereus. mSphere. 2021;6(2):e00007–21 . https://doi.org/10.1128/mSphere.00007-21.
23. Stewart GC. The Exosporium layer of bacterial spores: a connection to the environment and the infected host. Microbiol Mol Biol Rev. 2015;79(4):437–57. https://doi.org/10.1128/MMBR.00050-15.
24. Gu C, Jenkins SA, Xue Q, Xu Y. Activation of the classical complement pathway by *Bacillus* anthracis is the primary mechanism for spore phagocytosis and involves the spore surface protein BclA. J Immunol. 2012;188(9):4421–31. https://doi.org/10.4049/jimmunol.1102092.
25. Wang Y, Jenkins SA, Gu C, Shree A, Martinez-Moczygemba M, Herold J, et al. *Bacillus* anthracis spore surface protein BclA mediates complement factor H binding to spores and promotes spore persistence. PLoS Pathog. 2016;12(6):e1005678. https://doi.org/10.1371/journal.ppat.1005678.
26. Koshikawa T, Yamazaki M, Yoshimi M, Ogawa S, Yamada A, Watabe K, et al. Surface hydrophobicity of spores of *Bacillus* spp. J Gen Microbiol. 1989;135(10):2717–22. https://doi.org/10.1099/00221287-135-10-2717.
27. Rosenberg M. Microbial adhesion to hydrocarbons: twenty-five years of doing MATH. FEMS Microbiol Lett. 2006;262(2):129–34. https://doi.org/10.1111/j.1574-6968.2006.00291.x.
28. Sanchez B, Arias S, Chaignepain S, Denayrolles M, Schmitter JM, Bressollier P, et al. Identification of surface proteins involved in the adhesion of a probiotic *Bacillus* cereus strain to mucin and fibronectin. Microbiology. 2009;155:1708–16. https://doi.org/10.1099/mic.0.025288-0.
29. Mukherjee S, Kearns DB. The structure and regulation of flagella in *Bacillus* subtilis. Annu Rev Genet. 2014;48:319–40. https://doi.org/10.1146/annurev-genet-120213-092406.

30. Tian T, Sun B, Shi H, Gao T, He Y, Li Y, et al. Sucrose triggers a novel signaling cascade promoting *Bacillus* subtilis rhizosphere colonization. ISME J. 2021;15(9):2723–37. https://doi.org/10.1038/s41396-021-00966-2.
31. Maan H, Itkin M, Malitsky S, Friedman J, Kolodkin-Gal I. Resolving the conflict between antibiotic production and rapid growth by recognition of peptidoglycan of susceptible competitors. Nat Commun. 2022;13(1):431. https://doi.org/10.1038/s41467-021-27904-2.
32. Dai T, Wen D, Bates CT, Wu L, Guo X, Liu S, et al. Nutrient supply controls the linkage between species abundance and ecological interactions in marine bacterial communities. Nat Commun. 2022;13(1):175. https://doi.org/10.1038/s41467-021-27857-6.
33. Meyer FM, Jules M, Mehne FM, Le Coq D, Landmann JJ, Gorke B, et al. Malate-mediated carbon catabolite repression in *Bacillus subtilis* involves the HPrK/CcpA pathway. J Bacteriol. 2011;193(24):6939–49. https://doi.org/10.1128/JB.06197-11.
34. Deutscher J, Francke C, Postma PW. How phosphotransferase system-related protein phosphorylation regulates carbohydrate metabolism in bacteria. Microbiol Mol Biol Rev. 2006;70(4):939–1031. https://doi.org/10.1128/mmbr.00024-06.
35. Sonenshein AL. Control of key metabolic intersections in *Bacillus subtilis*. Nat Rev Microbiol. 2007;5(12):917–27. https://doi.org/10.1038/nrmicro1772.
36. Liu Y, Zhu Y, Ma W, Shin HD, Li J, Liu L, et al. Spatial modulation of key pathway enzymes by DNA-guided scaffold system and respiration chain engineering for improved N-acetylglucosamine production by *Bacillus subtilis*. Metab Eng. 2014;24:61–9. https://doi.org/10.1016/j.ymben.2014.04.004.
37. Sassone-Cors M, Chairatana P, Zhen T, Perez-Lopez A, Edwards RA, Georg MD, et al. Siderophore-based immunization strategy to inhibit growth of enteric pathogens. Proc Natl Acad Sci USA. 2016;113(47):13462–7. https://doi.org/10.1073/pnas.1606290113.
38. Dimopoulou A, Theologidis I, Benaki D, Koukounia M, Zervakou A, Tzima A, et al. Direct antibiotic activity of Bacillibactin Broadens the biocontrol range of *Bacillus amyloliquefaciens* MBI600. mSphere. 2021;6(4):e0037621. https://doi.org/10.1128/mSphere.00376-21.
39. Cai G, Wu D, Li X, Lu J. Levan from *Bacillus amyloliquefaciens* JN4 acts as a prebiotic for enhancing the intestinal adhesion capacity of Lactobacillus reuteri JN101. Int J Biol Macromol. 2020;146:482–7. https://doi.org/10.1016/j.ijbiomac.2019.12.212.
40. Mg E. Role of oxygen gradients in shaping redox relationships between the human intestine and its microbiota. Free Radical Biol Med. 2013;55:130–40. https://doi.org/10.1016/j.freeradbiomed.2012.10.554.
41. Litvak Y, Mon KKZ, Nguyen H, Chanthavixay G, Liou M, Velazquez EM, et al. Commensal *Enterobacteriaceae* protect against *Salmonella* colonization through oxygen competition. Cell Host Microbe. 2019;25(1):128–39 e5. https://doi.org/10.1016/j.chom.2018.12.003.
42. Litvak Y, Byndloss MX, Baumler AJ. Colonocyte metabolism shapes the gut microbiota. Science. 2018;362(6418):eaat9076. https://doi.org/10.1126/science.aat9076.
43. Vacca I. The microbiota maintains oxygen balance in the gut. Nat Rev Microbiol. 2017;15(10):574–5. https://doi.org/10.1038/nrmicro.2017.112.
44. Arjes HA, Vo L, Dunn CM, Willis L, DeRosa CA, Fraser CL, et al. Biosurfactant-mediated membrane depolarization maintains viability during oxygen depletion in *Bacillus subtilis*. Curr Biol. 2020;30(6):1011–22 e6. https://doi.org/10.1016/j.cub.2020.01.073.
45. Cochrane SA, Vederas JC. Lipopeptides from *Bacillus* and *Paenibacillus* spp.: a gold mine of antibiotic candidates. Med Res Rev. 2016;36(1):4–31. https://doi.org/10.1002/med.21321.
46. Olishevska S, Nickzad A, Deziel E. *Bacillus* and *Paenibacillus* secreted polyketides and peptides involved in controlling human and plant pathogens. Appl Microbiol Biotechnol. 2019;103(3):1189–215. https://doi.org/10.1007/s00253-018-9541-0.
47. Tran C, Horyanto D, Stanley D, Cock IE, Chen X, Feng Y. Antimicrobial properties of *Bacillus* probiotics as animal growth promoters. Antibiotics. 2023;12(2):0407. https://doi.org/10.3390/antibiotics12020407.
48. Pinchuk IV, Bressollier P, Verneuil B, Fenet B, Sorokulova IB, Megraud F, et al. In vitro anti-*Helicobacter pylori* activity of the probiotic strain *Bacillus subtilis* 3 is due to secretion of antibiotics. Antimicrob Agents Chemother. 2001;45(11):3156–61. https://doi.org/10.1128/AAC.45.11.3156-3161.2001.
49. Crits-Christoph A, Diamond S, Butterfield CN, Thomas BC, Banfield JF. Novel soil bacteria possess diverse genes for secondary metabolite biosynthesis. Nature. 2018;558(7710):440–4. https://doi.org/10.1038/s41586-018-0207-y.
50. Chu J, Koirala B, Forelli N, Vila-Farres X, Ternei MA, Ali T, et al. Synthetic-bioinformatic natural product antibiotics with diverse modes of action. J Am Chem Soc. 2020;142(33):14158–68. https://doi.org/10.1021/jacs.0c04376.
51. Harwood CR, Mouillon J-M, Pohl S, Arnau J. Secondary metabolite production and the safety of industrially important members of the Bacillus subtilis group. FEMS Microbiol Rev. 2018;42(6):721–38. https://doi.org/10.1093/femsre/fuy028.
52. Xia L, Miao Y, Cao A, Liu Y, Liu Z, Sun X, et al. Biosynthetic gene cluster profiling predicts the positive association between antagonism and phylogeny in Bacillus. Nat Commun. 2022;13(1):1023. https://doi.org/10.1038/s41467-022-28668-z.
53. Steinke K, Mohite OS, Weber T, Kovacs AT. Phylogenetic distribution of secondary metabolites in the *Bacillus subtilis* species complex. mSystems. 2021;6(2):e00057–21. https://doi.org/10.1128/mSystems.00057-21.
54. Li Y, Rebuffat S. The manifold roles of microbial ribosomal peptide-based natural products in physiology and ecology. J Biol Chem. 2020;295(1):34–54. https://doi.org/10.1074/jbc.REV119.006545.
55. Halimi B, Dortu C, Arguelles-Arias A, Thonart P, Joris B, Fickers P. Antilisterial activity on poultry meat of amylolysin, a bacteriocin from *Bacillus amyloliquefaciens* GA1. Probiotics Antimicrob Proteins. 2010;2(2):120–5. https://doi.org/10.1007/s12602-010-9040-9.
56. Wang J, Zhang L, Teng K, Sun S, Sun Z, Zhong J. Cerecidins, novel lantibiotics from *Bacillus cereus* with potent antimicrobial activity. Appl Environ Microbiol. 2014;80(8):2633–43. https://doi.org/10.1128/aem.03751-13.
57. Bouhss A, Al-Dabbagh B, Vincent M, Odaert B, Aumont-Nicaise M, Bressolier P, et al. Specific interactions of clausin, a new lantibiotic, with lipid precursors of the bacterial cell wall. Biophys J. 2009;97(5):1390–7. https://doi.org/10.1016/j.bpj.2009.06.029.
58. Ahire JJ, Kashikar MS, Madempudi RS. Survival and germination of *Bacillus clausii* UBBC07 spores in *in vitro* human gastrointestinal tract simulation model and evaluation of clausin production. Front Microbiol. 2020;11:1010. https://doi.org/10.3389/fmicb.2020.01010.
59. Hyronimus B, Le Marrec C, Urdaci MC. Coagulin, a bacteriocin-like inhibitory substance produced by *Bacillus coagulans* I4. J Appl Microbiol. 1998;85(1):42–50. https://doi.org/10.1046/j.1365-2672.1998.00466.x.
60. Fuchs SW, Jaskolla TW, Bochmann S, Kotter P, Wichelhaus T, Karas M, et al. Entianin, a novel subtilin-like lantibiotic from *Bacillus subtilis* subsp. spizizenii DSM 15029T with high antimicrobial activity. Appl Environ Microbiol. 2011;77(5):1698–707. https://doi.org/10.1128/AEM.01962-10.
61. Collins FWJ, O'Connor PM, O'Sullivan O, Rea MC, Hill C, Ross RP. Formicin – a novel broad-spectrum two-component lantibiotic produced by *Bacillus paralicheniformis* APC 1576. Microbiology. 2016;162(9):1662–71. https://doi.org/10.1099/mic.0.000340.
62. Lawton EM, Cotter PD, Hill C, Ross RP. Identification of a novel two-peptide lantibiotic, haloduracin, produced by the alkaliphile *Bacillus halodurans* C-125. FEMS Microbiol Lett. 2007;267(1):64–71. https://doi.org/10.1111/j.1574-6968.2006.00539.x.
63. Oman TJ, Lupoli TJ, Wang TS, Kahne D, Walker S, van der Donk WA. Haloduracin alpha binds the peptidoglycan precursor lipid II with 2:1 stoichiometry. J Am Chem Soc. 2011;133(44):17544–7. https://doi.org/10.1021/ja206281k.
64. Begley M, Cotter PD, Hill C, Ross RP. Identification of a novel two-peptide lantibiotic, lichenicidin, following rational genome mining for LanM proteins. Appl Environ Microbiol. 2009;75(17):5451–60. https://doi.org/10.1128/AEM.00730-09.
65. Panina IS, Balandin SV, Tsarev AV, Chugunov AO, Tagaev AA, Finkina EI, et al. Specific binding of the alpha-component of the lantibiotic lichenicidin to the peptidoglycan precursor lipid II predetermines its antimicrobial activity. Int J Mol Sci. 2023;24(2):1332. https://doi.org/10.3390/ijms24021332.
66. Ivanovics G, Alfoldi L, Nagy E. Mode of action of megacin. J Gen Microbiol. 1959;21:51–60. https://doi.org/10.1099/00221287-21-1-51.

67. Brusilow WS, Nelson DL. Improved purification and some properties of megacin Cx, a bacteriocin produced by *Bacillus* megaterium. J Biol Chem. 1981;256(1):159–64.
68. Sass P, Jansen A, Szekat C, Sass V, Sahl HG, Bierbaum G. The lantibiotic mersacidin is a strong inducer of the cell wall stress response of *Staphylococcus aureus*. BMC Microbiol. 2008;8:186. https://doi.org/10.1186/1471-2180-8-186.
69. Chatterjee S, Chatterjee DK, Jani RH, Blumbach J, Ganguli BN, Klesel N, et al. Mersacidin, a new antibiotic from *Bacillus*. *In vitro* and *in vivo* antibacterial activity. J Antibiot. 1992;45(6):839–45. https://doi.org/10.7164/antibiotics.45.839.
70. Basi-Chipalu S, Dischinger J, Josten M, Szekat C, Zweynert A, Sahl HG, et al. Pseudomycoicidin, a Class II Lantibiotic from *Bacillus pseudomycoides*. Appl Environ Microbiol. 2015;81(10):3419–29. https://doi.org/10.1128/AEM.00299-15.
71. Molohon KJ, Blair PM, Park S, Doroghazi JR, Maxson T, Hershfield JR, et al. Plantazolicin is an ultranarrow-spectrum antibiotic that targets the *Bacillus anthracis* membrane. ACS Infectious Diseases. 2016;2(3):207–20. https://doi.org/10.1021/acsinfecdis.5b00115.
72. Garcia De Gonzalo CV, Denham EL, Mars RA, Stülke J, Van Der Donk WA, van Dijl JM. The phosphoenolpyruvate:sugar phosphotransferase system is involved in sensitivity to the glucosylated bacteriocin sublancin. Antimicrob Agents Chemother. 2015;59(11):6844–54. https://doi.org/10.1128/aac.01519-15.
73. Pm H. Sublichenin, a new subtilin-like lantibiotics of probiotic bacterium *Bacillus licheniformis* MCC 2512 with antibacterial activity. Microb Pathog. 2019;128:139–46. https://doi.org/10.1016/j.micpath.2018.12.044.
74. Parisot J, Carey S, Breukink E, Chan WC, Narbad A, Bonev B. Molecular mechanism of target recognition by subtilin, a class I lanthionine antibiotic. Antimicrob Agents Chemother. 2008;52(2):612–8. https://doi.org/10.1128/AAC.00836-07.
75. Phelan RW, Barret M, Cotter PD, O'Connor PM, Chen R, Morrissey JP, et al. Subtilomycin: a new lantibiotic from *Bacillus subtilis* strain MMA7 isolated from the marine sponge *Haliclona simulans*. Mar Drugs. 2013;11(6):1878–98. https://doi.org/10.3390/md11061878.
76. Thennarasu S, Lee DK, Poon A, Kawulka KE, Vederas JC, Ramamoorthy A. Membrane permeabilization, orientation, and antimicrobial mechanism of subtilosin A. Chem Phys Lipids. 2005;137(1–2):38–51. https://doi.org/10.1016/j.chemphyslip.2005.06.003.
77. Algburi A, Zehm S, Netrebov V, Bren AB, Chistyakov V, Chikindas ML. Subtilosin prevents biofilm formation by inhibiting bacterial quorum sensing. Probiotics Antimicrob Proteins. 2017;9(1):81–90. https://doi.org/10.1007/s12602-016-9242-x.
78. Favret ME, Yousten AA. Thuricin: the bacteriocin produced by *Bacillus thuringiensis*. J Invertebr Pathol. 1989;53(2):206–16. https://doi.org/10.1016/0022-2011(89)90009-8.
79. Mo T, Ji X, Yuan W, Mandalapu D, Wang F, Zhong Y, et al. Thuricin Z: a narrow-spectrum sactibiotic that targets the cell membrane. Angew Chem Int Ed Engl. 2019;58(52):18793–7. https://doi.org/10.1002/anie.201908490.
80. Wang G, Feng G, Snyder AB, Manns DC, Churey JJ, Worobo RW. Bactericidal thurincin H causes unique morphological changes in *Bacillus cereus* F4552 without affecting membrane permeability. FEMS Microbiol Lett. 2014;357(1):69–76. https://doi.org/10.1111/1574-6968.12486.
81. Shoji J, Hinoo H, Wakisaka Y, Koizumi K, Mayama M. Isolation of three new antibiotics, thiocillins I, II and III, related to micrococcin P. Studies on antibiotics from the genus *Bacillus*. VIII. J Antibiot. 1976;29(4):366–74. https://doi.org/10.7164/antibiotics.29.366.
82. Siewert G, Strominger JL. Bacitracin: an inhibitor of the dephosphorylation of lipid pyrophosphate, an intermediate in the biosynthesis of the peptidoglycan of bacterial cell walls. Proc Natl Acad Sci USA. 1967;57(3):767–73. https://doi.org/10.1073/pnas.57.3.767.
83. McLeod C. Circulin, an antibiotic from a member of the *Bacillus circulans* Group: I. Bacteriological Studies J Bacteriol. 1948;56(6):749–54.
84. Howell SF. Polypeptin, an antibiotic from a member of the *Bacillus circulans* group. II. Purification, crystallization, and properties of polypeptin. J Biol Chem. 1950;186(2):863–77.
85. Storm DR, Rosenthal KS, Swanson PE. Polymyxin and related peptide antibiotics. Annu Rev Biochem. 1977;46:723–63. https://doi.org/10.1146/annurev.bi.46.070177.003451.
86. Shoji J, Sakazaki R, Wakisaka Y, Koizumi K, Matsuura S, Miwa H, et al. Isolation of octapeptin D (studies on antibiotics from the genus *Bacillus*. *XXVII*). J Antibiot. 1980;33(2):182–5. https://doi.org/10.7164/antibiotics.33.182.
87. Velkov T, Gallardo-Godoy A, Swarbrick JD, Blaskovich MAT, Elliott AG, Han M, et al. Structure, function, and biosynthetic origin of octapeptin antibiotics active against extensively drug-resistant gram-negative bacteria. Cell Chem Biol. 2018;25(4):380–91e5. https://doi.org/10.1016/j.chembiol.2018.01.005.
88. Tareq FS, Shin HJ. Bacilotetrins A and B, anti-staphylococcal cyclic-lipotetrapeptides from a marine-derived *Bacillus subtilis*. J Nat Prod. 2017;80(11):2889–92. https://doi.org/10.1021/acs.jnatprod.7b00356.
89. Luo C, Liu X, Zhou X, Guo J, Truong J, Wang X, et al. Unusual biosynthesis and structure of locillomycins from *Bacillus subtilis* 916. Appl Environ Microbiol. 2015;81(19):6601–9. https://doi.org/10.1128/AEM.01639-15.
90. Peypoux F, Besson F, Michel G, Lenzen C, Dierickx L, Delcambe L. Characterization of a new antibiotic of iturin group: bacillomycin D. J Antibiot. 1980;33(10):1146–9. https://doi.org/10.7164/antibiotics.33.1146.
91. Wu T, Chen M, Zhou L, Lu F, Bie X, Lu Z. Bacillomycin D effectively controls growth of *Malassezia globosa* by disrupting the cell membrane. Appl Microbiol Biotechnol. 2020;104(8):3529–40. https://doi.org/10.1007/s00253-020-10462-w.
92. Besson F, Peypoux F, Michel G. Action of mycosubtilin and of bacillomycin L on *Micrococcus luteus* cells and protoplasts: influence of the polarity of the antibiotics upon their action on the bacterial cytoplasmic membrane. FEBS Lett. 1978;90(1):36–40. https://doi.org/10.1016/0014-5793(78)80292-0.
93. Maget-Dana R, Peypoux F. Iturins, a special class of pore-forming lipopeptides: biological and physicochemical properties. Toxicology. 1994;87:151–74. https://doi.org/10.1016/0300-483x(94)90159-7.
94. Peypoux F, Besson F, Michel G, Delcambe L. Preparation and antibacterial activity upon *Micrococcus luteus* of derivatives of iturin A, mycosubtilin and bacillomycin L, antibiotics from Bacillus subtilis. J Antibiot. 1979;32(2):136–40. https://doi.org/10.7164/antibiotics.32.136.
95. Liu Y, Ding S, Dietrich R, Martlbauer E, Zhu K. A biosurfactant-inspired heptapeptide with improved specificity to kill MRSA. Angew Chem Int Ed Engl. 2017;56(6):1486–90. https://doi.org/10.1002/anie.201609277.
96. Coronel JR, Marques A, Manresa A, Aranda FJ, Teruel JA, Ortiz A. Interaction of the lipopeptide biosurfactant lichenysin with phosphatidylcholine model membranes. Langmuir. 2017;33(38):9997–10005. https://doi.org/10.1021/acs.langmuir.7b01827.
97. Coronel-Leon J, Marques AM, Bastida J, Manresa A. Optimizing the production of the biosurfactant lichenysin and its application in biofilm control. J Appl Microbiol. 2016;120(1):99–111. https://doi.org/10.1111/jam.12992.
98. Naruse N, Tenmyo O, Kobaru S, Kamei H, Miyaki T, Konishi M, et al. Pumilacidin, a complex of new antiviral antibiotics. Production, isolation, chemical properties, structure and biological activity. J Antibiot. 1990;43(3):267–80. https://doi.org/10.7164/antibiotics.43.267.
99. Saggese A, Culurciello R, Casillo A, Corsaro MM, Ricca E, Baccigalupi L. A marine isolate of *Bacillus pumilus* secretes a pumilacidin active against staphylococcus aureus. Mar Drugs. 2018;16(6):180. https://doi.org/10.3390/md16060180.
100. Liu J, Li W, Zhu X, Zhao H, Lu Y, Zhang C, et al. Surfactin effectively inhibits *Staphylococcus aureus* adhesion and biofilm formation on surfaces. Appl Microbiol Biotechnol. 2019;103(11):4565–74. https://doi.org/10.1007/s00253-019-09808-w.
101. Chen X, Lu Y, Shan M, Zhao H, Lu Z, Lu Y. A mini-review: mechanism of antimicrobial action and application of surfactin. World J Microbiol Biotechnol. 2022;38(8):143. https://doi.org/10.1007/s11274-022-03323-3.
102. Deleu M, Paquot M, Nylander T. Effect of fengycin, a lipopeptide produced by *Bacillus subtilis*, on model biomembranes. Biophys J. 2008;94(7):2667–79. https://doi.org/10.1529/biophysj.107.114090.
103. Ongena M, Jacques P, Touré Y, Destain J, Jabrane A, Thonart P. Involvement of fengycin-type lipopeptides in the multifaceted biocontrol potential of *Bacillus subtilis*. Appl Microbiol Biotechnol. 2005;69(1):29–38. https://doi.org/10.1007/s00253-005-1940-3.
104. Yu WB, Yin CY, Zhou Y, Ye BC. Prediction of the mechanism of action of fusaricidin on *Bacillus subtilis*. PLoS ONE. 2012;7(11):e50003. https://doi.org/10.1371/journal.pone.0050003.

105. Kajimura Y, Kaneda M, Fusaricidins B, C and D, new depsipeptide antibiotics produced by *Bacillus polymyxa* KT-8: isolation, structure elucidation and biological activity. J Antibiot. 1997;50(3):220–8.
106. Barsby T, Kelly MT, Gagné SM, Andersen RJ. Bogorol A produced in culture by a marine *Bacillus* sp. reveals a novel template for cationic peptide antibiotics. Org Lett. 2001;3(3):4. https://doi.org/10.1021/ol006942q.
107. Shoji J, Hinoo H, Wakisaka Y, Koizumi K, Mayama M. Isolation of two new related peptide antibiotics, cerexins A and B (studies on antibiotics from the genus *Bacillus*. I). J Antibiot. 1975;28(1):56–9. https://doi.org/10.7164/antibiotics.28.56.
108. Tareq FS, Lee MA, Lee HS, Lee YJ, Lee JS, Hasan CM, et al. Non-cytotoxic antifungal agents: isolation and structures of gageopeptides A-D from a *Bacillus* strain 109GGC020. J Agric Food Chem. 2014;62(24):5565–72. https://doi.org/10.1021/jf502436r.
109. Tareq FS, Lee MA, Lee HS, Lee JS, Lee YJ, Shin HJ. Gageostatins A-C, antimicrobial linear lipopeptides from a marine *Bacillus subtilis*. Mar Drugs. 2014;12(2):871–85. https://doi.org/10.3390/md12020871.
110. Tareq FS, Lee MA, Lee SH, Lee YJ, Lee JS, Hasan CM, et al. Gageotetrins A-C, noncytotoxic antimicrobial linear lipopeptides from a marine bacterium *Bacillus subtilis*. Org Lett. 2014;16(3):29. https://doi.org/10.1021/ol403657r.
111. Bann SJ, Ballantine RD, Cochrane SA. The tridecaptins: non-ribosomal peptides that selectively target Gram-negative bacteria. RSC Med Chem. 2021;12(4):538–51. https://doi.org/10.1039/d0md00413h.
112. Silo-Suh LA, Stabb EV, Raffel SJ, Handelsman J. Target range of zwittermicin A, an aminopolyol antibiotic from *Bacillus cereus*. Curr Microbiol. 1998;37(1):6–11. https://doi.org/10.1007/s002849900328.
113. Foster JW, Woodruff HB. Bacillin, a new antibiotic substance from a soil isolate of *Bacillus subtilis*. J Bacteriol. 1946;51:363–9. https://doi.org/10.1128/JB.51.3.363-369.1946.
114. Wu L, Wu H, Chen L, Yu X, Borriss R, Gao X. Difficidin and bacilysin from *Bacillus amyloliquefaciens* FZB42 have antibacterial activity against *Xanthomonas oryzae* rice pathogens. Sci Rep. 2015;5:12975. https://doi.org/10.1038/srep12975.
115. Gao XY, Liu Y, Miao LL, Li EW, Hou TT, Liu ZP. Mechanism of anti-Vibrio activity of marine probiotic strain *Bacillus pumilus* H2, and characterization of the active substance. AMB Express. 2017;7(1):23. https://doi.org/10.1186/s13568-017-0323-3.
116. Muller S, Strack SN, Hoefler BC, Straight PD, Kearns DB, Kirby JR. Bacillaene and sporulation protect *Bacillus subtilis* from predation by *Myxococcus xanthus*. Appl Environ Microbiol. 2014;80(18):5603–10. https://doi.org/10.1128/AEM.01621-14.
117. Podnar E, Erega A, Danevcic T, Kovacec E, Lories B, Steenackers H, et al. Nutrient availability and biofilm polysaccharide shape the bacillaene-dependent antagonism of *Bacillus subtilis* against *Salmonella* typhimurium. Microbiol Spectr. 2022;10(6):e0183622. https://doi.org/10.1128/spectrum.01836-22.
118. Kim DH, Kim HK, Kim KM, Kim CK, Jeong MH, Ko CY, et al. Antibacterial activities of macrolactin A and 7-O-succinyl macrolactin A from *Bacillus polyfermenticus* KJS-2 against vancomycin-resistant enterococci and methicillin-resistant *Staphylococcus aureus*. Arch Pharm Res. 2011;34(1):147–52. https://doi.org/10.1007/s12272-011-0117-0.
119. Yuan J, Zhao M, Li R, Huang Q, Rensing C, Raza W, et al. Antibacterial compounds-macrolactin alters the soil bacterial community and abundance of the gene encoding PKS. Front Microbiol. 2016;7:1904. https://doi.org/10.3389/fmicb.2016.01904.
120. Petchiappan A, Chatterji D. Antibiotic resistance: current perspectives. ACS Omega. 2017;2(10):7400–9. https://doi.org/10.1021/acsomega.7b01368.
121. Montalbán-López M, Sánchez-Hidalgo M, Valdivia E, Martínez-Bueno M, Maqueda M. Are bacteriocins underexploited? Novel applications for old antimicrobials. Curr Pharm Biotechnol. 2011;12(8):1205–20. https://doi.org/10.2174/138920111796117364.
122. Winn M, Fyans JK, Zhuo Y, Micklefield J. Recent advances in engineering nonribosomal peptide assembly lines. Nat Prod Rep. 2016;33(2):317–47. https://doi.org/10.1039/c5np00099h.
123. Bleich R, Watrous JD, Dorrestein PC, Bowers AA, Shank EA. Thiopeptide antibiotics stimulate biofilm formation in *Bacillus subtilis*. Proc Natl Acad Sci USA. 2015;112(10):3086–91. https://doi.org/10.1073/pnas.1414272112.
124. Le Marrec C, Hyronimus B, Bressollier P, Verneuil B, Urdaci MC. Biochemical and genetic characterization of coagulin, a new antilisterial bacteriocin in the pediocin family of bacteriocins, produced by *Bacillus coagulans* I(4). Appl Environ Microbiol. 2000;66(12):5213–20. https://doi.org/10.1128/AEM.66.12.5213-5220.2000.
125. Gotze S, Stallforth P. Structure elucidation of bacterial nonribosomal lipopeptides. Org Biomol Chem. 2020;18(9):1710–27. https://doi.org/10.1039/c9ob02539a.
126. Pitt ME, Cao MD, Butler MS, Ramu S, Ganesamoorthy D, Blaskovich MAT, et al. Octapeptin C4 and polymyxin resistance occur via distinct pathways in an epidemic XDR *Klebsiella pneumoniae* ST258 isolate. J Antimicrob Chemother. 2019;74(3):582–93. https://doi.org/10.1093/jac/dky458.
127. Andric S, Rigolet A, Arguelles Arias A, Steels S, Hoff G, Balleux G, et al. Plant-associated *Bacillus* mobilizes its secondary metabolites upon perception of the siderophore pyochelin produced by a *Pseudomonas* competitor. ISME J. 2023;17(2):263–75. https://doi.org/10.1038/s41396-022-01337-1.
128. Madslien EH, Rønning HT, Lindbäck T, Hassel B, Andersson MA, Granum PE. Lichenysin is produced by most *Bacillus licheniformis* strains. J Appl Microbiol. 2013;115(4):1068–80. https://doi.org/10.1111/jam.12299.
129. Hamley IW. Lipopeptides: from self-assembly to bioactivity. Chem Commun. 2015;51(41):8574–83. https://doi.org/10.1039/c5cc01535a.
130. Erega A, Stefanic P, Danevcic T, Smole Mozina S, Mandic Mulec I. Impact of *Bacillus subtilis* antibiotic bacilysin and *Campylobacter jejuni* efflux pumps on pathogen survival in mixed biofilms. Microbiol Spectr. 2022;10(4):e0215622. https://doi.org/10.1128/spectrum.02156-22.
131. Chevrette MG, Thomas CS, Hurley A, Rosario-Melendez N, Sankaran K, Tu Y, et al. Microbiome composition modulates secondary metabolism in a multispecies bacterial community. Proc Natl Acad Sci USA. 2022;119(42):e2212930119. https://doi.org/10.1073/pnas.2212930119.
132. Baranova MN, Kudzhaev AM, Mokrushina YA, Babenko VV, Kornienko MA, Malakhova MV, et al. Deep functional profiling of wild animal microbiomes reveals probiotic *Bacillus pumilus* strains with a common biosynthetic fingerprint. Int J Mol Sci. 2022;23(3):1168. https://doi.org/10.3390/ijms23031168.
133. Im E, Choi YJ, Kim CH, Fiocchi C, Pothoulakis C, Rhee SH. The angiogenic effect of probiotic *Bacillus polyfermenticus* on human intestinal microvascular endothelial cells is mediated by IL-8. Am J Physiol Gastrointest Liver Physiol. 2009;297(5):G999–G1008. https://doi.org/10.1152/ajpgi.00204.2009.
134. Müller M, Fink K, Geisel J, Kahl F, Jilge B, Reimann J, et al. Intestinal colonization of IL-2 deficient mice with non-colitogenic *B. vulgatus* prevents DC maturation and T-cell polarization. PloS ONE. 2008;3(6):e2376. https://doi.org/10.1371/journal.pone.0002376.
135. Guo M, Wu F, Hao G, Qi Q, Li R, Li N, et al. *Bacillus subtilis* improves immunity and disease resistance in rabbits. Front Immunol. 2017;8:354. https://doi.org/10.3389/fimmu.2017.00354.
136. Peng M, Liu J, Liang Z. Probiotic *Bacillus subtilis* CW14 reduces disruption of the epithelial barrier and toxicity of ochratoxin A to Caco-2 cells. Food Chem Toxicol. 2019;126:25–33. https://doi.org/10.1016/j.fct.2019.02.009.
137. Liu Z, Jiang Z, Zhang Z, Liu T, Fan Y, Liu T, et al. *Bacillus coagulans* in combination with chitooligosaccharides regulates gut microbiota and ameliorates the DSS-induced colitis in mice. Microbiol Spectr. 2022;10(4):e0064122. https://doi.org/10.1128/spectrum.00641-22.
138. Wang N, Gao J, Yuan L, Jin Y, He G. Metabolomics profiling during biofilm development of *Bacillus licheniformis* isolated from milk powder. Int J Food Microbiol. 2021;337:108939. https://doi.org/10.1016/j.ijfoodmicro.2020.108939.
139. Gao Y, Li D, Tian Z, Hou L, Gao J, Fan B, et al. Metabolomics analysis of soymilk fermented by *Bacillus subtilis* BSNK-5 based on UHPLC-Triple-TOF-MS/MS. LWT. 2022;160:113311. https://doi.org/10.1016/j.lwt.2022.113311.
140. Krautkramer KA, Fan J, Backhed F. Gut microbial metabolites as multikingdom intermediates. Nat Rev Microbiol. 2021;19(2):77–94. https://doi.org/10.1038/s41579-020-0438-4.
141. Pujo J, Petitfils C, Le Faouder P, Eeckhaut V, Payros G, Maurel S, et al. Bacteria-derived long chain fatty acid exhibits anti-inflammatory properties in colitis. Gut. 2021;70(6):1088–97. https://doi.org/10.1136/gutjnl-2020-321173.

142. Nogal A, Valdes AM, Menni C. The role of short-chain fatty acids in the interplay between gut microbiota and diet in cardio-metabolic health. Gut Microbes. 2021;13(1):1–24. https://doi.org/10.1080/19490976.2021.1897212.
143. Jacobson A, Lam L, Rajendram M, Tamburini F, Honeycutt J, Pham T, et al. A gut commensal-produced metabolite mediates colonization resistance to *Salmonella* infection. Cell Host Microbe. 2019;24:20. https://doi.org/10.1016/j.chom.2018.07.002.
144. Jeong S, Lee Y, Yun CH, Park OJ, Han SH. Propionate, together with triple antibiotics, inhibits the growth of *Enterococci*. J Microbiol. 2019;57(11):1019–24. https://doi.org/10.1007/s12275-019-9434-7.
145. Sorbara MT, Dubin K, Littmann ER, Moody TU, Fontana E, Seok R, et al. Inhibiting antibiotic-resistant Enterobacteriaceae by microbiota-mediated intracellular acidification. J Exp Med. 2019;216(1):84–98. https://doi.org/10.1084/jem.20181639.
146. Roe AJ, McLaggan D, Davidson I, O'Byrne C, Booth IR. Perturbation of anion balance during inhibition of growth of *Escherichia coli* by weak acids. J Bacteriol. 1998;180(4):767–72. https://doi.org/10.1128/JB.180.4.767-772.1998.
147. Russell JB, Diez-Gonzalez F. The effects of fermentation acids on bacterial growth. Adv Microb Physiol. 1998;39:205.
148. Venegas DP, De la Fuente MK, Landskron G, Gonzalez MJ, Quera R, Dijkstra G, et al. Short Chain Fatty Acids (SCFAs)-mediated gut epithelial and immune regulation and its relevance for inflammatory bowel diseases. Front Immunol. 2019;10:277. https://doi.org/10.3389/fimmu.2019.00277.
149. Ratajczak W, Ryl A, Mizerski A, Walczakiewicz K, Sipak O, Laszczynska M. Immunomodulatory potential of gut microbiome-derived short-chain fatty acids (SCFAs). Acta Biochim Pol. 2019;66(1):1–12. https://doi.org/10.18388/abp.2018_2648.
150. Smith PM, Howitt MR, Panikov N, Michaud M, Gallini CA, Bohlooly YM, et al. The microbial metabolites, short-chain fatty acids, regulate colonic Treg cell homeostasis. Science. 2013;341(6145):569–73. https://doi.org/10.1126/science.1241165.
151. Vinolo MA, Rodrigues HG, Nachbar RT, Curi R. Regulation of inflammation by short chain fatty acids. Nutrients. 2011;3(10):858–76. https://doi.org/10.3390/nu3100858.
152. Morita N, Umemoto E, Fujita S, Hayashi A, Kikuta J, Kimura I, et al. GPR31-dependent dendrite protrusion of intestinal CX3CR1 cells by bacterial metabolites. Nature. 2019;566(7742):110–4. https://doi.org/10.1038/s41586-019-0884-1.
153. Lee Y, Yoshitsugu R, Kikuchi K, Joe GH, Tsuji M, Nose T, et al. Combination of soya pulp and *Bacillus coagulans* lilac-01 improves intestinal bile acid metabolism without impairing the effects of prebiotics in rats fed a cholic acid-supplemented diet. Br J Nutr. 2016;116(4):603–10. https://doi.org/10.1017/s0007114516002270.
154. Calvigioni M, Bertolini A, Codini S, Mazzantini D, Panattoni A, Massimino M, et al. HPLC-MS-MS quantification of short-chain fatty acids actively secreted by probiotic strains. Front Microbiol. 2023;14:1124144. https://doi.org/10.3389/fmicb.2023.1124144.
155. Santos JEA, de Brito MV, Pimenta ATA, da Silva GS, Zocolo GJ, Muniz CR, et al. Antagonism of volatile organic compounds of the *Bacillus* sp. against *Fusarium kalimantanense*. World J Microbiol Biotechnol. 2022;39(2):60. https://doi.org/10.1007/s11274-022-03509-9.
156. Chen Y, Gozzi K, Yan F, Chai Y. Acetic acid acts as a volatile signal to stimulate bacterial Biofilm formation. mBio. 2015;6(3):e00392. https://doi.org/10.1128/mBio.00392-15.
157. Bai L, Gao M, Cheng X, Kang G, Cao X, Huang H. Engineered butyrate-producing bacteria prevents high fat diet-induced obesity in mice. Microb Cell Fact. 2020;19(1):94. https://doi.org/10.1186/s12934-020-01350-z.
158. Shao J, Li S, Zhang N, Cui X, Zhou X, Zhang G, et al. Analysis and cloning of the synthetic pathway of the phytohormone indole-3-acetic acid in the plant-beneficial *Bacillus amyloliquefaciens* SQR9. Microb Cell Fact. 2015;14:130. https://doi.org/10.1186/s12934-015-0323-4.
159. Gao T, Wong Y, Ng C, Ho K. L-lactic acid production by *Bacillus subtilis* MUR1. Bioresour Technol. 2012;121:105–10. https://doi.org/10.1016/j.biortech.2012.06.108.
160. El-Adawy M, El-Aziz MA, El-Shazly K, Ali NG, El-Magd MA. Dietary propionic acid enhances antibacterial and immunomodulatory effects of oxytetracycline on Nile tilapia, Oreochromis niloticus. Environ Sci Pollut Res Int. 2018;25(34):34200–11. https://doi.org/10.1007/s11356-018-3206-5.
161. Cibis KG, Gneipel A, Konig H. Isolation of acetic, propionic and butyric acid-forming bacteria from biogas plants. J Biotechnol. 2016;220:51–63. https://doi.org/10.1016/j.jbiotec.2016.01.008.
162. Bjerre K, Cantor MD, Norgaard JV, Poulsen HD, Blaabjerg K, Canibe N, et al. Development of *Bacillus subtilis* mutants to produce tryptophan in pigs. Biotechnol Lett. 2017;39(2):289–95. https://doi.org/10.1007/s10529-016-2245-6.
163. Han Y, Xu X, Wang J, Cai H, Li D, Zhang H, et al. Dietary *Bacillus licheniformis* shapes the foregut microbiota, improving nutrient digestibility and intestinal health in broiler chickens. Front Microbiol. 2023;14:1113072. https://doi.org/10.3389/fmicb.2023.1113072.
164. Huang Q, Liu H, Zhang J, Wang S, Liu F, Li C, et al. Production of extracellular amylase contributes to the colonization of *Bacillus cereus* 0–9 in wheat roots. BMC Microbiol. 2022;22(1):205. https://doi.org/10.1186/s12866-022-02618-7.
165. Wang J, Ni X, Wen B, Zhou Y, Liu L, Zeng Y, et al. *Bacillus* strains improve growth performance via enhancing digestive function and anti-disease ability in young and weaning rex rabbits. Appl Microbiol Biotechnol. 2020;104(10):4493–504. https://doi.org/10.1007/s00253-020-10536-9.
166. Senol M, Nadaroglu H, Dikbas N, Kotan R. Purification of Chitinase enzymes from *Bacillus subtilis* bacteria TV-125, investigation of kinetic properties and antifungal activity against *Fusarium culmorum*. Ann Clin Microbiol Antimicrob. 2014;13:35. https://doi.org/10.1186/s12941-014-0035-3.
167. Mahajan PM, Nayak S, Lele SS. Fibrinolytic enzyme from newly isolated marine bacterium *Bacillus subtilis* ICTF-1: media optimization, purification and characterization. J Biosci Bioeng. 2012;113(3):307–14. https://doi.org/10.1016/j.jbiosc.2011.10.023.
168. Palanichamy E, Repally A, Jha N, Venkatesan A. Haloalkaline Lipase from *Bacillus flexus* PU2 efficiently inhibits biofilm formation of aquatic pathogen *Vibrio parahaemolyticus*. Probiotics Antimicrob Proteins. 2022;14(4):664–74. https://doi.org/10.1007/s12602-022-09908-6.
169. Ghasemi S, Ahmadian G, Sadeghi M, Zeigler DR, Rahimian H, Ghandili S, et al. First report of a bifunctional chitinase/lysozyme produced by *Bacillus pumilus* SG2. Enzyme Microb Technol. 2011;48(3):225–31. https://doi.org/10.1016/j.enzmictec.2010.11.001.
170. Wei X, Luo M, Xie Y, Yang L, Li H, Xu L, et al. Strain screening, fermentation, separation, and encapsulation for production of nattokinase functional food. Appl Biochem Biotechnol. 2012;168(7):1753–64. https://doi.org/10.1007/s12010-012-9894-2.
171. Kim JY, Gum SN, Paik JK, Lim HH, Kim KC, Ogasawara K, et al. Effects of nattokinase on blood pressure: a randomized, controlled trial. Hypertens Res. 2008;31(8):1583–8. https://doi.org/10.1291/hypres.31.1583.
172. Zhang Z, Yang J, Xie P, Gao Y, Bai J, Zhang C, et al. Characterization of a thermostable phytase from *Bacillus licheniformis* WHU and further stabilization of the enzyme through disulfide bond engineering. Enzyme Microb Technol. 2020;142:109679. https://doi.org/10.1016/j.enzmictec.2020.109679.
173. Murugesan GR, Romero LF, Persia ME. Effects of protease, phytase and a *Bacillus* sp. direct-fed microbial on nutrient and energy digestibility, ileal brush border digestive enzyme activity and cecal short-chain fatty acid concentration in broiler chickens. PLoS One. 2014;9(7):e101888. https://doi.org/10.1371/journal.pone.0101888.
174. Ripert G, Racedo SM, Elie AM, Jacquot C, Bressollier P, Urdaci MC. Secreted compounds of the probiotic bacillus clausii strain O/C inhibit the cytotoxic effects induced by *Clostridium difficile* and *Bacillus cereus* toxins. Antimicrob Agents Chemother. 2016;60(6):3445–54. https://doi.org/10.1128/AAC.02815-15.
175. Park S, Lee JJ, Yang BM, Cho JH, Kim S, Kang J, et al. Dietary protease improves growth performance, nutrient digestibility, and intestinal morphology of weaned pigs. J Anim Sci Technol. 2020;62(1):21–30. https://doi.org/10.5187/jast.2020.62.1.21.
176. Bhaskar N, Sudeepa ES, Rashmi HN, Tamil SA. Partial purification and characterization of protease of *Bacillus proteolyticus* CFR3001 isolated from fish processing waste and its antibacterial activities. Bioresour Technol. 2007;98(14):2758–64. https://doi.org/10.1016/j.biortech.2006.09.033.
177. Di Luccia B, D'Apuzzo E, Varriale F, Baccigalupi L, Ricca E, Pollice A. *Bacillus megaterium* SF185 induces stress pathways and affects the cell

cycle distribution of human intestinal epithelial cells. Benef Microbes. 2016;7(4):609–20. https://doi.org/10.3920/BM2016.0020.
178. Esmaeilishirazifard E, Dariush A, Moschos SA, Keshavarz T. A novel antifungal property for the *Bacillus licheniformis* ComX pheromone and its possible role in inter-kingdom cross-talk. Appl Microbiol Biotechnol. 2018;102(12):5197–208. https://doi.org/10.1007/s00253-018-9004-7.
179. Chung KS, Shin JS, Lee JH, Park SE, Han HS, Rhee YK, et al. Protective effect of exopolysaccharide fraction from *Bacillus subtilis* against dextran sulfate sodium-induced colitis through maintenance of intestinal barrier and suppression of inflammatory responses. Int J Biol Macromol. 2021;178:363–72. https://doi.org/10.1016/j.ijbiomac.2021.02.186.
180. Cai G, Liu Y, Li X, Lu J. New levan-type exopolysaccharide from *Bacillus amyloliquefaciens* as an antiadhesive agent against enterotoxigenic *Escherichia coli*. J Agric Food Chem. 2019;67(28):8029–34. https://doi.org/10.1021/acs.jafc.9b03234.
181. Wu Y, Wang Y, Yang H, Li Q, Gong X, Zhang G, et al. Resident bacteria contribute to opportunistic infections of the respiratory tract. PLoS Pathog. 2021;17(3):e1009436. https://doi.org/10.1371/journal.ppat.1009436.
182. McReynolds M, Chellappa K, Chiles E, Jankowski C, Shen Y, Chen L, et al. NAD^+ flux is maintained in aged mice. 2020. https://doi.org/10.21203/rs.3.rs-86538/v1.
183. Ginsberg D, Bachrach U, Keynan A. Spermidine levels and its relationship to DNA synthesis in outgrowing spores and vegetative cells of *Bacillus subtilis*. FEBS Lett. 1982;137(2):181–5. https://doi.org/10.1016/0014-5793(82)80344-x.
184. Ma L, Ni Y, Wang Z, Tu W, Ni L, Zhuge F, et al. Spermidine improves gut barrier integrity and gut microbiota function in diet-induced obese mice. Gut Microbes. 2020;12(1):1–19. https://doi.org/10.1080/19490976.2020.1832857.
185. Chandrasekaran M, Paramasivan M, Chun SC. *Bacillus subtilis* CBR05 induces Vitamin B6 biosynthesis in tomato through the de novo pathway in contributing disease resistance against *Xanthomonas campestris* pv. *vesicatoria*. Sci Rep. 2019;9(1):6495. https://doi.org/10.1038/s41598-019-41888-6.
186. Biedendieck R, Knuuti T, Moore SJ, Jahn D. The "beauty in the beast"-the multiple uses of *Priestia megaterium* in biotechnology. Appl Microbiol Biotechnol. 2021;105(14–15):5719–37. https://doi.org/10.1007/s00253-021-11424-6.
187. Ryan-Harshman M, Aldoori W. Vitamin B12 and health. Can Fam Physician. 2008;54(4):536–41.
188. Koshihara Y, Hoshi K, Shiraki M. Vitamin K2 (menatetrenone) inhibits prostaglandin synthesis in cultured human osteoblast-like periosteal cells by inhibiting prostaglandin H synthase activity. Biochem Pharmacol. 1993;46(8):1355–62.
189. Yamaguchi M, Taguchi H, Gao YH, Igarashi A, Tsukamoto Y. Effect of vitamin K2 (menaquinone-7) in fermented soybean (*natto*) on bone loss in ovariectomized rats. J Bone Miner Metab. 1999;17(1):23–9.
190. Guo S, Xv J, Li Y, Bi Y, Hou Y, Ding B. Interactive effects of dietary vitamin K(3) and *Bacillus subtilis* PB6 on the growth performance and tibia quality of broiler chickens with sex separate rearing. Animal. 2020:1–9. https://doi.org/10.1017/S1751731120000178.
191. Shivaramaiah S, Pumford NR, Morgan MJ, Wolfenden RE, Wolfenden AD, Torres-Rodríguez A, et al. Evaluation of *Bacillus* species as potential candidates for direct-fed microbials in commercial poultry. Poult Sci. 2011;90(7):1574–80. https://doi.org/10.3382/ps.2010-00745.
192. Ghasemi S, Ahmadian G, Sadeghi M, Zeigler DR, Rahimian H, Ghandili S, et al. First report of a bifunctional chitinase/lysozyme produced by *Bacillus pumilus* SG2. Enzyme Microbial Technol. 2011;48(3):225–31. https://doi.org/10.1016/j.enzmictec.2010.11.001.
193. Gu MJ, Song SK, Park SM, Lee IK, Yun CH. *Bacillus subtilis* protects porcine intestinal barrier from deoxynivalenol via improved zonula occludens-1 expression. Asian-Australas J Anim Sci. 2014;27(4):580–6. https://doi.org/10.5713/ajas.2013.13744.
194. Hosoi T, Ametani A, Kiuchi K, Kaminogawa S. Improved growth and viability of lactobacilli in the presence of *Bacillus subtilis* (*natto*), catalase, or subtilisin. Can J Microbiol. 2000;46(10):892–7. https://doi.org/10.1139/w00-070.
195. Alamri S, Hashem M, Mostafa Y. *In vitro* and *in vivo* biocontrol of soilborne phytopathogenic fungi by certain bioagents and their possible mode of action. Biocontrol Sci. 2012;17(4):155–67. https://doi.org/10.4265/bio.17.155.
196. Fujiya M, Musch MW, Nakagawa Y, Hu S, Alverdy J, Kohgo Y, et al. The *Bacillus subtilis* quorum-sensing molecule CSF contributes to intestinal homeostasis via OCTN2, a host cell membrane transporter. Cell Host Microbe. 2007;1(4):299–308. https://doi.org/10.1016/j.chom.2007.05.004.
197. Ibáñez de Aldecoa AL, Zafra O, González-Pastor JE. Mechanisms and regulation of extracellular DNA release and its biological roles in microbial communities. Front Microbiol. 2017;8:1390.
198. Santos VSV, Silveira E, Pereira BB. Toxicity and applications of surfactin for health and environmental biotechnology. J Toxicol Environ Health B Crit Rev. 2018;21(6–8):382–99.
199. Schneider KB, Palmer TM, Grossman AD. Characterization of *comQ* and *comX*, two genes required for production of ComX pheromone in *Bacillus subtilis*. J Bacteriol. 2002;184:410–19.
200. Vogel K, Blümer N, Korthals M, Mittelstädt J, Garn H, Ege M, et al. Animal shed *Bacillus licheniformis* spores possess allergy-protective as well as inflammatory properties. J Allergy Clin Immunol. 2008;122(2):307–12. e8. https://doi.org/10.1016/j.jaci.2008.05.016.
201. Magnusdottir S, Ravcheev D, de Crecy-Lagard V, Thiele I. Systematic genome assessment of B-vitamin biosynthesis suggests co-operation among gut microbes. Front Genet. 2015;6:148. https://doi.org/10.3389/fgene.2015.00148.
202. Raux E, Lanois A, Warren MJ, Rambach A, Thermes C. Cobalamin (vitamin B12) biosynthesis: identification and characterization of a *Bacillus* megaterium cobI operon. Biochem J. 1998;335(1):159–66.
203. Ozols A, Smirnova G, Leont'Eva N. The regulatory mechanism of the activity of the saccharase-isomaltase complex of the brush border in rat enterocytes. Fiziologicheski Zhurnal Imeni Imsechenova. 1996;82(8–9):96.
204. Rosenberg J, Yeak KC. A two-step evolutionary process establishes a non-native vitamin B6 pathway in *Bacillus subtilis*. Environ Microbiol. 2018;20(1):156–68. https://doi.org/10.1111/1462-2920.13950.
205. Zhu J, Chen Y, Wu Y, Wang Y, Zhu K. Commensal bacteria contribute to the growth of multidrug-resistant *Avibacterium paragallinarum* in chickens. Front Microbiol. 2022;13:1010584. https://doi.org/10.3389/fmicb.2022.1010584.
206. Imai S, Guarente L. NAD+ and sirtuins in aging and disease. Trends Cell Biol. 2014;24(8):464–71. https://doi.org/10.1016/j.tcb.2014.04.002.
207. Jones SE, Paynich ML, Kearns DB, Knight KL. Protection from intestinal inflammation by bacterial exopolysaccharides. J Immunol. 2014;192(10):4813–20. https://doi.org/10.4049/jimmunol.1303369.
208. Carfrae LA, Brown ED. Nutrient stress is a target for new antibiotics. Trends Microbiol. 2023. https://doi.org/10.1016/j.tim.2023.01.002.
209. Caulier S, Nannan C, Gillis A, Licciardi F, Bragard C, Mahillon J. Overview of the antimicrobial compounds produced by members of the *Bacillus subtilis* group. Front Microbiol. 2019;10:302. https://doi.org/10.3389/fmicb.2019.00302.
210. Liu Y, Ding S, Shen J, Zhu K. Nonribosomal antibacterial peptides that target multidrug-resistant bacteria. Nat Prod Rep. 2019;36(4):573–92. https://doi.org/10.1039/c8np00031j.
211. Deehan EC, Yang C, Perez-Munoz ME, Nguyen NK, Cheng CC, Triador L, et al. Precision microbiome modulation with discrete dietary fiber structures directs short-chain fatty acid production. Cell Host Microbe. 2020;27(3):389–404 e6. https://doi.org/10.1016/j.chom.2020.01.006.
212. Araújo JR, Tazi A, Burlen-Defranoux O, Vichier-Guerre S, Nigro G, Licandro H, et al. Fermentation products of commensal bacteria alter enterocyte lipid metabolism. Cell Host Microbe. 2020;27(3):358–75.e7. https://doi.org/10.1016/j.chom.2020.01.028.
213. Huus KE, Bauer KC, Brown EM, Bozorgmehr T, Woodward SE, Serapio-Palacios A, et al. Commensal bacteria modulate immunoglobulin a binding in response to host nutrition. Cell Host Microbe. 2020;27(6):909–21 e5. https://doi.org/10.1016/j.chom.2020.03.012.

214. Cui Y, Wang S, Ding S, Shen J, Zhu K. Toxins and mobile antimicrobial resistance genes in *Bacillus* probiotics constitute a potential risk for One Health. J Hazard Mater. 2020;382:121266. https://doi.org/10.1016/j.jhazmat.2019.121266.
215. Deng F, Chen Y, Sun T, Wu Y, Su Y, Liu C, et al. Antimicrobial resistance, virulence characteristics and genotypes of *Bacillus* spp. from probiotic products of diverse origins. Food Res Int. 2021;139:109949. https://doi.org/10.1016/j.foodres.2020.109949.

Publisher's Note