npj | biofilms and microbiomes

Review

Published in partnership with Nanyang Technological University

https://doi.org/10.1038/s41522-025-00713-x

Exploring the bioactive landscape: peptides and non-peptides from the human microbiota

Abdul Bari Shah[1,2], Hyeonjae Cho[1,2] & Sang Hee Shim[1] ✉

The human microbiota, consisting of trillions of bacteria from six main phyla, produces peptide and non-peptide secondary metabolites which have antibacterial properties vital to medicine and biotechnology. These metabolites influence biological processes linked to diseases, yet much remains unknown. This review explores their structures and functions, aiming to spur novel metabolite discovery and advance drug development.

The human body comprises distinct parts, each fulfilling specific functions in the body. The microbiota, which exists in large quantities, is a part of the body that inhabits various regions. Microbes are present in several organs throughout the body, including the gastrointestinal, reproductive, oral, and skin systems. They have distinct populations and play crucial roles in the functioning of these organs and overall biological processes. They affect various physiological systems in the body, including the neurological, endocrine, metabolic, and immune systems[1,2]. The human microbiota consists of not only bacteria but also yeasts and viruses, which inhabit specific organs. The bacteria mainly belong to the following phyla: Firmicutes, Bacteroidetes, Actinobacteria, Fusobacteria, Proteobacteria, and Verrucomicrobia. These bacteria encompass a diverse array of genera including commensal, mutualistic, or harmful species. Various factors, including nutrition, lifestyle, hormonal changes, heredity, and underlying diseases, can significantly alter the overall balance of the microbiota, leading to the development of numerous diseases[1]. The microbiota genome contains 150 times more genetic information than the total human genome, indicating that it is a vital organ in the human body[3]. Fungi and viruses are essential constituents of the human intestine[4]. The microbiota includes *Candida albicans*, a prevalent fungus passed from mother to infant after parturition. Although typically innocuous, it may contribute to the onset of inflammatory bowel disease. Fungi colonize various body sites, including the gastrointestinal tract, skin, respiratory tract, and genitourinary tract, where they play essential roles in host functions. Similarly, viral communities are crucial to the human microbiome, with plant-derived and large viruses frequently detected in the gut. Numerous studies have established correlations between fungal and viral species and the development of inflammatory and autoimmune disorders[5–7].

Recently, the microbiota has been shown to play a significant role in a multitude of diseases. For instance, recent research has established a connection between the microbiota of the gut and neurodegenerative diseases such as Alzheimer's disease. The microbes present in the gut have an effect on the functioning of the brain[8]. A potential correlation exists between vaginal/endometrial microbiota and reproductive success, underscoring the need of comprehending the genitourinary microbiota in assessing obstetric outcomes. A pilot investigation with 34 women receiving hormonal stimulation revealed a considerable disparity between vaginal and endometrial microbiota[9]. *Dysosmobacter welbionis* is a newly isolated human commensal bacterium that enhances host metabolism and represents a promising candidate for the development of next-generation beneficial bacteria targeting obesity and associated metabolic disorders[10]. Furthermore, scientists have coined the phrase "organ-gut-microbiota axis" to characterize the several directions in which the trillions of intestinal bacteria interact with other body organs[11]. A comprehensive understanding of the microbiota is essential for developing novel therapeutic and preventive strategies, highlighting the importance of advancing current and future microbiome research methodologies.

One element of the microbiota is the production of beneficial metabolites that play crucial roles in numerous disorders. Peptides derived from these bacteria are the main substances that exhibit high antibacterial activity and have been functioning in this capacity for many decades. Additionally, the bacteria release non-peptide metabolites that have significant implications for human health and related illnesses[12]. Current genomic and sequencing technologies make it easier to determine how different metabolites are produced, which play a vital role in the domain of human diseases. In genome mining, the major actors are the biosynthetic gene clusters (BGCs) that represent a clear picture of these metabolites. In addition, advanced computational techniques make it easier to predict their presence and role, making the drug discovery field very advanced. For example, sequence homology-based prediction approaches have been widely used in tools such as antiSMASH and PRISM4. Furthermore, machine learning-based approaches, such as those used in RiPPMiner and DeepRiPP, are currently employed for RiPP prediction[13–15]. In this review, we focus on metabolites isolated from the human microbiota and their biological

[1]Natural Products Research Institute, College of Pharmacy, Seoul National University, Seoul, Republic of Korea. [2]These authors contributed equally: Abdul Bari Shah, Hyeonjae Cho. ✉e-mail: sanghee_shim@snu.ac.kr

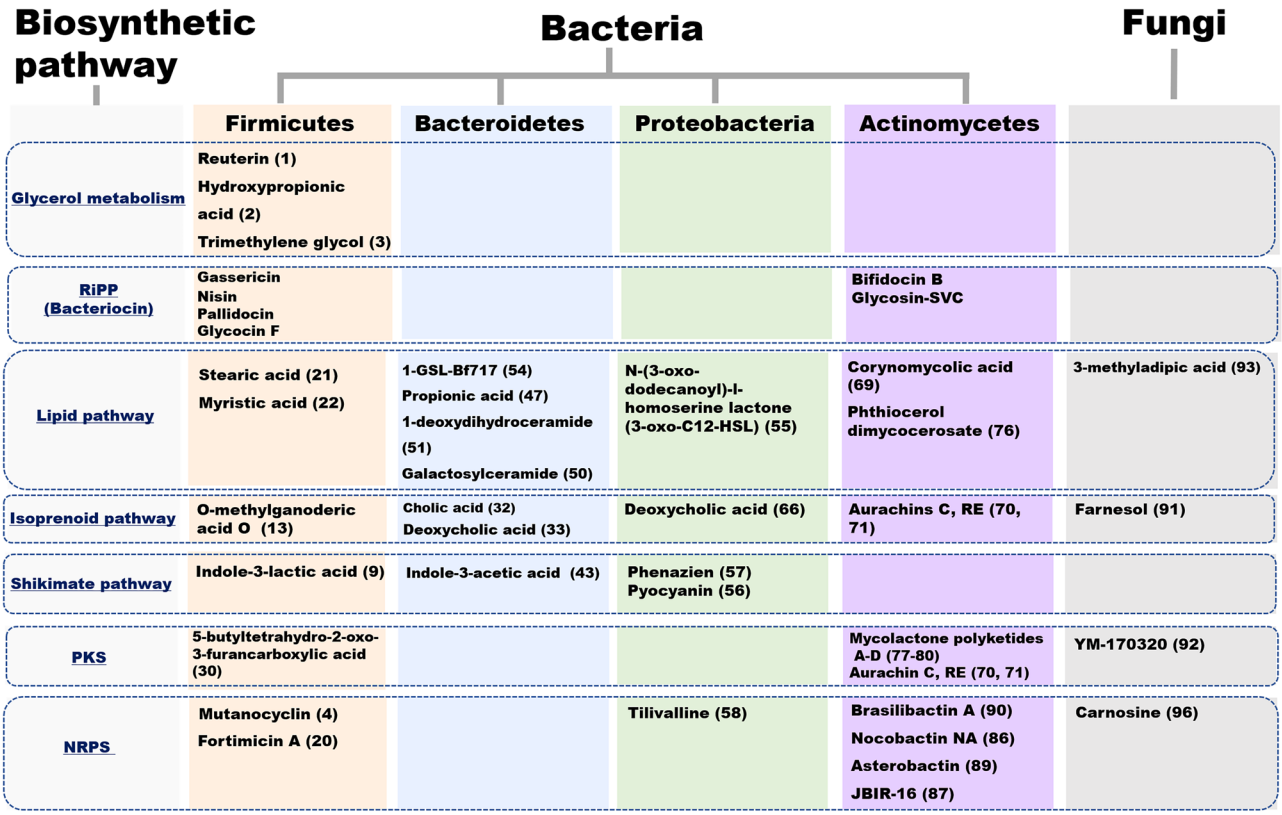

Fig. 1 | Clustering of human microbiome metabolites based on related biosynthetic pathways and phylum origins.

applications. Essential information was gathered from various scientific sources including Google Scholar, Web of Science, and PubMed. The structures in the figures were created using ChemDraw 22.2.0 and the remaining figure was created using https://app.biorender.com/.

Importance of metabolites from the human microbiota

Over the past decade, many sophisticated techniques such as metabolomics, genomic investigations, and culturomics have enabled the extensive investigation of human microbiota metabolites[16]. Antibiotics, which are antimicrobial metabolites, mostly originate from the human microbiota, either directly or indirectly. However, antibiotic use leading to antimicrobial resistance is a significant and urgent problem that must be addressed promptly. Failure to do so could lead to unmanageable and disastrous events in human history[17,18]. The metabolites produced by the human microbiota are emerging as essential elements in precision medicine, enabling personalized diagnostics and treatment approaches by illustrating how these bacteria influence human health and disease susceptibility. Key aspects of this evolving role include biomarker potential, insights into disease mechanisms, and individualized treatment strategies[19–21]. The following sections will explore the various microbiota-derived metabolites relevant to precision medicine.

We have extensively documented peptides derived from the human microbiota and their corresponding biological functions[22]. However, our previous study did not address the nonpeptide portion, which plays a crucial role in human health. Here, we provide a detailed exploration of these aspects. Non-peptide metabolites derived from the human microbiota mostly consist of the sphingolipid pathway, isoprenoid pathway, polyketides, and various other compounds[23]. Firmicutes primarily contribute to the synthesis of short-chain fatty acids (SCFAs), Bacteroidetes are responsible for the degradation of polysaccharides and the generation of SCFAs, and Actinobacteria play a role in the creation of vitamins and SCFAs. In addition, the peptide portion is discussed in terms of its chemistry. On the contrary, dysbiosis is a primary cause of microbiota imbalance, significantly affecting metabolite production and altering bacterial types and quantities. This results in changes to beneficial metabolites, such as SCFAs, while simultaneously increasing harmful metabolites that contribute to various diseases[24,25]. However, many species within the human microbiota remain underexplored in terms of metabolite production and isolation. This limited investigation is primarily due to the insufficient study of microbiota-derived metabolites. Most studies focus on non-human microbiota or fungi, with particular emphasis on individual plants. The human microbiota is highly diverse, including many uncultured species and numerous metabolite production pathways remain unexplored. Additionally, it is essential to employ various approaches, such as culture-independent methods, and to advance multi-omics technologies[26,27]. A simple representation of the metabolites from the human microbiota is shown in Fig. 1.

Different phyla within the human microbiota contributing to non-peptides

As mentioned previously, six principal phyla influence the metabolite makeup of the human microbiota (Table 1). Firmicutes and Bacteroidetes comprise approximately 90% of the human microbiome. Firmicutes have a greater impact on the metabolite profile than any other phyla. The *Firmicutes* genus encompasses multiple genera including *Bacillus*, *Lactobacillus*, *Clostridium*, *Ruminococcus*, *Enterococcus*, and *Staphylococcus*. In contrast, Bacteroidetes include species such as *Bacteroides*, *Odoribacter*, and *Alistipes*, which are the primary inhabitants of the gastrointestinal tract. Proteobacteria, which includes genera such as *Escherichia*, *Salmonella*, *Helicobacter*, and *Klebsiella*, are another important phylum. It contains many opportunistic pathogens and its imbalance is often linked to inflammation and various diseases[28]. Actinomycetota (formerly Actinobacteria) consists of beneficial genera such as *Bifidobacterium* and *Collinsella*. These microbes contribute to gut health and immunity, and some species are widely utilized as probiotics owing to their health-promoting effects[29]. A simple representation of the human microbiome and the niches from which they are derived is shown in Fig. 2.

Non-peptide metabolites from Firmicutes and their biological properties

Bacillus and Lactobacillus play a vital role in the human body by releasing many bioactive compounds, including lipopeptides, bacteriocins, and most importantly, polyketides. These genera serve as probiotics, resulting in many beneficial effects on the human body[30,31] (Table 2). Lactobacilli occupy the digestive system, oral cavity, and reproductive organs and contribute to metabolite profiles in the form of phenolic acids, carboxylic acids, hydrogen peroxide, and many others, displaying diverse ranges of biological activities[32,33]. *Lactobacillus reuteri* is a naturally occurring bacterium in the human gastrointestinal tract. It has numerous advantageous effects including the production of beneficial metabolites, combating harmful bacteria, maintaining a healthy balance of bacteria, enhancing the immune system, and functioning as a probiotic microorganism[33]. Reuterin (**1**), a growth inhibitor has been isolated from *L. reuteri* 1063 together with β-hydroxypropionicacid (**2**) and trimethylene glycol (**3**)[34]. The structures of the three compounds are shown in Fig. 3. Reuterin is a low-molecular-weight water-soluble molecule that contains both aldehyde and hydroxyl functional groups. It exhibits a wide range of antimicrobial effects and, in particular, does not affect normal bacteria present in the human microbiota, while targeting the harmful bacteria[35]. The effects of reuterin, also known as 3-hydroxypropionaldehyde, on *Escherichia coli* cells expressing a gene responsive to oxidative stress, were investigated. To demonstrate its involvement in oxidative stress, *E. coli* was genetically altered to modify OxyR. In addition, the antibacterial effect of reuterin was inhibited by adding cysteine to the growth media of *E. coli* and *Clostridium difficile*. The presence of *E. coli* prompts the development or release of reuterin by *L. reuteri*, suggesting a detrimental effect on numerous cellular targets[36]. The synergistic activity of reuterin against many foodborne pathogenic bacteria, including nisin, lacticin 481, and enterocin AS-48, results in improved antibacterial activity[37].

L. reuteri also results in the formation of another bioactive non-peptide metabolite called reutericyclin. The inhibitory activity of this compound has been observed across a wide range of bacteria, including the following Lactobacillus species: *Bacillus subtilis*, *B. cereus*, *Enterococcus faecalis*, *Staphylococcus aureus*, and *Listeria innocua*. Additionally, it is effective against a lipopolysaccharide-mutant strain of *E. coli*. The bactericidal activity of this compound has also been shown to be effective against *S. aureus*, *B. subtilis*, and *L. sanfranciscensis*[38]. This compound has also been reported in another Firmicute called *Streptococcus mutans*, which was able to produce mutanocyclin (**4**) and reutericyclins A–C (**5**–**7**), which display many biological functions, including biofilm inhibition, and acts on *Limosilactobacillus fermentum*[39]. *S. mutans* is a bacteria inherently found in the human oral microbiome and is a primary contributor to dental caries and cavities[40]. Mutanocyclin exhibits potent antifungal activity against *Candida albicans*. In these fungi, it modulates the activity of the PKA catabolic subunit Tpk2 and its binding partner Sfl1, resulting in increased resistance and sensitivity. The mutanocyclin response is influenced by three GPI-anchored proteins and filamentous regulators, indicating that transcriptional regulation and cell wall composition play roles in inhibiting filamentous growth. Both in vivo and in vitro experiments have confirmed the fungicidal properties of mutanocyclin[41]. Recently, a Lactobacillus genus was studied against the fungus *C. albicans*, in which the bioassay-guided isolation from

Table 1 | Different phyla within the human microbiota

Phylum	Major Genera	Notes
Firmicutes	*Bacillus* *Lactobacillus* *Clostridium* *Ruminococcus* *Enterococcus* *Staphylococcus*	- comprise 90% of the human microbiome with Bacteroidetes - the greatest impact on the metabolite profile
Bacteroidetes	*Bacteroides* *Odoribacter* *Alistipes*	- primary inhabitants of the gastrointestinal tract
Proteobacteria	*Escherichia* *Salmonella* *Helicobacter* *Klebsiella*	- includes many opportunistic pathogens - inflammation or disease caused by their imbalance
Actinomycetota	*Bifidobacterium* *Collinsella*	- contributes to gut health and immunity - some are probiotics

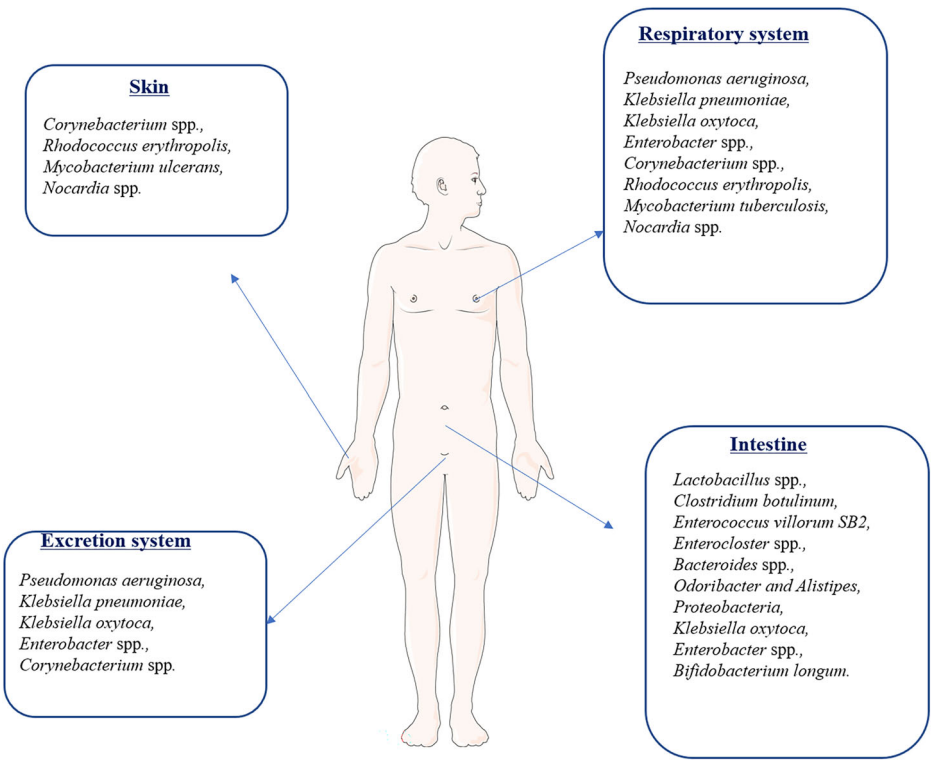

Fig. 2 | Different microorganisms derived from different niches in the human body (elements created using Servier Medical Art, licensed under CC BY 4.0).

Table 2 | Non-peptidyl metabolites from Firmicutes

Organism	Metabolites	Activity	Ref.
Lactobacillus reuteri	reuterin (**1**), β-hydroxypropionic acid (**2**), trimethylene glycol (**3**)	- wide range of antimicrobial effects	34
	reutericyclins A–C (**5**–**7**), mutanocyclin (**4**)	- broad-spectrum antibacterial; biofilm inhibition; antifungal activity against *Candida albicans*	39
Lactobacillus genus	1-acetyl-β-carboline (**8**)	- fungicidal activity against *Candida albicans*	42
Lactobacillus gallinarum	indole-3-lactic acid (**9**)	- reduction of intestinal tumor growth in mice models	43
Clostridium botulinum AIP981.10	clostridiolysin S, botulinolysin, phospholipase C, C3 exoenzyme	- role in inflammation, symbiosis, and association with gastrointestinal disorders	46,47
Enterococcus villorum SB2	hordatine B (**10**), quercetin 3-*O*-manoglucoside (**11**), hydroxycitraniaxanthin (**12**), *O*-methylganoderic acid O (**13**), thalicsessine (**14**), austinol (**15**), valdiate (**16**)	- antimicrobial	51
	5-hydroxykynurenamine (**17**), (2*S*,4 *R*)-4-(9H-pyrido[3,4-b]indol-1-yl)-1,2,4-butanetriol (**18**)	- indole derivatives	
	indoleacrylic acid (**19**), fortimicin A (**20**), $_{L}$-theanine (**27**), glycerol-1-propanoate (**29**)	- antimicrobial and gut health enhancement activities	
	stearic acid (**21**), myristic acid (**22**), p-mentha-1,3,5,8-tatraene (**23**), 6-hydroxypseudooxynicotine (**24**), $_{D/L}$-glycerol-1-phosphate (**25**), 4-β-D-glucan (**26**), 5-butyltetrahydro-2-oxo-3-furancarboxylic acid (**30**)	- fatty acids with potential bioactivities	
Enterocloster spp.	urolithin G (**31**)	- antioxidant and anti-inflammatory properties	53

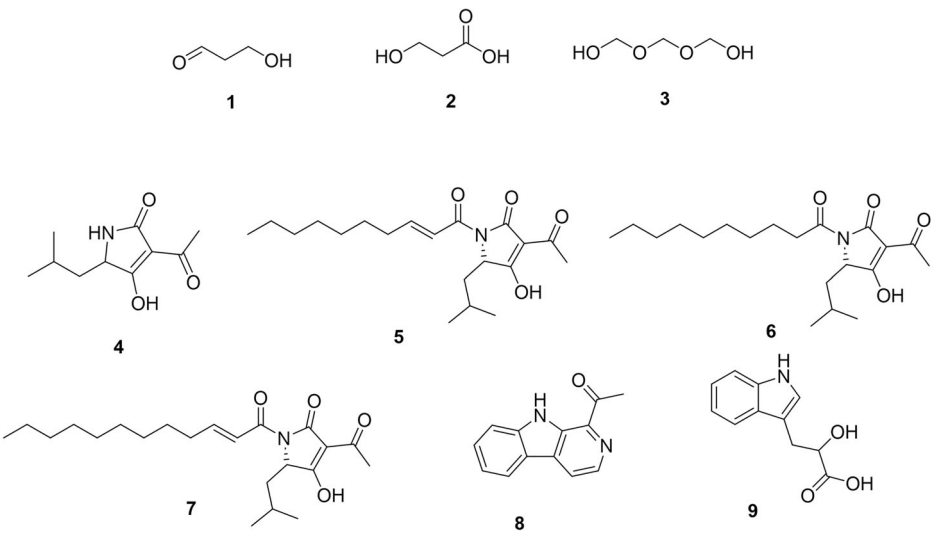

Fig. 3 | Structures of reuterin (**1**), β-hydroxypropionicacid (**2**), trimethylene glycol (**3**), mutanocyclin (**4**), reutericyclins A–C (**5**–**7**), 1-acetyl-β-carboline (**8**), and indole-3-lactic acid (**9**).

Lactobacillus resulted in 1-acetyl-β-carboline (**8**)[42]. Moreover, indole-3-lactic acid (**9**) has also been detected in *L. gallinarum*. This compound was used to decrease the quantity and growth of intestinal tumors in male and female mouse models of intestinal tumorigenesis in comparison with *E. coli* MG1655 and phosphate-buffered saline[43]. The structures of compounds (**4**–**9**) are shown in Fig. 3.

Clostridium is a well-known symbiotic bacterium that inhabits the gastrointestinal tract. It also plays a vital role in inflammation and allergies. Many disorders, such as botulism and tetanus, are caused by bacteria within this genus and are involved in diarrhea[44,45]. Typically, Clostridia produce toxins. Bouvet et al. conducted a case study on Clostridium, specifically focusing on the isolation of *Clostridium botulinum* AIP981.10 from a blood culture collected from a patient with a fatal infection. Remarkably, they observed that this strain could not generate fatal toxins. In addition to clostridiolysin S, it contains genes for botulinolysin, phospholipase C, and the C3 exoenzyme. Its genomic profile indicates a phylogenetic association between AIP981.10 and strains belonging to *Clostridium botulinum* group III. Furthermore, the genomic sequences of botulinolysin and phospholipase C exhibited notable similarity to those of *C. botulinum* C and D. However, they displayed a comparatively lower degree of homology with the genes of *C. novyi* and *C. haemolyticum*[46,47]. Another genus in the gastrointestinal tract that belongs to the lactic acid bacteria family is

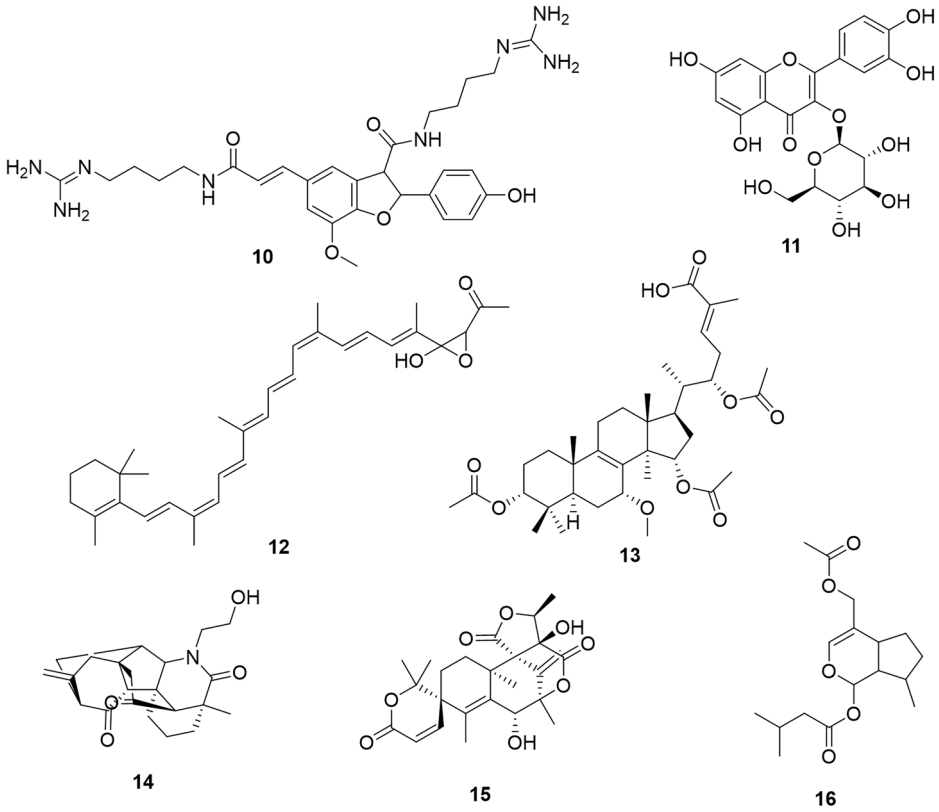

Fig. 4 | Structures of hordatine B (**10**), quercetin 3-O-manoglucoside (**11**), 7',8'-dihydro-8'-hydroxycitraniaxanthin (**12**), O-methylganoderic acid O (**13**), thalicsessine (**14**), austinol (**15**), and valdiate (**16**).

Enterococci[48,49]. Enterococci are a natural component of the human microbiota, often found in the lower gastrointestinal tract, mouth cavity, and vaginal tract. They are opportunistic pathogens capable of causing infections in individuals who are immunocompromised or have significant underlying health conditions[50]. *Enterococcus villorum SB2* isolated from the female reproductive system exhibited the occurrence of many metabolites including flavonoids (hordatine B (**10**), quercetin 3-O-manoglucoside (**11**)), terpenoids (7',8'-dihydro-8'-hydroxycitraniaxanthin (**12**), *O*-methylganoderic acid O (**13**), thalicsessine (**14**), urolithin G (**15**), and valdiate (**16**)), indole derivatives produced by tryptophan metabolism (5-hydroxykynurenamine (**17**), 2*S*,4*R*-4-(9H-pyrido[3,4-b]indol-1-yl)-1,2,4-butanetriol (**18**), and indoleacrylic acid (**19**)), antimicrobial compounds (fortimicin A (**20**)), fatty acids (stearic acid (**21**) and myristic acid (**22**)), p-mentha-1,3,5,8-tatraene (**23**), 6 hydroxypseudooxynicotine (**24**), DL-glycerol 1-phosphate (**25**), and 4-beta-D-glucan (**26**). Furthermore, many other metabolites have been reported, such as analogs of an amino acid to glutamate (L-theanine (**27**)), galactose, lactate, ketohexose deoxy sugar (L-fuculose (**28**)), acetylated glycerols (glycerol-1-propanoate (**29**)), and gutyrolactones (5-butyltetrahydro-2-oxo-3-furancarboxylic acid (**30**))[51]. Bhagwat et al. examined 13 strains of Enterococci derived from humans that produce significant enzymes such as amylase, protease, lipase, bile salt hydrolase, conjugated linoleic acid, and lactic acid. These findings suggest that starter cultures possess qualities that may be beneficial to the food and dairy industries. Biogenic amines such as arginine and tryptamine were also synthesized by these strains[52].

In addition, a new urolithin derived from urolithin D was discovered and thoroughly analyzed. Urolithin G (3,4,8-trihydroxy urolithin) (**31**), derived from urolithin D by in vitro incubation with various human gut Enterocloster species, was detected in the feces of 12% of overweight participants following the use of a pomegranate extract rich in ellagitannins. Urolithin G is distinguished by the presence of a catechol group in ring A and a solitary hydroxyl group in ring B, a distinctive characteristic that is absent in both human and animal samples[53]. The structures of (**10**–**31**) are shown in Figs. 4 and 5.

Non-peptides from Bacteroidetes and their biological activities

Bacteroidaceae, along with Firmicutes, are crucial because of their increased prevalence compared to other phyla. This phylum is primarily involved in the process of metabolizing polysaccharides[54]. Their contribution to the bioactive compound profile is lower than that of Firmicutes. However, certain genera produce compounds that are described in Table 3.

Bacteroides fragilis is a bacterial species commonly found in the human colon, where it plays a crucial role in gut microbiota and contributes to overall health maintenance. It produces cholic acid (**32**) and deoxycholic acid (**33**)[55] and exhibits antibacterial properties. However, it can also act as an opportunistic pathogen, potentially causing infections[56]. Numerous species i.e., *B. ovatus, B. eggerthii, B. fragilis, B. thetaiotaomicron*, and *Parabacteroides distasonis* were evaluated for the production of metabolites, and as a result, benzoic acid (**34**), phenyl acid (**35**), phenyl propionic acid (**36**), phenyl pyruvic acid (**37**), phenyl lactic acid (**38**), methyl benzene (**39**), 4-hydroxyphenyl acetic acid (**40**), 4-hydroxy benzoic acid (**41**), p-cresol (**42**) (in some of them), indole 3-acetic acid (**43**), indole 3-lactic acid (**44**), and methyl indole (**45**) (in some of them) were found[57]. The structures of these compounds, along with **46** and **47** are shown in Fig. 6.

B. fragilis also produces oligosaccharide, polysaccharide A, and glycolipid α-galactosylceramide (**46**) which display immunomodulatory effects; other *Bacteroides* spp. produce propionic acid (**47**) with a similar effect[23]. Sphingolipids play a crucial role in the structure of cellular membranes and act as important signaling molecules in eukaryotes, which are vital in regulating inflammation and immunity. They have recently gained interest due to their status as the metabolite that exhibits the most notable variations in abundance in the stool of patients with inflammatory bowel disease. Most sphingolipids, such as ceramide phosphoinositol (**48**), dihydroceramides (**49**), galactosylceramide (**50**), 1-deoxydihydroceramide (**51**), ceramide phosphoethanolamine (**52**), 1-*O*-(α-D-galactosyl)-N-hexacosanoylphytosphingosine (KRN7000) (**53**), and GSL-Bf717 (**54**) are derived from human *Bacteroides*[58–60]. Their structures are displayed in Fig. 7. The genera odoribacter and alistipes from *Bacteroides* are widely recognized for their ability to synthesize sulfonolipids. The utilization of sulfonolipids as

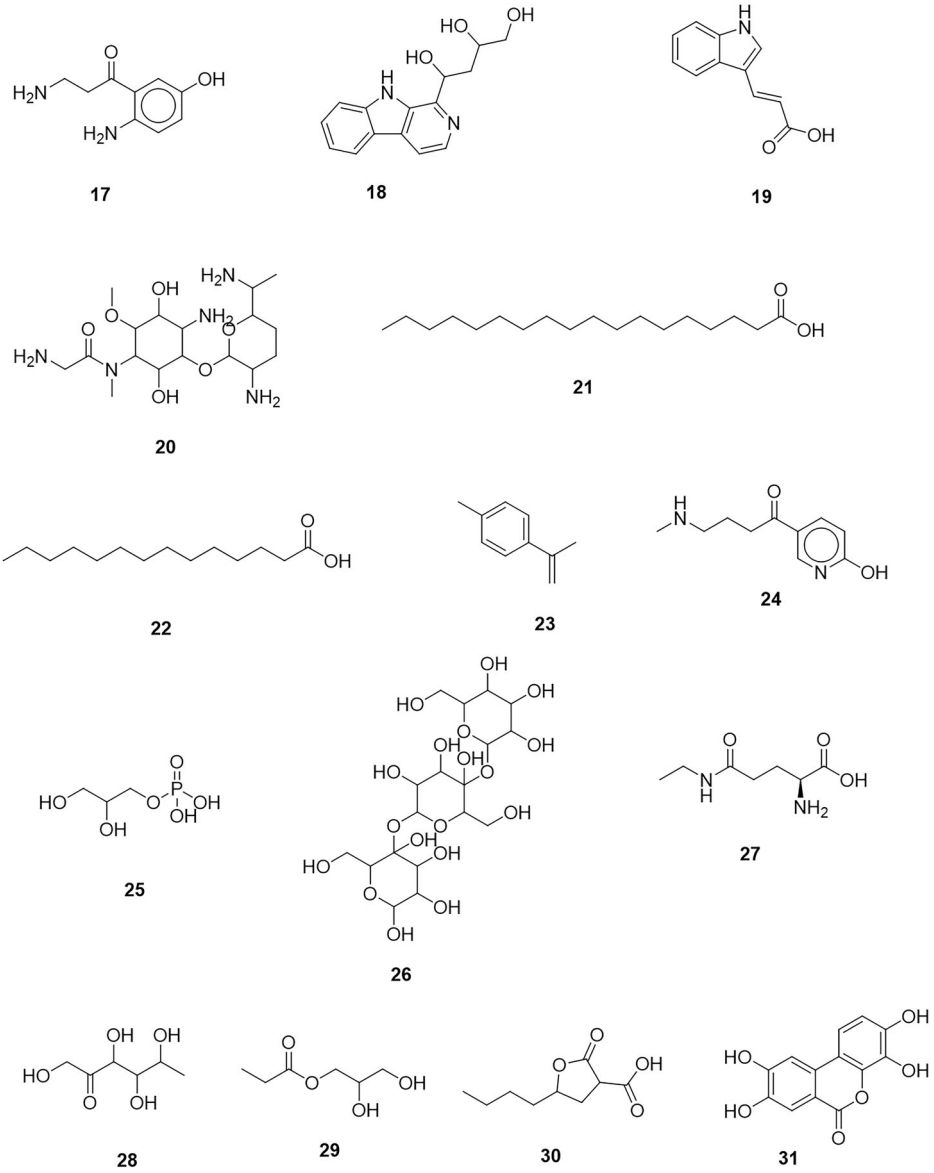

Fig. 5 | Structures of 5-hydroxykynurenamine (**17**), 2S,4R-4-(9H-pyrido[3,4-b]indol-1-yl)-1,2,4-butanetriol (**18**), indoleacrylic acid (**19**), fortimicin A (**20**), stearic acid (**21**), myristic acid (**22**), p-mentha-1,3,5,8-tatraene (**23**), 6 hydroxypseudooxynicotine (**24**), $_{DL}$-glycerol 1-phosphate (**25**), 4-beta-D-glucan (**26**), L-theanine (**27**), L-fuculose (**28**), glycerol-1-propanoate (**29**), 5-butyltetrahydro-2-oxo-3-furancarboxylic acid (**30**), and 3,4,8-trihydroxy urolithin (**31**).

a bacterial metabolite marker holds great potential for future investigations into the gut microbiota[61].

Non-peptides from Proteobacteria and their biological activities

Proteobacteria is currently the most abundant phylum in the bacterial domain. However, their existence as part of the human microbiota is relatively less than that of the former two phyla. Proteobacteria are widely distributed throughout the body and play a crucial role[62]. *E.* coli is a prominent bacterium found in the Proteobacteria group and has numerous biological uses. The primary byproducts of their metabolism consist predominantly of peptides, which will be subsequently addressed[63,64] Table 4).

Pseudomonas, a member of the same phylum, produces a metabolite called N-(3-oxo-dodecanoyl)-l-homoserine lactone (3-oxo-C12-HSL) (**55**), which serves as a signaling molecule and enhances inflammation during *Pseudomonas aeruginosa* infection[65] (Table 4). Pseudomonas is typically absent from the human gut microbiota; however, it may colonize the gut following antibiotic treatment. This may elevate the likelihood of lung infections[66]. Pyocyanin (**56**) is a virulence factor found in *P. aeruginosa* that has varied effects on different systems of the body, including the central nervous, cardiovascular, respiratory, and urological systems[67]. *P. aeruginosa*, a frequently observed source of biofilm infections, synthesizes a chemical called phenazine (**57**) in this particular setting. Phenazine aids in maintaining cellular redox equilibrium by accepting electrons[68]. Exopolysaccharides and rhamnolipids have also been reported in pseudomonas[69,70]. The structures of (**55**–**57**) are shown in Fig. 8.

Siderophores are released by *Klebsiella pneumoniae* during infection. These siderophores affect tissue location, infection propagation, and viability of the host[71]. One of the toxins, a non-peptide pyrrolobenzodiazepine, was isolated from *K. oxytoca;* the toxin was tilivalline (**58**) and displayed cytotoxic activity[72].

The human pathogenic bacterium Enterobacter is mainly associated with infections and healthcare facilities that lead to many diseases[73]. It can result in opportunistic infections, which arise when the body's defenses are compromised, potentially disseminating to the bloodstream and leading to life-threatening conditions[74]. Different toxins are generated by this genus such as endotoxins and uremic toxins, such as indole-3 acetic acid (**59**), 4-hydroxy phenyl lactate (**60**), trimethylamine-N-oxide (**61**), indoxyl sulfate (**62**), p-cresol sulfate (**63**), and imidazole propionate (**64**)[75]. The structures of these compounds are shown in Fig. 9.

The inhibition of *Campylobacter jejuni* colonization by the gut microbiota is counteracted by butyric acid, a molecule generated by

Table 3 | Compounds produced by Bacteroidetes (except peptides)

Organism	Metabolite(s)	Activity	Ref.
Bacteroides fragilis	cholic acid (32), deoxycholic acid (33)	- antibacterial	55
	α-galactosylceramide (46), propionic acid (**47**)	- immunomodulatory	23
Bacteroides spp.	benzoic acid (**34**), phenyl acid (**35**), phenyl propionic acid (**36**), phenyl pyruvic acid (**37**), phenyl lactic acid (**38**), methyl benzene (**39**), 4-hydroxyphenyl acetic acid (**40**), 4-hydroxy benzoic acid (**41**), p-cresol (**42**), indole 3-acetic acid (**43**), indole 3-lactic acid (**44**), methyl indole (**45**)	- antibacterial - antioxidant	57
	ceramide phosphoinositol (**48**), dihydroceramides (**49**), galactosylceramide (**50**), 1-deoxydihydroceramide (**51**), 1-ceramide phosphoethanolamine (**52**), 1-1-*O*-(α-D-galactosyl)-*N*-hexacosanoylphytosphingosine (**53**), 1-GSL-Bf717 (**54**)	- potential markers for the gut microbiota and regulators of inflammation and immunity	58–60
Odoribacter and Alistipes	sulfonolipids	- potential markers for bacterial metabolite studies of the gut microbiota	61

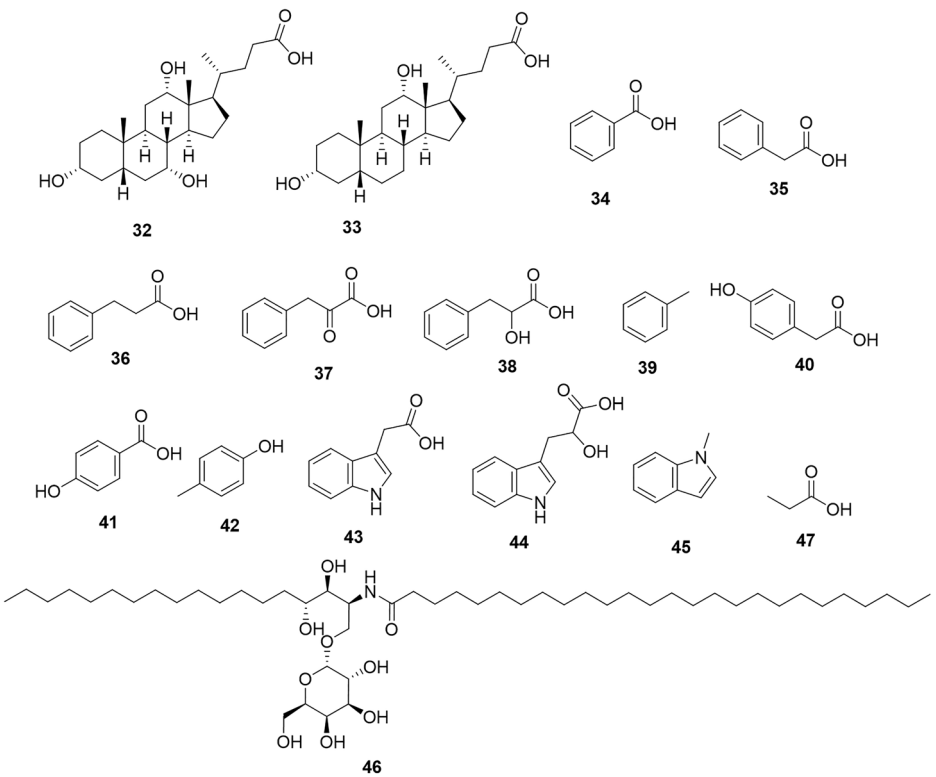

Fig. 6 | Structures of cholic acid (**32**), deoxycholic acid (**33**), benzoic acid (**34**), phenyl acid (**35**), phenyl propionic acid (**36**), phenyl pyruvic acid (**37**), phenyl lactic acid (**38**), methyl benzene (**39**), 4-hydroxyphenyl acetic acid (**40**), 4-hydroxy benzoic acid (**41**), p-cresol (**42**), indole 3-acetic acid (**43**), indole 3-lactic acid (**44**), methyl indole (**45**), α-galactosylceramide (**46**), and propionic acid (**47**).

microbes. Figure 10 shows that butyric acid (**65**) and deoxycholic acid (**66**) both reduced the severity of *C. jejuni*-induced colitis[12,76].

Non-peptides from Actinobacteria (Actinomycetota) and their biological activities

Actinobacteria constitute a small portion of the human microbiota, however, they play a vital role in the body and are mainly found on the skin and mucosal surfaces[77–79]. Many genera in this phylum are important for infection, and some produce metabolites.

For example, *Bifidobacterium longum BL*-10 exhibits robust antioxidant properties that are attributed to the presence of distinct genes. *B. longum* is a prevalent bacterium in the human gastrointestinal tract linked to several health advantages; it is among the first bacteria to inhabit the gut and remains there throughout a person's life[80]. Bifidobacteria has been found to produce

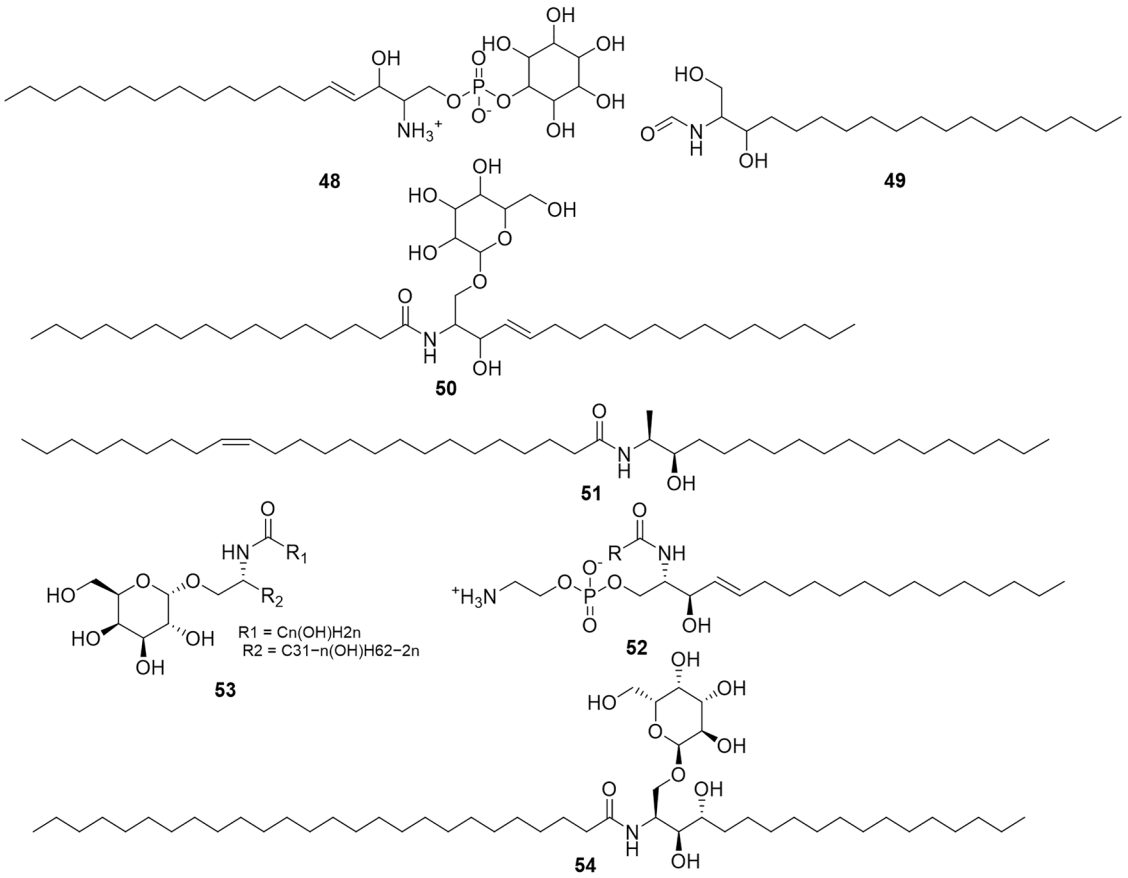

Fig. 7 | Structures of ceramide phosphoinositol (**48**), dihydroceramides (**49**), galactosylceramide (**50**), 1-deoxydihydroceramide (**51**), ceramide phosphoethanolamine (**52**), 1-O-(α-D-galactosyl)-N-hexacosanoylphytosphingosine (KRN7000) (**53**), and GSL-Bf717 (**54**).

Table 4 | Compounds produced by Proteobacteria (except peptides)

Organism	Metabolite(s)	Activity/Effect	Ref.
Pseudomonas aeruginosa	*N*-(3-oxo-dodecanoyl)-l-homoserine lactone (3-oxo-C12-HSL) (**55**)	- signaling molecule that enhances inflammation during infection.	65
	Pyocyanin (**56**)	- virulence factor affecting the central nervous, cardiovascular, respiratory, and urological systems.	67
	Phenazine (**57**)	- chemical aiding in maintaining cellular redox equilibrium; supports biofilm formation.	68
	Exopolysaccharides, Rhamnolipids	- biofilm-associated compounds.	69,70
Klebsiella pneumoniae	Siderophores	- compounds influencing infection propagation, tissue targeting, and host viability.	71
Klebsiella oxytoca	Tilivalline (**58**)	- non-peptide pyrrolobenzodiazepine toxin with cytotoxic activity.	72
Enterobacter spp.	Indole-3 acetic acid (**59**), 4-Hydroxy phenyl lactate (**60**), Trimethylamine-N-oxide (**61**), Indoxyl sulfate (**62**), p-Cresol sulfate (**63**), Imidazole propionate (**64**)	- toxins and uremic toxins associated with infections and health-care-related diseases.	75

phenylacetic acid (**68**), which is a metabolite derived from amino acids[12]. However, harmful bacteria, such as *Corynebacterium*, are normally present in the respiratory organs and are associated with many diseases. Corynomycolic acid (**67**) and corynebactin (**69**) have been isolated from the skin of corynebacterium spp[12]. The structures of (**67**–**69**) are shown in Fig. 11.

Another type of bacteria that causes diseases is *Rhodococcus* spp., which exists in several regions of the body, including the gastrointestinal tract, skin, and mouth. *Rhodococcus erythropolis* exhibits significant antibacterial activity against a wide range of microbes. *R. erythropolis* JCM 6824 produces quinolone-type antibiotics such as aurachin RE (**70**) and aurachin C (**71**). The former exhibits antibacterial activity by attacking gram-positive bacteria[81,82]. Furthermore, *R. erythropolis* generates siderophores such as heterobactin A (**72**) and B (**73**)[12]. Humimycin A (**74**) and B (**75**) have also been isolated from *R. erythropolis* and *R. equi;* both humimycins exhibit antibacterial activity against methicillin-resistant *Staphylococcus aureus*[83]. The structures of (**70**–**75**) are shown in Fig. 12.

Mycobacterium species are associated with many human diseases. This genus is particularly important because it is one of the most renowned pathogens responsible for tuberculosis[84]. Some lipids called phthiocerol dimycocerosates have been identified in *Mycobacterium tuberculosis*. These

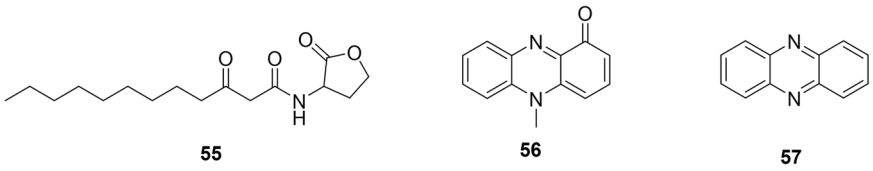

Fig. 8 | Structures of N-(3-oxo-dodecanoyl)-l-homoserine lactone (3-oxo-C12-HSL) (**55**), pyocyanin (**56**), and phenazine (**57**).

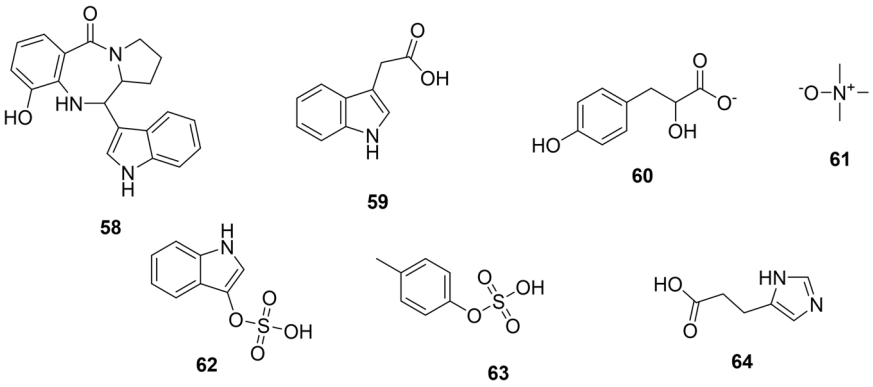

Fig. 9 | Structures of tilivalline (**58**), indole-3 acetic acid (**59**), 4-hydroxy phenyl lactate (**60**), trimethylamine-N-oxide (**61**), indoxyl sulfate (**62**), p-cresol sulfate (**63**), and imidazole propionate (**64**).

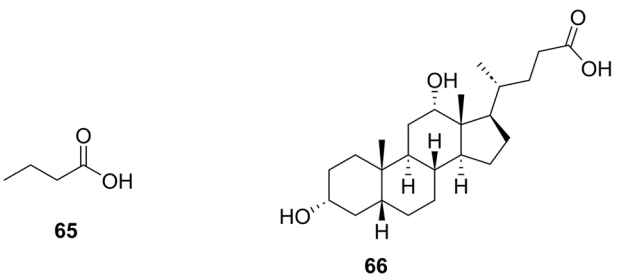

Fig. 10 | Structures of butyric acid (**65**) and deoxycholic acid (**66**).

bacteria contain many of the lipids that are prevalent in their pathogenicity. The structure of phthiocerol dimycocerosate from *M. leprae* is shown in Fig. 13 (**76**)[85,86]. Lipoarabinomannan is a glycolipid that is essential for the structural integrity of the cell wall of *M. tuberculosis*. Lipoarabinomannan has also been detected in the urine of patients diagnosed with tuberculosis[87]. *M. ulcerans*, a different species, is the primary cause of Buruli ulcers, a debilitating skin disorder characterized by extensive ulceration of the epidermis. Different geographical regions of the 34 *M. ulcerans* isolates produce structural variants of mycolactone polyketides A–D (**77**–**80**) and lactone (Fig. 13). The polyketide-derived macrolide toxin plays a significant role in the tissue destruction and immunological suppression observed in cases of Buruli ulcers[88].

Nocardia is a pathogenic bacterium that causes nocardiosis in humans. It is a member of the Actinobacteria family and is recognized for producing a diverse array of compounds with antimicrobial and antitumor properties. Nocardia produces many compounds such as brasilinolide A (**81**), brasilinolide B (**82**), nocardicyclin A (**83**), nocardicyclin B (**84**), and transvalencin Z (**85**)[89–91]. *Norcardia* spp. yield numerous siderophores. Examples include nocobactin NA (**86**), JBIR-16 (**87**), nocardamine (**88**), asterobactin (**89**), and brasilibactin A (**90**)[92]. Other phyla, namely, Fusobacteria and Verrucomicrobia, have not been studied in terms of their metabolites. The structures of (**81**–**90**) are shown in Figs. 14 and 15.

Fungi in the human microbiota and their metabolites and biological activities

Fungi are important constituents of the human microbiota, although they are less prevalent than bacteria and account for 0.1% of the total gut microbiota. They are found in different environments, including the gastrointestinal system, skin, oral cavity, and urogenital tract[93,94]. The human gut mycobiome consists of more than 66 genera and 184 species of fungi, with *Candida*, *Saccharomyces*, *Cladosporium*, *Malassezia*, and *Rhodotorula* being the most prevalent.

Different fungi in humans cause different diseases; for instance, the presence of *Candida* species in the gastrointestinal tract can result in the development of candidiasis when they become excessively abundant. *Candida albicans* is a common commensal in the oral cavity; however, excessive proliferation can lead to the development of an oral thrush[95,96]. On the contrary, Malassezia species, such as *Malassezia furfur*, have been associated with skin disorders such as dandruff and seborrheic dermatitis. Furthermore, notably, fungi present in the urogenital tract encompass *Candida* species that can cause vaginal yeast infections; however, research on this aspect is limited. Although fungi are less abundant than bacteria, they play a significant role in microbial diversity, which affects human health through interactions within the microbiota and metabolite synthesis. For example, fungi are known to interact with various gut bacteria, a well-documented example being the overgrowth of *Candida* following antibiotic treatment in humans, highlighting their competitive relationship. Additionally, a study using gnotobiotic mice demonstrated that a small fungal community (comprising five species) can induce significant ecological shifts in gut bacterial assembly. The same study further revealed that interkingdom interactions (bacteria-fungi) play a crucial role in shaping the early-stage assembly of both bacterial and fungal communities. Moreover, fungal metabolites impact metabolic diseases. For example, candidalysin damages hepatocytes and promotes IL-1β secretion via NLRP3 inflammasome activation, whereas altenusin improves metabolic parameters by reducing fat mass, hepatic steatosis, and insulin resistance. Additionally, dehydrocurvularin, (S)-curvularin, galiellalactone, and oxacyclododecindione regulate glucose tolerance and hepatic steatosis by inhibiting TGF-β/Smad signaling. These compounds also exhibit anti-inflammatory effects by downregulating pro-inflammatory cytokines and markers[97]. Additional investigation into the role of fungi in the microbiota is crucial for a thorough understanding of the interactions between hosts and microbes, as well as their consequences in health and diseases[98–100].

Patients with cystic fibrosis are most often affected by *P. aeruginosa*. *C. albicans* and *Aspergillus fumigatus* may coexist with *P. aeruginosa* in the cystic fibrotic lung environment; however, the disease implications of this coexistence are unknown. Recent scientific investigations have confirmed

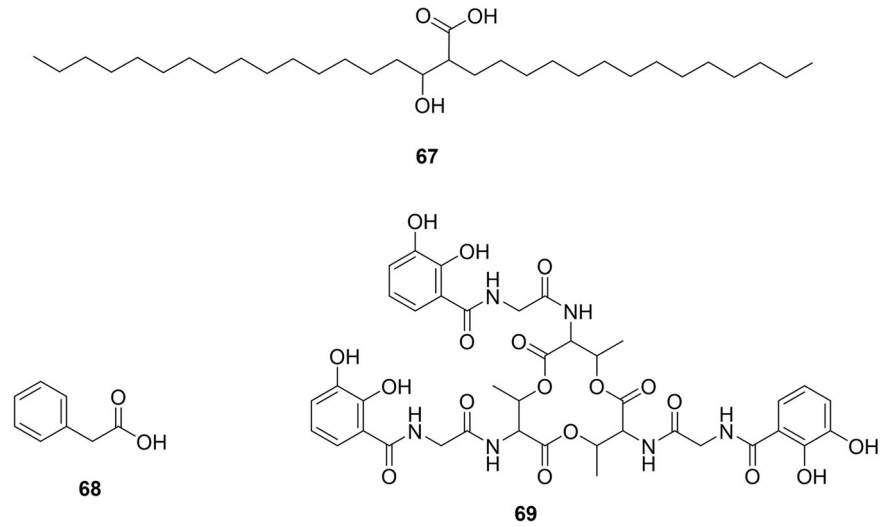

Fig. 11 | Structures of phenylacetic acid (**67**), corynomycolic acid (**68**), and corynebactin (**69**).

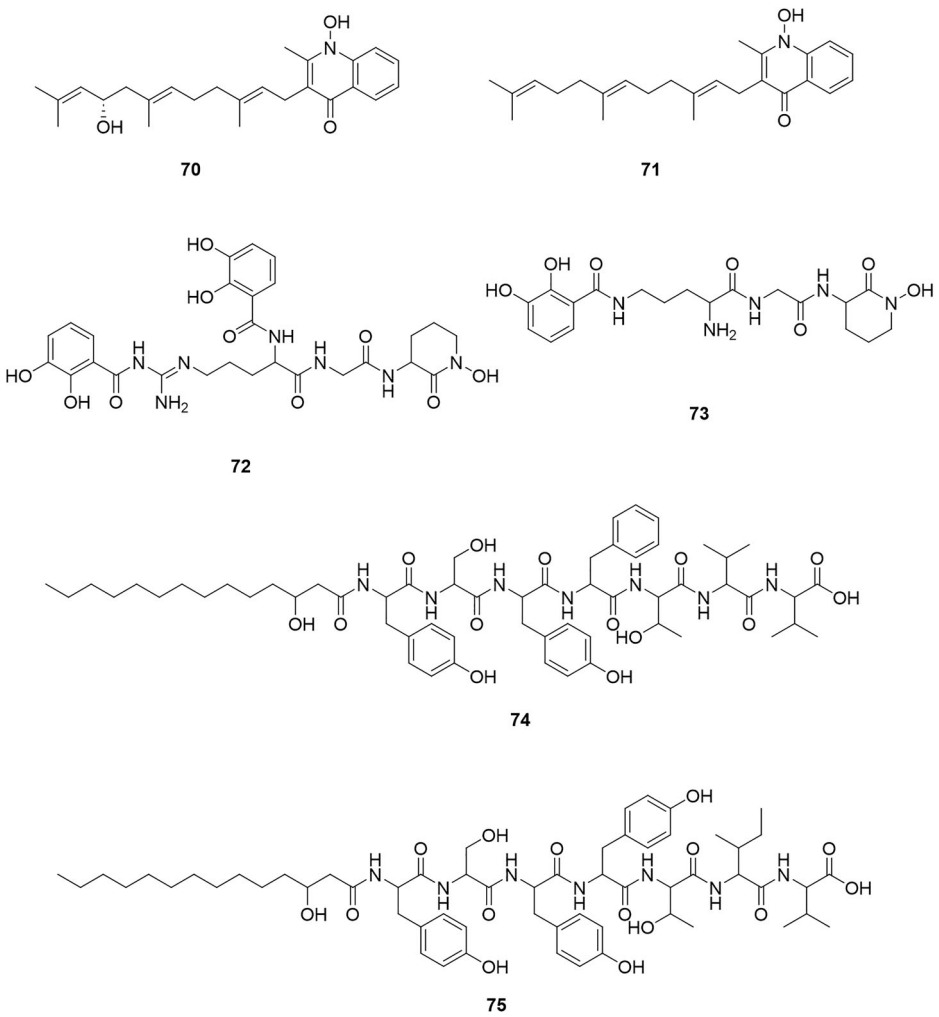

Fig. 12 | Structures of aurachin RE (**70**), aurachin C (**71**), heterobactin A and B (**72** and **73**), and humimycin A and B (**74** and **75**).

the presence of *P. aeruginosa* and *C. albicans* signaling pathways. More specifically, 3-oxo-C12HSL, a chemical produced by bacteria, can affect the shape of *Candida*, whereas farnesol (**91**), a metabolite produced by fungi, can lower the concentrations of pyocyanin and the *Pseudomonas* quinolone signal[98,101,102]. *C. tropicalis*, a pathogenic fungus frequently present in the human oral cavity, skin, and digestive tract, produces a lipopeptide called YM-170320 (**92**), which can inhibit the formation of ergosterol production in fungi[103,104].

Shuai et al. conducted a study examining fungal communities in the human gut. Their goal was to evaluate the factors affecting the stability of the gut mycobiome in middle-aged and elderly adults. In addition, their study identified 47 fungal metabolites, 13 of which were identified as fatty acids.

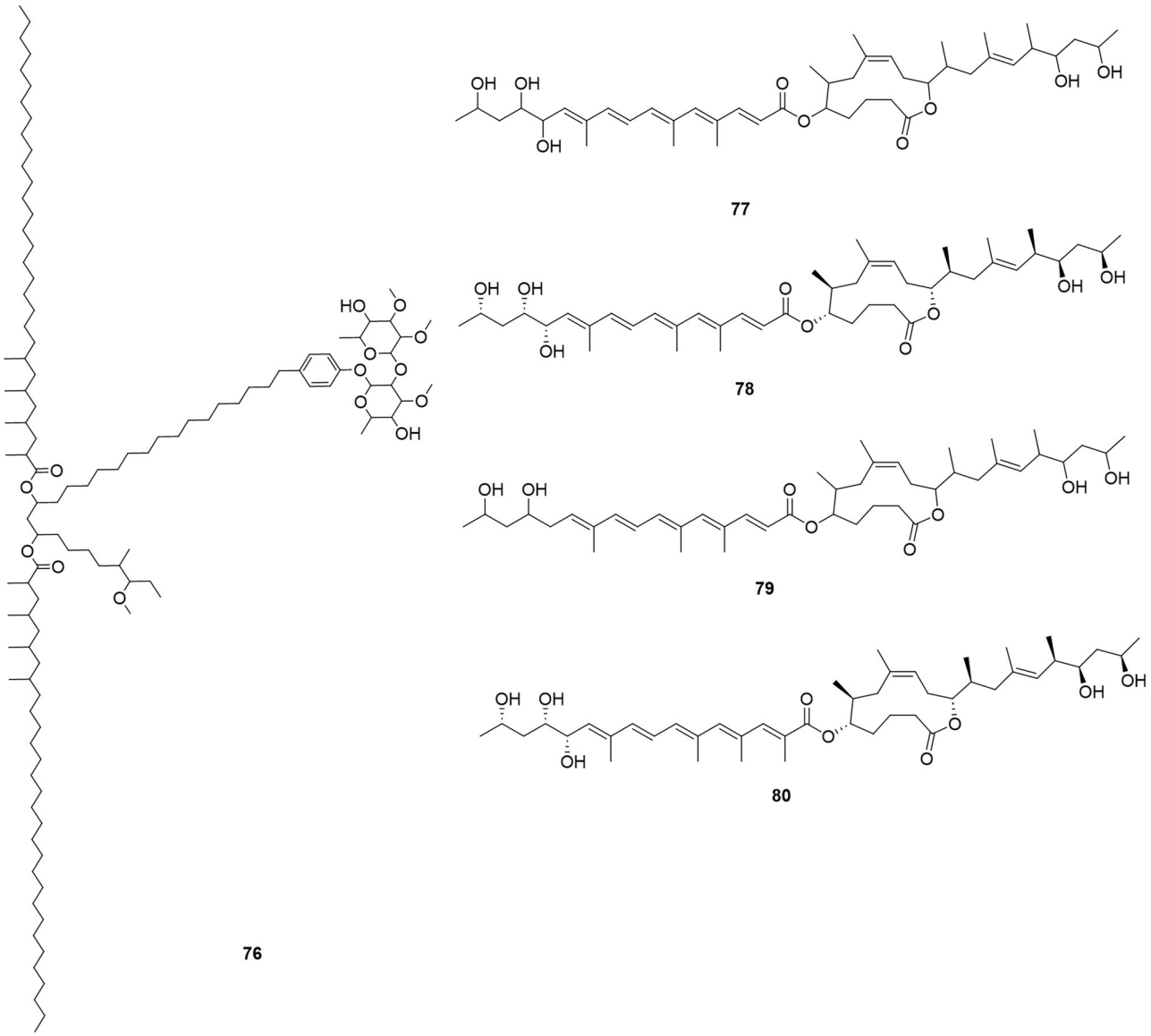

Fig. 13 | Structures of phthiocerol dimycocerosate (**76**) and mycolactone polyketides A–D (**77**–**80**).

The main compounds influencing the diversity of the total gut mycobiome are 3-methyladipic acid (**93**), tridecanoic acid (**94**), and ethylmethylacetic acid (**95**). In addition, most of the fecal metabolites showed a correlation with particular fungal taxa metabolites, such as carnosine (**96**), D-gluconolactone (**97**), and L-threonine (**98**)[105]. The structures of (**91**–**98**) are shown in Fig. 16.

A. fumigatus is the predominant species in the *Aspergillus* genus that is responsible for producing infectious lung illnesses. This species is known for its capacity to produce a diverse array of extrolites, including secondary metabolites, acids, and proteins such as hydrophobins and extracellular enzymes. A previous study showed 226 active bioactive metabolites from *A. fumigatus*, which were classified into 24 different biosynthetic families. Within these groups, a range of secondary metabolites were identified, such as gliotoxins, trypacidin, fumigaclavines, verruculogens, fumiquinazolines, monomethylsulochrins, fumagillins, fumigatins, pseurotins, chloroanthraquinones, fumitremorgins, helvolic acids, and pyripyropenes with the help of high-performance liquid chromatography (HPLC) in conjunction with diode array and mass spectrometric detection[106,107]. Overall, there are approximately a billion cases of human fungal infections, leading to 1.6 million fatalities[108,109]. Although the sources of this mycobiome are not human, they still have an impact on the human body, as mentioned. Thus, it is imperative to identify the specific metabolites produced by these pathogenic fungi when they infect the human body. *Rhodotorula* spp., widely distributed in the environment, belong to basidiomycetous fungi. Transmission and colonization in humans primarily occur through air and food. While intestinal colonization is common, overgrowth is usually suppressed as the body's temperature exceeds their optimal growth range. However, excessive presence may increase the risk of fungemia and subsequent organ infections, particularly in individuals with weakened immune systems. Conversely, in a well-balanced colonization state, these fungi can be beneficial, as they produce valuable nutrients such as proteins, lipids, folate, and carotenoids[110].

Dietary factors, especially prebiotics, play a crucial role in shaping metabolites generated by human microbiota. They serve as substrates for particular gut bacteria, facilitating fermentation processes that yield beneficial metabolites such as SCFAs. These metabolites can positively influence host health by regulating immune function, enhancing gut barrier integrity, and affecting metabolic processes. Dietary fiber is the main substrate for bacterial metabolite production, especially those abundant in prebiotics such as inulin and fructooligosaccharides (FOS). Bacterial fermentation of prebiotics results in the production of SCFAs, including acetate, propionate, and butyrate, which are key metabolites influencing host health[111,112]. This

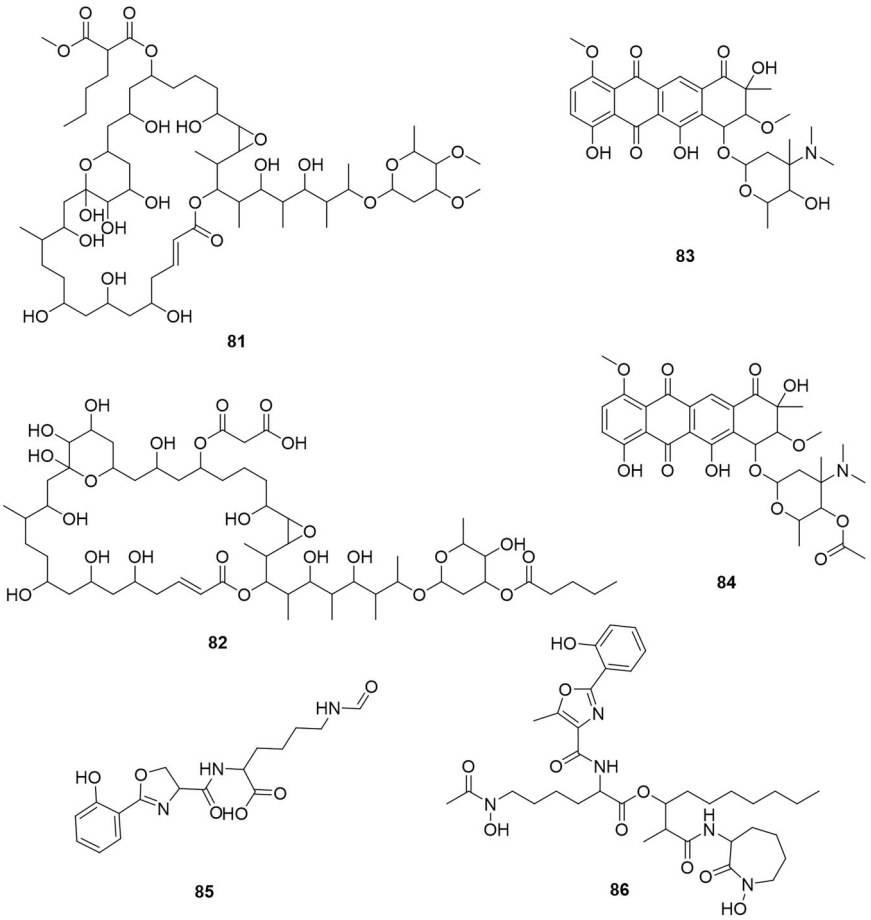

Fig. 14 | Structures of brasilinolides A and B (**81** and **82**), nocardicyclins A and B (**83** and **84**), transvalencin Z (**85**), and nocobactin NA (**86**).

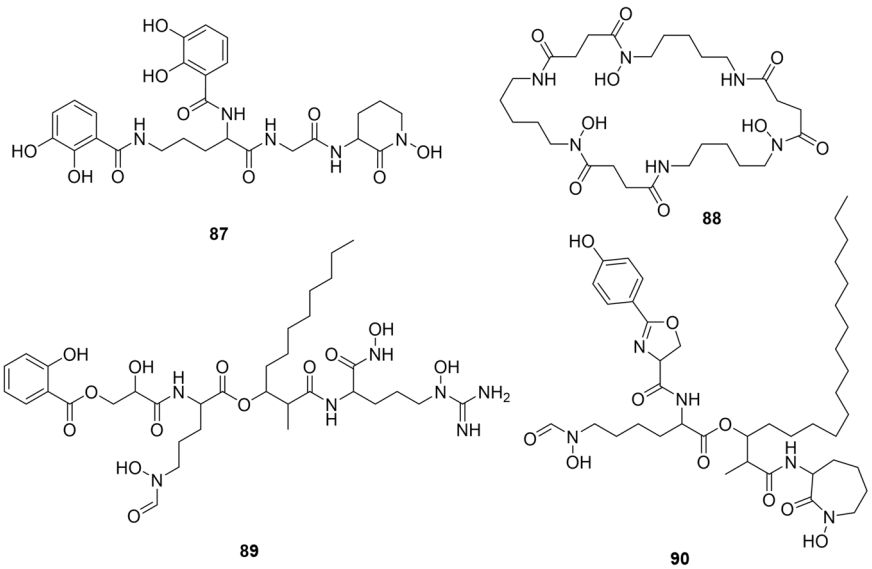

Fig. 15 | Structures of JBIR-16 (**87**), nocardamine (**88**), asterobactin (**89**), and brasilibactin A (**90**).

highlights the significant influence of dietary factors on microbiota-derived metabolites and overall human health (Tables 5, 6).

Important peptides from the human microbiota

Peptides originating from the human microbiome function primarily as antibacterial agents. These microbiota can have commensal and mutualistic relationships, as well as pathogenic effects, leading to the production of various peptides. Commensals typically produce bacteriocins and peptides that specifically target harmful bacteria[113]. The biological roles of these peptides were studied in detail in our recent review article[22]. Here, we highlight the important peptides and their sources that can aid in drug discovery and the identification of a new framework from the human microbiota (Table 7).

Nisin was discovered in *Lactococcus lactis subsp. lactis*. This antibacterial peptide is synthesized by specific *Streptococcus* species. Nisin A (Fig. 17), the first identified form, is a polypeptide consisting of 34 amino

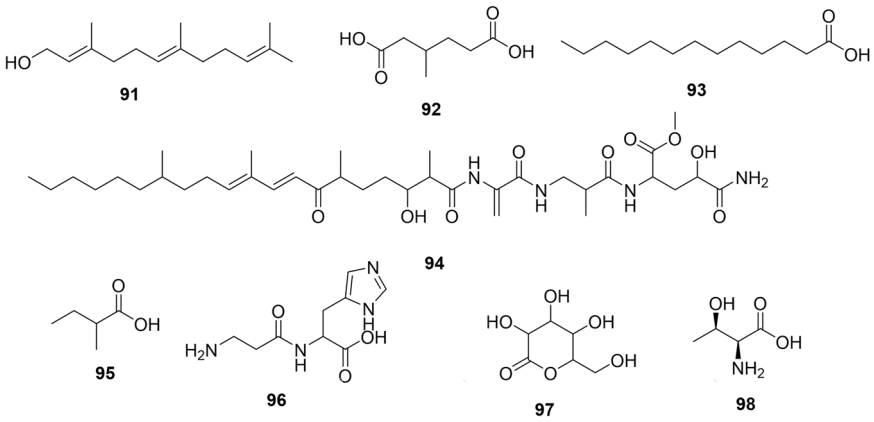

Fig. 16 | Structures of farnesol (**91**), YM-170320 (**92**), 3-methyladipic acid (**93**), tridecanoic acid (**94**), ethylmethylacetic acid (**95**), carnosine (**96**), D-gluconolactone (**97**), and L-threonine (**98**).

Table 5 | Compounds produced by Actinobacteria (except peptides)

Organism	Metabolite(s)	Activity/Effect	Ref.
Bifidobacterium longum	Phenylacetic acid (**68**)	- antioxidant properties	80
Corynebacterium spp.	Corynomycolic acid (**67**), Corynebactin (**69**)	- associated with respiratory diseases; metabolites isolated from skin isolates.	12
Rhodococcus erythropolis	Aurachin RE (**70**), Aurachin C (**71**)	- Aurachin RE targets gram-positive bacteria.	81,82
	Heterobactin A (**72**), Heterobactin B (**73**)	- siderophores with antibacterial activities	12
	Humimycin A (**74**), Humimycin B (**75**)	- active against MRSA	83
Mycobacterium tuberculosis	Phthiocerol Dimycocerosate (**76**)	- lipids linked to pathogenesis.	85,86
	Lipoarabinomannan	- structural integrity of cell wall; detected in urine of tuberculosis patients	87
Mycobacterium ulcerans	Mycolactone polyketides A (**77**), B (**78**), C (**79**), D (**80**)	- macrolide toxins causing tissue destruction and immunological suppression in Buruli ulcer cases	88
Nocardia spp.	Brasilinolide A (**81**), Brasilinolide B (**82**)	- antimicrobial and antitumor properties	89–92
	Nocardicyclin A (**83**), Nocardicyclin B (**84**)	- antimicrobial properties	
	Transvalencin Z (**85**)	- antimicrobial properties	
	Nocobactin NA (**86**), JBIR-16 (**87**), Nocardamine (**88**), Asterobactin (**89**), Brasilibactin A (**90**)	- siderophores contributing to various bioactivities	

Table 6 | Compounds produced by fungi in the human microbiota (except peptides)

Organism	Metabolite(s)	Activity/Effect	Ref.
Candida tropicalis	YM-170320 (**92**)	- inhibits ergosterol production in fungi.	103,104
Aspergillus fumigatus	gliotoxins, trypacidin, fumigaclavines, fumiquinazolines, helvolic acids, 226 additional metabolites.	- lung infections and produces extrolites	106,107
Candida albicans	farnesol (**91**)	- reduces pyocyanin and *Pseudomonas* quinolone signaling molecules.	100,102,103
Various fungi (gut mycobiome)	3-methyladipic acid (**93**), tridecanoic acid (**94**), ethylmethylacetic acid (**95**), carnosine (**96**), D-gluconolactone (**97**), L-threonine (**98**)	- influence the diversity and stability of the gut mycobiome	105

acids with a molecular weight of 3500 Da. It comprises two distinct groups: methyllanthionine and lanthionine. During biosynthesis, the nisin leader peptide plays a crucial role in facilitating interactions between precursor nisin and its modification enzymes, NisB and NisC, which are responsible for posttranslational maturation. NisB dehydrates serines and threonines, while NisC catalyzes the subsequent coupling of the formed dehydroamino acids to form lanthionines[114]. This peptide has been approved by the FDA and is considered safe according to GRAS standards. In addition to its use as a food preservative, it is used in biomedicine[115–117]. Various variants of nisin have been identified since 1928. They include nisin A[118], nisin Z[119], nisin

Table 7 | Representative peptides produced by the human microbiota

Organism	Metabolite(s)	Activity/Effect	Ref.
Lactococcus lactis subsp. lactis	nisin A	antibacterial, FDA-approved	118
Lactococcus lactis	nisin Z	antibacterial	119
Lactococcus lactis	nisin Q	antibacterial	120
Lactococcus lactis	nisin F	antibacterial	121
Streptococcus uberis	nisin U, U2	antibacterial	122
S. gallolyticus subsp. Pasteurianus	nisin P	antibacterial	123
Blautia obeum	nisin O1–O4	antibacterial	125
Staphylococcus capitis	nisin J	antibacterial	124
Lactobacillus gasseri (LA39)	gassericin A	antibacterial	128
Lactobacillus gasseri (SBT 2055)	gassericin T	antibacterial	129
Lactobacillus gasseri (JV-V03)	lactocillin	antibacterial	14
Lactobacillus plantarum (LL441)	plantaricin C	antibacterial, membrane disruption	132
Lactobacillus plantarum (C11)	plantaricin A, EF, JK	antibacterial	133
Lactobacillus acidophilus (M46)	acidocin B	antibacterial	135
Lactobacillus acidophilus (JCM1132)	acidocin J1132	antibacterial	27
Lactobacillus rhamnosus (68)	rhamnosin A	antibacterial	136
Lactobacillus amylovorus (DCE 471)	amylovorin L471 (lactobin A)	antibacterial	137
Lactobacillus johnsonii	lactacin F (lactacin A + lafX)	antibacterial	138
Streptococcus salivarius (UCC118)	salivaricin ABP-118	antibacterial	140
Streptococcus salivarius	salivaricin D	antibacterial	141
Clostridium botulinum (213B)	boticin B	antibacterial	146,147
Clostridium beijerinckii (ATCC 25752)	circularin A	antibacterial	
Clostridium tyrobutyricum (ADRIAT 932)	closticin 574	antibacterial	
Enterococcus faecium	bacteriocin 43	antibacterial	148
Enterococcus faecalis	bacteriocins 31 and 32	antibacterial	150,151
Enterococcus faecalis (RC714)	bacteriocin RC714	antibacterial	151
Staphylococcus epidermidis	epilancin 15X, epidermin, Pep5	antibacterial	153–156
Staphylococcus epidermidis (K7)	epilancin K7	antibacterial	
Staphylococcus epidermidis (BN 280)	epicidin 280	antibacterial	161
Staphylococcus lugdunensis	lugdunin	antibacterial	164
Staphylococcus hominis	micrococcin P1	antibacterial	165
Streptococcus mutans (UA159)	mutanamide	antibacterial	166,167
Streptococcus mutans	mutacin I and BNY266	antibacterial	168,169
Escherichia coli (LR05)	microcin L	antibacterial	173
Escherichia coli (Nissle 1917)	microcins M and H47	antibacterial	174,175
Escherichia coli (AY25)	microcin J25	antibacterial	177,178
Escherichia coli	microcin V (colicin V), microcin B	antibacterial	
Klebsiella pneumoniae	colibactin	cytotoxic	183
Klebsiella oxytoca	tilivalline, tilimycin	cytotoxic	185,186
Bacteroides vulgatus	commendamide	bioactive	
Bifidobacterium bifidum	bifidocin B	antibacterial	186
Bifidobacterium infantis	bifidin I	antibacterial	187

Q[120], and nisin F[121] from *L. lactis*, nisin U and U2 from *Streptococcus uberis*[122], nisin P from *S. gallolyticus* subsp. Pasteurianus (human fecal isolate)[123], nisin J from *Staphylococcus capitis*[124], nisin O1 to O4 from *Blautia obeum*[125], and nisin H (non-human source) from *S. hyointestinalis*[126].

Gassericins and plantaricins are bacteriocins, and several such peptides have been isolated from the human microbiota. Gassericins are primarily produced by *Lactobacillus gasseri* and exhibit antimicrobial properties. Their biosynthesis involves leader peptide cleavage, enzymatic cyclization, and ABC transporter-mediated secretion. The circular nature of gassericin enhances its stability and prolongs its bioactivity[127]. To date, several gassericins have been isolated, including gassericin A (Fig. 17), which has been isolated from the LA39 strain of *L. gasseri*. This strain was isolated from human feces and exhibited high antibacterial activity[128]. Another strain, SBT 2055, of the same species resulted in the isolation of gassericin T with potent antibacterial properties[129]. Reutericin 6 was first isolated from *L. reuteri* LA6b[130]; however, it was later named gasserinin A after it was first reported in 1991[131]. *L. gasseri* JV-V03 resulted in the isolation of bioactive peptides

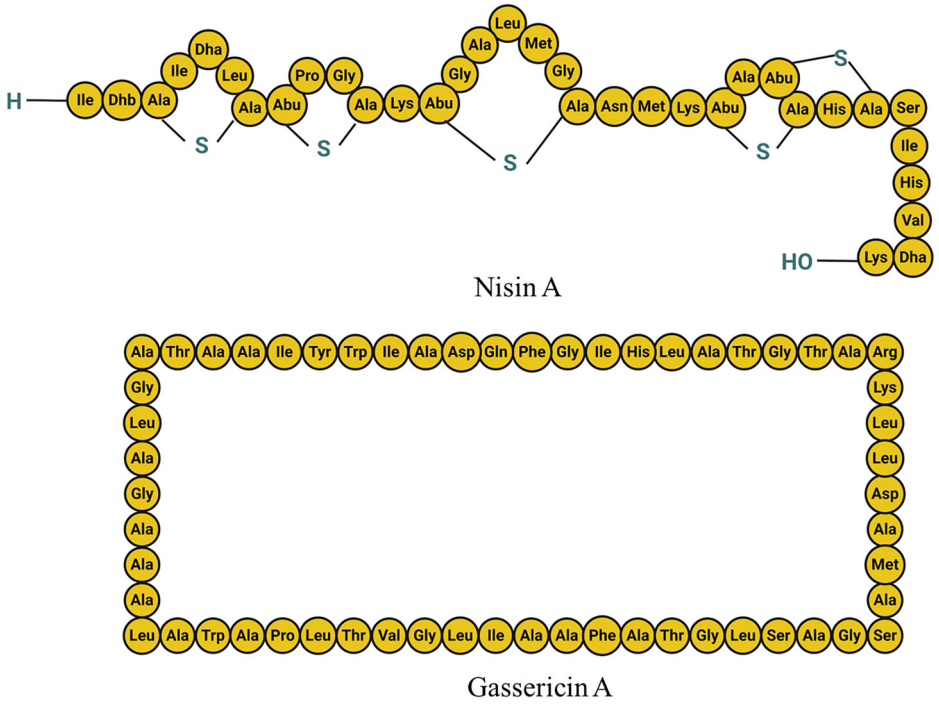

Fig. 17 | Putative structures of nisin A and gassericin A.

from a thiopeptide group called lactocillin, which exhibits antibacterial action[14]. On the contrary, plantaricins and bacteriocins have been reported from *L. plantarum*; for example, plantaricin C was isolated from the LL441 strain of *L. plantarum*, which displayed antibacterial activity by targeting the cytoplasmic membrane permeability barrier[132]. A C11 strain resulted in the isolation of plantaricin A, which displayed antimicrobial properties[133]. Plantiricins EF and JK have been purified from *L. plantarum* C11, which demonstrates antagonistic antibacterial activity; notably, when plantaricins E and F and J and K are together, better bioactivity is achieved[134].

Furthermore, in terms of peptides from Lactobacillus, *L. acidophilus* M46 produced acidocin B, which displayed antibacterial activities against a range of bacteria[135]; a strain of the same species, JCM1132, resulted in the isolation and purification of acidocin J1132[27]. *L. rhamnosus* 68 produces rhamnosin A, which displayed antibacterial activity against *Micrococcus lysodeikticus*[136]. The hydrophobic bacteriocin amylovorin L471 (lactobin A) is found in *L. amylovorus* DCE 471[137]. The combination of two peptides, namely lactacin A and LafX, created another peptide named lactacin F, which was isolated from *L. johnsonii* and displayed antibacterial activity against other lactobacillus[138]. Salivaricins are antibiotics derived mainly from *Streptococcus salivarius*. They exhibit antibacterial properties against a wide range of bacteria, particularly those found in the respiratory system[139]. During the isolation of salivaricins from the human microbiota, *L. salivarius subsp. salivarius* UCC118, which is present in the gut, gave rise to salivaricin ABP-118[140]. Furthermore, salivaricin D has been found in *S. salivarius*, which is found on human faces[141]. Regarding other salivaricins, A was isolated from *S. salivarius* 20P3, B was isolated from *S. salivarius* K12, D was isolated from S. *salivarius* 5M6c, and salivaricin 9 was isolated from *S. salivarius* NU1[142–144].

Clostridium, which belongs to the Firmicutes phylum, like *Lactobacillus* and others, is normally present in the gastrointestinal tract. It contains one of the most well-known species that causes many diseases, *Clostridioides difficile*[145]. Boticin B, circularin A, and closticin 574 were the main peptides isolated from this genus; they were isolated from *C. botulinum* 213 B, *C. beijerinckii* ATCC 25752, and *C. tyrobutyricum* ADRIAT 932, respectively[146,147]. Enterococci in the gastrointestinal tract play important roles in the synthesis of many bioactive compounds[34,35]. Bacteriocin 43 was found in *Enterococcus faecium*[148], bacteriocin 32 and 31 in *E. faecalis*[149,150], and bacteriocin RC714 was also found in *E. faecalis*[151]. All these compounds exhibited antibacterial properties. *S. faecalis* S-48, also called *E. faecalis*, produces another AMP, AS-48[152]. *Ruminococcus*, which is prevalent in the human microbiota, resulted in the isolation of ruminococcin A from *Ruminococcus gnavus*[153], and through a computational approach, ruminopeptin was identified in *R. bromii*[154].

Many types of Staphylococcus live on epithelial surfaces, such as the skin and nasal passages, and are highly valued in the human microbiome. Epilancin 15X was isolated from *Staphylococcus epidermidis* and has a structure similar to that of epilancin K7 isolated from *S. epidermidis* K7, which exhibits antimicrobial properties[153–157]. Furthermore, epidermins from *S. epidermidis* Tu 3298[158], epidermicin NI01 from *S. epidermidis* 224[159], gallidermin from *S. gallinarum*[160], epicidin 280 from *S. epidermidis* BN 280[161], pep5 from *S. epidermidis*[162], and epilancin A37 have been reported in the *Staphylococcus* genus[163]. Lugdunin, the first non-ribosomally synthesized peptide from the human microbiota, was isolated from *S. lugdunensis*[164]. Similarly, *S. hominis* from the human microbiota produces micrococcin P1[165].

Streptococcus mutans is the primary cause of dental caries and is typically found in the human microbiome. Different streptococci from the human microbiota produce many important peptides; for example, one of the oral pathogens, *S. mutants* UA159, yields mutanamide[166,167]. The lantibiotics mutacin 1140 and mutacin-BNY266 have been reported in *S. mutans*[168,169]. Gallocin A, a combination of two peptides, GllA1 and GllA2, has been detected in *S. gallolyticus* subsp. *Gallolyticus*; notably, both peptides are essential for biological activity, and a single peptide of the pair cannot affect the target bacteria[170]. In the same series, gallocin D was isolated from *S. gallolyticus* LL009 and displayed potent activity against vancomycin-resistant enterococci[171].

Escherichia, a well-known human microbiota belonging to the phylum Proteobacteria, is widely distributed throughout the human body[44,172]. A definite type of peptide, namely microcins, has been found in specific species of *Escherichia coli*; for example, microcin L has been found in *E. coli* LR05[173], microcin M and microcin H47 in *E. coli* Nissle 1917[174,175], microcin J25 in

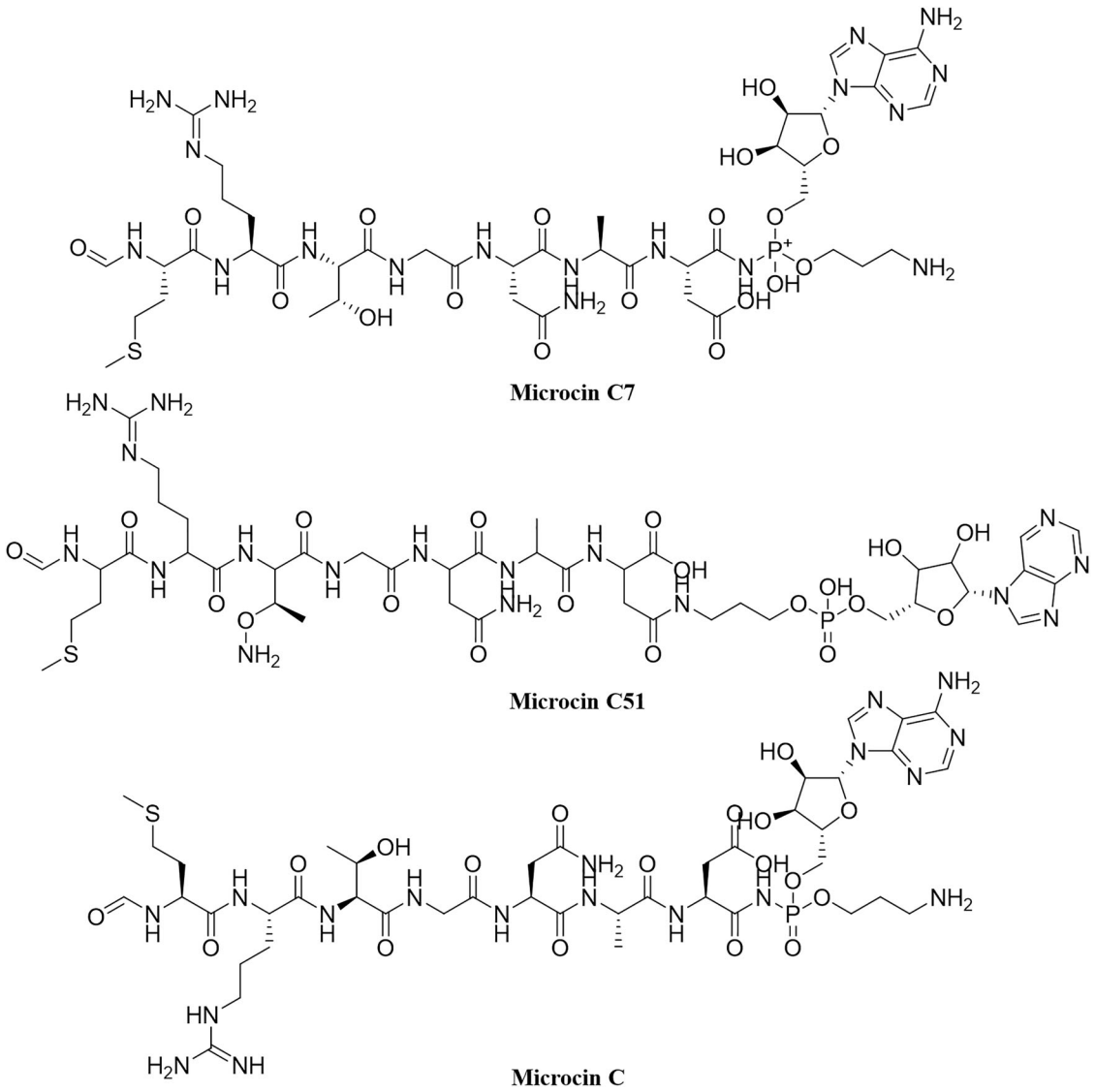

Fig. 18 | Structures of Microcin C7, C51, and C.

E. coli AY25[176], and microcin V (previously called colicin V) and microcins C7, C51, B, and C in *E. coli* with antimicrobial activities[13,177,178]. The structures of some microcins are shown in Fig. 18. In other genera of Proteobacteria, *Pseudomonas aerugonisa* produces the siderophore pyoverdine[179], and pyocins S2 and 2 have also been reported from similar species[180]. The Klebsiella genus, commonly present in the human microbiota as a pathogen and one of the species of *Klebsiella pneumoniae*, has been given higher importance because of pneumonia[181,182]. Different metabolites, including colibactin *K. pneumoniae*[183], pyrrolobenzodiazepines tilivalline, and tilimycin, have been isolated from *K. oxytoca*, and displayed cytotoxic activities[72,184,185].

Another major phylum in the human microbiota is Actinobacteria, which is usually present in different parts of the human body. This phylum contains the pathogenic bacteria that cause tuberculosis[78]. Bifidobacterium is a genus that produces BLD 1648 from *bifidobacterium longum* DJO10A[132], bifidocin B from *B. bifidum*[186], and bifidin I from *B. infantis* BCRC 14602[187]. Nocardithiocin is a thiopeptide that has been reported in *Nocardia pseudobrasiliensis* IFM 0757[188]. Other compounds from this phylum have been identified in the non-peptide fraction. Bacteroidaceae are also widely distributed in the human microbiota and play a substantial role in the breakdown of polysaccharides[37,189]. Commendamide, a bioactive peptide, has been isolated from *Bacteroides vulgatus*[190]. Additionally, bacteroidetocin A and B have been reported in this phylum[191].

Future challenges and conclusive remarks

Following an extensive literature review, we found that the human microbiota not only contains peptides, but various non-peptide metabolites have also been reported. The human microbiota consists of trillions of microorganisms comprising six major phyla. Among them, Firmicutes contributes the most to the metabolite profile. The peptide portion of Firmicutes mainly displays antimicrobial activity, and because of the current global threat of antimicrobial resistance, this phylum can contribute enormously to this phenomenon. Current genomics and computational techniques make it possible, to a great extent, to identify novel metabolites from these bacteria. However, uncovering many bacterial metabolites from the human microbiota and use them against many fatal diseases for which antimicrobials are on the frontline of treatment. Furthermore, most species within these major phyla remain unexplored for metabolite isolation and characterization, leaving significant potential for discovering novel metabolites. Enhancing current techniques is essential for advancing microbiome research. Novel culture-based methods, improved genomic and computational tools, and refined chromatographic techniques are required to better identify metabolite-producing microbiota. Ethical and regulatory challenges must

also be addressed, such as biobank management and probiotic safety. Clinically, microbiome therapeutics, including prebiotics, probiotics, and microbiota transplants, are being developed to treat diseases and improve drug efficacy. Major challenges include identifying key microbial contributors to health and disease and designing targeted interventions despite individual microbiome variability. Future research should focus on defined microbial communities in gnotobiotic models, targeted bacterial interventions, metabolomics for functional metabolite identification, and advanced computational tools. In addition, current metabolomic techniques face significant challenges that limit our ability to link specific microbial metabolites to biological outcomes, mainly due to issues with detection sensitivity, incomplete metabolite annotation, and variability in sample preparation and analysis, which together hinder consistent identification and quantification of metabolites. Moreover, the dynamic nature of metabolite production, which is affected by factors such as diet, circadian rhythms, and disease, coupled with high inter-individual variability in the microbiome, complicates establishing clear causal relationships. While techniques such as mass spectrometry and NMR spectroscopy offer valuable insights, limitations such as ion suppression, matrix effects, and the inability to capture transient metabolite changes in single-time-point measurements often result in data that are difficult to interpret in terms of biological function. These technical constraints, alongside the complexity of host-microbe interactions and metabolic redundancy, underscore the need for more standardized protocols and integrative multi-omics approaches to better understand the roles of microbial metabolites in human health.

In this review, we carefully evaluated most of the human microbiota and specifically focused on their metabolites. We have previously analyzed the biological activities of peptides in depth. Here, we mentioned all the metabolites, both peptides and non-peptides, and provided a clear picture of the human microbiota. This information will not only help to find existing metabolites in the human microbiota but will also serve as a tool for the discovery of new and novel metabolites from these microbes, which can ultimately lead to the discovery of future breakthrough products and save millions of people around the world.

Data Availability

No datasets were generated or analysed during the current study.

Received: 12 December 2024; Accepted: 28 April 2025;
Published online: 08 May 2025

References

1. Ogunrinola, G. A., Oyewale, J. O., Oshamika, O. O. & Olasehinde, G. I. The Human Microbiome and Its Impacts on Health. *Int J. Microbiol* **2020**, 8045646 (2020).
2. Afzaal, M. et al. Human gut microbiota in health and disease: Unveiling the relationship. *Front. Microbiol*. **13**, 999001 (2022).
3. Hou, K. et al. Microbiota in health and diseases. *Sig Transduct. Target Ther.* **7**, 1–28 (2022).
4. Matijašić, M. et al. Gut Microbiota beyond Bacteria—Mycobiome, Virome, Archaeome, and Eukaryotic Parasites in IBD. *Int. J. Mol. Sci.* **21**, 2668 (2020).
5. Iliev, I. D. & Cadwell, K. Effects of Intestinal Fungi and Viruses on Immune Responses and Inflammatory Bowel Diseases. *Gastroenterology* **160**, 1050–1066 (2021).
6. Kapitan, M., Niemiec, M. J., Steimle, A., Frick, J. S. & Jacobsen, I. D. Fungi as Part of the Microbiota and Interactions with Intestinal Bacteria. in *Fungal Physiology and Immunopathogenesis* (ed. Rodrigues, M. L.) 265–301 https://doi.org/10.1007/82_2018_117 (Springer International Publishing, Cham, 2019).
7. Scarpellini, E. et al. The human gut microbiota and virome: Potential therapeutic implications. *Digestive Liver Dis.* **47**, 1007–1012 (2015).
8. Ceppa, F. A. et al. Human Gut-Microbiota Interaction in Neurodegenerative Disorders and Current Engineered Tools for Its Modeling. *Front. Cell. Infect. Microbiol*. **10**, 297 (2020).
9. Riganelli, L. et al. Structural Variations of Vaginal and Endometrial Microbiota: Hints on Female Infertility. *Front. Cell. Infect. Microbiol*. **10**, 350 (2020).
10. Roy, T. L. et al. Dysosmobacter welbionis is a newly isolated human commensal bacterium preventing diet-induced obesity and metabolic disorders in mice. *Gut* **71**, 534–543 (2022).
11. Gut Microbiome Communication: The Gut-Organ Axis. *ASM.org* https://asm.org:443/Articles/2023/January/Gut-Microbiome-Communication-The-Gut-Organ-Axis.
12. Mousa, W. K., Athar, B., Merwin, N. J. & Magarvey, N. A. Antibiotics and specialized metabolites from the human microbiota. *Nat. Prod. Rep.* **34**, 1302–1331 (2017).
13. Chong, J. & Xia, J. Computational Approaches for Integrative Analysis of the Metabolome and Microbiome. *Metabolites* **7**, 62 (2017).
14. Donia, M. S. et al. A systematic analysis of biosynthetic gene clusters in the human microbiome reveals a common family of antibiotics. *Cell* **158**, 1402–1414 (2014).
15. Russell, A. H. & Truman, A. W. Genome mining strategies for ribosomally synthesised and post-translationally modified peptides. *Comput Struct. Biotechnol. J.* **18**, 1838–1851 (2020).
16. Lagier, J.-C. et al. Culturing the human microbiota and culturomics. *Nat. Rev. Microbiol* **16**, 540–550 (2018).
17. Antimicrobial resistance. https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance.
18. Nicholson, J. K. et al. Host-Gut Microbiota Metabolic Interactions. *Science* **336**, 1262–1267 (2012).
19. Olalekan, S. O. et al. Gut microbiota-derived metabolites: implications for metabolic syndrome and therapeutic interventions. *Egypt. J. Intern. Med.* **36**, 72 (2024).
20. Vo, D.-K. & Trinh, K. T. L. Emerging Biomarkers in Metabolomics: Advancements in Precision Health and Disease Diagnosis. *Int. J. Mol. Sci.* **25**, 13190 (2024).
21. Jung, Y. H., Chae, C. W. & Han, H. J. The potential role of gut microbiota-derived metabolites as regulators of metabolic syndrome-associated mitochondrial and endolysosomal dysfunction in Alzheimer's disease. *Exp. Mol. Med.* **56**, 1691–1702 (2024).
22. Shah, A. B. & Shim, S. H. Human microbiota peptides: important roles in human health. *Nat. Prod. Rep*. https://doi.org/10.1039/D4NP00042K (2024).
23. Donia, M. S. & Fischbach, M. A. Small molecules from the human microbiota. *Science* **349**, 1254766 (2015).
24. Zhao, M. et al. Immunological mechanisms of inflammatory diseases caused by gut microbiota dysbiosis: A review. *Biomedicine Pharmacother.* **164**, 114985 (2023).
25. Bock, P. M., Martins, A. F. & Schaan, B. D. Understanding how pre- and probiotics affect the gut microbiome and metabolic health. *Am. J. Physiol.-Endocrinol. Metab.* **327**, E89–E102 (2024).
26. Koppel, N. & Balskus, E. P. Exploring and Understanding the Biochemical Diversity of the Human Microbiota. *Cell Chem. Biol.* **23**, 18–30 (2016).
27. Garcia-Gutierrez, E., Mayer, M. J., Cotter, P. D. & Narbad, A. Gut microbiota as a source of novel antimicrobials. *Gut Microbes* **10**, 1–21 (2019).
28. Binda, C. et al. Actinobacteria: A relevant minority for the maintenance of gut homeostasis. *Dig. Liver Dis.* **50**, 421–428 (2018).
29. Shin, N. R. et al. Proteobacteria: microbial signature of dysbiosis in gut microbiota. *Trends Biotechnol.* **33**, 496–503 (2015).
30. Abdel-Nasser, A., Hathout, A. S., Badr, A. N., Barakat, O. S. & Fathy, H. M. Extraction and characterization of bioactive secondary metabolites from lactic acid bacteria and evaluating their antifungal and antiaflatoxigenic activity. *Biotechnol. Rep. (Amst.)* **38**, e00799 (2023).
31. Crowley, S., Mahony, J. & van Sinderen, D. Current perspectives on antifungal lactic acid bacteria as natural bio-preservatives. *Trends Food Sci. Technol.* **33**, 93–109 (2013).

32. Mu, Q., Tavella, V. J. & Luo, X. M. Role of Lactobacillus reuteri in Human Health and Diseases. *Front. Microbiol.* **9**, 757 (2018).
33. Talarico, T. L., Casas, I. A., Chung, T. C. & Dobrogosz, W. J. Production and isolation of reuterin, a growth inhibitor produced by Lactobacillus reuteri. *Antimicrob. Agents Chemother.* **32**, 1854–1858 (1988).
34. Dalal, K. S., Patil, S. P., Pendharkar, G. B., Dalal, D. S. & Chaudhari, B. L. Reuterin: A Broad Spectrum Antimicrobial Agent and Its Applications. in *Industrial Microbiology and Biotechnology: Emerging concepts in Microbial Technology* (ed. Verma, P.) 585–604 (Springer Nature, Singapore, 2023). https://doi.org/10.1007/978-981-99-2816-3_20.
35. Schaefer, L. et al. The antimicrobial compound reuterin (3-hydroxypropionaldehyde) induces oxidative stress via interaction with thiol groups. *Microbiology* **156**, 1589 (2010).
36. Arqués, J. L., Rodríguez, E., Nuñez, M. & Medina, M. Combined effect of reuterin and lactic acid bacteria bacteriocins on the inactivation of food-borne pathogens in milk. *Food Control* **22**, 457–461 (2011).
37. Gänzle, M. G., Höltzel, A., Walter, J., Jung, G. & Hammes, W. P. Characterization of Reutericyclin Produced by Lactobacillus reuteri LTH2584. *Appl. Environ. Microbiol.* **66**, 4325 (2000).
38. Uranga, C., Nelson, K. E., Edlund, A. & Baker, J. L. Tetramic Acids Mutanocyclin and Reutericyclin A, Produced by Streptococcus mutans Strain B04Sm5 Modulate the Ecology of an in vitro Oral Biofilm. *Front. Oral. Health* **2**, 796140 (2022).
39. Fang, Y. et al. Roles of Streptococcus mutans in human health: beyond dental caries. *Front. Microbiol*. **15**, 1503657 (2024).
40. Tao, L. et al. Streptococcus mutans suppresses filamentous growth of Candida albicans through secreting mutanocyclin, an unacylated tetramic acid. *Virulence* **13**, 542–557 (2022).
41. MacAlpine, J. et al. A small molecule produced by Lactobacillus species blocks Candida albicans filamentation by inhibiting a DYRK1-family kinase. *Nat. Commun.* **12**, 6151 (2021).
42. Sugimura, N. et al. Lactobacillus gallinarum modulates the gut microbiota and produces anti-cancer metabolites to protect against colorectal tumourigenesis. *Gut* **71**, 2011–2021 (2022).
43. Dieterle, M. G., Rao, K. & Young, V. B. Novel therapies and preventative strategies for primary and recurrent Clostridium difficile infections. *Ann. N. Y Acad. Sci.* **1435**, 110–138 (2019).
44. Guo, P., Zhang, K., Ma, X. & He, P. Clostridium species as probiotics: potentials and challenges. *J. Anim. Sci. Biotechnol.* **11**, 24 (2020).
45. Baldassi, L. Clostridial toxins: potent poisons, potent medicines. *J. Venom. Anim. Toxins incl. Trop. Dis.* **11**, 391–411 (2005).
46. Bouvet, P. et al. An Atypical Clostridium Strain Related to the Clostridium botulinum Group III Strain Isolated from a Human Blood Culture. *J. Clin. Microbiol.* **52**, 339–343 (2020).
47. Bette, P. et al. A comparative biochemical, pharmacological and immunological study of Clostridium novyi alpha-toxin, C. difficile toxin B and C. sordellii lethal toxin. *Toxicon* **29**, 877–887 (1991).
48. Ben Braïek, O. & Smaoui, S. Enterococci: Between Emerging Pathogens and Potential Probiotics. *Biomed. Res. Int.* **2019**, 5938210 (2019).
49. Hanchi, H., Mottawea, W., Sebei, K. & Hammami, R. The Genus Enterococcus: Between Probiotic Potential and Safety Concerns—An Update. *Front. Microbiol*. **9**, 1791 (2018).
50. Krawczyk, B., Wityk, P., Gałęcka, M. & Michalik, M. The Many Faces of Enterococcus spp.—Commensal, Probiotic and Opportunistic Pathogen. *Microorganisms* **9**, 1900 (2021).
51. Gaur, S. S. & Annapure, U. S. Untargeted metabolite profiling of Enterococcus villorum SB2, isolated from the vagina of pregnant women, by HR-LCMS. *World J. Microbiol Biotechnol.* **38**, 219 (2022).
52. Bhagwat, A. & Annapure, U. S. In vitro assessment of metabolic profile of *Enterococcus* strains of human origin. *J. Genet. Eng. Biotechnol.* **17**, 11 (2019).
53. Beltrán, D. et al. NMR Spectroscopic Identification of Urolithin G, a Novel Trihydroxy Urolithin Produced by Human Intestinal Enterocloster Species. *J. Agric Food Chem.* **71**, 11921–11928 (2023).
54. Amini Khiabani, S., Haghighat, S., Tayebi Khosroshahi, H., Asgharzadeh, M. & Samadi Kafil, H. Diversity of Bacteroidaceae family in gut microbiota of patients with chronic kidney disease and end stage renal disease. *Health Promot Perspect.* **13**, 237–242 (2023).
55. Gautier, T. et al. Bacteroides fragilis derived metabolites, identified by molecular networking, decrease Salmonella virulence in mice model. *Front Microbiol* **13**, 1023315 (2022).
56. Elsaghir, H. & Reddivari, A. K. R. Bacteroides Fragilis. in *StatPearls* (StatPearls Publishing, Treasure Island (FL), 2025).
57. Russell, W. R. et al. Major phenylpropanoid-derived metabolites in the human gut can arise from microbial fermentation of protein. *Mol. Nutr. Food Res.* **57**, 523–535 (2013).
58. An, D. et al. Sphingolipids from a Symbiotic Microbe Regulate Homeostasis of Host Intestinal Natural Killer T Cells. *Cell* **156**, 123–133 (2014).
59. Le, H. H., Lee, M.-T., Besler, K. R. & Johnson, E. L. Host hepatic metabolism is modulated by gut microbiota-derived sphingolipids. *Cell Host Microbe* **30**, 798–808.e7 (2022).
60. Brown, E. M. et al. Bacteroides-Derived Sphingolipids Are Critical for Maintaining Intestinal Homeostasis and Symbiosis. *Cell Host Microbe* **25**, 668–680.e7 (2019).
61. Walker, A. et al. Sulfonolipids as novel metabolite markers of Alistipes and Odoribacter affected by high-fat diets. *Sci. Rep.* **7**, 11047 (2017).
62. Rizzatti, G., Lopetuso, L. R., Gibiino, G., Binda, C. & Gasbarrini, A. Proteobacteria: A Common Factor in Human Diseases. *BioMed. Res. Int.* **2017**, e9351507 (2017).
63. Kaper, J. B., Nataro, J. P. & Mobley, H. L. Pathogenic Escherichia coli. *Nat. Rev. Microbiol* **2**, 123–140 (2004).
64. Mueller, M. & Tainter, C. R. Escherichia coli Infection. in *StatPearls* (StatPearls Publishing, Treasure Island (FL), 2024).
65. Cooley, M. A., Whittall, C. & Rolph, M. S. *Pseudomonas* signal molecule 3-oxo-C12-homoserine lactone interferes with binding of rosiglitazone to human PPARγ. *Microbes Infect.* **12**, 231–237 (2010).
66. Wheatley, R. M. et al. Gut to lung translocation and antibiotic mediated selection shape the dynamics of Pseudomonas aeruginosa in an ICU patient. *Nat. Commun.* **13**, 6523 (2022).
67. Hall, S. et al. Cellular Effects of Pyocyanin, a Secreted Virulence Factor of Pseudomonas aeruginosa. *Toxins* **8**, 236 (2016).
68. Schiessl, K. T. et al. Phenazine production promotes antibiotic tolerance and metabolic heterogeneity in Pseudomonas aeruginosa biofilms. *Nat. Commun.* **10**, 762 (2019).
69. Soberón-Chávez, G., González-Valdez, A., Soto-Aceves, M. P. & Cocotl-Yañez, M. Rhamnolipids produced by Pseudomonas: from molecular genetics to the market. *Micro. Biotechnol.* **14**, 136–146 (2020).
70. Balíková, K. et al. Role of Exopolysaccharides of Pseudomonas in Heavy Metal Removal and Other Remediation Strategies. *Polymers* **14**, 4253 (2022).
71. Holden, V. I., Breen, P., Houle, S., Dozois, C. M. & Bachman, M. A. Klebsiella pneumoniae Siderophores Induce Inflammation, Bacterial Dissemination, and HIF-1α Stabilization during Pneumonia. *mBio* **7**, e01397–16 (2016).
72. Schneditz, G. et al. Enterotoxicity of a nonribosomal peptide causes antibiotic-associated colitis. *Proc. Natl Acad. Sci. USA* **111**, 13181–13186 (2014).
73. Ramirez, D. & Giron, M. Enterobacter Infections. in *StatPearls* (StatPearls Publishing, Treasure Island (FL), 2024).

74. Yin, Q. et al. Ecological dynamics of Enterobacteriaceae in the human gut microbiome across global populations. *Nat. Microbiol* **10**, 541–553 (2025).
75. Boopathi, S. et al. Gut Enterobacteriaceae and uraemic toxins - Perpetrators for ageing. *Exp. Gerontol.* **173**, 112088 (2023).
76. Du, K. et al. Combination of organic acids benzoate, butyrate, caprylate, and sorbate provides a novel antibiotics-independent treatment option in the combat of acute campylobacteriosis. *Front Microbiol* **14**, 1128500 (2023).
77. Wu, C. Human Microbiome, Actinobacteria in. in *Encyclopedia of Metagenomics* (ed. Nelson, K. E.) 1–7 https://doi.org/10.1007/978-1-4614-6418-1_76-9. (Springer, New York, NY, 2013).
78. Binda, C. et al. Actinobacteria: A relevant minority for the maintenance of gut homeostasis. *Digestive Liver Dis.* **50**, 421–428 (2018).
79. Dekaboruah, E., Suryavanshi, M. V., Chettri, D. & Verma, A. K. Human microbiome: an academic update on human body site specific surveillance and its possible role. *Arch. Microbiol* **202**, 2147–2167 (2020).
80. Díaz, R., Torres-Miranda, A., Orellana, G. & Garrido, D. Comparative Genomic Analysis of Novel Bifidobacterium longum subsp. longum Strains Reveals Functional Divergence in the Human Gut Microbiota. *Microorganisms* **9**, 1906 (2021).
81. Kitagawa, W. & Tamura, T. A Quinoline Antibiotic from Rhodococcus erythropolis JCM 6824. *J. Antibiot.* **61**, 680–682 (2008).
82. Kitagawa, W. & Tamura, T. Three Types of Antibiotics Produced from Rhodococcus erythropolis Strains. *Microbes Environ.* **23**, 167–171 (2008).
83. Chu, J. et al. Discovery of MRSA active antibiotics using primary sequence from the human microbiome. *Nat. Chem. Biol.* **12**, 1004–1006 (2016).
84. Cloud, J. L. et al. Identification of Mycobacterium spp. by Using a Commercial 16S Ribosomal DNA Sequencing Kit and Additional Sequencing Libraries. *J. Clin. Microbiol.* **40**, 400–406 (2002).
85. Block, A. M. et al. Mycobacterium tuberculosis Requires the Outer Membrane Lipid Phthiocerol Dimycocerosate for Starvation-Induced Antibiotic Tolerance. *mSystems* **8**, e0069922 (2023).
86. Draper, P., Payne, S. N., Dobson, G. & Minnikin, D. E. Isolation of a Characteristic Phthiocerol Dimycocerosate from Mycobacterium leprae. *Microbiology* **129**, 859–863 (1983).
87. Flores, J., Cancino, J. C. & Chavez-Galan, L. Lipoarabinomannan as a Point-of-Care Assay for Diagnosis of Tuberculosis: How Far Are We to Use It? *Front. Microbiol*. **12**, 638047 (2021).
88. Mve-Obiang, A., Lee, R. E., Portaels, F. & Small, P. L. C. Heterogeneity of Mycolactones Produced by Clinical Isolates of Mycobacterium ulcerans: Implications for Virulence. *Infect. Immun.* **71**, 774–783 (2003).
89. Mikami, Y. et al. A New Antifungal Macrolide Component, Brasilinolide B, Produced by Nocardia brasiliensis. *J. Antibiot.* **53**, 70–74 (2000).
90. Mukai, A. et al. Transvalencin Z, a New Antimicrobial Compound with Salicylic Acid Residue from Nocardia transvalensis IFM 10065. *J. Antibiot.* **59**, 366–369 (2006).
91. Tanaka, Y., Gräfe, U., Yazawa, K., Mikami, Y. & Ritzau, M. Nocardicyclins A and B: New Anthracycline Antibiotics Produced by Nocardia pseudobrasiliensis. *J. Antibiot.* **50**, 822–827 (1997).
92. Mukai, A., Komaki, H., Takagi, M. & Shin-ya, K. Novel siderophore, JBIR-16, isolated from Nocardia tenerifensis NBRC 101015. *J. Antibiot.* **62**, 601–603 (2009).
93. Chen, Y. et al. Gut Fungal Microbiota Alterations in Pulmonary Arterial Hypertensive Rats. *Biomedicines* **12**, 298 (2024).
94. Zhang, F., Aschenbrenner, D., Yoo, J. Y. & Zuo, T. The gut mycobiome in health, disease, and clinical applications in association with the gut bacterial microbiome assembly. *Lancet Microbe* **3**, e969–e983 (2022).
95. Schmidt, A. Malassezia furfur: a fungus belonging to the physiological skin flora and its relevance in skin disorders. *Cutis* **59**, 21–24 (1997).
96. Peroumal, D., Sahu, S. R., Kumari, P., Utkalaja, B. G. & Acharya, N. Commensal Fungus Candida albicans Maintains a Long-Term Mutualistic Relationship with the Host To Modulate Gut Microbiota and Metabolism. *Microbiol. Spectr.* **10**, e02462–22.
97. Wang, L. et al. Gut mycobiome and metabolic diseases: The known, the unknown, and the future. *Pharmacol. Res.* **193**, 106807 (2023).
98. McAlester, G., O'Gara, F. & Morrissey, J. P. Signal-mediated interactions between Pseudomonas aeruginosa and Candida albicans. *J. Med Microbiol* **57**, 563–569 (2008).
99. Lapiere, A. & Richard, M. L. Bacterial-fungal metabolic interactions within the microbiota and their potential relevance in human health and disease: a short review. *Gut. Microbes* **14**, 2105610 (2022).
100. Begum, N. et al. Host-mycobiome metabolic interactions in health and disease. *Gut Microbes* **14**, 2121576 (2022).
101. Magee, L. C., Louis, M., Khan, V., Micalo, L. & Chaudary, N. Managing Fungal Infections in Cystic Fibrosis Patients: Challenges in Clinical Practice. *Infect. Drug Resist* **14**, 1141–1153 (2021).
102. Grainha, T., Jorge, P., Alves, D., Lopes, S. P. & Pereira, M. O. Unraveling Pseudomonas aeruginosa and Candida albicans Communication in Coinfection Scenarios: Insights Through Network Analysis. *Front Cell Infect. Microbiol* **10**, 550505 (2020).
103. Sugawara, T. et al. YM-170320, a Novel Lipopeptide Antibiotic Inducing Morphological Change of Colonies in a Mutant of Candida tropicalis pK233. *J. Antibiot.* **51**, 435–438 (1998).
104. Wang, D. et al. Candida tropicalis distribution and drug resistance is correlated with ERG11 and UPC2 expression. *Antimicrobial Resistance Infect. Control* **10**, 54 (2021).
105. Shuai, M. et al. Mapping the human gut mycobiome in middle-aged and elderly adults: multiomics insights and implications for host metabolic health. *Gut* **71**, 1812–1820 (2022).
106. Kwon-Chung, K. J. & Sugui, J. A. Aspergillus fumigatus—What Makes the Species a Ubiquitous Human Fungal Pathogen? *PLoS Pathog.* **9**, e1003743 (2013).
107. Frisvad, J. C., Rank, C., Nielsen, K. F. & Larsen, T. O. Metabolomics of Aspergillus fumigatus. *Med Mycol.* **47**(Suppl 1), S53–S71 (2009).
108. Dagenais, T. R. T. & Keller, N. P. Pathogenesis of Aspergillus fumigatus in Invasive Aspergillosis. *Clin. Microbiol Rev.* **22**, 447–465 (2009).
109. Rokas, A. Evolution of the human pathogenic lifestyle in fungi. *Nat. Microbiol* **7**, 607–619 (2022).
110. Hof, H. Rhodotorula spp. in the gut - foe or friend? *GMS Infect. Dis.* **7**, Doc02 (2019).
111. Bongomin, F., Gago, S., Oladele, R. O. & Denning, D. W. Global and Multi-National Prevalence of Fungal Diseases-Estimate Precision. *J. Fungi (Basel)* **3**, 57 (2017).
112. Peredo-Lovillo, A., Romero-Luna, H. E. & Jiménez-Fernández, M. Health promoting microbial metabolites produced by gut microbiota after prebiotics metabolism. *Food Res. Int.* **136**, 109473 (2020).
113. Holscher, H. D. Dietary fiber and prebiotics and the gastrointestinal microbiota. *Gut Microbes* **8**, 172–184 (2017).
114. Nisin biosynthesis and its properties. *Biotechnol. Lett.* **27**, 1641–1648 (2005)
115. Heilbronner, S., Krismer, B., Brötz-Oesterhelt, H. & Peschel, A. The microbiome-shaping roles of bacteriocins. *Nat. Rev. Microbiol* **19**, 726–739 (2021).
116. de Arauz, L. J., Jozala, A. F., Mazzola, P. G. & Vessoni Penna, T. C. Nisin biotechnological production and application: a review. *Trends Food Sci. Technol.* **20**, 146–154 (2009).
117. Rogers, L. A. & Whittier, E. O. Limiting factors in the lactic fermentation. *J. Bacteriol.* **16**, 211–229 (1928).
118. Shin, J. M. et al. Biomedical Applications of Nisin. *J. Appl Microbiol* **120**, 1449–1465 (2016).

119. Mulders, J. W. M., Boerrigter, I. J., Rollema, H. S., Siezen, R. J. & de VOS, W. M. Identification and characterization of the lantibiotic nisin Z, a natural nisin variant. *Eur. J. Biochem.* **201**, 581–584 (1991).
120. ZENDO, T. et al. Identification of the Lantibiotic Nisin Q, a New Natural Nisin Variant Produced by Lactococcus lactis 61-14 Isolated from a River in Japan. *Biosci., Biotechnol., Biochem.* **67**, 1616–1619 (2003).
121. de Kwaadsteniet, M., ten Doeschate, K. & Dicks, L. M. T. Characterization of the Structural Gene Encoding Nisin F, a New Lantibiotic Produced by a Lactococcus lactis subsp. lactis Isolate from Freshwater Catfish (Clarias gariepinus). *Appl. Environ. Microbiol.* **74**, 547–549 (2008).
122. Wirawan, R. E., Klesse, N. A., Jack, R. W. & Tagg, J. R. Molecular and Genetic Characterization of a Novel Nisin Variant Produced by Streptococcus uberis. *Appl. Environ. Microbiol.* **72**, 1148–1156 (2006).
123. Garcia-Gutierrez, E. et al. First evidence of production of the lantibiotic nisin P. *Sci. Rep.* **10**, 3738 (2020).
124. O'Sullivan, J. N. et al. Nisin J, a Novel Natural Nisin Variant, Is Produced by Staphylococcus capitis Sourced from the Human Skin Microbiota. *J. Bacteriol.* **202**, e00639–19 (2020).
125. Hatziioanou, D. et al. Discovery of a novel lantibiotic nisin O from Blautia obeum A2-162, isolated from the human gastrointestinal tract. *Microbiol. (Read.)* **163**, 1292–1305 (2017).
126. O'Connor, P. M. et al. Nisin H Is a New Nisin Variant Produced by the Gut-Derived Strain Streptococcus hyointestinalis DPC6484. *Appl. Environ. Microbiol.* **81**, 3953–3960 (2015).
127. Arnison, P. G. et al. Ribosomally synthesized and post-translationally modified peptide natural products: overview and recommendations for a universal nomenclature. *Nat. Prod. Rep.* **30**, 108–160 (2013).
128. Itoh, T., Fujimoto, Y., Kawai, Y., Toba, T. & Saito, T. Inhibition of food-borne pathogenic bacteria by bacteriocins from Lactobacillus gasseri. *Lett. Appl. Microbiol.* **21**, 137–141 (1995).
129. Kawai, Y. et al. Primary amino acid and DNA sequences of gassericin T, a lactacin F-family bacteriocin produced by Lactobacillus gasseri SBT2055. *Biosci. Biotechnol. Biochem* **64**, 2201–2208 (2000).
130. Kabuki, T., Saito, T., Kawai, Y., Uemura, J. & Itoh, T. Production, purification and characterization of reutericin 6, a bacteriocin with lytic activity produced by *Lactobacillus reuteri* LA6. *Int. J. Food Microbiol.* **34**, 145–156 (1997).
131. Pandey, N., Malik, R. K., Kaushik, J. K. & Singroha, G. Gassericin A: a circular bacteriocin produced by Lactic acid bacteria Lactobacillus gasseri. *World J. Microbiol Biotechnol.* **29**, 1977–1987 (2013).
132. Gonzalez, B. et al. Bactericidal Mode of Action of Plantaricin C. *Appl Environ. Microbiol* **62**, 2701–2709 (1996).
133. Sand, S. L., Nissen-Meyer, J., Sand, O. & Haug, T. M. Plantaricin A, a cationic peptide produced by *Lactobacillus plantarum*, permeabilizes eukaryotic cell membranes by a mechanism dependent on negative surface charge linked to glycosylated membrane proteins. *Biochimica et. Biophysica Acta (BBA) - Biomembranes* **1828**, 249–259 (2013).
134. Anderssen, E. L., Diep, D. B., Nes, I. F., Eijsink, V. G. H. & Nissen-Meyer, J. Antagonistic Activity of Lactobacillus plantarum C11: Two New Two-Peptide Bacteriocins, Plantaricins EF and JK, and the Induction Factor Plantaricin A. *Appl Environ. Microbiol* **64**, 2269–2272 (1998).
135. Leer, R. J., van der Vossen, J. M. B. M., van Giezen, M., van Noort Johannes, M. & Pouwels, P. H. Genetic analysis of acidocin B, a novel bacteriocin produced by Lactobacillus acidophilus. *Microbiology* **141**, 1629–1635 (1995).
136. Dimitrijević, R. et al. The identification of a low molecular mass bacteriocin, rhamnosin A, produced by Lactobacillus rhamnosus strain 68. *J. Appl Microbiol* **107**, 2108–2115 (2009).
137. Callewaert, R. et al. Characterization and production of amylovorin L471, a bacteriocin purified from Lactobacillus amylovorus DCE 471 by a novel three-step method. *Microbiol. (Read.)* **145**, 2559–2568 (1999).
138. Abee, T., Klaenhammer, T. R. & Letellier, L. Kinetic studies of the action of lactacin F, a bacteriocin produced by Lactobacillus johnsonii that forms poration complexes in the cytoplasmic membrane. *Appl Environ. Microbiol* **60**, 1006–1013 (1994).
139. Barbour, A., Wescombe, P. & Smith, L. Evolution of Lantibiotic Salivaricins: New Weapons to Fight Infectious Diseases. *Trends Microbiol.* **28**, 578–593 (2020).
140. Flynn, S. et al. Characterization of the genetic locus responsible for the production of ABP-118, a novel bacteriocin produced by the probiotic bacterium Lactobacillus salivarius subsp. salivarius UCC118. *Microbiol. (Read.)* **148**, 973–984 (2002).
141. Birri, D. J., Brede, D. A., Nes, I. F. & Salivaricin, D. a Novel Intrinsically Trypsin-Resistant Lantibiotic from Streptococcus salivarius 5M6c Isolated from a Healthy Infant. *Appl Environ. Microbiol* **78**, 402–410 (2012).
142. Ross, K. F., Ronson, C. W. & Tagg, J. R. Isolation and characterization of the lantibiotic salivaricin A and its structural gene salA from Streptococcus salivarius 20P3. *Appl Environ. Microbiol* **59**, 2014–2021 (1993).
143. Barbour, A., Philip, K. & Muniandy, S. Enhanced Production, Purification, Characterization and Mechanism of Action of Salivaricin 9 Lantibiotic Produced by Streptococcus salivarius NU10. *PLOS ONE* **8**, e77751 (2013).
144. Hyink, O. et al. Salivaricin A2 and the Novel Lantibiotic Salivaricin B Are Encoded at Adjacent Loci on a 190-Kilobase Transmissible Megaplasmid in the Oral Probiotic Strain Streptococcus salivarius K12. *Appl Environ. Microbiol* **73**, 1107–1113 (2007).
145. Bien, J., Palagani, V. & Bozko, P. The intestinal microbiota dysbiosis and Clostridium difficile infection: is there a relationship with inflammatory bowel disease? *Ther. Adv. Gastroenterol.* **6**, 53–68 (2013).
146. Dineen, S. S., Bradshaw, M. & Johnson, E. A. Cloning, Nucleotide Sequence, and Expression of the Gene Encoding the Bacteriocin Boticin B from Clostridium botulinum Strain 213B. *Appl. Environ. Microbiol.* **66**, 5480–5483 (2000).
147. Kemperman, R. et al. Identification and Characterization of Two Novel Clostridial Bacteriocins, Circularin A and Closticin 574. *Appl Environ. Microbiol* **69**, 1589–1597 (2003).
148. Todokoro, D., Tomita, H., Inoue, T. & Ike, Y. Genetic analysis of bacteriocin 43 of vancomycin-resistant Enterococcus faecium. *Appl Environ. Microbiol* **72**, 6955–6964 (2006).
149. Inoue, T., Tomita, H. & Ike, Y. Bac 32, a novel bacteriocin widely disseminated among clinical isolates of Enterococcus faecium. *Antimicrob. Agents Chemother.* **50**, 1202–1212 (2006).
150. Tomita, H., Fujimoto, S., Tanimoto, K. & Ike, Y. Cloning and genetic organization of the bacteriocin 31 determinant encoded on the Enterococcus faecalis pheromone-responsive conjugative plasmid pYI17. *J. Bacteriol.* **178**, 3585–3593 (1996).
151. del Campo, R. et al. Bacteriocin production in vancomycin-resistant and vancomycin-susceptible Enterococcus isolates of different origins. *Antimicrob. Agents Chemother.* **45**, 905–912 (2001).
152. Gálvez, A., Maqueda, M., Valdivia, E., Quesada, A. & Montoya, E. Characterization and partial purification of a broad spectrum antibiotic AS-48 produced by Streptococcus faecalis. *Can. J. Microbiol* **32**, 765–771 (1986).
153. Marcille, F. et al. Distribution of Genes Encoding the Trypsin-Dependent Lantibiotic Ruminococcin A among Bacteria Isolated from Human Fecal Microbiota. *Appl. Environ. Microbiol.* **68**, 3424–3431 (2002).
154. Schneider, B. A. & Balskus, E. P. Discovery of small molecule protease inhibitors by investigating a widespread human gut bacterial biosynthetic pathway. *Tetrahedron* **74**, 3215–3230 (2018).

155. Ekkelenkamp, M. B. et al. Isolation and structural characterization of epilancin 15X, a novel lantibiotic from a clinical strain of *Staphylococcus epidermidis*. *FEBS Lett.* **579**, 1917–1922 (2005).
156. Van De Kamp, M. et al. Sequence Analysis by NMR Spectroscopy of the Peptide Lantibiotic Epilancin K7 from Staphylococcus epidermidis K7. *Eur. J. Biochem.* **227**, 757–771 (1995).
157. Van De Kamp, M. et al. Elucidation of the Primary Structure of the Lantibiotic Epilancin K7 from Staphylococcus epidermidis K7. *Eur. J. Biochem.* **230**, 587–600 (1995).
158. Allgaier, H., Jung, G., Werner, R. G., Schneider, U. & Zähner, H. Epidermin: sequencing of a heterodet tetracyclic 21-peptide amide antibiotic. *Eur. J. Biochem.* **160**, 9–22 (1986).
159. Sandiford, S. & Upton, M. Identification, Characterization, and Recombinant Expression of Epidermicin NI01, a Novel Unmodified Bacteriocin Produced by Staphylococcus epidermidis That Displays Potent Activity against Staphylococci. *Antimicrob. Agents Chemother.* **56**, 1539–1547 (2012).
160. Brötz, H. et al. Role of lipid-bound peptidoglycan precursors in the formation of pores by nisin, epidermin and other lantibiotics. *Mol. Microbiol.* **30**, 317–327 (1998).
161. Heidrich, C. et al. Isolation, Characterization, and Heterologous Expression of the Novel Lantibiotic Epicidin 280 and Analysis of Its Biosynthetic Gene Cluster. *Appl. Environ. Microbiol.* **64**, 3140–3146 (1998).
162. Fontana, M. B. C., de Bastos, M., do & Brandelli, C. F. A. Bacteriocins Pep5 and Epidermin Inhibit Staphylococcus epidermidis Adhesion to Catheters. *Curr. Microbiol* **52**, 350–353 (2006).
163. Puls, J.-S. et al. Staphylococcus epidermidis bacteriocin A37 kills natural competitors with a unique mechanism of action. *ISME J.* **18**, wrae044 (2024).
164. Zipperer, A. et al. Human commensals producing a novel antibiotic impair pathogen colonization. *Nature* **535**, 511–516 (2016).
165. Liu, Y. et al. Skin microbiota analysis-inspired development of novel anti-infectives. *Microbiome* **8**, 85 (2020).
166. Zvanych, R. et al. Systems biosynthesis of secondary metabolic pathways within the oral human microbiome member Streptococcus mutans. *Mol. BioSyst.* **11**, 97–104 (2014).
167. Joyner, P. M. et al. Mutanobactin A from the human oral pathogen Streptococcus mutans is a cross-kingdom regulator of the yeast-mycelium transition. *Org. Biomol. Chem.* **8**, 5486–5489 (2010).
168. Hillman, J. D. et al. Genetic and Biochemical Analysis of Mutacin 1140, a Lantibiotic from Streptococcus mutans. *Infect. Immun.* **66**, 2743–2749 (1998).
169. Mota-Meira, M., Lacroix, C., LaPointe, G. & Lavoie, M. C. Purification and structure of mutacin B-Ny266: a new lantibiotic produced by Streptococcus mutans. *FEBS Lett.* **410**, 275–279 (1997).
170. Proutière, A. et al. Gallocin A, an Atypical Two-Peptide Bacteriocin with Intramolecular Disulfide Bonds Required for Activity. *Microbiol. Spectr.* **11**, e05085-22 (2023).
171. Hill, D. et al. Extensive bacteriocin gene shuffling in the Streptococcus bovis/Streptococcus equinus complex reveals gallocin D with activity against vancomycin resistant enterococci. *Sci. Rep.* **10**, 13431 (2020).
172. Saksena, S., Forbes, K., Rajan, N. & Giles, D. Phylogenetic investigation of Gammaproteobacteria proteins involved in exogenous long-chain fatty acid acquisition and assimilation. *Biochem Biophys. Rep.* **35**, 101504 (2023).
173. Gaillard-Gendron, S. et al. Isolation, purification and partial amino acid sequence of a highly hydrophobic new microcin named microcin L produced by Escherichia coli. *FEMS Microbiol. Lett.* **193**, 95–98 (2000).
174. Patzer, S. I., Baquero, M. R., Bravo, D., Moreno, F. & Hantke, K. The colicin G, H and X determinants encode microcins M and H47, which might utilize the catecholate siderophore receptors FepA, Cir, Fiu and IroN. *Microbiol. (Read.)* **149**, 2557–2570 (2003).
175. Laviña, M., Gaggero, C. & Moreno, F. Microcin H47, a chromosome-encoded microcin antibiotic of Escherichia coli. *J. Bacteriol.* **172**, 6585–6588 (1990).
176. Salomón, R. A. & Farías, R. N. Microcin 25, a novel antimicrobial peptide produced by Escherichia coli. *J. Bacteriol.* **174**, 7428–7435 (1992).
177. Cascales, E. et al. Colicin biology. *Microbiol Mol. Biol. Rev.* **71**, 158–229 (2007).
178. Khmel, I. A. et al. Isolation and characterization of Escherichia coli strains producing microcins of B and C types. *FEMS Microbiol Lett.* **111**, 269–274 (1993).
179. Kang, D., Kirienko, D. R., Webster, P., Fisher, A. L. & Kirienko, N. V. Pyoverdine, a siderophore from Pseudomonas aeruginosa, translocates into C. elegans, removes iron, and activates a distinct host response. *Virulence* **9**, 804–817 (2018).
180. Watanabe, T. & Saito, H. Cytotoxicity of pyocin S2 to tumor and normal cells and its interaction with cell surfaces. *Biochimica et. Biophysica Acta (BBA) - Gen. Subj.* **633**, 77–86 (1980).
181. Onori, R. et al. Tracking Nosocomial Klebsiella pneumoniae Infections and Outbreaks by Whole-Genome Analysis: Small-Scale Italian Scenario within a Single Hospital. *J. Clin. Microbiol.* **53**, 2861–2868 (2015).
182. Le, T. et al. Clinical and microbiological characteristics of nosocomial, healthcare-associated, and community-acquired Klebsiella pneumoniae infections in Guangzhou, China. *Antimicrobial Resistance Infect. Control* **10**, 41 (2021).
183. Strakova, N., Korena, K. & Karpiskova, R. *Klebsiella pneumoniae* producing bacterial toxin colibactin as a risk of colorectal cancer development - A systematic review. *Toxicon* **197**, 126–135 (2021).
184. Dornisch, E. et al. Biosynthesis of the Enterotoxic Pyrrolobenzodiazepine Natural Product Tilivalline. *Angew. Chem. Int Ed. Engl.* **56**, 14753–14757 (2017).
185. Hering, N. A. et al. Tilivalline- and Tilimycin-Independent Effects of Klebsiella oxytoca on Tight Junction-Mediated Intestinal Barrier Impairment. *Int J. Mol. Sci.* **20**, 5595 (2019).
186. Yildirim, Z. & Johnson, M. G. Characterization and Antimicrobial Spectrum of Bifidocin B, a Bacteriocin Produced by *Bifidobacterium bifidum* NCFB 1454†‡. *J. Food Prot.* **61**, 47–51 (1998).
187. Cheikhyoussef, A. et al. Bifidin I – A new bacteriocin produced by *Bifidobacterium infantis* BCRC 14602: Purification and partial amino acid sequence. *Food Control* **21**, 746–753 (2010).
188. Mukai, A. et al. Nocardithiocin, a novel thiopeptide antibiotic, produced by pathogenic Nocardia pseudobrasiliensis IFM 0757. *J. Antibiot.* **62**, 613–619 (2009).
189. Kollarcikova, M. et al. Different Bacteroides Species Colonise Human and Chicken Intestinal Tract. *Microorganisms* **8**, 1483 (2020).
190. Cohen, L. J. et al. Functional metagenomic discovery of bacterial effectors in the human microbiome and isolation of commendamide, a GPCR G2A/132 agonist. *Proc. Natl Acad. Sci. USA* **112**, E4825–E4834 (2015).
191. Coyne, M. J. et al. A family of anti-Bacteroidales peptide toxins wide-spread in the human gut microbiota. *Nat. Commun.* **10**, 3460 (2019).

Acknowledgements

This research was supported by the Bio and Medical Technology Development Program of the National Research Foundation (NRF), funded by the Korean government (MSIT) (No. RS-2024-00352229), and the National Research Foundation (NRF) of Korea (NRF-2021R1A2C1004958 and NRF-2022R1A4A3022401).

Author contributions

Conceptualization and writing of the original draft: A.B.S. Formal analysis and investigation: C.H. Writing, editing, supervision, and funding: S.H.S. All the authors have read and agreed to the published version of the manuscript.

Competing interests

The authors declare no competing interests.

Additional information

Correspondence and requests for materials should be addressed to Sang Hee Shim.

Reprints and permissions information is available at http://www.nature.com/reprints

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.