Antimicrobial Resistance and Recent Alternatives to Antibiotics for the Control of Bacterial Pathogens with an Emphasis on Foodborne Pathogens

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Abstract: Antimicrobial resistance (AMR) is one of the most important global public health problems. The imprudent use of antibiotics in humans and animals has resulted in the emergence of antibiotic-resistant bacteria. The dissemination of these strains and their resistant determinants could endanger antibiotic efficacy. Therefore, there is an urgent need to identify and develop novel strategies to combat antibiotic resistance. This review provides insights into the evolution and the mechanisms of AMR. Additionally, it discusses alternative approaches that might be used to control AMR, including probiotics, prebiotics, antimicrobial peptides, small molecules, organic acids, essential oils, bacteriophage, fecal transplants, and nanoparticles.

Keywords: antimicrobial resistance; antibiotics alternatives; quorum sensing; prebiotics; probiotics; small molecules; antimicrobial peptides; bacteriophage; essential oils; fecal transplant; nanoparticles; organic acids; vaccines; antibodies

1. Introduction

Antimicrobial resistance (AMR) is a major public health concern worldwide [1]. Infections with antibiotic-resistant pathogens have a negative influence on the health of humans and other animals because they increase the risk of treatment failures and illness severity [2,3]. Over the past few decades, the misuse of antibiotics in both humans and food-producing animals has resulted in the emergence and dissemination of antibiotic-resistant bacteria [4–6]. Between 2000 and 2010, 76% of the global increase in antibiotic use was reported in BRICS countries (Brazil, Russia, India, China, and South Africa) [7]. For example, in 2010, India was the largest antibiotic consumer (12.9×10^9 units; 10.7 units/person), followed by China (10.0×10^9 units; 7.5 units per person), then the US (6.8×10^9 units; 22.0 units per person) [8]. Between 2000 and 2015, global antibiotic use significantly increased by 65% (21.1–34.8 billion) DDDs (defined daily doses), especially in low- and

middle-income countries [9]. In the US, approximately 80% of antibiotics are used in live-stock production [10]. The uses of sub-therapeutic doses of antibiotics in food-producing animals as growth promoters, therapeutic doses for control, and treatment of infectious diseases [11,12] have also contributed to the development of antimicrobial-resistant microorganisms. Transmission of resistant bacteria from food-producing animals to humans through direct contact, handling, or eating their product poses a substantial threat to human health [13,14]. Antibiotic resistance illnesses currently cause approximately 1.2 million deaths worldwide [15]. However, if no steps are taken to control the spread of antibiotic resistance, the estimated number of deaths will rise to 10 million, with an economic loss of more than $100 trillion by 2050 [15,16]. In the US, more than two million infections with antibiotic-resistant bacteria occur each year; with ~$20 billion in economic losses [16]. Notably, foodborne illnesses caused by *Campylobacter*, *Salmonella*, *E. coli* O157, *Listeria monocytogenes*, *Staphylococcus aureus*, and *Clostridium perfringens* can affect one in six people annually, leading to approximately 128,000 hospitalizations and 3000 deaths, with about $90 billion in the US [17,18]. Many of these pathogens are on the global priority pathogens list of antibiotic-resistant bacteria provided by the National Institute of Health (NIH) and World Health Organization (WHO) [19,20]. Therefore, there is a critical need to control AMR pathogens. In this review, we will highlight the evolution of the AMR problem, the mechanism of acquiring resistance, and the novel non-antibiotic approaches that can be used for reducing the burden of antimicrobial-resistant pathogens.

2. Evolution, Source, and Transmission of AMR

The non-prudent use of antibiotics in livestock production has resulted in an alarming surge of antibiotic-resistant pathogens [21]. The first effective antimicrobial sulfonamide drug Prontosil was discovered in 1932 and approved for human use in 1935 [22]. Resistance to sulfonamide was observed in 1939 due to limitations in safety and efficacy [23]. Despite compelling evidence that the discovery of antimicrobials was revolutionary for controlling many serious and life-threating diseases, one of the major shortcomings associated with their prolonged use is that many pathogenic bacteria may develop or acquire resistance traits over time through a large variety of mechanisms [24]. For example, *S. aureus* was initially sensitive to penicillin; however, it became resistant over time due to the development and production of penicillinase that inactivates the inhibitory impact of penicillin [21]. The evolution and resistance acquisition of different antibiotics is shown in Figure 1. The FDA is carefully seeking to produce new antibiotics to overcome microbial resistance. Eravacycline dihydrochloride (Xerava) is a new synthetic fluorocycline belonging to tetracycline-class antibiotics that was discovered in 2018 [25,26]. It has potent antibacterial activity against Gram-negative and Gram-positive bacteria that usually have tetracycline-specific resistance mechanisms [27]. It inhibits bacterial growth by binding to the bacterial 30S ribosomal subunit [26]. Additionally, levonadifloxacin L-arginine tetrahydrate and the combination of levonadifloxacin and lipoglycopeptide dalbavancin were approved in 2019 by the FDA as antibiotics to treat acute bacterial skin and skin structure infections (ABSSSI) [28]. In 2020, the FDA approved pretomanid in combination with bedaquiline and linezolid for the treatment of drug-resistant *Mycobacterium tuberculosis* [29] and approved remdesivir in combination with baricitinib for the treatment of other pathogens [30,31]. In 2021, ozenoxacin was approved for the treatment of impetigo and bacterial infections caused by *S. pyogenes* or *S. aureus* in children [32,33] and rifapentine for the treatment of tuberculosis [33].

AMR can be caused by (1) microbial genetic mutations [34], (2) incomplete courses of antibiotic, enabling some pathogens to survive and develop resistance to antibiotics [35], (3) overuse of antibiotics [36], (4) using antibiotics at doses lower than recommended, (5) consumption of animal products containing antibiotic residues and (6) using antibiotics containing fertilizers in agriculture and/or animal farming [37]. The continuous environmental overlapping between livestock and human activity provides many opportunities for the transmission of antimicrobial-resistant bacteria or development of their AMR genes in both directions [38]. AMR can be transmitted through (1) direct close contact between hu-

man and livestock [39,40], (2) ingestion of contaminated food and water, (3) contaminated bio wastes, (4) transportation/importation of animal products across the world, (5) clonal transfer of resistance bacteria or horizontal transmission of AMR genes [36], (6) soil, manure of animals, waste water and sewage, or vectors such as invertebrates (insects and bugs) and wild animals [41,42].
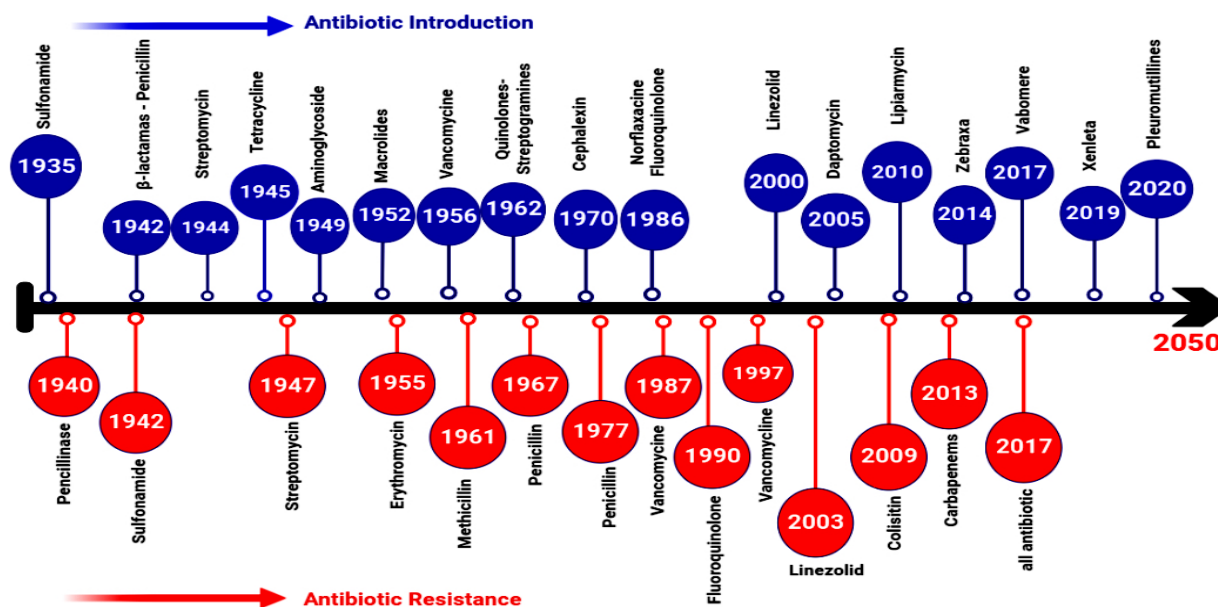

Figure 1. Timeline illustrates antibiotics evolution.

3. Mechanism of Acquiring AMR

Antibiotic resistance (AR) in the bacteria can be intrinsic or acquired. Intrinsic resistance is seen in naturally resistant bacteria that exhibit certain inherited properties. For example, the presence of lipopolysaccharide (LPS) in the cell walls of Gram-negative bacteria provides an innate barrier against the penetration of antimicrobials [43]. This intrinsic resistance includes limiting the drug's uptake and increasing its efflux or inactivation [44]. Meanwhile, acquired antibiotic resistance mechanisms include modification of drug targets, drug efflux, and inactivation [44]. In addition to the aforementioned mechanisms, adaptive mutations are exhibited by bacteria in response to the use of antibiotics as a means of resistance [45,46]. Prior studies reported that adaptive resistance is responsible for in vitro and in vivo differences in antibiotic effectiveness and the failure of clinical antibiotic therapies [24]. Bacterial genetic plasticity aids the acquisition of AR. It appears as either mutations in bacterial genes or gain of foreign DNA fragments coding resistance determinants through horizontal gene transfer (HGT) of antibiotic resistance genes (ARGs) [47]. Antibiotic-sensitive bacteria acquire resistance-modulating genes through HGT, which enables bacteria to share their genetic material by one of three techniques, including transduction, conjugation, and transformation [24]. Regarding transduction, the genetic material from a donor-resistant bacterium is transferred to another bacterium by a bacteriophage, a virus that infects and replicates inside bacterial cells. Basically, the bacteriophage attaches to the donor bacterium and injects its genetic material into it, which incorporates itself within the bacterial genome; by the replication of the bacteriophage, multiple bacteriophages are produced carrying genomes containing resistance genes. When the newly created bacteriophage infects another bacterium, it injects the resistance-genes-containing genome into it [48]. Conjugation, which is referred to as bacterial sex, occurs when the donor bacterial cell, containing a resistance-gene-encoding plasmid, attaches to the recipient bacterium. This process requires a pilus (physical attachment between bacterial cells through which the plasmid is transferred) and a type IV secretion system to be accomplished successfully [49]. Unlike transduction and conjugation, transformation

occurs after the death of bacteria carrying resistance genes. By bacterial lysis, genetic material is released and naked DNA is picked up by another bacterium and is incorporated into its genome [50]. After bacteria acquire resistance genes by any of the aforementioned mechanisms, genes are expressed in one or more of the following ways (Figure 2):
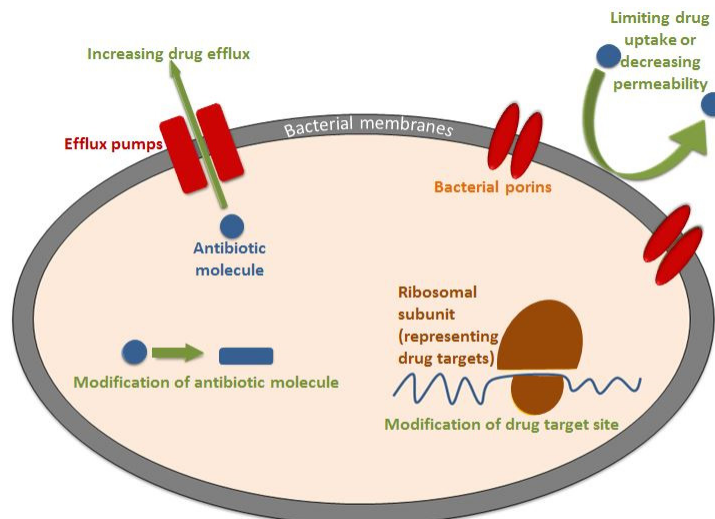
Figure 2. Mechanisms of antimicrobial resistance in bacterial cells.

3.1. Limiting Drug Uptake and Decreasing Permeability

3.1.1. Lipopolysaccharide (LPS) of Outer Bacterial Membrane

Bacterial LPS is a conserved major biologically active component of bacterial outer membranes, primarily in Gram-negative bacteria. LPS has a direct role in AMR as a physical barrier limiting the penetration of antimicrobials into bacterial cells. This may explain, at least in part, why-Gram positive bacteria have a lower ability to limit the antimicrobials' uptake than Gram-negative ones [51].

3.1.2. Bacterial Porins

Bacterial porins are membrane protein channels present in the outer membrane of Gram-negative bacteria. They modulate crossing of hydrophilic molecules, including hydrophilic antibiotics such as β-lactams [52]. The bacteria can also limit drug uptake via the modification of their porin channels, either by decreasing their numbers, as in *Enterobacteriaceae* resistance to carbapenems, or by alteration of porin's selectivity through mutation, as in resistance of *Neisseria gonorrhoeae* to β-lactam and tetracycline and resistance of *Enterobacter aerogenes* to imipenem and some cephalosporins [44]. This clearly indicates that the outer membrane of Gram-negative bacteria contains overlapping defensive systems that confer not only protection against antibiotics but also to the host antimicrobial factors.

3.1.3. Biofilm Formation

Biofilm is the aggregation of bacterial cells in the form of clusters. Bacterial cells piled up on one another prevent access of antimicrobials into the bacterial cells [53]. The capacity for biofilm formation is widely distributed in bacteria, with approximately 40–80% of terrestrial cells existing in biofilms as a defense mechanism [54]. Biofilm formation supports antimicrobial resistance either directly, by acting as a physical barrier, or indirectly, by facilitating horizontal transfer of resistance genes amongst bacterial cells by conjugation, transduction, and transformation [54]; this is in addition to protection against the host's immune defenses. Bacteria are able to develop biofilms on inanimate surfaces as well as inside living tissues [55]. For example, the resistance of cystic fibrosis of the lung (caused by *Pseudomonas aeruginosa* infection) to antibiotics is thought to be due to bacterial biofilm formation. Mechanical disruption or removal of biofilms will therefore improve the action of antibiotics by exposing the causative agent to their effects [56,57].

3.2. Enzymatic Destruction of Antibiotic Molecules

Resistant bacteria produce antibiotic-degrading enzymes which destroy certain sites in the antibiotic, rendering it ineffective. These enzymes work by acetylation, phosphorylation, glycosylation, or hydroxylation of certain sites in the antibiotic molecule that interfere with the binding of the corresponding drugs to their ribosomal targets [45]. For example, β-lactams-hydrolyzing enzymes impede the ability of β-lactams to inhibit bacterial cell wall biosynthesis [58]. Additionally, macrolides are encountered by resisting bacteria through modification of macrolide esterases (Eres) and macrolide phosphotransferases (MPHs) enzymes [59]. Aminoglycoside (AGS)-resistant bacteria encode aminoglycoside-modifying enzymes (AMEs) in their chromosomes or in mobile genetic elements (MGEs), which is the most commonly utilized mechanism by bacteria for battling the effect of AGS [60].

3.3. Drug Target Site Modification

Resistant bacteria inhibit antimicrobials from binding by altering their antimicrobial's target proteins. It was noticed that most of the bacterial genes involved in these changes are encoded on mobile genetic elements (MGEs) [45]. The changes can be achieved in several ways, including replacement of target sites, enzymatic alterations of binding sites, and mutations in genes encoding target sites [61]. Vancomycin-resistant *S. aureus* is an example of resistance by replacement of a target site, where it replaces the alanine subunit in its cell wall peptides, the target site of vancomycin, with a lactate subunit to which vancomycin cannot bind properly. Eventually, the cross-linking enzyme of the bacterial cell wall can fit into its site and perform its function [62]. Furthermore, macrolides-resisting bacteria showed enzymatic alterations of their binding sites by methylation of the 50S ribosomes, macrolides targets. They carry erm (erythromycin ribosomal methylation) genes, which encode an enzyme responsible for catalyzing the methylation process. The methylated ribosome becomes an unfit target for macrolide antibiotics, thus preventing antibiotic access into the bacterial cell wall [45]. Also, rifampicin-resistant bacteria mutate the rpob gene, which encodes the β subunit of DNA-dependent RNA polymerase (RNAP) that carries the rifampicin binding site, resulting in the substitution of an amino acid in the RPOB protein. Overall, mutations in genes' encoding target sites decrease the affinity of antibiotics to their targets inside bacteria [63].

3.4. Antibiotic-Specific Efflux Pumps

The plasma membranes of bacteria carry protein structures called bacterial efflux pumps (EPs) [64]. These pumps can recognize foreign structures accessing the bacterial cells through their cell wall and pump them out, thus preventing their intracellular accumulation and interaction with their target cells [65]. Efflux pumps can be either substrate-specific for certain antibiotic families or have broad antibiotic activity as in multi-drug-resistant bacteria [66]. However, single efflux pumps may target multiple antibiotics [67]. Thus, multi-drug resistance (MDR) can be achieved by bacteria through either expression of a single efflux pump or overexpression of multiple efflux pumps as in *P. aeruginosa* [68] and the SmeDEF or SmeVWX efflux systems of *Stenotrophomonas maltophilia* [69]. There are five families of efflux pumps, including small multidrug resistance (SMR), resistance-nodulation-division (RND), multidrug and toxic compound extrusion (MATE), the major facilitator superfamily (MFS), and the ATP-binding cassette (ABC) families [70]. All types are found in bacteria, except for the RND family, which is exclusive to Gram-negative bacteria. The over-expression of efflux pumps is associated with clinical antibiotic resistance [71].

4. Novel Strategies to Combat AMR

4.1. Small Molecules (SMs)

SMs are non-peptide organic molecules that are synthetic or obtained from natural product extracts. They have drug-like properties that can interact with biological molecules, including protein and nucleic acids, and can alter their normal functions. The low molecular weight (~200–500 Da) and high hydrophilicity of these molecules allow their effective

absorption by both host and pathogen barriers [72,73]. SMs can be modified to enhance the qualities desired for specific applications, such as stability and solubility under adverse environmental conditions. These properties can be exploited to enhance the SMs' antimicrobial efficacy and their mass applicability. High-throughput screening (HTS) of SM libraries is commonly used for the development of antibacterial drugs and identification of SM candidates that inhibit either bacterial growth in whole-cell assays or the activity of a main bacterial enzyme or protein [74]. Indeed, a cost-effective, cell-based HTS expedient approach has been recently developed to enhance anti-bacterial molecule discovery [75,76]. A summary of the SMs identified using HTS is shown in Table 1. SM antimicrobials targeting bacterial membranes are highly desired because they have low potential for resistance development by pathogens, can potentiate the activity of many antibiotics, are effective against slow-growing bacteria and biofilms, and have high stability in serum and good tissue penetration [77]. They have been reported to be effective against several MDR bacteria, such as *E. coli*, *P. aeruginosa*, *Enterococcus faecium*, methicillin resistant *S. aureus* (MRSA), *Klebsiella pneumoniae*, *Acinetobacter baumannii*, and *Enterobacter* species [78–80]. Recently, SMs were used for the treatment of plant pathogens such as *Xanthomonas* spp., *Erwinia tracheiphila*, *Acidovorax citrulli* and *Salmonella* infection [81–84], as well as for the potentiation of antibiotics, which can help in reducing the resistance of the treated bacteria [85].

4.1.1. Mechanisms of Actions of SMs

The low molecular weights of SMs facilitate their infiltration into target cells [86]. Following infiltration, SMs interfere with or inhibit certain molecules involved in cellular pathways [87]. Examples of these cellular pathways include (1) biosynthesis of microbial cell envelopes that can be inhibited by SMs through inhibition of the dephosphorylation of the central lipid carrier undecaprenyl pyrophosphate (C_{55}-PP) to C_{55}-P, such as THCz, which in turn, interferes with lipid II (peptidoglycan), lipid III$_{WTA}$ (wall teichoic acid), and lipid I$_{cap}$ (capsule), involved in cell envelope biosynthesis pathways, (2) interference with bacterial cell division through inhibition of a key component in that process, FtsZ [88], and (3) encountering quorum sensing through inhibition of LsrK, which is an essential component for initiation of the QS cascade [89].

4.1.2. Limitations of SMs

Despite their beneficial effects, there are functional limitations of SMs. Limitations include their action inside the recipient's body, irrespective of the physiologic status. The likelihood of binding to non-target molecules inside the human body leads to undesirable effects [90]. In addition to these limitations, there are also some structural design constrains, such as the difficulty of designing SMs to target unstructured disordered polypeptide, as well as their low affinity to bind or modify the relatively flat protein surface mediators [91]. Moreover, it is challenging to accurately determine the modulating proteins to be targeted by SMs [91].

Table 1. Identified SMs against different pathogens and their potential targets.

Bacteria	Name of the SMs	Evaluation	Targets	References
M. tuberculosis	Benzimidazole and nitro-triazole	In vitro	Inhibit cell wall biosynthesis	[92]
Uropathogenic *E. Coli*	120304 and 175472	In vitro	TonB system	[93]
E. coli and *P. aeruginosa*	Nitrofurans	In vitro	Inhibit bacterial growth through reduction of the nitro group to an amine, followed by damage to bacterial DNA	[94]
P. aeruginosa and *S.* Typhimurium	Class 2,4-disubstituted-4H-[1,3,4]-thiadiazine-5-ones, Fluorothiazinon (FT)	In vitro, in mice	Suppress T3SS	[95,96]
Bacillus subtilis	Adamantane derivatives (T6102)	In vitro	Inhibit bacterial protein synthesis and bacterial growth	[97]

Table 1. *Cont.*

Bacteria	Name of the SMs	Evaluation	Targets	References
S. aureus and *S. epidermidis*	3-methoxybenzamide derivatives (PC190723)	In vitro (CD-1 mouse hepatocytes), in mice	Disrupt FtsZ	[98]
S. aureus	ZY-214-4 ($C_{19}H_{11}BrNO_4$)	In vitro	Suppress biofilm formation	[99]
Mycoplasma gallisepticum	SM4 and SM9	In vitro, in chickens	Alter cell membrane conformation	[76]
M. bovis	Methanesulphonic acid, 3-[(2E)-3-(3,4-dihydroxyphenyl) prop-2-enoyloxy](1S,3R,4R,5R)-1,4,5-trihydroxycyclohexane carboxylic acid, S-carboxymethyl-l-cysteine, l-aspartic acid, dihydrotachysterol, eriodictyol and (+)-a-tocopherol acid succinate)	In vitro	NI*	[100]
C. jejuni	Campynexin A	In vitro, in chickens	Inhibit flagellar expression	[101]
C. jejuni	Piperazine, aryl amine, piperidine, sulfonamide and pyridazinone molecules	In vitro	NI*	[75]
C. jejuni	TH-4 and TH-8	In vitro, in chickens	Alter cell membrane integrity	[102]
S. Typhimurium	JD1	In vitro, in mice	Inhibit bacterial growth by distorting cytoplasmic membranes through increasing fluidity and disrupting barrier function	[103]
S. Typhimurium	Imidazole and methoxybenzylamine	In vitro, *Galleria mellonella* larvae, in chickens	Alter cell membrane integrity	[104]
Avian pathogenic E. coli (APEC)	QSI-5 and GI-7	In vitro, *Galleria mellonella* larvae, in chickens	Inhibit quorum-sensing autoinducer-2 and outer membrane proteins	[105–108]
E. faecium	6-indolyl compounds	In vitro	NI*	[109]
Clostridium difficle R20291	2-aminoimidazole (2-AI)	In vitro	NI*	[110]
Chlamydia	INPs (Innate Pharmaceuticals AB)	Epithelial cells	Supress Type III secretion	[111]
Clostridium botulinum		In vitro, In mice	Inhibit neurotoxin serotype A	[112]
L. monocytogenes	Pimozide (antipsychotic drug)	In vitro: murine bone marrow-derived macrophages (BMM)	Decrease the vacuole escape and cell-to-cell spread of *L. monocytogenes*	[113]
L. monocytogenes	SM-3, 5, 7	In vitro: on catfish fillets	Block the LapB gene, that encodes cell wall surface anchor protein	[114]
S. aureus, S. epidermidis, S. pyogenes, S. pneumoniae and *Bacillus cereus*	F19 and F12	In vitro on human THP-1 monocytes and mouse macrophage cell line - In mice	Host cell lysis	[115]

NI*: Not identified.

4.2. Quorum-Sensing/Antivirulence Inhibitors

Bacterial cells adapt to their surrounding environment and regulate their density and behavior via a cell-to-cell communication process named quorum sensing (QS). This process is mediated by bacterial secretion of extracellular signaling molecules called autoinducers (AIs) [116]. The bacteria produce and release AIs to coordinate their gene expression for survival as multicellular organisms. Additionally, AIs are also key regulators of biofilm formation, stress adaptation, secondary metabolite production, swarming motility, enzyme production, and virulence factor production [117,118]. Active transport or diffusion is used to release autoinducers into the environment to achieve efficient communication between bacterial cells [119]. As the bacterial population density rises, AIs build up in the environment, and, after this reaches a certain threshold, bacteria use them as extracellular signaling molecules to adjust their density and coordinate their gene expression [120].

QS systems are based on three fundamental concepts. (1) One is the bacterial cells' density: at a high cell density, the cumulative generation of AIs results in local accumulation at a high concentration, which facilitates detection and response. However, at a low cell density, the AIs diffuse away, as they are present at concentrations below the detection threshold [121]. (2) Receptors generated in the cytoplasm or on the membrane are used

to identify AIs. (3) The recognition of AIs leads to increased bacterial synthesis of AIs in addition to stimulation of gene expression required for cooperative behaviors [122].

Generally, the bacterial QS systems are classified into three types: (1) LuxI/LuxR–type QS, which is found in Gram-negative bacteria and uses acyl-homoserine lactones (AHL) as signaling molecules [123], (2) oligopeptide-two-component-type QS, which is found in Gram-positive bacteria and utilizes oligopeptides as signaling molecules, and (3) luxS-encoded autoinducer-2 (AI-2) QS, a general system, which is found in both Gram-negative and Gram-positive bacteria and uses AI-2 as signaling molecules [117]. The AIs are categorized into acylated homoserine lactones (AHLs), utilized by Gram-negative bacteria, oligopeptides, utilized by Gram-positive bacteria, and furanosyl borate diester, utilized by Gram-negative and Gram-positive bacteria. In addition, there are other signaling molecules of the QS system called autoinducer-3 (AI-3), which are utilized by *P. aeruginosa* and do not belong to any of the previous classes. This complex network of signals allows the bacterial community to react and adapt to different environments [124].

Interrupting the connection system between bacterial cells results in a reduction in bacterial biofilm formation and pathogenicity [124,125]. Therefore, many strategies have been developed to hinder this connection and control the QS-dependent bacterial infections [126]. The inactivation, blocking, or degradation of QS signal molecules refers to QS inhibition or quorum quenching (QQ) [26]. The perfect QS inhibitors (QSIs) are low-mass compounds with a great selectivity for the QS regulator and no deleterious side effects on the bacterium or a potential eukaryotic host. They must also be chemically stable and extremely efficient [124]. QSIs may be natural or artificial molecules. In fact, many anti-QS compounds are isolated from plants and microbes. Natural products, including plant extracts, as shown in Table 1, are the main source of QS Inhibitors (QSIs), because they contain compounds such as phenylpropanoids, flavonoids, benzoates, and gallotannins [127]. For example, grape seed extract reduces autoinducing activity and inhibits flagellum synthesis and Shiga toxin production in *E. coli* (STEC), verotoxigenic *E. coli* (VTEC), and enteroaggregative *E. coli* (EAEC) [128]. In addition, *Melia dubia* bark extracts suppress α-toxin hemolysin production, biofilm formation, and the mobility of enterohemorrhagic *E. coli* [EHEC] [129]. Furthermore, rosemary, ginger, and broccoli extracts inhibit the synthesis of AI-2 and the production of virulence factors and affect the mobility-type swarming of EHEC [130]. On the other hand, synthetic QSIs, as displayed in Table 2, include chitosan, limonene nanoemulsion, and N-phenyl-4-phenylaminothioxomenthyl amino-benzenesulfonamide, inhibiting the QS system in uropathogenic *E. coli* (UPEC), EHEC, and *S. enterica* serovar Typhimurium, respectively. The mechanisms by which QSIs inhibit QS signals include inhibition of the synthesis of AI-2 by blocking AI synthase and methyltransferase, blocking the LsrB receptor protein, inhibition of the QseC regulator protein responsible for inducing virulence factor gene expression, and inhibition of the transcriptional protein regulator LsrR or the SdiA LuxR solo regulator. Examples of QSI enzymes include AHL acylases and AHL oxidoreductase; the latter has a modified chemical structure among the AHLs [131]. The acyl side chains of the homoserine lactone are cleaved by AHL acylases, a new family of N-terminal nucleophile (NTN) that renders the AHLs activity [132]. Acyl homoserine lactone acylases have been isolated from *Streptomyces* sp. strain M664 as AhlM [133], while AHL oxidoreductase was first isolated from *Rhodococcus erythropolis* [132].

4.2.1. Mechanisms of Action of QSIs

The mechanism of inhibition of QS systems includes different pathways: (1) prevention of AI synthesis [134], (2) AI receptor antagonism, (3) blocking the targets downstream of receptor binding [135], (4) application of antibodies for sequestration of AIs, (5) breakdown of AI-catalytic antibodies (abzymes) or enzymes (i.e., lactonases, acylase, and oxidoreductase) [133,136], (6) attenuation of AI secretion/transport [130], and (7) competition with autoinducing signal molecules to bind to the transcriptional protein regulators of bacterial QS systems, including *LuxS*, *LsrB*, *LsrR*, and *QscE* regulator proteins in foodborne bacteria, such as *E. coli* and *Salmonella* [136].

4.2.2. Limitations of QSIs

Limitations of QSIs include (1) the development of resistance to QSIs: bacteria might evolve and develop resistance to QSIs due to the presence of plenty of QS systems in bacteria. Bacteria can regulate and induce their QS system by activating and enhancing the production of QS signal molecules, which enhance virulence factor production to promote bacterial resilience to the environment [137]. (2) Modification of virulence genes: Gram-negative bacteria can evade the action of QSIs by developing mutations in the amino acid residue of the LuxR protein regulator, which encodes virulence factors, motility, biofilm formation, and antibiotics biosynthesis [138]. (3) Indole signaling: QS systems in *E. coli* and *Salmonella* respond to indole in a nutrient-poor environment that enhances the production of virulence factors, plasmid stability, adaptation, and resistance to antibiotics. During these conditions, indole competes with AIs to bind with the AHL domain of the SdiA transcriptional regulator. Indole also competes with other QSIs that cause reduction of *P. aeruginosa*'s virulence factors, resulting in bacterial resistance from anthranilate breakdown [129,139]. (4) Disturbance of microbiota homeostasis: QSIs cause distribution of AI-2 signaling and affect human microflora activities, including adherence, biofilm formation, and production of antimicrobial metabolites, resulting in disturbance of human microbiota homeostasis [140].

Table 2. Quorum-sensing inhibitors with their target.

Compound Name	Source	Target Pathogen	Mechanism of Inhibition	References
C1-C10	Synthetic	APEC O78	Inhibit quorum sensing via inhibiting AI-2 production, genes associated with biofilm formation, such as the hha gene, and genes associated with bacterial cell morphology, motility, and division.	[107]
Savirin	Synthetic	*S. aureus*	Inhibits the signaling cascade of bacteria and biofilm formation by targeting AgrA to disrupt agr operon-mediated QS.	[141]
N-phenyl-4-(3-phenylthioureido) benzene sulfonamide	Synthetic	*E. coli* [EHEC]	Inhibits biofilm formation and virulence factors by modifying the AI-3 receptor (QseC).	[142]
Anti-autoinducer monoclonal antibody AP4-24H11	Synthetic	*S. aureus* [RN4850]	Inhibits the QS signaling molecule autoinducing peptide (AIP)-4 by targeting AgrA, resulting in QS inhibition and biofilm formation.	[143]
Limonene nanoemulsion	Synthetic	*E. coli* [EHEC]	Reduces AI-2 synthesis; inhibits the production of *E. coli flagellum* by inhibiting QseB and the promoter region of *flhDC* binding that encodes bacterial motility	[144]
N-phenyl-4-phenylaminothioxomen hyl amino-benzenesulfonamide	Synthetic	*E. coli* [EHEC] *S.* Typhimurium	Inhibits the histidine kinase QseC and results in a decrease in the expression of virulence factors.	[145]
Thiophene inhibitor (TF101)	Synthetic	*E. coli* (EPEC)	Inhibit the expression of the *lsrB* gene which encodes the AI-2 receptor, and interferes with *fimH*, which encodes virulence factors and inhibits biofilm formation.	[146]
Grape seed extract	Grape seed extract	*E. coli* (STEC), *E. coli* (VTEC), *E. coli* (EAEC)	Reduces the synthesis of AI and its activity by blocking AI synthase activity. Inhibits the production of *E. coli* flagellum by inhibiting QseB and the promoter region of *flhDC* binding that encodes bacterial motility and inhibit Shiga toxin production.	[128]
Thymol-carvacrol-chemotype (I and II) oils	*Lippia origanoides* *Thymus vulga0ris* oil	*E. coli* [O157:H7] *E. coli* [O33]	Inhibits the synthesis of AI-3 and prevents the formation of biofilm.	[147]
furocoumarin	Grapefruit juice	*S.* Typhimurium *E. coli* [O157:H7]	Inhibits the activity of AI-2, interferes with the activity of AI-1 molecules (AHLs), and inhibits biofilm formation.	[148]
Broccoli extracts	Basil, oregano, thyme, rosemary, ginger, and turmeric	*E. coli* [EHEC]	Inhibits the activity of AI-2 synthase and inhibits synthesis of AI-2. Affects *E. coli* mobility and inhibits production of virulence factors.	[149]
Acetic acid, citric acid, and lactic acid	Vinegar, Lemon, fermented soy products, yogurt	*S.* Typhimurium *E. coli* [O157:H7]	Inhibit the producing of the signaling molecules AI-2 by inhibiting AI-2 synthase. They also inhibit the activity of biofilm formation.	[150]
Star anise (Illicium verum Hook. f.)	Chinese fruit evergreen tree Illicium verum	*S.* Typhimurium	Interferes with promoter region *flhDC* operon which regulates the mobility. Interferes with the signal receptors *lux*, *rhl*, and *las* systems and inhibits biofilm formation.	[151]

Table 2. *Cont.*

Compound Name	Source	Target Pathogen	Mechanism of Inhibition	References
Chitosan	Shells of crustaceans	*E. coli* [UPEC]	Reduces *E. coli* mobility by inhibiting QseB binding to the promoter region of *flhDC*. Inhibits AI-2 production and biofilm formation.	[152]
(Z)-4-Bromo-5-(bromomethylene)-3-methylfuran-2(5H)-one	Synthetic	*E. coli* [RP437]	Reduces the activity of AI-2 by reducing the activity of AI-2 synthase.	[153]
Punicalagin	Pomegranate rind	*S.* Typhimurium [SL1344]	Decreases the expression of the genes *fliA*, *fliY*, *fljB*, *flhC*, and *fimD* encoding the swimming and swarming motility of *Salmonella* and represses the expression of *sdiA* and *srgE* QS-related genes.	[154]
2,3-methyl-N-(2′-phenylethyl)-butyramide	*Halobacillus salinus*	*E. coli* [JB525]	Inhibits biofilm formation and decreases the expression of virulence factors by competing with signaling molecules (AHL) for receptor binding.	[155,156]
N-(2′-phenylethyl)-isobutyramide	*Halobacillus salinus*	*E. coli* [JB525]	Competes with signaling molecules (AHL) for receptor binding and inhibits bacterial QS resulting in biofilm formation.	[155,156]
Cyclo(L-Pro-L-Val)	*Haloterrigena hispanica*	*E. coli* [JB525]	Inhibits biofilm formation by interacting with signaling molecules (AHL).	[157]
Diketopiperazines (DKPs): Cyclo(L-Pro-L-Phe), Cyclo(L-Pro-L-Leu), Cyclo(L-Pro-L-isoLeu), Cyclo(L-Pro-D-Phe)	*Marinobacter* sp.	*E. coli* [pSB401]	Inhibits bacterial biofilm formation by inhibiting the production of AHL signaling molecules.	[158]
Kojic acid	*Altenaria* sp., from marine green algae *Ulva pertusa*	*E. coli* [pSB401]	Interferes with N-hexanoyl-L-homoserine lactone (C6-HSL) and with LuxR reporters.	[159]
O-prenylated flavonoid buchapine and 3-(3-methyl-2-butenyl)-4-[(3-methyl-2-butenyl)oxy]-2(1H)-quinolinone	*Melicope lunu-ankenda* (leaves extract)	*E. coli* [pSB401]	Inhibits biofilm formation and decreases violacein production, motility, and bioluminescence production by downregulating the expression of lecA and lux genes.	[160,161]
Sesquiterpenes, monoterpenes, hydrocarbon, and phenolic compounds. Eugenyl acetate, eugenol, and β-caryophyllene	*Syzygium aromaticum* (bud)	*E. coli* [pSB1075]	Targets lecA and lux genes resulting in the inhibition of QS-regulated phenotypes and violacein factor production, which are considered secondary metabolites responsible for growth and propagation and are a useful indicator of QS systems in bacteria.	[162]
Fructose-furoic acid	*Aloe africana* (plant extract)	*E. coli* [UPEC]	Represses the expression of biofilm phenotypic characters by competing with quorum regulator (SdiA) native ligand C8HSL.	[163]
Cembranoids	*Pseudoplexaura flagellosa* and *Eunicea knighti*	*E. coli* [pSB403] *S. aureus*	Inhibits biofilm formation by interacting with LuxR receptors.	[164]
Brominated alkaloids compounds	*Flustra foliacea*	*E. coli* [pSB403]	Inhibits biofilm formation by targeting CepR and LuxR and interferes with N-acyl-homoserine lactone.	[165]

4.3. Probiotics

Probiotics are microorganisms that live in a symbiotic relationship with the host. They provide health benefits and perform several biological functions when provided in adequate amounts. Probiotics were discovered and selected based on certain criteria, which ensure safety and effectiveness requirements [166]. The FAO/WHO have specified several parameters that should be assessed in vitro when selecting probiotics, such as safety, efficacy, cost effectiveness, function, and technological and physiological applications. The selected probiotics can be characterized by a lack of pathogenicity, tolerance to changes in the human gastrointestinal microenvironment, capacity for adherence to and colonization of the intestinal epithelium, antimicrobial activity, genetic and phenotypic stability, and immunomodulatory capabilities [167]. Several in vitro tests can be used to evaluate the efficacy of probiotics before starting the clinical trials, such as the agar spot test [168], the agar well diffusion assay [169], microdilution [170], antibiofilm analysis [171], 3D cell cultures, and use of human tissues and animal models [172–174].

Additionally, probiotics have been found to help with a variety of pathological conditions, including constipation, diarrhea, polycystic ovarian syndrome, ulcerative colitis, stress and anxiety, inflammatory bowel disease, breast cancer, and diabetes [175]. Probiotics are classified into four categories: (1) viable and active probiotics, (2) viable/non-active probiotics, in the forms of spores or vegetative cells, (3) dead/nonviable probiotics [176],

and (4) next-generation probiotics [177]. The biological properties of probiotics have been extensively investigated, but only a few studies focused on their antimicrobial properties as novel antibiotic alternatives.

1. Viable and active probiotics

According to the FAO/WHO, probiotics delivered into the body via the gastrointestinal tract (GIT) need to be viable and active in vitro (externally), resistant to GIT conditions, and viable and active in vivo (internally) [178]. Viable and active probiotics provide health benefits to the host via (1) increasing the hydrogen ion concentration (low pH value) in the gut, (2) enhancing synthesis of essential vitamins and enzymes, (3) production of antimicrobial substances, (4) restoring intestinal microbiota after diarrhea, (5) lowering serum cholesterol, (6) boosting the immune system, (7) production of antioxidants, (8) reduction of food allergy sensitivities, and (9) increasing lactose and calcium absorption [179]. Probiotics should be alive when traveling from the mouth to the gut and resist saliva enzymes, gastric fluid (acid and enzymes), bile salts, competitive gut microbiota, and inhibitory GIT conditions. Lactic acid bacteria (LAB) are considered the major probiotic bacteria that are used as viable cells, including homofermentative lactobacilli, which are represented by three groups, (i) the *L. acidophilus* group (*L. acidophilus*, *L. johnsonii*, *L. crispatus* and *L. gasseri*), (ii) the *L. salivarius* group, and (iii) the *L. casei* group (*L. paracasei*, *L. zeae* and *L. rhamnosus*). Additionally, Reuter and coworkers reported that *L. fermentum* is the predominant heterofermentative lactobacilli associated with the human GIT [180]. Other LABs that have been isolated either from dairy products or human GIT are *Bifidobacterium animalis*, *B. bifidum*, *B. breves*, *B. infantis*, *B. lactis*, *B. longum*, and *E. faecium*. In addition, non-lactic acid producers include *B. cereus*, *E. coli* Nissle 1917, *Sporolactobacillus inulinus*, *Propionibacterium freudenreichii*, and *Saccharomyces cerevisiae* [181]. Applications of selected probiotics against pathogenic bacteria and their mechanisms of action are summarized in Table 3 and Figure 3.
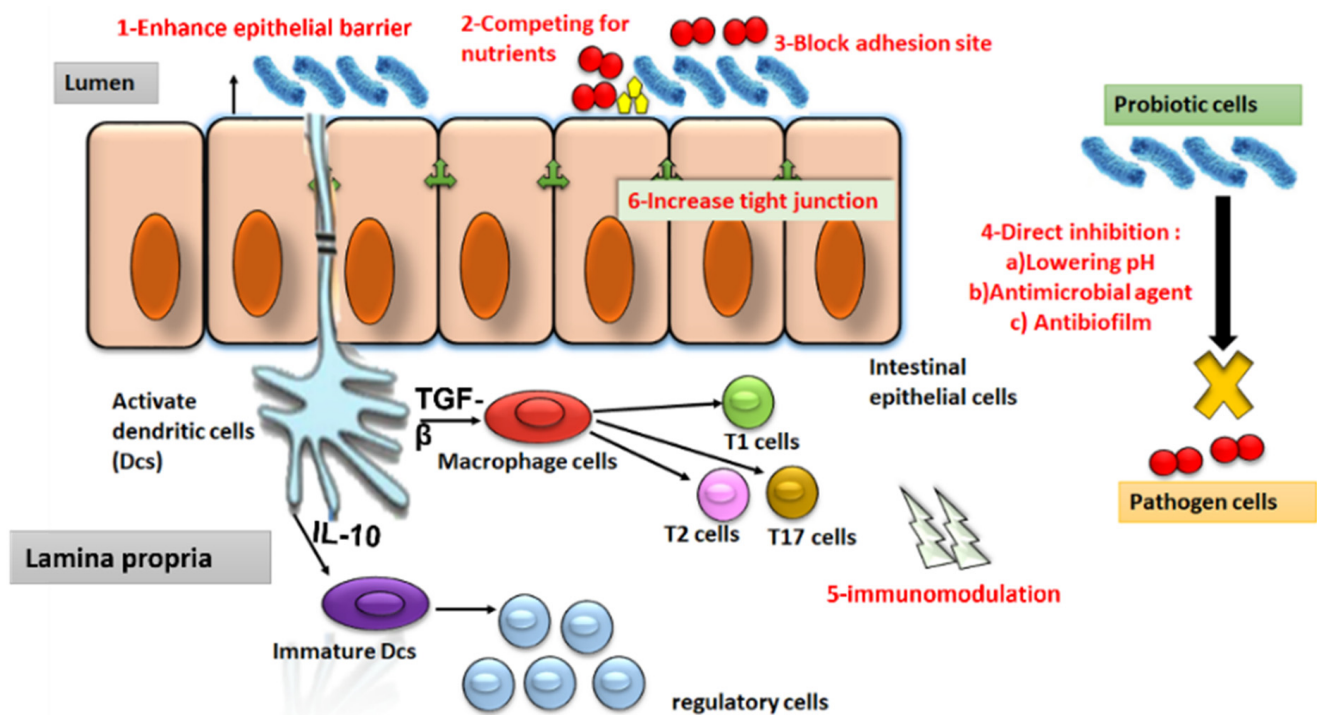

Figure 3. Mechanism of probiotics action.

2. Viable and inactive probiotics

These are viable probiotics but are not metabolically active. They are considered dormant probiotics because they are exposed to detrimental stresses such as temperature, extreme pH values, high osmotic pressure, and high O_2 supplementation (for anaer-

obes) [182,183]. *Bacillus* species, such as *B. coagulans*, *B. subtilis*, *B. clausii*, and *B. licheniformis*, have lately been authorized as inactive viable probiotics and utilized in human diets as well as for the treatment of intestinal and urinary problems [184]. Bacteriocins are produced by *Bacillus* spp. and are effective against Gram-positive and Gram-negative bacteria and fungus found in the food. As a result, they are commonly used in the food industry as natural preservatives [185]. *B. clausii* have been reported to treat child diarrhea, allergic children's immune systems, respiratory infections, and *Helicobacter pylori* infections (Table 3) [186].

3. Dead/nonviable probiotics (postbiotics/parabiotics)

The host can be protected from harmful microbes by using dead/nonviable probiotic cells [176]. Different procedures are performed for obtaining nonviable/inviable/inactivated/dead probiotic cells, including exposure to ultraviolet (UV) radiation for 530 min, heat at 121 °C for 560 min, and ionizing radiation (10 kGy). Protein denaturation, enzyme inactivation, nucleotide destruction, DNA breakage, and cell structural deformation are among the structural and functional changes associated with the inactivation pathway. This is called parabiotic/postbiotics, and is considered a new horizon in microbial therapy and the food industry [187]. In mice, heat-inactivated *L. plantarum* has prevented *S. enterica* infection in multiple organs, including the liver, spleen, and blood, by reducing pathogenic cell translocation and adhesion into intestinal cells [188]. Through enhancing the host immune responses (local and systemic), heat-inactivated *Leuconostoc mesenteroides* cells prevented *L. monocytogenes* invasion into Caco-2 cells [189]. Along similar lines, inactivated heat-killed yogurt prevent cytokine-induced barrier disruption in human intestinal epithelial cells [190]. Inactivated *L. paracasei* and *L. rhamnosus* cells have been found to prevent colon and stomach cancer by reducing proliferative activity and improving cancer cell apoptosis [191]. They can also lessen allergic rhinitis symptoms by maintaining cell wall integrity [192]. In hamsters with allergic rhinitis, administration of heat-inactivated *E. faecalis* FK-23 cells increased the number of T-regulatory cells in the spleen and altered the body's immune responses [193]. Heat-killed *L. rhamnosus* CNCM-I-3698 and *L. farciminis* CNCM-I-3699 exhibited coaggregation potential against foodborne pathogens, such as *Campylobacter*, *Salmonella*, *E. coli*, and *L. monocytogenes* [194]. It is noteworthy that the strongest coaggregation was mediated by a carbohydrate–lectin interaction between the heat-killed strains and *C. jejuni* CIP 70.2 and resulted in inhibition of its attachment to intestinal tissues [194]. Additionally, *L. brevis* cells have been shown to suppress the transcription of tumor necrosis factor, reduce the expression of sterol regulatory element binding protein 1 and 2, and enhance the induction of heat-shocked protein in the gut [195]. Lipoteichoic acid (LTA) is a microbe-associated molecular pattern (MAMP) expressed by Gram-positive bacteria and detected by the Toll-like receptor 2 (TLR-2) expressed on the surface of gut enterocytes. Ligation of LTA to TLR-2 initiates cellular signals, leading to induction of an inflammatory cytokine response. LTA derived from probiotic *Lactobacillus* strains has anti-biofilm properties against oral and enteric pathogens, such as *S. mutans*, *S. aureus*, and *E. faecalis*, by inhibiting biofilm formation and destroying pre-existing biofilms [187]. Parabiotics and postbiotics have several advantages over live probiotics, including easier creation and storage, possession of particular mechanisms of action, better accessibility of MAMP during contact with pattern recognition receptors (PRR), and greater likelihood of inducing targeted reactions through specific ligand–receptor interactions [187].

4. Next-generation and genetically modified probiotics

Next-generation probiotics (NGP) are those commensal and typical occupants of GIT microbial strains that enhance host defense against gastrointestinal pathogens [196]. Most NGP are gut bacteria that are nutritionally finicky and oxygen-sensitive, such as genera *Bacteroides*, *Clostridium*, *Faecalibacterium*, and *Akkermansia*, as well as genetically engineered (GE) strains [177]. As such, they are difficult to mass-produce and keep alive during processing and eventual product formulation [197]. They also require careful target consumer selection and circumstances; unlike other conventional probiotics, they are not suited to or safe for all users [196]. For example, *Bacteroides* spp. are essential gut micro-

biota members with a high capacity to metabolize complex polysaccharides that can help other bacteria. *Bacteroide* spp. such as *B. thetaiotamicron* have been found to interact with intestinal cells and modulate the expression of the host genes by inducing dendritic cell immunotolerance [198,199]. With its zwitterionic polysaccharide, *B. fragilis* can stimulate the host immune system. *C. butyricum* is a spore-forming, Gram-positive, butyrate-producing anaerobe of human and animal guts. While butyrate is known to exert beneficial effects on the host, supplementation of *C. butyricum* to newborns can induce necrotizing enterocolitis and type *E botulism* [198,199]. *Faecalibacterium prausnitzii* is a non-spore-forming, Gram-negative, butyrate-producing anaerobe (extremely oxygen-sensitive, EOS). The lower abundance or absence of *F. prausnitzii* has been linked to a variety of gastrointestinal illnesses [200]. This species is technologically problematic because of its great sensitivity to oxygen. Many experiments with *F. prausnitzii* have used culture supernatants (SN) instead of live cells to circumvent concerns with viability and stability [177]. The butyrate synthesis and immunomodulatory activities of *F. prausnitzii* have been related to its potential health benefits [177]. Additionally, *F. prausnitzii* (live cells or SN) was found to prevent colitis caused by dinitrobenzene sulfonic acid (DNBS), trinitrobenzene sulfonic acid (TNBS), or dextran sodium sulfate (DSS) (doses 10^9 CFU/day) [201]. Live cells of *F. prausnitzii* were proven to reduce the incidence of diarrhea and mortality-associated diarrhea in dairy calves and increase body weight [202].

4.3.1. Mechanisms of Action of Probiotics

Probiotics exert their effects via (1) the sustainability of host–microbe interactions and pathogen prevention through competitive exclusion. Probiotics competitively exclude pathogens by a variety of mechanisms, including competing with them for nutrients, blocking the epithelial adhesion sites, and decreasing the intestinal lumen pH [203]. (2) Production of antibacterial compounds. Compounds that are produced in the metabolome of probiotics include organic acids (butyric, lactic, and acetic acids), bacteriocins, hydrogen peroxide, amines and peptides, which not only antagonize opportunistic pathogens but also play a crucial role in regulation of host cellular proliferation, differentiation, inflammation, angiogenesis, and metastasis [204]. The mechanisms by which probiotics antagonize microbial growth include a reduction in intestinal pH [205], pathogen agglutination, toxic substance entrapment and metabolization [206], alteration of the intestine's motility [207], and production of bacteriocins, H_2O_2, and organic acids (Figure 3) [176]. (3) Promoting the synthesis and secretion of mucus by intestinal goblet cells to form a protective layer against pathogens [208]. (4) Stimulation of the host immune system [178,209]. (5) Production of vitamins, minerals and trace elements and important digestive enzymes (e.g., b-galactosidase) [210]. (6) Inhibition of the adherence and colonization of opportunistic and pathogenic bacteria. (7) Enhancing and maintaining gut mucosal integrity.

4.3.2. Limitations of Probiotics

Despite variable scientific evidence reporting the beneficial health impact of probiotics, concerns continue to grow about their clinical applications due to some obstacles, including: (i) the loss of viability of true probiotics during the preservation period, particularly at room temperature [211], (ii) different colonization patterns and variable tolerance to gut conditions, (iii) the potential of acquisition of virulence genes from opportunistic or pathogenic organisms, (iv) the capacity of some probiotic strains to transfer antibiotic resistance genes within the GIT [212], and (v) the probability of production of toxic substances, such as the heat-stable amylosin toxin from *Bacillus amyloliquefaeiens*, *B. subtilis*, and *B. mojavensis*, which may induce food poisoning [213].

Table 3. Applications of selected probiotics against pathogenic bacteria and their mode of action.

Probiotic	Target Pathogen	Additional Benefits	Monitoring	References
Nissle *E. coli* 1917 (EcN)	*C. jejuni*	In vitro: enhance tight junction functions and modulate the innate immune response on HT-29 cells. In chickens: reduce *C. Jejuni* colonization in the cecum up to 2.5 logs; enhance the immune response and intestinal morphology of the treated chickens without showing adverse effect on the gut microbe.	In vitro (HT-29 cell line) In chickens	[172–174,214]
L. plantarum	*L. monocytogenes*, *S.* Enteritidis, *E. coli* O157:H7 and *Staphylococcus*	Attach to epithelial cells, stimulate the production of IL-10 in the colon, and enhance the induction of dopamine and serotonin.	In vitro & in mice	[188,215]
L. paracasei & *L. rhamnosus*	*E. coli* V517, *S.* Enteritidis *OMS-Ca*, *S. aureus* 76 and *L. monocytogenes* ATCC 15313	Boost mineral bioavailability in food products, reduce serum parathyroid hormone via synthesis of short-chain fatty acids, enhance mineral solubilization and absorption, production of phytase, and hydrolyze glycoside linkages of estrogenic food products.	In vitro	[191,216,217]
L. helveticus	*L. monocytogenes* ATCC 19115, *S.* Typhimurium ATCC 14028, *S. aureus* ATCC 25923, and *E. coli* O157:H7 ATCC 43889	Stop GIT infections, improve protection against pathogens, enhance the immune system of the host, and makeup the composition GIT microbiota.	In vitro	[218,219]
L. reuteri	*E. coli* ATCC25922, *S. typhi* NCDC113, *L. monocytogenes* ATCC53135, and *E. faecalis* NCDC115.	Reduce pro-inflammatory cytokines production, promote regulatory T cells, strengthen the intestinal barrier, and decrease microbial translocation from the gut lumen to the tissues.	In vivo	[220,221]
L. acidophilus	*S. aureus*, *P. aeruginosa*, *L. monocytogenes*, *V. parahaemolyticus*, *V. cholerae*, *H. pylori*, *Klebsiella*, *Salmonella*, *Shigella*, *Bacillus*, *Clostridium*, *Mucor*, *Aspergillus*, *Fusarium*, *Trichoderma* and *Candida* spp.	Production of lactacins B and F, acidophilin, acidocin, acidophilucin, and acidophilicin.	In vitro	[222]
L. rhamnosus GG and *B. lactis* Bb12	APEC	Reduce the number of colonized APEC in chicken cecum with modulation of the gut microbiota.	In vitro In chickens	[223]
S. lactis and *L. delbrueckii* subsp. *Bulgaricus*	*E. coli* ATCC25922 and *S. aureus* ATCC25923	Inhibit proliferation via production of acid metabolites.	In vitro & in vivo	[224]
B. animalis AHC7	*S.* Typhimurium	Mediate weakness of activation of NF-κB that includes recognition of the pathogen by dendritic cells and production of T cells.	In humans	[225]
B. adolescentis and *B. pseudocatenulatum*, and *B. longum*	Vancomycin-resistant *S. aureus* and *Enterococcus*, *Propionibacterium acnes*, *S. aureus*, and *S. Epidermidis*	Reduce pathogen growth and cell adhesion.	In vitro	[226]
B. bifidum and *B.m infantis*	*S. enterica* serotype Enteritidis	Reduce pathogen growth via production of acids, hydrogen proxide, and bacteriocins.	In vitro	[227]
B. lactis	*S.* Typhimurium	Stimulate transient pro-inflammatory host responses in the epithelial cells of the intestine.	In vivo (rats)	[228]
Propionibacterium freudenreichii	Multidrug-resistant *S.* Heidelberg	Anti-inflammatory effect.	In vitro (HT-29 cell line)	[229,230]
Pediococcus acidilactici Kp1	*L. monocytgenes*, *S. enterica*, *Shigella sonnei*, *Klebsiella oxytoca*, *Enterobacter cloaca* and *S. pyogenes*.	Hender the adherence of pathogens to the intestinal mucosa by forming a barrier via auto-aggregation; production of bacteriocin-like inhibitory substances.	In vitro	[231]
Leuconostoc mesenteroides	*L. innocua*, *L. ivanovii*, or *S. aureus*	Production of bacteriocin, which inhibits the growth of pathogens, and lowering the medium pH.	In vivo (mice)	[189,232]
E. faecium NCIMB 11181	*C. perfringens*	Ameliorate necrotic enteritis and reduce intestinal barrier injury.	In chickens)	[233]
S. salivarius K12	*S. mutans* and *S. hominis*	Antibiofilm of *Schaalia odontolytica* P10 and *Enterobacter cloacae*.	In vitro	[234]
S. thermophilus SMQ-301	*S. aureus*, *E. coli*, and *Gardnerella vaginalis*	Potential candidate for novel biotherapeutic interventions against inflammation caused in septic mice.	In vitro, in vivo	[235,236]
B. coagulans subtilis, *B. laterosporus*	*E. coli*, *P. aeruginosa*, *K. pneumoniae*, *B. subtilis*, *S. aureu*, and *Candida albicans*	Stimulate human immune cells and change the induction of anti-inflammatory cytokines and chemokines.	In vitro (cell lines)	[237]

Table 3. *Cont.*

Probiotic	Target Pathogen	Additional Benefits	Monitoring	References
Saccharomyces boulardii	*S. aureus, E. coli, Klebsiella oxytoca, Yersinia enterocolitica, C. perfringens, C. difficile, Salmonella* sp., *Shigella* sp., *Candida albicans* and *Entamoeba hystolitica*	Affect the epithelial reconstitution; anti-secretory, anti-inflammatory, and immunomodulating effects.	In vivo (Lymphocyte-transferred SCID mice)	[238–240]
C. butyricum (CBM 588)	*E. coli* [EHEC] O157:H7	Inhibit growth by limiting the adhesion of pathogen to epithelial cells and the production of butyric acid.	In vivo (mice)	[241,242]
L. salivarius, L. johnsonii, L. reuteri, L. crispatus, and *L. gasseri*	*C. jejuni* 81-176	Inhibit the quorum-sensing signals of *C. jejuni.* Reduce the expression of *C. jejuni* virulence-related genes, including genes responsible for motility (*flaA, flaB,* and *flhA*), invasion (*ciaB*), and AI-2 production (*luxS*). Enhance the phagocytic activity of macrophages. Increase the expression of cytokines and co-stimulatory molecules in macrophages.	In vitro	[243]
Microbial consortia (Aviguard and CEL)	*C. jejuni* 81-176	Enhance the intestinal mucosa via the modulation of gut microbiome composition by increasing the relative abundance of Bacteroidaceae and Rikenellaceae	In vivo (chicken)	[244]
L. johnsonii, Ligilactobacillus salivarius, Limosilactobacillus reuteri, and *L. crispatus*	*C. perferingens*	Induce significant alterations in cytokine gene expression in the intestine. Modify the gut microbiome composition. Improve intestinal morphology.	In vivo (chicken)	[245]

4.4. Prebiotics

Prebiotics are defined as "non-digestible food materials that beneficially impact the host by selectively enhancing the growth and/or metabolism of bacterial species inhabiting the GIT, and thus improve the host health" [246]. Prebiotics are also defined as "any substrate preferentially consumed by host microorganisms that result in increasing the health benefit" [246]. Evidence indicates that prebiotics are promising alternatives in the medicinal and food industries. Prebiotics are characterized by (1) the ability to withstand the acidic environment during passage through the digestive tract (GIT) [247], (2) resistance to digestive enzymes but susceptibility to probiotic-hydrolyzing enzymes [248,249], (3) non-direct absorbance [250], (4) maintenance of gut microbial ecology [248], and (5) the ability to stimulate the host immune response [247]. Prebiotics are non-digestible oligosaccharides (fructans, inulins, xylans, galactans, and mannan), fibers (pectin, non-starch polysaccharides (such as β-glucan), xylooligosaccharides, andisomaltooligosaccharide), and seeds containing gums [251,252]. Human milk oligosaccharide is considered an endogenous source of prebiotics that increases the population of *Bifidobacterium* spp. in breastfeeding newborns, thereby enhancing their immunity [253]. To use prebiotics as alternatives to antibiotics, specific criteria must be met. Prebiotics should have a well-identified source chemical composition and structure, be a pure product, be at a suitable dose, and have been assessed in animal models or 3D cells to confirm their safety and beneficial health impact on the microflora [252]. When used as feed additives for livestock and poultry, prebiotics have shown an ability to improve host health and productivity via selective stimulation of proliferation and metabolism of the gut microbiota, such as *Akkermansia* spp., *Christensenella* spp., *Propionibacterium* spp., *Faecalibacterium* spp. and *Roseburia* spp., *Lactobacillus* spp., *and Bifidobacterium* spp. [254]. In the context of their benefits for human health, fermentation of the prebiotics konjac glucomannan hydrolysate and inulin in a batch culture of human feces has been associated with the production of short-chain fatty acids and proliferation of the genera *Bifidobacterium*, *Lactobacillus* and *Enterococcus* [255]. A meta-analysis of 64 studies reported that addition of dietary fibers stimulated *Bifidobacterium* spp. and *Lactobacillus* spp. resulting in an increase in the concentration of fecal short-chain fatty acids (SCFAs) in healthy adults [256]. Moreover, other studies have revealed that these bacteria play a key role in maintaining the composition of GIT microflora, enhancing the food and mineral absorption, and promoting the host defense system [257].

Prebiotics have also shown potential to eliminate harmful bacteria, such as *Salmonella*, *Campylobacter*, *Clostridium* and *E. coli* [258,259]; however, their mechanism of action remains to be elucidated. Fermentation of prebiotics by the gut's resident microbiota and the subsequent production of SCFAs results in a reduction in the gut pH, which, in turn, make the condition unfavorable for the growth and colonization of invading pathogens [260]. It was reported that the activity of probiotic *Bifidobacterium* strains against *C. difficile* was significantly stimulated in the presence of five prebiotics (oligosaccharides) [261]. Similarly, the activity of *Pediococcus acidilactici* was enhanced against *E. coli*, *Salmonella*, *E. fecalis* and *S. aureus* in the presence of garlic and basil (natural prebiotics) [262]. Moreover, the use of the prebiotics mannan-oligosaccharides and fructooligosaccharides, as poultry feed supplements, reduced the colonization of *Campylobacter* and *Salmonella* in the GIT of poultry [259]. Supplementation of weaning pigs with prebiotic oligofructose resulted in a significant increase in the number of *Bifidobacteria* and *Lactobacilli* and a significant reduction in the number of clostridia, enterobacteria, and enterococci [263]. A reduction in disease severity was observed following treatment of patients with *C. difficile*-associated diarrhea with inulin and oligofructose [264].

4.4.1. Mechanisms of Action of Prebiotics

There is no distinctive mechanism by which prebiotics eliminate the pathogenic bacteria, stimulate the host GIT microflora, or enhance immunity. Indeed, the mechanisms of action of prebiotics are very complex, as they are associated with a set of actions on the host physiology and intestinal microflora balance [252],. Nonetheless, it is well documented that fermentation or degradation of prebiotics beneficially affect the host by (1) mediating the growth and proliferation of beneficial intestinal microbes [260], (2) blocking adhesion sites on the epithelial cells (the catabolic end products released from the bifidogenic degradation of prebiotics might block the adhesion sites on the epithelial cells), (3) acting as receptor analogues and blocking lectin receptors that present on the surface of the pathogens [265], and (4) producing SCFAs, such as acetate, propionate, lactate, and butyrate, which result in lowering of the pH of the intestine, leading to suppression of the growth and colonization of pathogenic bacteria [266]. Additionally, SCFAs serve as a source of energy for the intestinal cells, in addition to their role in maintaining intestinal integrity by enhancing the expression of the tight junction proteins [267].

4.4.2. Limitations of Prebiotics

Prebiotics lack life-threatening or severe side effects. However, there are a few moderate side effects that have been reported [249], including osmotic diarrhea, bloating, cramping, and flatulence. It should be noted that these side effects depend upon the chemical composition of the prebiotics and the length of side chain, with short side chains reported to have more side effects than long ones [268]. Additionally, prebiotic dose is a critical factor that affects their safety profile. The commercially recommended dose of prebiotics is 1.5–5 g per portion [268].

4.5. Antimicrobial Peptides (AMPs)

AMPs are naturally produced by various immune cells and play a vital role in the innate immune systems of various animals, plants, and microorganisms [269]. AMPs, have a wide spectrum of antimicrobial activity against bacteria, fungi, viruses, and parasites [270]. In addition to their antimicrobial activities, AMPs possess biological functions, such as immune modulation, angiogenesis, antitumor activity, and wound healing [271,272]. AMPs are considered promising alternatives to antibiotics, due to many advantages; (1) they act on multiple target sites on the intracellular targets and plasma membranes of pathogenic bacteria, (2) they have potent killing activity against drug-resistant bacteria [270,273], (3) they are a component of the innate immune system, (4) their natural production by the host cells saves time and energy compared to antibody synthesis via acquired immunity, and (5) they reach the target sites faster than immunoglobulin [269]. AMPs are classified

into several subgroups based on their amino acid sequences (10–100), the net charge of the peptide (+2 to +9), and their protein structure and sources [274]. These subgroups include (1) anionic AMPs, which consist of 5–70 amino acid residues and have a net charge range of −1 to −8 [275]. Their structural characteristics include α-helical peptides and cyclic cystine knots [275]. They use the negatively charged content of the microbial membrane to form salt bridges, leading to disruption of the microbial membrane [276]. (2) Cationic α-helical AMPs are ≤40 amino acids in length (50% hydrophobic in nature) and have a charge of +2 to +9 and the C-terminus amidated [277]. The structure of cationic α-helical AMPs is disordered in aqueous solutions [278]. They are capable of forming amphiphilic structures when interacting with target cells [279]. (3) Cationic AMPs, where the peptides consist of 2–8 cysteine residues forming 1–4 pairs of intramolecular disulfide bonds. These disulfide bonds play a crucial role in β-sheet AMP stabilization and biological functions [280]. (4) Extended cationic AMPs containing amino acids including tryptophan, arginine, proline, histidine and glycine and lacks the regular secondary structures [279]. (5) Fragments from antimicrobial proteins that have a broad-spectrum bactericidal effect, such as lysozyme [281]. The helix–loop–helix (HLH) region in the human and chicken lysozyme has a strong effect on the growth of pathogenic bacteria and fungi [282].

Many antimicrobial peptides, isolated from different sources, have shown activity against a wide variety of pathogenic bacteria. For example, magainin-2 (α-helix (TFE)) was originally isolated from frogs and has been shown to be active against *P. gingivalis*, *F. nucleatum*, *P. intermedia*, *E. coli*, and *S. aureus* [283]. Cecropin and cecropin P1 (α-helix structure) were isolated from silk moth and pig, respectively. These peptides inhibited the growth of *E. coli* ML-35p [284], *S. aureus*, *B. subtilis*, *M. luteus*, *P. aeruginosa*, *S.* Typhimurium, *S. marcescens* and *E. coli* [285]. In addition, apo-lactoferrin (α-helix structure), discovered in bovine and human PDB code (1BOL), inhibited the growth of *E. coli* O157:H7 [286]. Melittin (α-helix structure), extracted from bee, was active against *S. salivarius*, *S. mitis*, *S. mutans*, *S. sanguinis*, *S. sobrinus*, *L. casei*, and *E. faecalis* [287]. Temporin A and temporin L, extracted from frog, were active against MRSA [288], *B. megaterium* Bm11, *S. aureus* Cowan I, and *E.coli* D21 [289]. Moreover, buforin II and clavanin A (α-helix structure), discovered in extended toad and Styela clava, respectively, possess inhibitory activity against *B. subtilis*, *S. aureus*, *E. coli*, *S.* Typhimurium [290], *E. coli* ML35p and *L. monocytogenes* [291]. Furthermore, protegrin-1 (β-sheet structure), isolated from human and porcine, has demonstrated antagonistic activity against MRSA and *P. aeruginosa* [292]. Tachyplesin-I (β-sheet structure), discovered in horseshoe crab, was shown to inhibit the growth of *S. Typhimurium* [293]. Furthermore, hepcidin (β-structure), extracted from humans, has demonstrated capabilities to inhibit *E. coli, S. aureus*, and *S. epidermidis* [294]. Daptomycin (cyclic lipopeptide membrane), isolated from *Streptomyces roseosporus*, can kill MRSA [295] and nisin (lantibiotic), isolated from *L. lactis*, was shown to kill MRSA, *S. pneumoniae*, *Enterococci* and *C. difficile* [296]. NPSRQERR [P1], PDENK [P2], and VHTAPK [P3]), derived from *L. rhamnosus* GG, showed inhibitory activity against APEC in chicken [297].

4.5.1. Mechanisms of Action of AMPs

The antibacterial activity of AMPs depends mainly on the type and the nature of the AMPs as well as the targeted bacterial pathogens. AMPs exert their antibacterial activity through either direct killing mechanisms where they cause membrane disruption, eventually causing bacterial cell death, and/or indirect mechanisma via modulation of the immune system (Figure 4) [298,299]. Cationic AMPs exert antibacterial activity by interacting with negatively charged bacterial membranes, leading to increased membrane permeability and cell lysis [269]. α-helical AMPs can bind to an anionic lipid microbial membrane and modify its disordered structure in aqueous solution into an amphiphilic α-helical structure to enhance its interaction with the microbial membrane [300]. Other modes of action of cationic AMPs were found to be dependent upon the pH of the medium. At neutral pH, AMP (clavanin A) adopts the membrane permeation mode of α-helical peptides [301], while at a slightly acidic pH, it induces cell death by disturbing membrane

proteins. Additionally, AMPs such as buforin II, indolicidin, and Peptide-P2 [302] can pass through the bacterial membranes and bind to DNA, inhibiting enzyme synthesis and indirectly stopping DNA replication and transcription [303]. Some AMPs, such as PR-39, a proline- and arginine-rich AMP, oncocin-type peptide, and Api137, an apidaecin-type peptide, inhibit protein synthesis via inhibition of mRNA translation, blocking the assembly of the ribosome 50S large subunit, or binding to the tunnel of ribosomes and preventing the transition from the initial stage to the elongation stage of translation [304]. Microcin J25 was found to bind to the secondary channel of the RNA polymerase and block trigger-loop folding. LL-37 was shown to inhibit *E. coli* via stopping the activity of palmitoyl transferase PagP [305]. NP-6 was found to inhibit the β-galactosidase activity of *E. coli* [306]. Further, cycloserine was also found to inhibit bacterial cell wall biosynthesis via blocking of the activity of alanine racemase and D-Ala-D-Ala ligase and, consequently, the synthesis of the D-Ala-D-Ala dipeptide of lipid II of the peptidoglycan precursor [269]. This suggests that HNP1 kills bacteria by interacting with lipid II. Teixobactin inhibits the synthesis of bacterial cell walls by binding to a highly conserved motif of lipid II and lipid III (precursors of cell wall teichoic acid) [298]. Amyloidogenic peptide and amyloids cause direct protein coaggregation leading to suppression of intracellular transport processes and eventual bacterial death [307].
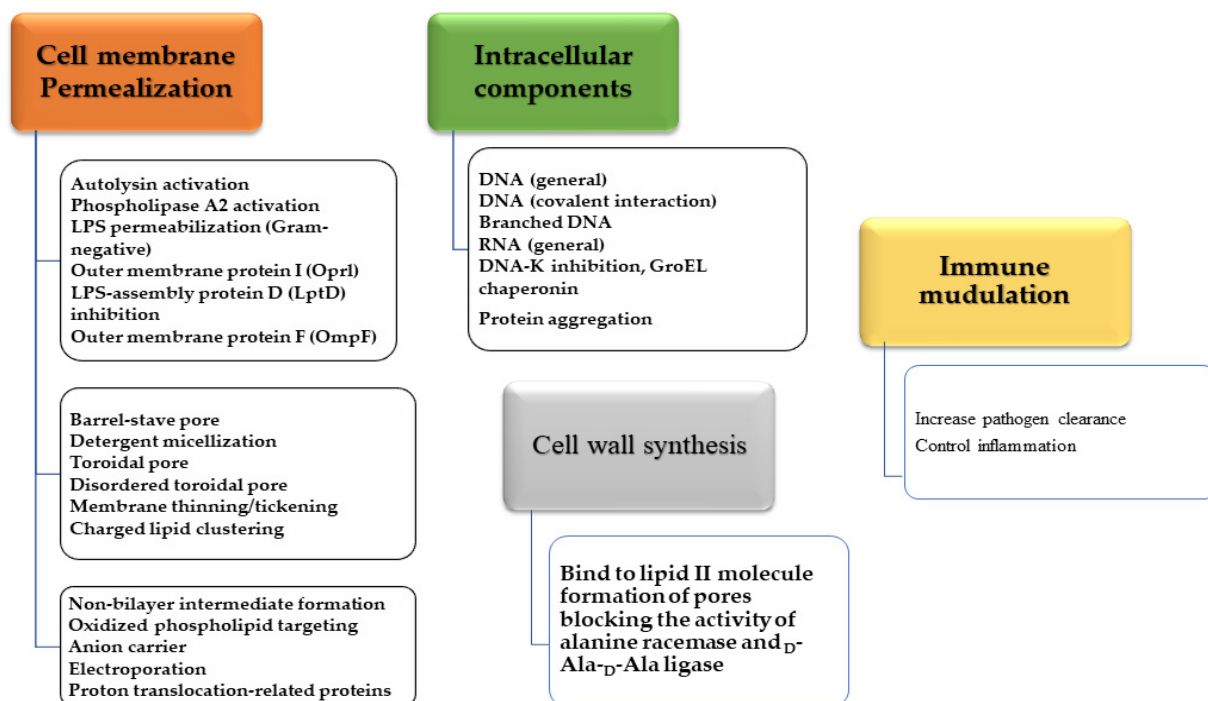
Figure 4. The mechanisms of antibacterial action of AMPs.

4.5.2. Limitation of AMPs

Although large numbers of AMPs have been discovered and characterized, a small number have been applied in clinical trials and a limited number have been approved by the FDA [298]. Most clinically applied AMPs are limited to topical applications, due to their systemic toxicity, the susceptibility of the peptides to protease degradation, and rapid kidney clearance if they are administrated orally [308]. Additionally, oral administration of AMPs can lead to proteolytic digestion by GIT enzymes, such as trypsin and pepsin, while systemic administration leads to a short half-life, protease degradation, and cytotoxic profiles in blood [309].

4.6. Bacteriophages

Phages or bacterial viruses are obligate parasites that infect bacteria and archaea. Phages are classified according to their size, shape, type of nucleic acid and mechanism of action in the host bacterial cell [310]. The genomic sequences of phages range from a few thousand base pairs to 498 kilobase pairs in phage G, the biggest phage ever sequenced [311]. Some phages have wide host ranges; however, the majority of them have high host specificity [312]. Based on the last classification, bacteriophages are classified as virulent (e.g., lysis of the bacterial cells to release new phages) or temperate (e.g., incorporation of its genetic material in the host genome and the host changes its genetic characters) bacteriophages [310]. In vitro trials showed that phages have many advantages over antibiotics, including (1) high host specificity (phages can target one strain of bacteria without perturbing the human or animal gut microbiota, while antibiotics do not distinguish between pathogenic and beneficial bacteria); (2) cost effectiveness and time saving [313]; (3) inhibition of multi-drug-resistant bacteria while antibiotics increase them; (4) ease of delivery to the target site and ability to penetrate the blood–brain barrier [314]; (5) no antagonistic effect detected between phages when given as a cocktail (mixture of different phages); (6) that phages could prevent biofilm formation [315]; and (7) phages might be used as an alternative in antibiotic-allergic patients; however, very few reports discussed this [316]. Several studies have reported that phage therapy development might be a potential solution to bacterial antibiotic resistance as well as the treatment of numerous bacterial infectious illnesses [317]. As the poultry gut is considered the main reservoir of *Campylobacter*, most *Campylobacter* phages have been isolated from avian GIT. Many studies have demonstrated that administration of individual phages resulted in a significant decrease in the number of *Campylobacter* without altering the GIT microbiota [318]. The most multi-drug-resistant bacterial strains, such as *E. faecium*, *S. aureus*, *K. pneumoniae*, *A. baumannii*, *P. aeruginosa*, and *Enterobacter* spp, have been reported to cause serious human diseases. The specific types of phages that have been applied for treatment of these pathogens are summarized in Table 4.

4.6.1. Mechanisms of Action of Bacteriophages

The majority of phages are virulent (lytic) with a negligible probability of becoming temperate (lysogenic) [314]. The lytic cycle of virulent phages starts by attachment of tailed phage to the cell surface receptors of a host. This interaction is two steps, a reversible phase followed by an irreversible phase. After the irreversible attachment, the lysis enzymes break down the host cell wall and the phage ejects its genetic material into the host cell with the assistance of processive host enzymes. The phage genome then manipulates the host cell metabolism by redirecting it for DNA replication and protein biosynthesis to the production of phage particles (nucleic acids and capsids); the host cell genome is degraded at this stage, followed by phage particle assembly and host cell lysis. The new viral particles are then released to re-attach to a new host cell. The lytic cycle of bacteriophages is performed by key phage proteins (holins) that permeabilize the host cell membrane and endolysins that degrade cell wall peptidoglycan. Consequently, the bacterial cells lose their cell wall integrity and the selective permeability of cell membranes, eventually resulting in cell lysis due to osmotic disruption [319].

4.6.2. Limitations of Phage Therapy

The main limitations for application of phage therapy are: (1) high host specificity. This can be overcome by using a cocktail of phages that may kill a broader host range. However, this is only feasible in chronic infection, not acute infection. Thus, a stable cocktail and/or phage lytic enzymes are recommended as alternatives [312]. (2) The targeted bacteria may develop resistance over time against phage attachment and adsorption by altering the receptor sites [312]. (3) Some bacteria produce endotoxins during lysis by phages, which may lead to septic shock. However, it should be noted that induction of endotoxins by antibiotic treatments like amikacin, cefoxitin, and imipenem was reported

to be higher than that released from coliphage treatments [320]. (4) It is difficult to obtain regulatory approval for phage-based therapeutics in in vivo trials [317]. (5) It is difficult to control the stability and purity of phages that are prepared for clinical trials, which may result in low-quality control data [321]. (6) Temperate phages are not preferable for therapeutic applications, due to the fact that phage-induced changes in the host DNA may lead to spread of antibiotic resistance [319,322]. (7) There is a significant decrease in phage concentrations by the reticuloendothelial system or neutralization by antibodies during therapeutic application [323].

Table 4. Examples of identified phages against pathogenic bacteria.

| Phage	Target Bacteria	PFU	Application	Reference
Cocktail of 12 natural virulent bacteriophages	*P. aeruginosa*	10^6	In vivo in human	[324]
coliphage PhiX174	*S. aureus*	NI	Patients with *S. aureus* bacteremia	[325]
Phage cocktail DS-6A, GR-21/T, My-327	*Mycobacterium abscessus*	10^9	A cystic fibrosis patient	[326]
cocktail 1 (*P. aeruginosa* 24, *P. aeruginosa* 25, and *P. aeruginosa* 7)	*P. aeruginosa*	6.2×10^{10}	Mice with chronic bacterial lung infections	[327]
IME-AB2	*A. baumannii*	62 PFU/cell	Reduce lung inflammation in mice	[328]
Pyo phage phage cocktail from the Eliava Institute	*S. aureus*, *E. coli*, *Streptococcus*, *P. aeruginosa*, or *Proteus mirabilis*	10^7–10^9	Patients with urinary tract infections	[329]
T4-like coliphage cocktail	*E. coli*	3.6×10^8	Diarrhea infected children	[330]
WPP-201 phage coctail	*P. aeruginosa*, *S. aureus*, and *E. coli*	8×10^7	Leg ulcer patients	[331]
P. aeruginosa phages 14/1 (Myoviridae) and PNM (Podoviridae) and *S. aureus* phage ISP (Myoviridae),	*P. aeruginosa* and *S. aureus*	10^9	Colonized burn wounds	[332]
PP01 phage,	*E. coli* O157: H7	10^5	In vitro	[333]
PlySs2 and PlySs9	*S. uberis*	NI	In vitro (bovine mastitis)	[334]
PlySs2	*S. equi*, *S. agalactiae*, *S. dysgalactiae*, *S. pyogenes*, *S. sanguinis*, *S. pneumoniae* and group E streptococci	NI	In vitro and in vivo (mice)	[335]
Φ7-izsam and Φ16-izsam	*C. jejuni*	10^7	In chickens	[336]
Phage cocktail e11/2, e4/1c, pp01	*E. coli* O157:H7	ND	Meat surface	[337]
Phage Cj6	*C. jejuni*	5×10^8	Raw and cooked beef	[338]
Phage Φ2	*C. jejuni*	10^7	Chicken skin	[339]
Salmonella phage (P7)	*Salmonella*	5×10^8	Raw and cooked beef	[338]
phage SJ2	*S.* Enteritidis	104	Cheddar cheese made from raw and pasteurized milk	[340]
phage A511	*L. monocytogenes*	5.2×10^7	Red smear cheese	[341]
Cocktail of the two lytic phages	*S. aureus*	10^6	Fresh and hard cheese type	[342]

PFU; plaque-forming units per mL, NI; Not identified.

4.7. Nanoparticles (NPs)

NPs are considered one of the potential alternative candidates of antibiotics for controlling multi-drug-resistant microorganisms [343]. They have demonstrated therapeutic potential due to their unique chemical and physical characteristics [344]. NPs have a tiny size (1–100 nm) with a large surface area to interact with target organisms [345]. They can be chemically or naturally synthesized from different sources with variable chemical structures that allow different chemical functionalities [346]. NPs exhibit antimicrobial activities through targeting critical active sites in pathogens, leading to partial or complete inhibition [346]. Organic or inorganic (metal and metal oxide) NPs can be synthesized from different sources. Inorganic NPs possess bactericidal activity against bacteria using multiple mechanisms and, therefore, they are denominated "nanobactericides". The nanobactericides activity of inorganic NPs is attributed to (1) their tiny size [346], (2) formation of weak and nonspecific interactions with bacterial surfaces [347], (3) Van der Waals forces (distance-dependent interactions between atoms or molecules) [348], and (4) attachment through specific receptor–ligand bonds [349]. Therefore, the bacterial cells' susceptibility to NPs depends on their structural components as well as their growth rate [350]. Gram-positive

bacteria are more susceptible to NPs than Gram-negative bacteria. Gram-positive bacteria have a permeable and negatively charged cell wall, making them an easy target for NP penetration, while the non-porous cell walls of Gram-negative bacteria serve as penetration barriers against the NPs [351]. Moreover, bacteria with slow growth rates are more sensitive to NPs than those with rapid growth rates. This is due to different stress-response genes' expressions in fast-growing bacteria [350].

4.7.1. Mechanisms of Action of NPs

The lethal impact of NPs on microbial cells is performed through (1) damaging the cell membrane and inhibition of permeability regulation due to direct attachment with the bacterial cell wall, (2) blocking electron transport and oxidative phosphorylation [352], (3) altering bacterial metabolism by interfering with enzymes, DNA and ribosomes, leading to protein and enzyme deactivation, prevention of DNA replication, and alteration of gene expression levels [353], (4) impeding the development of biofilms, (5) causing oxidative stress by releasing reactive oxygen species (ROS), and (6) excitation of host immune responses (Figure 5) [354,355]. Antimicrobial activities of NPs against different pathogenic bacteria, and mechanisms of action, are shown in Table 5.
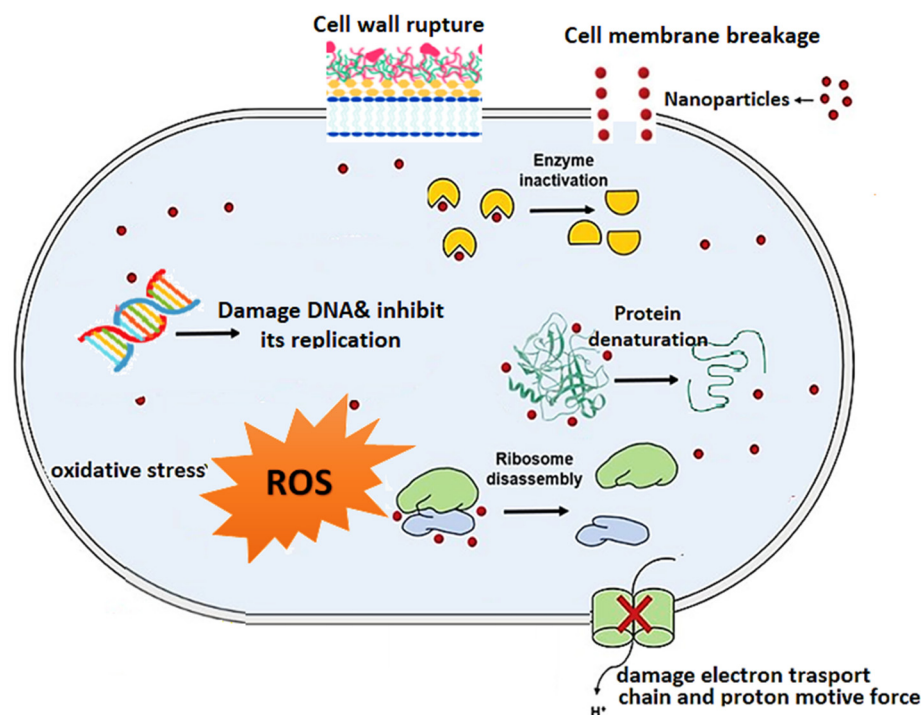
Figure 5. Mechanism of action of nanoparticles in bacterial cells.

4.7.2. Limitations of NPs

The major limitations of NPs are (1) local and systemic toxic complications in the human body and potential inhibition activity on gut microbiota [350]; (2) silver NPs' Ag accumulates in human organs such as colon, lung, bone marrow, liver, spleen, and the lymphatic system, leading to damage and/or decrease of organ efficacy and dysfunction [344] (additionally, Al_2O_3 NPs were reported to exhibit toxic effects on neurons [356]); (3) oxidative damage induced by CuO NPs, ZnO NPs, or TiO_2 NPs [344,357]; (4) the buildup of metallic NPs in various tissues might cause renal damage, and liver or lung toxicity [358]; (5) the lack of a well-described standard technique that is not influenced by the properties of the NPs; and (6) that although resistance of bacteria to NPs rarely happens, some literature mentions that bacteria may develop NP resistance following exposure to metal NPs, such as Ag, Au, or Cu [359–361], or metal-oxide NPs, such as Cu^{2+} and Cu-doped TiO_2 and Al_2O_3 NPs [362].

Table 5. Effects of nanoparticles on different pathogenic bacteria and the mechanism of their antimicrobial activity.

NPs	Particle Size	Target Bacteria	Mechanism of Action	Reference
Silver (Ag)	1–100 nm	*S. epidermidis*, MRSA, vancomycin-resistant *Enterococcus* (VRE), extended-spectrum beta lactamase (ESBL)-producing organisms, MDR *E. coli*, *P. aeruginosa*, *K. pneumoniae*, carbapenem and polymyxin B-resistant *A. baumannii*, and carbapenem resistant *P. aeruginosa*, *E. coli*	Generate reactive oxygen species (ROS), stopping cytochrome chains, membrane damage, dissipation of proton gradients, destabilization of RNA and DNA	[343,351,352,363]
Gold (Au)	1–100 nm	MRSA	Damage membranes and respiratory chains, inhibit ATPase activity, decrease the binding between tRNA and ribosomes and formation of pores in the cell wall	[344,351,352]
Copper (Cu)	2–350 nm	MDR *E. coli*, *A. baumannii*	Dissipation of cell membranes, generation of ROS, lipid peroxidation, protein oxidation, and DNA degradation	[343,364]
Silica (Si)	20–400 nm	MRSA	Generation of ROS and lysis of cell walls	[351,352]
Aluminum (Al)	10–100 nm	*E. coli*	Generation of ROS and lysis of cell walls	[344]
Iron oxide NP	1–100 nm	MDR *E. coli*, MRSA, *K. pneumoniae*,	ROS-generated oxidative stress: superoxide radicals (O^{-2}), hydroxyl radicals (OH^{-}), hydrogen peroxide (H_2O_2)	[351]
Titanium dioxide (TiO_2)	30–45 nm	*E. coli*, *P. aeruginosa*, *S. aureus*, *E. Faecium*	ROS generation and adsorption to the cell surface	[344]
Zinc oxide (ZnO)	10–100 nm	*Enterobacter aerogenes*, *E. coli*, *K. oxytoca*, *K. pneumoniae*, MRSA, *K. Pneumoniae*, ESBL-producing *E. coli*	Generation of ROS, disruption of membranes, adsorption to cell surface, and damage to lipids and proteins	[365]
Magnesium oxide (MgO)	15–100 nm	*S. aureus*, *E. coli*	ROS generation, lipid peroxidation	[343]

4.8. Organic Acids (OAs)

Organic acids are widely used as antimicrobials in food processing and many industries [366]. Bacteria, fungi, and yeast play a critical role in the synthesis of organic acids during their lifecycle with high yields that can be achieved using cost-effective substrates. The bioproduction of OAs depends on many factors, such as the species of microorganism, inoculum size, substrate or carbon source, and environmental conditions (aeration, temperature, pH and agitation) [367]. Increasing the acidity by adding an acidulant or integrating natural fermentation is one of the commonly used methods to minimize and/or inhibit microbial growth. Using organic acids as an alternative to antibiotics depends on several factors, such as chemical formula structure, molecular weight, the value of the dissociation constant (pKa), minimum inhibitory concentration (MIC), nature of the microorganism, and exposure time to the food [368], where the pKa is an important criterion because of the undissociated part of the acid that is responsible for the antimicrobial effect.

Common OAs that are microbially produced and commercially used for microbial inhibition and food processing (Table 6) include (1) acetic acid, which is produced after fermentation of many substrates, such as glucose, lactose, and sucrose. This has the European code E260 and is used in the production of vinegar, stabilizer, flavor enhancer, and firming agent [367]. (2) Adipic acid is a crucial intermediate in the pathways of cyclic alkanes, long-chain aliphatic dicarboxylic acids and cyclic alcohols [369]. It is commonly used in the synthesis of polymers, plasticizers, nylon, clothing, automobile parts, and lubricant [370]. (3) Butyric acid is used in the fuel, plastic pharmaceutical, and textile industries. (4) Citric

acid is used as a pH regulator, flavor enhancer, pharmaceutical reagent, and firming agent, in addition to its antimicrobial properties [371]. It is also used in soft candies, baked goods, gelatins, snacks, dairy products, and cheese warps as an antimicrobial and in the fuel industry. (5) Lactic acid is used in dairy products, biochemical processes, and the leather, pharmaceutical, textile, and biodegradable biopolymer industries [372]. (6) Malic acid, which is an intermediate compound in the tricarboxylic acid cycle, is naturally found in fruits including apricot, blackberry, cherry, mango, peach, and plum. It has been used in the food, water treatment, textile, metals, and pharmaceutical industries [373]. (7) Phenyl lactic acid naturally exists in honey and has an effective and broad microbial activity against bacteria, fungi, and yeast [374]. (8) Propionic acid naturally presents in apples, strawberries, grains, and cheese [375]. Adding propionic acid to chick diets was found to improve their growth, exert an antimicrobial effect in the intestine, and reduce the yellowness of the meat [376]. (9) Succinic acid is used in food preservation, perfume intermediates, herbicide production, and the plastics and textiles industries [377].

4.8.1. Mechanisms of Action of OAs

The inhibitory mechanism of OAs is mainly due to the passage of the compound in proton-like form into the pathogen's plasma membrane. When organic acid molecules pass through the cell membrane, they subsequently dissociate, resulting in the release of charged anions and protons that could not pass through the plasma membrane on their own [378]. It has been reported that these accumulating anions are poisonous and capable of blocking metabolic processes [379]. OAs limit microbial growth through altering lipophilic properties and, thus, allowing the uncharged form of weak acids to diffuse into the cytoplasm through the microbial plasma membrane until reaching an equilibrium. The decrease in the intracellular pH leads to microbial growth inhibition through denaturation of enzymes and structural proteins and DNA damage [380]. OAs were also reported to cause perturbation of membrane function by intercalation or chelation of ions essential to bacterial membrane stabilization [381]. There is also evidence that weak acids result in accumulation of anions inside the cytoplasm, which may have an osmotic effect and alter metabolic processes within the cells [380]. Furthermore, the inhibitory activity of mild organic acid might be due to an induced response involving an integral membrane protein (Hsp30) that strives to restore equilibrium. This protein inhibits the rise in membrane ATPase by serving as a 'molecular switch' to save the cellular energy reserves that the enzyme would otherwise utilize to establish equilibrium. However, this reaction is energy-intensive and the process reduces the available energy pools for growth and other vital metabolic functions [382].

4.8.2. Limitations of OAs

The increase in OAs concentrations could change the sensory quality (color, odor, flavor, and taste) of preserved food [383]. Some pathogens possess several mechanisms to counteract the inhibitory impact of OAs, which may result in resistance to their antimicrobial activity and/or to the harsh acidic conditions [384]. Additionally, the procedure to get production approval from regulatory agencies is very complex and time-consuming [382]. Direct applications in living organisms, such as poultry, may reduce their growth performance because OAs are rapidly metabolized in the foregut [385].

Table 6. The structures of commonly used organic acids, their main producers, and their activity against various pathogenic bacteria.

Organic Acid (pKa1)	Chemical Structure	Main Microbial Producers	Active against	References
Acetic acid (4.76)	$C_2H_4O_2$	*C. formicoaceticum, Acetobacter, Gluconobacter,*	*L. monocytogenes, S.* Typhimurium and *E. coli*	[367]
Adipic acid (4.41)	$C_6H_{10}O_4$	*E. coli*	*Alternaria solani, Botrytis cinerea, Phytophthora capsici,* and *P. citrophthora*	[386]
Butyric acid (4.82)	$C_4H_8O_2$	*C. butyricum, Butyrivibrio* sp., *Eubacterium* sp., *Fusobacterium, Megasphera* sp., *Sarcina* sp.	*S.* Enteritidis, *C. perfringens, E. faecalis,* and *S. pneumoniae*	[387,388]
Caprylic acid (4.89)	$C_8H_{16}O_2$	*Mixculture* from brewery wastewater	*Vibrio parahaemolyticus & Dermatophilus congolensis*	[389]
Citric acid (3.13)	$C_6H_8O_7$	*Aspergillus ficum, Acremonium, Bacillus, Bostrytis, Candida, Aschochyta, Eupenicillium, Debaromyces, Hansenula, Trichoderma, Mucor, Pichia, Saccharomyces, Talaromyces, Penicillium, Torulopsis, Yarrowia,* and *Zygosaccharomyces*	*Yersinia enterocolitica Shigella dysenteriae E. coli* O157:H7	[390,391]
Fumaric acid (3.02)	$C_4H_4O_4$	*Rhizopus arrhizus*	*Talaromyces flavus*	[392]
Lactic acid (3.86)	$C_3H_6O_3$	*Rhizopus oryzae, Aspergillus, Bacillus, Carnobacterium, Enterococcus, Escherichia, Lactobacillus, Lactococcus, Rhizopus, Saccharomyces*	*B. coagulans, L. monocytogenes*	[393]
Malic acid (3.40)	$C_4H_6O_5$	*Ustilago trichophora, E. coli, Saccharomyces, Aspergillus* sp. and *Zygosaccharomyces Aureobasidium pullulans*	*L. monocytogenes, E. coli* O157:H7, *S.* Enteritidis and *S. gaminara,*	[394]
Phenyllactic acid (4.31)	$C_9H_{10}O_3$	*B. coagulans, Lactobacillus, Enterococcus, Leuconostoc,* and *Weissella, Leuconostoc, L. plantarum* 1081, *L. acidophilus* 1063, *L. paracasei* 1501	*L. monocytogenes Aspergillus* spp. *Penicillium* spp.	[10,142]
Propionic acid (4.87)	$C_3H_6O_2$	*Propionibacterium acidipropionici*	*L. plantarum, Sarcina lutea, S. ellipsoideus, Proteus vulgaris, S. aureus,* and *Torula* spp. *E. coli* K12 and *Salmonella*	[154]
Succinic acid (4.21)	$C_4H_6O_4$	*Yarrowia lipolytica, Anaerobiospirillum succiniciproducens, Mannheimia succiniciproducens,* and *Actinobacillus succinogenes*	*S.* Typhimurium, *E. coli, B. subtilis,* and *S. suis*	[395,396]
Tartaric acid (2.98)	$C_4H_6O_6$	*Gluconobacter suboxydans*	*L. monocytogenes, E. coli* O157:H7 and *S. gaminara*	[397]
Valeric acid (4.82)	$C_5H_{10}O_2$	*Megasphaera elsdenii*	*C. jejuni*	[398]

4.9. Essential Oils (EOs)

Essential oils are volatile, aromatic, and oily liquids extracted from plant parts, such as seeds, leaves, buds, twigs, flowers, bark, herbs, wood, fruits, and roots [399]. Plants generate EOs as a natural defense against pathogens and herbivore feeding by reducing the appetite of herbivores. As a result, the Department of Health and Human Services has designated EOs as safe antibacterial additives [400]. To date, about 3000 EOs have been recorded, 300 of which are economically valued in the pharmaceutical, agronomic, food, sanitary, cosmetics and perfume industries [401]. EOs are complex natural mixes that contain anywhere from 20 to 60 distinct components in various proportions. The antibacterial effects of EOs are dictated by their primary ingredients (85%), which include terpenes, terpenoids, and aromatic and aliphatic groups from different natural sources [402]. These groups are characterized by low molecular weights, which are limonene (31%) and α-phellandrene (36%) in *Anethum graveolens* leaf oil, d-limonene (over 80%) in citrus peel

oils, α/β-thujone (57%) and camphor (24%) in *Artemisia herba-alba* oil, carvacrol (30%) and thymol (27%) in *Origanum compactum* oil, α-phellandrene (36%) and limonene (31%) in *Anethum graveolens* leaf oil, menthol (59%) and menthone (19%) in *Mentha piperita* oil, and carvone (58%) and d-limonene (37%) in *Anethum graveolens* seed oil [403].

Menthol, pulegone, linalool, thymol and camphor, extracted from *Salvia lavandulifolia Lavandulaangustifolia*, *Mentha piperita*, *Mentha pulegium*, and *Satureja montana*, respectively, have shown antagonistic effects against *P. aeruginosa*, *S. pyogenes*, *S. mutans*, *S. sanguis*, *S. salivarius*, and *E. feacalis* [404]. Thymol and carvacrol, extracted from many sources, such as *Origanum compactum*, *Lavandula latifolia*, *Lavandula angustifolia*, *Rosmarinus officinalis*, *Origanum vulgare*, *Thymus vulgaris*, and *Thymus zygis* chemotype thymol, have shown activity against *S. aureus*, *C. hystoliticum*, *C. perfringens*, *E. coli* O157:H7, *S.* Typhimurium, *S.* Enteritidis, and *L. monocytogenes* [404,405]. Linalool, linalyl acetate α-terpineol, β-caryophyllene and nerol, produced by *Mentha citrata* Ehrh, have shown inhibitory effects against *P. aeruginosa*, *K. pneumoniae*, *E. coli* (DH5α), *E. coli* (MTCC 723) and *S.* Typhimurium, *S. aureus*, *S. epidermidis* and *S. mutans* [406]. Additionally, E-anethole, linalool, 1,8-cineole, α-pinene, camphor, camphene, menthol, menthone, and limonene, produced by *Ocimum basilicum*, *Rosmarinus officinalis*, *O. majorana*, *Mentha piperita*, *Thymus vulgaris*, and *Pimpinella anisum*, have shown activity against *C. perfringens* [407]. *Epilobium parviflorum*, *Salvia desoleana*, *S. sclarea*, and *Allium sativum* were reported to produce palmitic acid, linoleic acid and α-linolenic acid, which have shown an ability to inhibit *E. faecalis*, *S. aureus*, *P. aeruginosa*, *S. epidermidis*, and *E. coli* [408]. Moreover, cinnamomum was reported to produce cinnamaldehyde, which was shown to inhibit *E. coli*, *S. aureus*, and *S.* Typhimurium [409]. Dipterocarpus gracilis was reported to produce elemicin and geranyl acetate, which were shown to suppress *B. cereus* and Proteus mirabilis [410].

4.9.1. Mechanisms of Action of EOs

EOs and their components are characterized by their hydrophobic nature that allows them to interact with the lipids of the microbial cell membrane [411]. They can sensitize cells and cause severe membrane damage, resulting in leaking of essential intracellular contents, bacterial cytoplasmic membrane collapse, and bacterial cell death. Cell wall breakdown, cytoplasmic membrane damage, cytoplasm coagulation, and membrane protein degradation are the common causes of the leakage [412]. EOs also directly target biofilm formation. A recent study has shown that EOs can limit biofilm formation by binding to them, in addition to reducing cell-wall-related virulence factors and the translation of particular target microorganism regulatory gene products [413]. EOs can also operate as transmembrane carriers by swapping their hydroxyl protons for potassium ion, causing the electrical potential and the pH gradient across the membrane to dissipate. They also result in a reduction in proton motive force and depletion of intracellular adenosine triphosphate (ATP) pools. Potassium deficiency can also be troublesome, since it is necessary for the activation of several cytoplasmic enzymes, the maintenance of osmotic pressure, and intracellular pH regulation [413]. A phenolic group in EOs exhibits a direct antibacterial activity by altering bacterial membrane permeability and energy production. Moreover, the hydroxyl groups of EOs are thought to attach to bacterial proteins and block the function of amino acid decarboxylases in *E. aerogenes* [405].

4.9.2. Limitations of EO Applications

Application of EOs in food processing reduces the availability of EOs as antimicrobial agents because food constituents contain many fatty, proteinaceous, and sugary components that may interfere with the action of EOs. Additionally, the concentration and the dose of EOs added to the food is 10–100 times lower than the in vitro concentrations, which may consequently result in a decreased efficiency of these EOs [414]. Moreover, addition of EOs in the food industry even at a low concentration may change the physical properties of the food product, such as odor and taste [415]. Since the optimum antimicrobial activity of EOs is at an acidic pH, many EOs are sensitive to high pH values [416]. The relation-

ships between the toxicity of bioactive components of Eos, their chemical structures and functional groups, the influence of hydrophobicity, and the makeup of the microbial lipid membrane should be investigated extensively before EOs are used [415].

4.10. Fecal Microbial Transplant (FMT)

FMT is a process of transferring processed fecal material from the intestine of a healthy donor to the intestine of a recipient patient [417]. Processed fecal matter can be administered to the recipient through several methods, such as a nasoduodenal tube [418], nasojejunal tube [419], colonoscopy, or retention enema [420]. Colonoscopy administration of fresh or frozen and thawed fecal matter from stool banks into the cecum and colon of *C. difficile*-infected children in Maryland resulted in complete resolution of CDI in recipients as well as reductions in both AMR and multidrug resistance genes. Moreover, FMT resulted in sustained elevations in alpha diversity post-FMT as well as significant changes in beta diversity, in addition to improving the biosynthetic pathways [420]. In another study performed in mice, when a combination of FMT and lytic phages was used for treatment of *S.* Typhimurium, a complete clearance of *Salmonella*, a reduction in inflammatory cytokines, and restoration of the intestinal microbial diversity was observed [421]. Additionally, patients with MRSA enteritis who were treated with FMT through nasointestinal tube, jejunostomy fistula tube or gastrostomy fistula tube had negative stool cultures for MRSA, and gut microbiota analysis also revealed that all recipients developed donor-related bacterial diversity [422]. FMT has also shown satisfactory results when given to patients infected with beta-lactamase-producing Enterobacteriaceae. Four weeks after the first FMT dose through nasoduodenal tube, decolonization was detected in 20% of the recipients, with recipients' microbial composition showing a shift toward the donors' microbial diversity [423]. Administration of fresh fecal matter using nasojejuneal tube into *K. pneumoniae*-infected patients stopped sepsis and resulted in elimination of *K. pneumoniae*, as demonstrated in the blood cultures and general improvement of the health status. Moreover, a restoration of microbial diversity was observed after 6 weeks of treatment [419]. Administration of fresh fecal matter using nasoduodenal gastroscope into the third part of the duodenum of chronically infected hepatitis B patients (CHB) also resulted in suppression of the hepatitis B virus as well as clearance of the HBeAg [418]. In addition to its use in the treatment of microbial infections, FMT has also shown potential to improve non-infectious GIT conditions, such as ulcerative colitis, where it resulted in a lowered pediatric ulcerative colitis activity index (PUCAI) following completion of the FMT treatment course [424]. Similar observations were made for other inflammatory bowel diseases [425]. Moreover, several experiments were undertaken to assess the safety and efficacy of FMT in treating other extra-intestinal disorders, such as obesity and metabolic disorders [426] and psoriatic arthritis [427].

4.10.1. Mechanisms of Action of FMT

Although the mechanism of treatment by FMT is not fully clear yet, it has been noticed that the restoration of healthy gut microbial diversity [428], including *Firmicutes* in recipients after FMT [428], is associated with improvement in the recipients' health status [429]. It has been hypothesized that restoration of gut beneficial microbes, such as *Roseburia hominis* and *Bacteroides ovatus*, inhibits the pathogens' growth [428] or competes with the pathogens for nutrients and growth environment [428]. The restored commensal microbes compete with *C. difficile* directly through competitive niche exclusion or indirectly through production of bacteriocins, such as thuricin CD [430].

4.10.2. Limitations of FMT

While the development of FMT may seem easy [431], there are still some challenges associated with its preparation. These challenges include donor selection, stool processing, method of sample administration, colonization resistance, and relapse of infection. The donor for FMT has to be healthy, free from autoimmune, metabolic, and malignant disorders as well as pathogenic microorganisms [417]. It was noticed that microbiota from donors

encounter resistance to colonizing the recipient's intestine from the recipient's gut flora, thus preventing them from performing their function [432]. Therefore, it is recommended that the donor should be one of the recipient's relatives to achieve what is called "donor–recipient microbial matching" to overcome colonization resistance [433]. Additionally, naso-gastric administration is associated with respiratory side effects, while diarrhea is a common adverse effect of a colonoscopy [434]. Processing of a donor's stool under aerobic conditions diminishes its quality, as it affects bacterial diversity by inhibiting the viability of normal anaerobes in the sample while inhibiting bacterial ability to produce short-chain fatty acids, which are crucial processes for homeostasis [432,435]. However, it is noteworthy that processing and freezing storage duration did not significantly impact the efficacy of FMT in *C. difficile* infection (CDI) [436]. For better FMT outcomes, proper site administration should be applied at the site of dysbiosis [432]. Relapse of infection is also one of adverse effects of FMT, as seen in about 20% of FMT-treated CDI [428]. It can be concluded that, to date, there is no perfect approach without adverse effects for FMT application. More studies concerning safety and efficacy are required to approve FMT for wide use in treatment.

4.11. Vaccines

Vaccines are preparations used to stimulate the body's immune response against diseases by exploiting the ability of the human immune system to respond to, and remember, the antigens of pathogens. Several vaccines have been developed to make a revolutionary change in the world, such as fowl (avian) cholera, anthrax, polio, norovirus, rift valley fever, and rabies vaccines [437–439]. Vaccines play a pivotal role in reducing the need for antibiotics and controlling the emergence of AMR bacterial strains [440]. Vaccines reduce the burden of antimicrobial resistance through disease prevention and thus reducing the use of antibiotics [441,442]. This occurs as a vaccine curbing the ability of the pathogen to establish a foothold in the host, by conferring immunity against these pathogens, thus minimizing the chances of some bacterial mutations and the development and spread of resistant genes to other bacteria [443,444]. For instance, a 67% reduction in the circulation of penicillin-resistant invasive pneumococcal strains was demonstrated in a group of children that received pneumococcal conjugate vaccine 9 (PCV9) compared to controls in South Africa [445]. Conjugate vaccines combine weak antigens with strong antigens (which serve as the carriers) to increase the response of the body to the weaker antigen. In this context, the typhoid conjugate vaccine (TCV) has been introduced in children in order to protect them extensively from drug-resistant *S.* Typhi [446]. It has been observed that TCV can avert 44% of typhoid cases, of which 35% are resistant to antibiotics [447]. Salmonellosis, caused by *Salmonella* spp., is one of the most common zoonotic diseases associated with consumption of dairy and beef [448]. *S. enterica* serotype Dublin, which infects cattle and can be shed in milk, colostrum, and feces, also poses a threat to public health. *S.* Dublin causes bloodstream infections in humans, with a relatively high case fatality [449]. Data from the CDC (Centers for Disease Control and Prevention) showed that *Salmonella* Dublin infections caused more hospitalization during 1996–2004. Additionally, a higher percentage of *Salmonella* isolates were resistant to more than seven classes of antimicrobial drugs during 2005–2013 (50.8%) compared to only 2.4% during the period 1996–2004. Resistant *S. enterica* causes at least 100,000 foodborne human infections annually [450]. A commercial modified-live *Salmonella* Dublin vaccine (EnterVene-d) is approved by the USDA for use in calves, but vaccination does not reduce the likelihood of contamination or the risk to public health; it only improves clinical outcome [451]. *C. perfringens* enterotoxin (CPE) and Shiga-toxin-producing *E. coli* (STEC) are also common causes of food poisoning. Research has been conducted on possible development of a vaccine for CPE and STEC in the form of a bivalent food poisoning vaccine. The bivalent vaccine uses a fused protein (Stx2B-C-CPE) consisting of the B subunit of *E. coli* Shiga toxin 2 fused to CPE to enhance its antigenicity [452]. Two other extremely important bacteria, *C. jejuni* and *C. perfringens,* have been the subject of many vaccine studies in poultry [453–456]. The efficacy and commercial potential

of these vaccines has been described and reviewed in detail elsewhere [457]. It is worth mentioning that the conserved N-glycan heptasaccharide conjugated to GlycoTag, or fused to the *E. coli* lipopolysaccharide core, has shown tremendous potential to reduce *C. jejuni* colonization in the gastrointestinal tract of chickens by up to 10 $\log_{10}$ [458]. Despite the demonstrated efficacy of this vaccine, its commercialization remains murky.

Vaccination can cause indirect effects on infections. While resistance is a predictable outcome of antibiotic use, resistance to vaccines is very rare [459]. Vaccines are administered prophylactically, whereas antibiotics are administered only once symptoms have begun to show. Thus, by the time antibiotics are administered, there are possibly already millions of copies of the pathogen, raising the probability of mutation occurring. Vaccines prevent the pathogen from gaining a foothold and multiplying in the first place. In many cases, the use of vaccines has globally eradicated some diseases, while decreases of 95% in the incidence of diseases like diphtheria, tetanus, and pertussis have been observed [460]. Much progress has been made in bacterial vaccine development. Bacterial vaccines can and should help address the global AMR problem. It is reasonable to believe that reductions in MDR infections as well as the prevention thereof can be achieved using bacterial vaccines. Attention should also be paid to the role of veterinary bacterial vaccines to reduce antibiotic use in animals, especially food-producing animals. The role of bacterial vaccines is set to expand dramatically in response to the crisis of AMR and MDR [461]. Although vaccines against major AMR pathogens are still missing, predictions of the impact of vaccines against AMR hint that vaccines could have a significant impact in controlling resistance [462].

4.11.1. Mechanisms of Action of Vaccines

Vaccine types are quite varied in their formulations and mechanisms of action. The mechanisms through which different types of vaccines work include: (1) live, attenuated vaccines: these vaccines contain a live version of the pathogen that has been attenuated or weakened to the point where it loses its pathogenicity, but is still capable of inducing an immune response [463]; (2) killed whole-cell vaccines: the pathogen is killed or inactivated by treatment with gamma irradiation or a chemical agent; this preserves the structure of the epitopes but removes the pathogen's ability to replicate or be virulent [464]; (3) toxoid vaccines: the pathogen's toxin is purified and treated with formalin to destroy its toxic activity, while retaining enough antigenic activity to protect against disease [465]; (4) subunit vaccines: these contain protein or glycoprotein components of a pathogen that are able to induce a protective immune response [466]; outer membrane vesicles (OMVs) are comprised of bacterial outer membrane constituents naturally released from Gram-negative bacteria, and contain key antigenic components that can elicit a protective immune response but cannot cause disease [467]; (5) protein–polysaccharide conjugates: conjugate vaccines are composed of covalently linked bacterial polysaccharides to proteins; polysaccharides on their own do not elicit T-Cell response, whereas polysaccharides linked to certain proteins do elicit a T-cell response [468]; (6) recombinant viral and bacterial vector vaccines: these use harmless bacteria or viruses as vectors to introduce the genetic code of the antigens of the pathogen to the cells, to train the immune response [469]; and (7) nanovaccines: a new generation of vaccines using NPs as carriers and/or adjuvants; nanovaccines could target the area of the body where the disease originated from, while other vaccines target the whole body [470]. Table 7 shows examples of vaccines that have been developed and approved or are still currently being developed against foodborne bacterial pathogens in humans and livestock.

Table 7. Vaccines against infectious bacterial pathogens, either approved or in the research stage.

Vaccine Name	Target Pathogen	Indicated for Use in	Notable Observations	Reference
M01ZH09 vaccine Live attenuated *S.* Typhi, strain *S.* Typhi ZH9	*S.* Typhi	Humans	Vaccine extremely well tolerated. Adverse events did not differ between cohorts or from subjects receiving placebo; M01ZH09 was highly immunogenic in all dose ranges. Serologic responses measured by *S.* Typhi LPS-specific IgA and IgG ELISA were seen in most volunteers at all dose levels and time points post-vaccination.	[471]
Whole cell *S. aureus* vaccine (StartVac)	*S. aureus*	Cattle	The 45% observed reduction in the basic reproduction ratio of *S. aureus* is encouraging, but highlights that vaccination is only an additional tool in the control of *S. aureus* infections on dairy farms. Efficacy was dependent upon the age group of the animals, where first-lactation animals showed a higher value. Compared with animals in third and higher lactation.	[472]
Whole cell *S. aureus* vaccine (Lysigin)	*S. aureus*	Cattle	Lower mean duration of clinical mastitis. No evidence that the vaccine reliably prevented *S. aureus*, but Lysigin showed a benefit in reducing the clinical severity and duration of clinical disease after challenging.	[473]
Modified live *S. dublin* vaccine (EnterVene-d)	*S. enterica* serotype Dublin	Cattle	The vaccine induced the immune response via stimulation of cell-mediated, humoral, and mucosal immunity. Calves that received colostrum from vaccinated cows had significantly higher *S.* Dublin titers compared to calves born to unvaccinated cows.	[474]
Alpha toxin (CPA) toxoid vaccine (NetVax)	*C. perfringens*	Poultry	Overall, the vaccine appeared to be safe, with no observed systemic reactions or adverse effects on performance or reproduction. Vaccination of broiler breeder hens induces the production of antibodies in the circulation of the hen, which remain at significant levels throughout the laying cycle. Antibodies are transferred from the hen to egg yolk, resulting in antibodies in the circulation of 7-day-old chicks.	[475]
N-glycan-based vaccine *	*C. jejuni*	Poultry	Reduce the cecal *Campylobacter* by 6 $\log_{10}$	[458]
AviPro Megan Vac 1	*S.* Typhimurium, *S.* Enteritidis and *S.* Heidelberg	Poultry	MV1 was effective at reducing cecal *S.* Enteritidis counts. The live attenuated vaccine had the added advantage of not persisting in the chicks.	[476]
PLGA-encapsulated CpG ODN and *C. jejuni* lysate	*C. jejuni*	Poultry	Reduced *C. jejuni* colonization by up to 2.4 $\log_{10}$, modulated intestinal immune responses, modulated the gut microbiome composition, enhanced the production of *C. jejuni*-specific antibodies	[453,454,456]

* Still in the research and development stage.

4.11.2. Limitations of Vaccines

(1) Highly variable pathogens pose a challenge, as their genetic diversity within and between hosts make it difficult to identify an antigen that can be used for vaccine development [477]. (2) Vaccine failure is always a risk. This refers to an organism contracting an illness despite being vaccinated against it. This is usually due to individual immune response differences [478]. (3) Live attenuated vaccines usually need the cold chain to stay potent, which adds extra cost that especially affect developing countries that lack widespread refrigeration [463]. (4) Killed whole-cell vaccines lead to a weaker immune response than live vaccines, thus requiring many booster doses to maintain immunity [463]. (5) Toxoid and subunit vaccines usually require adjuvants and several doses because they are not highly immunogenic. High doses may lead to toxoid tolerance [479]. (6) Virus-like particle (VLP) vaccines are multimeric structures with no viral genome, making them very unstable. The levels of expression of VLP vaccines in different platforms vary greatly [480]. (7) OMV vaccines have an incredibly low yield because they are released spontaneously by bacteria in low quantities. The key antigens on their surface can also be in low quantities [481]. (8) Polysaccharide–protein conjugate vaccines have inconsistent numbers of conjugates in each batch, affecting vaccine efficacy. The carrier protein k, and the linker between the polysaccharide and carrier protein, may also be immunogenic and trigger an immune response against itself [482]. (9) Bacteria, such as *Streptococcus pyogenes* and *S. aureus*, develop AMR gradually and with little selective pressure [442]. Similarly, *Bordetella pertussis* shows AMR towards unprotected or partially protected people, due to

incomplete vaccine protection [461]. Acellular vaccines against *B. pertussis* provide shorter protection than whole-cell vaccines [445]. Collectively, vaccination has a role in specific cases, and should be used in combination with other approaches to manage infection or lower the demand for antibiotics [462].
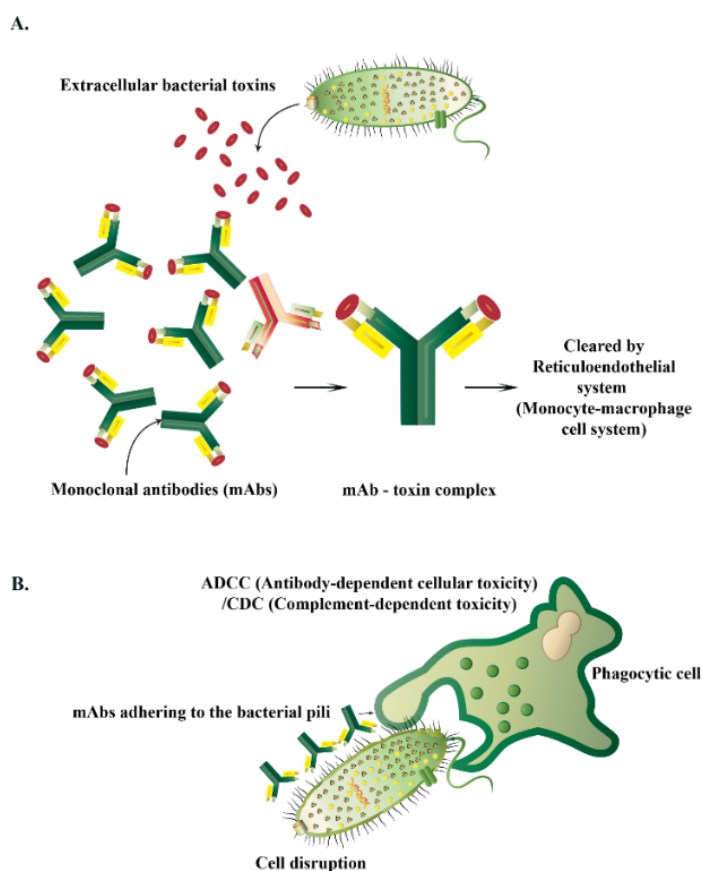
4.12. Antibodies

Antibodies, also known as immunoglobulins, are the most diverse set of proteins [483]. They have two major functions: antigen binding and effector functions [484]. Most of these effector functions are induced via the constant Fc (fragment crystallizable region, the tail region of an antibody) of the antibody, which can interact with complementary proteins and specialized Fc-receptors. This can activate or inhibit pathways, depending on the type of receptor [485]. Therapeutic antibacterial monoclonal antibodies (mAbs) are gaining traction as an alternative in treating infectious diseases [442]. Monoclonal antibodies could offer more effective ways of addressing antibiotic resistance and bacterial infections due to their superb specificity, by which they target conserved pathways. This allows for fewer off-target effects and less selective pressure for cross-resistance to other mAbs or antibiotics. Monoclonal antibodies also do not harm the beneficial microbiome [486,487] In 1879, Amil von Behring and Shibasaburo Kitasato were the first to develop antibodies called antitoxins that target specific toxins. Blood-serum-containing antitoxin was directly injected to convey immunity to diphtheria in humans [488,489]. The toxin/antitoxin approach provided a steady treatment against numerous pathogens, such as *Haemophilus influenzae*, *Neisseria meningitides*, *Corynebacterium diphtheria*, *Clostridium tetani*, *S. pneumonia*, and Group A *Streptococcus*. However, the antitoxin approach exhibits heterogeneity between lots, allergic reactions, and a limited spectrum, eventually leading to its replacement by antibiotics in 1930 [490]. Antibiotic production peaked for the next 80 years because of their safe application and their ease of formulation and manufacture [491]. However, due to the development of the hybridoma technology and recent advances in mAb engineering, awareness has shifted back to antibacterial mAbs [492].

4.12.1. Mechanisms of Action of mAbs

mAbs provide their anti-virulence effect through the following mechanisms: (1) mAbs binding to their target antigen: This can be a soluble ligand or a receptor; either way, the interaction is blocked between the ligand and receptor. This can also lead to internalization of receptors or apoptosis of the targeted cells [486]. (2) Blockage of the bacterial virulence factors (bacterial toxin neutralization): Neutralization of the toxin occurs when it binds to the mAb and forms an mAb–toxin complex. This complex eventually gets cleared by the reticuloendothelial system (Figure 6A). Monoclonal antibodies may also bind to the structural components of the cell surface, invoking immune-system-dependent cytotoxicity or direct bactericidal effects [493]. This also limits collateral damage, such as development of drug resistance, as mAbs often target virulence proteins rather than proteins required for survival, leading to lower virulence [494], while aiding both the host's adaptive and innate immune systems.

Several bacteria, such as *Bordetella pertussis*, *V. cholerae*, *Bacillus anthracis*, *C. diphtheriae*, *C. botulinum*, *C. tetani*, *C. difficile*, *C. perfringens*, *Salmonella* spp., and EHEC, secrete disease-causing toxins to which mAbs can bind [488]. Other virulence factors such as type III secretion systems (T3SS), adhesins, and pili, along with outer membrane transporters, which are exposed on the bacterial cell membrane, have also been identified as potential antibody targets. mAbs targeting these antigens cause bactericidal effects (Figure 6A) [495]. Ideally, these toxins (antigens) should be in abundance to allow the mAbs to bind to them specifically, avoiding any off-target binding. Additionally, the binding of these mAbs does not cause immediate bactericidal effects. Their action is closely associated with the phagocytic cells (antibody-dependent cellular cytotoxicity—ADCC) and/or complement (complement-dependent cytotoxicity—CDC), which eventually causes the bactericidal effect [496] (Figure 6B).

Many different mAbs are currently in clinical trial phases or have already been approved. For example, the isotype IgG1(κ) human monoclonal antibody auvratoxumab (MEDI-4893) targets pneumonia-causing *S. aureus* alpha-hemolysin toxin and neutralizes it, thereby preventing its colonization. This approach is much more effective than antibiotics because the use of antibodies is not expected to lead to resistance in the future. In addition to this, antibodies work irrespective of the antibiotic resistance status of the pathogen [494]. A new antibody–antibiotic conjugate (DSTA4637S) was developed to target intracellular *S. aureus*. It consists of anti-*S. aureus* thiomab human immunoglobulin G1 (IgG1) monoclonal antibody linked to a novel rifamycin-class antibiotic [497]. Following its phagocytosis by phagocytic cells, the intracellular cathepsins cleave the link between the mAbs and antibiotic, resulting in release of a rifamycin-class antibiotic, which subsequently kills the intracellular *S. aureus* [497].

Figure 6. Monoclonal antibodies' (mAbs) mode of action. (**A**) Depicts the neutralization of bacterial toxin by mAbs. Bacterial toxins are secreted by bacteria. The antibodies attach to the toxins and get cleared by the reticuloendothelial system. The reticuloendothelial system is a cluster of phagocytes that clear matter. (**B**) mAbs adhere to the pili structures of the bacteria. Pili are hair-like appendages found on the surface of many bacteria that function to attach cells to surfaces. The antibodies attach along with the phagocytic cells (antibody-dependent cellular cytotoxicity—ADCC) and/or complement (complement-dependent cytotoxicity—CDC) and eventually cause the bactericidal effect.

Co-mixtures of IgG1 human monoclonal antibodies with efficacy against botulinum toxin, produced by *C. botulinum*, (BoNT) serotypes A (BoNT/A, NTM-1631) and B (BoNT/B, NTM-1632), were developed [498]. Their mode of action involves high-affinity binding of the mixture to the toxin, blocking cellular binding epitopes on the toxin, and increasing hepatic clearance of the toxin–Ab immune complexes. The results revealed that NTM-1632 does not bind human epitopes, which means that it is less likely to have off-target effects and can be used post-exposure without having any negative consequences [498]. Similarly, Obiltoxaximab (Anthim®, ETI-204) is a monoclonal IgG1(κ) antibody that is being devel-

oped for the prevention and treatment of *B. anthracis* and works by neutralizing the free protective antigen of *B. anthracis*, thereby inhibiting the toxin [499]. Another mAb, raxibacumab (ABthrax) is a human IgG1(λ) monoclonal antibody that is capable of neutralizing lethal antigens of *B. anthracis*, inhibiting cell death [500]. A human chimeric monoclonal antibody (isotype IgG), pagibaximab, is currently in phase II of clinical trials for treatment of *S. epidermidis* (lipoteichoic acid) causing staphylococcal sepsis. Pagibaximab enhances serum opsonophagocytic activity, making all staphylococci opsonizable [501]. In addition, setoxaximab/pritoxaximab are mouse/human chimeric IgG1(κ) antibodies that target Shiga toxin 1 and Shiga toxin 2, produced by *E. coli*. The combination is named Shigamab and developed for the treatment of hemolytic–uremic syndrome (HUS). The neutralizing mAbs target their specific Shiga toxin, eliminating it from circulation [502]. Shigamab was found to be safe and well tolerated in phase I and II clinical studies. An additional pre-clinical study has also been completed in a HUS baboon model, in which Shigamab was shown to protect the animals against a lethal dose of toxin when administered up to 48 h post-intoxication. A human IgG1 monoclonal antibody, Aerucin, is being developed by Aridis Pharmaceuticals. Aerucin targets *P. aeruginosa* alginate using opsonophagocytosis as the mechanism of action. Specific OprF/I IgG antibodies were detected in all IC43 administered groups. From day 0 to day 14, a four-fold or more increase in the antibody titers was observed in >90% of subjects. At 90 days, titers started to decline but remained higher than the placebo groups for up to six months [503]. Additionally, DSTA4637S was safe and well tolerated in healthy volunteers in the phase 1 single-ascending-dose study. DSTA4637S for *S. aureus* infections is safe and has a favorable PK profile [497]. However, antibody–antibiotic conjugates can still increase the incidence of AMR, whereas pure mAb treatments, such as suvratoxamab, are not likely to. In terms of *P. aeruginosa,* a phase II clinical trial (NCT03027609) of Aerucin saw no significant difference between Aerucin and placebo patient groups for treatment of *P. aeruginosa* patients, whereas panobacumab improved clinical outcome in a short time [504].

4.12.2. Limitations of Abs

Despite the undeniable impact of mAbs in controlling many diseases, there are still some challenges concerning mAbs: (1) Production expenses: currently, mammalian cells, which allow human-like N-glycosylation and other post-translational modifications, are used to produce mAbs. This requires specialized eukaryotic machinery produce mAbs in the active form [505]. Mammalian cells also have several drawbacks when it comes to bioprocessing and scale-up, which results in long processing times and elevated costs. Moreover, high doses of the antibodies are required to reach clinical efficacy [506]. These factors limit the availability of the wide use of mAbs. (2) Systemic administration of mAbs is unsuitable for non-invasive routes of administration, such as oral, nasal, or pulmonary, as they are susceptible to chemical and enzymatic degradation in the gastrointestinal tract. In murine models, mAbs have been shown to largely remain in the blood.

Only about 20% of the administered dose reached the target tissue. Penetration and retention in the target area rely on the characteristics of the mAbs, such as molecular size, shape, affinity and valency [505]. By using methods such as in vivo gene transfer, costs can be greatly reduced, as one injection can produce mAbs in vivo long-term [507]. However, hybridoma mAb technology carries with it the risk of cancer, as the cell lines used are immortalized using the Epstein–Barr virus. There is also the risk of contamination of different cell lines, genetic instability of the cell line, and consistency and level of the expression and stoichiometric ratio of both the heavy and light chains [208,508]. Imbalances in the chain production can be toxic to the cell [509]. Nonetheless, mAbs remain one of the most promising technologies in the age of growing AMR threats.

4.13. Conclusions and Future Perspectives

The alarming rise in the emergence and spread of AMR and the associated global impact necessitate an urgent intervention of alternatives to combat the growing threat

of antibiotic-resistant bacteria. Beside their potential adverse events, the inappropriate prescription or dispensing of antibiotics for humans and their irrational use in animal agriculture are among the factors contributing to the growing incidence of AMR in humans. As such, averting AMR could be achieved by focusing on two aspects: one is to implement antimicrobial stewardship programs through promoting prudent use of antibiotics in healthcare and agricultural settings, and the other is to develop effective antimicrobial alternatives to substitute antibiotics in animal food production. In fact, developed countries, including Europe and North America, have taken steps to ban the use of sub-therapeutic doses of antibiotics as growth promoters in livestock and poultry production; however, such steps have yet to be implemented in developing countries. Thus, a global solution is crucial to tackle AMR, as the world has become increasingly interconnected. Research efforts have been made to limit AMR in both humans and animals by exploring various interventions, including SMs, QSIs, probiotics, prebiotics, phage therapy, nanoparticles, EOs, AMPs, OAs, FMT, vaccines, and immune-based strategies, as potential replacements for antibiotics. Despite the promising role of most of these strategies in promoting host immunity and in antagonizing a range of human and animal pathogens, their variable effects, combined with their limited spectrum, safety concerns, and poor efficacy, are among the potential limitations to their use. Nonetheless, the exuberant development of molecular technologies may improve the efficacy of existing strategies and reduce their limitations. For instance, the recent breakthroughs in CRISPR-Cas9-based genome editing offer a revolutionary platform for designing safe and effective vaccines. Likewise, computational molecular biology has directed vaccine development towards genome-based reverse vaccinology approaches, a process of analyzing the whole genome sequence for identification of novel target antigens. The processes of 16S rRNA next-generation sequencing and bioinformatics analysis have enabled the identification of bacterial strains at species level. This technology can be utilized to not only identify novel probiotic species, but also to develop a consortium of beneficial microbes, which may offer a safer and acceptable alternative to FMT. With millions of people travelling around the world and the uncontrollable spread of AMR, holistic AMR control requires global solidarity to expand and implement robust antimicrobial stewardship programs in both medical and veterinary practices.

References

1. WHO. Antimicrobial Resistance. Available online: https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance (accessed on 31 October 2022).
2. Friedman, N.D.; Temkin, E.; Carmeli, Y. The negative impact of antibiotic resistance. *Clin. Microbiol. Infect.* **2016**, *22*, 416–422. [CrossRef] [PubMed]
3. Helmy, Y.A.; El-Adawy, H.; Abdelwhab, E.M. A Comprehensive Review of Common Bacterial, Parasitic and Viral Zoonoses at the Human-Animal Interface in Egypt. *Pathogens* **2017**, *6*, 33. [CrossRef] [PubMed]
4. Kraemer, S.A.; Ramachandran, A.; Perron, G.G. Antibiotic Pollution in the Environment: From Microbial Ecology to Public Policy. *Microorganisms* **2019**, *7*, 180. [CrossRef] [PubMed]
5. Hailu, W.; Helmy, Y.A.; Carney-Knisely, G.; Kauffman, M.; Fraga, D.; Rajashekara, G. Prevalence and Antimicrobial Resistance Profiles of Foodborne Pathogens Isolated from Dairy Cattle and Poultry Manure Amended Farms in Northeastern Ohio, the United States. *Antibiotics* **2021**, *10*, 1450. [CrossRef]

6. Deblais, L.; Kathayat, D.; Helmy, Y.A.; Closs, G.; Rajashekara, G. Translating 'big data': Better understanding of host-pathogen interactions to control bacterial foodborne pathogens in poultry. *Anim. Health Res. Rev.* **2020**, *21*, 15–35. [CrossRef]

7. Van Boeckel, T.P.; Brower, C.; Gilbert, M.; Grenfell, B.T.; Levin, S.A.; Robinson, T.P.; Teillant, A.; Laxminarayan, R. Global trends in antimicrobial use in food animals. *Proc. Natl. Acad. Sci. USA* **2015**, *112*, 5649–5654. [CrossRef]

8. Van Boeckel, T.P.; Glennon, E.E.; Chen, D.; Gilbert, M.; Robinson, T.P.; Grenfell, B.T.; Levin, S.A.; Bonhoeffer, S.; Laxminarayan, R. Reducing antimicrobial use in food animals. *Science* **2017**, *357*, 1350–1352. [CrossRef]

9. Klein, E.Y.; Van Boeckel, T.P.; Martinez, E.M.; Pant, S.; Gandra, S.; Levin, S.A.; Goossens, H.; Laxminarayan, R. Global increase and geographic convergence in antibiotic consumption between 2000 and 2015. *Proc. Natl. Acad. Sci. USA* **2018**, *115*, E3463–E3470. [CrossRef]

10. FDA. *Summary Report on Antimicrobials Sold or Distributed for Use in Food-Producing Animals*; Department of Health and Human Services: Washington, DC, USA, 2011.

11. Kassem, I.I.; Kehinde, O.O.; Helmy, Y.A.; Kumar, A.; Chandrashekhar, K.; Pina-Mimbela, R.; Rajashekara, G. Campylobacter in poultry: The conundrums of highly adaptable and ubiquitous foodborne pathogens. In *Foodborne Diseases: Case Studies of Outbreaks in the Agri-Food Industries*; Soon, J.M., Manning, L., Wallace, C.A., Eds.; CRC Press: Boca Raton, FL, USA, 2016.

12. Kassem, I.; Helmy, Y.A.; Kashoma, I.P.; Rajashekara, G. The emergence of antibiotic resistance on poultry farms. In *Achieving Sustainable Production of Poultry Meat: Safety, Quality and Sustainability*; Ricke, S., Ed.; Burleigh Dodds Science Publishing: Sawston, UK, 2016; Volume 1, ISBN 978-1-78676-064-7.

13. Founou, L.L.; Founou, R.C.; Essack, S.Y. Antibiotic Resistance in the Food Chain: A Developing Country-Perspective. *Front. Microbiol.* **2016**, *7*, 1881. [CrossRef]

14. Algammal, A.M.; Enany, M.E.; El-Tarabili, R.M.; Ghobashy, M.O.; Helmy, Y.A. Prevalence, antimicrobial resistance profiles, virulence and enterotoxins-determinant genes of MRSA isolated from subclinical bovine mastitis in Egypt. *Pathogens* **2020**, *9*, 362. [CrossRef]

15. Murray, C.J.; Ikuta, K.S.; Sharara, F.; Swetschinski, L.; Aguilar, G.R.; Gray, A.; Han, C.; Bisignano, C.; Rao, P.; Wool, E.; et al. Global burden of bacterial antimicrobial resistance in 2019: A systematic analysis. *Lancet* **2022**, *399*, 629–655. [CrossRef] [PubMed]

16. O'Neill, J. Tackling Drug-Resistant Infections Globally: Final Report and Recommendations. 2016. Available online: http://amr-review.org/sites/default/files/160525_Final%20paper_with%20cover.pdf (accessed on 31 October 2022).

17. Scharff, R.L. Food Attribution and Economic Cost Estimates for Meat- and Poultry-Related Illnesses. *J. Food Prot.* **2020**, *83*, 959–967. [CrossRef] [PubMed]

18. CDC. *Burden of Foodborne Illness: Findings*; Centers for Disease Control and Prevention, United States Department of Health and Human Services: Atlanta, GA, USA, 2018. Available online: https://www.cdc.gov/foodborneburden/2011-foodborne-estimates.html (accessed on 31 October 2022).

19. WHO. WHO Publishes List of Bacteria for Which New Antibiotics Are Urgently Needed. Available online: https://www.who.int/news/item/27-02-2017-who-publishes-list-of-bacteria-for-which-new-antibiotics-are-urgently-needed (accessed on 31 October 2022).

20. NIAID. NIAID Emerging Infectious Diseases/Pathogens. Available online: https://www.niaid.nih.gov/research/emerging-infectious-diseases-pathogens (accessed on 31 October 2022).

21. Truman, A. Antibiotics: Past, present and future Matthew I Hutchings, Andrew W Truman 2 and Barrie Wilkinson 2. *Curr. Opin. Microbiol.* **2019**, *51*, 72–80.

22. Sköld, O. Sulfonamide resistance: Mechanisms and trends. *Drug Resist. Updates* **2000**, *3*, 155–160. [CrossRef] [PubMed]

23. Pancu, D.F.; Scurtu, A.; Macasoi, I.G.; Marti, D.; Mioc, M.; Soica, C.; Coricovac, D.; Horhat, D.; Poenaru, M.; Dehelean, C. Antibiotics: Conventional Therapy and Natural Compounds with Antibacterial Activity—A Pharmaco-Toxicological Screening. *Antibiotics* **2021**, *10*, 401. [CrossRef] [PubMed]

24. Christaki, E.; Marcou, M.; Tofarides, A. Antimicrobial Resistance in Bacteria: Mechanisms, Evolution, and Persistence. *J. Mol. Evol.* **2020**, *88*, 26–40. [CrossRef] [PubMed]

25. Hussar, D.A. New Drugs 2019, part 4. *Nursing2020* **2019**, *49*, 34–43. [CrossRef]

26. Andrei, S.; Droc, G.; Stefan, G. FDA approved antibacterial drugs: 2018–2019. *Discoveries* **2019**, *7*, e102. [CrossRef]

27. Voulgaris, G.L.; Voulgari, M.L.; Falagas, M.E. Developments on antibiotics for multidrug resistant bacterial Gram-negative infections. *Expert Rev. Anti-Infect. Ther.* **2019**, *17*, 387–401. [CrossRef]

28. Saxena, D.; Kaul, G.; Dasgupta, A.; Chopra, S. Levonadifloxacin arginine salt to treat acute bacterial skin and skin structure infection due to *S. aureus* including MRSA. *Drugs Today* **2020**, *56*, 583–598. [CrossRef]

29. Stancil, S.L.; Mirzayev, F.; Abdel-Rahman, S.M. Profiling Pretomanid as a Therapeutic Option for TB Infection: Evidence to Date. *Drug Des. Dev. Ther.* **2021**, *15*, 2815. [CrossRef] [PubMed]

30. Helmy, Y.A.; Fawzy, M.; Elaswad, A.; Sobieh, A.; Kenney, S.P.; Shehata, A.A. The COVID-19 Pandemic: A Comprehensive Review of Taxonomy, Genetics, Epidemiology, Diagnosis, Treatment, and Control. *J. Clin. Med.* **2020**, *9*, 1225. [CrossRef] [PubMed]

31. Hedman, H.D.; Krawczyk, E.; Helmy, Y.A.; Zhang, L.; Varga, C. Host Diversity and Potential Transmission Pathways of SARS-CoV-2 at the Human-Animal Interface. *Pathogens* **2021**, *10*, 180. [CrossRef] [PubMed]

32. Ilić, T.; Pantelić, I.; Savić, S. The implications of regulatory framework for topical semisolid drug products: From critical quality and performance attributes towards establishing bioequivalence. *Pharmaceutics* **2021**, *13*, 710. [CrossRef] [PubMed]

33. WHO. *Report of the Meeting to Review the Paediatric Antituberculosis Drug Optimization Priority List*; WHO: Geneva, Switzerland, 2021.

34. Peterson, E.; Kaur, P. Antibiotic resistance mechanisms in bacteria: Relationships between resistance determinants of antibiotic producers, environmental bacteria, and clinical pathogens. *Front. Microbiol.* **2018**, *9*, 2928. [CrossRef]

35. Collignon, P.J.; McEwen, S.A. One health—Its importance in helping to better control antimicrobial resistance. *Trop. Med. Infect. Dis.* **2019**, *4*, 22. [CrossRef]

36. Alduhaidhawi, A.H.M.; AlHuchaimi, S.N.; Al-Mayah, T.A.; Al-Ouqaili, M.T.; Alkafaas, S.S.; Muthupandian, S.; Saki, M. Prevalence of CRISPR-Cas Systems and Their Possible Association with Antibiotic Resistance in Enterococcus faecalis and *Enterococcus faecium* Collected from Hospital Wastewater. *Infect. Drug Resist.* **2022**, *15*, 1143. [CrossRef]

37. Goldman, E. Antibiotic abuse in animal agriculture: Exacerbating drug resistance in human pathogens. *Hum. Ecol. Risk Assess.* **2004**, *10*, 121–134. [CrossRef]

38. Hassell, J.M.; Begon, M.; Ward, M.J.; Fèvre, E.M. Urbanization and disease emergence: Dynamics at the wildlife–livestock–human interface. *Trends Ecol. Evol.* **2017**, *32*, 55–67. [CrossRef]

39. Ventola, C.L. The antibiotic resistance crisis: Part 1: Causes and threats. *Pharm. Ther.* **2015**, *40*, 277.

40. Terefe, Y.; Deblais, L.; Ghanem, M.; Helmy, Y.A.; Mummed, B.; Chen, D.; Singh, N.; Ahyong, V.; Kalantar, K.; Yimer, G.; et al. Co-occurrence of Campylobacter species in children from eastern Ethiopia, and their association with environmental enteric dysfunction, diarrhea, and host microbiome. *Front. Public Health* **2020**, *8*, 99. [CrossRef] [PubMed]

41. Hendriksen, R.S.; Munk, P.; Njage, P.; Van Bunnik, B.; McNally, L.; Lukjancenko, O.; Röder, T.; Nieuwenhuijse, D.; Pedersen, S.K.; Kjeldgaard, J.; et al. Global monitoring of antimicrobial resistance based on metagenomics analyses of urban sewage. *Nat. Commun.* **2019**, *10*, 1124. [CrossRef] [PubMed]

42. Zurek, L.; Ghosh, A. Insects represent a link between food animal farms and the urban environment for antibiotic resistance traits. *Appl. Environ. Microbiol.* **2014**, *80*, 3562–3567. [CrossRef] [PubMed]

43. Zhang, G.; Meredith, T.C.; Kahne, D. On the essentiality of lipopolysaccharide to Gram-negative bacteria. *Curr. Opin. Microbiol.* **2013**, *16*, 779–785. [CrossRef]

44. Reygaert, W.C. An overview of the antimicrobial resistance mechanisms of bacteria. *AIMS Microbiol.* **2018**, *4*, 482. [CrossRef]

45. Munita, J.M.; Arias, C.A. Mechanisms of Antibiotic Resistance. *Microbiol. Spectr.* **2016**, *4*, 15. [CrossRef]

46. Motta, S.S.; Cluzel, P.; Aldana, M. Adaptive resistance in bacteria requires epigenetic inheritance, genetic noise, and cost of efflux pumps. *PLoS ONE* **2015**, *10*, e0118464. [CrossRef]

47. Miller, W.R.; Munita, J.M.; Arias, C.A. Mechanisms of antibiotic resistance in enterococci. *Expert Rev. Anti-Infect. Ther.* **2014**, *12*, 1221–1236. [CrossRef]

48. Schneider, C.L. Bacteriophage-mediated horizontal gene transfer: Transduction. In *Bacteriophages*; Biology, Technology, Therapy; Springer: Cham, Switzerland, 2021; pp. 151–192.

49. Sørensen, S.J.; Bailey, M.; Hansen, L.H.; Kroer, N.; Wuertz, S. Studying plasmid horizontal transfer in situ: A critical review. *Nat. Rev. Microbiol.* **2005**, *3*, 700–710. [CrossRef]

50. Sun, D. Pull in and push out: Mechanisms of horizontal gene transfer in bacteria. *Front. Microbiol.* **2018**, *9*, 2154. [CrossRef]

51. Rosenfeld, Y.; Shai, Y. Lipopolysaccharide (Endotoxin)-host defense antibacterial peptides interactions: Role in bacterial resistance and prevention of sepsis. *Biochim. Biophys. Acta (BBA)-Biomembr.* **2006**, *1758*, 1513–1522. [CrossRef]

52. Aguilella, V.M.; Queralt-Martín, M.; Alcaraz, A. Bacterial porins. In *Electrophysiology of Unconventional Channels and Pores*; Springer: Berlin/Heidelberg, Germany, 2015; pp. 101–121.

53. Vestby, L.K.; Grønseth, T.; Simm, R.; Nesse, L.L. Bacterial biofilm and its role in the pathogenesis of disease. *Antibiotics* **2020**, *9*, 59. [CrossRef]

54. Flemming, H.-C.; Wuertz, S. Bacteria and archaea on Earth and their abundance in biofilms. *Nat. Rev. Microbiol.* **2019**, *17*, 247–260. [CrossRef]

55. Bjarnsholt, T. The role of bacterial biofilms in chronic infections. *Apmis* **2013**, *121*, 1–58. [CrossRef]

56. Høiby, N.; Ciofu, O.; Bjarnsholt, T. *Pseudomonas aeruginosa* biofilms in cystic fibrosis. *Future Microbiol.* **2010**, *5*, 1663–1674. [CrossRef]

57. Jiang, Y.; Geng, M.; Bai, L. Targeting Biofilms Therapy: Current Research Strategies and Development Hurdles. *Microorganisms* **2020**, *8*, 1222. [CrossRef]

58. Singh, T.; Singh, P.K.; Das, S.; Wani, S.; Jawed, A.; Dar, S.A. Transcriptome analysis of beta-lactamase genes in diarrheagenic *Escherichia coli*. *Sci. Rep.* **2019**, *9*, 3626. [CrossRef]

59. Golkar, T.; Zieliński, M.; Berghuis, A.M. Look and outlook on enzyme-mediated macrolide resistance. *Front. Microbiol.* **2018**, *9*, 1942. [CrossRef]

60. Garneau-Tsodikova, S.; Labby, K.J. Mechanisms of resistance to aminoglycoside antibiotics: Overview and perspectives. *Medchemcomm* **2016**, *7*, 11–27. [CrossRef]

61. Shah, R.A. Mechanisms of Bacterial Resistance. In *Overcoming Antimicrobial Resistance of the Skin*; Springer: Berlin/Heidelberg, Germany, 2021; pp. 3–25.

62. Kumar, P. Pharmacology of specific drug groups. In *Pharmacology and Therapeutics for Dentistry*, 7th ed.; Elsevier: Amsterdam, The Netherlands, 2017; pp. 457–487.

63. Xu, M.; Zhou, Y.N.; Goldstein, B.P.; Jin, D.J. Cross-resistance of Escherichia coli RNA polymerases conferring rifampin resistance to different antibiotics. *J. Bacteriol.* **2005**, *187*, 2783–2792. [CrossRef]

64. Handzlik, J.; Matys, A.; Kieć-Kononowicz, K. Recent advances in multi-drug resistance (MDR) efflux pump inhibitors of Gram-positive bacteria *S. aureus*. *Antibiotics* **2013**, *2*, 28–45. [CrossRef] [PubMed]

65. Neuberger, A.; Du, D.; Luisi, B.F. Structure and mechanism of bacterial tripartite efflux pumps. *Res. Microbiol.* **2018**, *169*, 401–413. [CrossRef] [PubMed]

66. Anes, J.; McCusker, M.P.; Fanning, S.; Martins, M. The ins and outs of RND efflux pumps in *Escherichia coli. Front. Microbiol.* **2015**, *6*, 587. [CrossRef]

67. Blanco, P.; Hernando-Amado, S.; Reales-Calderon, J.A.; Corona, F.; Lira, F.; Alcalde-Rico, M.; Bernardini, A.; Sanchez, M.B.; Martinez, J.L. Bacterial multidrug efflux pumps: Much more than antibiotic resistance determinants. *Microorganisms* **2016**, *4*, 14. [CrossRef]

68. Rahbar, M.; Hamidi-Farahani, R.; Asgari, A.; Esmailkhani, A.; Soleiman-Meigooni, S. Expression of RND efflux pumps mediated antibiotic resistance in *Pseudomonas aeruginosa* clinical strains. *Microb. Pathog.* **2021**, *153*, 104789.

69. Zhang, L.; Li, X.-Z.; Poole, K. SmeDEF multidrug efflux pump contributes to intrinsic multidrug resistance in Stenotrophomonas maltophilia. *Antimicrob. Agents Chemother.* **2001**, *45*, 3497–3503. [CrossRef]

70. Sharma, A.; Gupta, V.K.; Pathania, R. Efflux pump inhibitors for bacterial pathogens: From bench to bedside. *Indian J. Med. Res.* **2019**, *149*, 129–145. [CrossRef]

71. Alcalde-Rico, M.; Hernando-Amado, S.; Blanco, P.; Martínez, J.L. Multidrug efflux pumps at the crossroad between antibiotic resistance and bacterial virulence. *Front. Microbiol.* **2016**, *7*, 1483. [CrossRef]

72. Leeson, P.D.; Springthorpe, B. The influence of drug-like concepts on decision-making in medicinal chemistry. *Nat. Rev. Drug Discov.* **2007**, *6*, 881–890. [CrossRef]

73. Hong-Geller, E.; Micheva-Viteva, S. Small molecule screens to identify inhibitors of infectious disease. In *Drug Discovery*; El Shelmy, H.A., Ed.; InTech: London, UK, 2013; pp. 157–175.

74. Selin, C.; Stietz, M.S.; Blanchard, J.E.; Gehrke, S.S.; Bernard, S.; Hall, D.G.; Brown, E.D.; Cardona, S.T. A Pipeline for Screening Small Molecules with Growth Inhibitory Activity against Burkholderia cenocepacia. *PLoS ONE* **2015**, *10*, e0128587. [CrossRef]

75. Kumar, A.; Drozd, M.; Pina-Mimbela, R.; Xu, X.; Helmy, Y.A.; Antwi, J.; Fuchs, J.R.; Nislow, C.; Templeton, J.; Blackall, P.J.; et al. Novel Anti-Campylobacter Compounds Identified Using High Throughput Screening of a Pre-selected Enriched Small Molecules Library. *Front. Microbiol.* **2016**, *7*, 405. [CrossRef]

76. Helmy, Y.A.; Kathayat, D.; Ghanem, M.; Jung, K.; Closs, G., Jr.; Deblais, L.; Srivastava, V.; El-Gazzar, M.; Rajashekara, G. Identification and characterization of novel small molecule inhibitors to control Mycoplasma gallisepticum infection in chickens. *Vet. Microbiol.* **2020**, *247*, 108799. [CrossRef]

77. Mingeot-Leclercq, M.-P.; Decout, J.-L. Bacterial lipid membranes as promising targets to fight antimicrobial resistance, molecular foundations and illustration through the renewal of aminoglycoside antibiotics and emergence of amphiphilic aminoglycosides. *MedChemComm* **2016**, *7*, 586–611. [CrossRef]

78. Garg, S.K.; Singh, O.; Juneja, D.; Tyagi, N.; Khurana, A.S.; Qamra, A.; Motlekar, S.; Barkate, H. Resurgence of Polymyxin B for MDR/XDR Gram-Negative Infections: An Overview of Current Evidence. *Crit. Care Res. Pract.* **2017**, *2017*, 3635609. [CrossRef]

79. Hubbard, A.T.; Barker, R.; Rehal, R.; Vandera, K.A.; Harvey, R.D.; Coates, A.R. Mechanism of Action of a Membrane-Active Quinoline-Based Antimicrobial on Natural and Model Bacterial Membranes. *Biochemistry* **2017**, *56*, 1163–1174. [CrossRef]

80. Hart, E.M.; Mitchell, A.M.; Konovalova, A.; Grabowicz, M.; Sheng, J.; Han, X.; Rodriguez-Rivera, F.P.; Schwaid, A.G.; Malinverni, J.C.; Balibar, C.J. A small-molecule inhibitor of BamA impervious to efflux and the outer membrane permeability barrier. *Proc. Natl. Acad. Sci. USA* **2019**, *116*, 21748–21757. [CrossRef]

81. Vrisman, C.M.; Deblais, L.; Helmy, Y.A.; Johnson, R.; Rajashekara, G.; Miller, S.A. Discovery and Characterization of Low-Molecular Weight Inhibitors of Erwinia tracheiphila. *Phytopathology* **2020**, *110*, 989–998. [CrossRef]

82. Srivastava, V.; Deblais, L.; Kathayat, D.; Rotondo, F.; Helmy, Y.A.; Miller, S.A.; Rajashekara, G. Novel Small Molecule Growth Inhibitors of Xanthomonas spp. Causing Bacterial Spot of Tomato. *Phytopathology* **2021**, *111*, 940–953. [CrossRef]

83. Lu, Y.; Deblais, L.; Rajashekara, G.; Miller, S.A.; Helmy, Y.A.; Zhang, H.; Wu, P.; Qiu, Y.; Xu, X. High-throughput screening reveals small molecule modulators inhibitory to Acidovorax citrulli. *Plant Pathol.* **2020**, *69*, 818–826. [CrossRef]

84. Deblais, L.; Vrisman, C.; Kathayat, D.; Helmy, Y.A.; Miller, S.A.; Rajashekara, G. Imidazole and Methoxybenzylamine Growth Inhibitors Reduce Salmonella Persistence in Tomato Plant Tissues. *J. Food Prot.* **2019**, *82*, 997–1006. [CrossRef]

85. Kathayat, D.; Antony, L.; Deblais, L.; Helmy, Y.A.; Scaria, J.; Rajashekara, G. Small Molecule Adjuvants Potentiate Colistin Activity and Attenuate Resistance Development in Escherichia coli by Affecting pmrAB System. *Infect. Drug Resist.* **2020**, *13*, 2205–2222. [CrossRef]

86. Li, Q.; Kang, C. Mechanisms of Action for Small Molecules Revealed by Structural Biology in Drug Discovery. *Int. J. Mol. Sci.* **2020**, *21*, 5262. [CrossRef]

87. Hatcher, H.M. 4—Principles of systemic therapy. In *Specialist Training in Oncology*; Ajithkumar, T.V., Hatcher, H.M., Eds.; Mosby: Maryland Heights, MO, USA, 2011; pp. 30–44.

88. Carro, L. Recent Progress in the Development of Small-Molecule FtsZ Inhibitors as Chemical Tools for the Development of Novel Antibiotics. *Antibiotics* **2019**, *8*, 217. [CrossRef]

89. Linciano, P.; Cavalloro, V.; Martino, E.; Kirchmair, J.; Listro, R.; Rossi, D.; Collina, S. Tackling Antimicrobial Resistance with Small Molecules Targeting LsrK: Challenges and Opportunities. *J. Med. Chem.* **2020**, *63*, 15243–15257. [CrossRef]

90. La Manna, S.; Di Natale, C.; Florio, D.; Marasco, D. Peptides as Therapeutic Agents for Inflammatory-Related Diseases. *Int. J. Mol. Sci.* **2018**, *19*, 2714. [CrossRef]

91. Gurevich, E.V.; Gurevich, V.V. Therapeutic potential of small molecules and engineered proteins. *Handb. Exp. Pharmacol.* **2014**, *219*, 1–12. [CrossRef]

92. Stanley, S.A.; Grant, S.S.; Kawate, T.; Iwase, N.; Shimizu, M.; Wivagg, C.; Silvis, M.; Kazyanskaya, E.; Aquadro, J.; Golas, A.; et al. Identification of novel inhibitors of M. tuberculosis growth using whole cell based high-throughput screening. *ACS Chem. Biol.* **2012**, *7*, 1377–1384. [CrossRef]

93. Yep, A.; McQuade, T.; Kirchhoff, P.; Larsen, M.; Mobley, H.L. Inhibitors of TonB function identified by a high-throughput screen for inhibitors of iron acquisition in uropathogenic Escherichia coli CFT073. *MBio* **2014**, *5*, e01089-13. [CrossRef]

94. De La Fuente, R.; Sonawane, N.D.; Arumainayagam, D.; Verkman, A.S. Small molecules with antimicrobial activity against E. coli and P. aeruginosa identified by high-throughput screening. *Br. J. Pharmacol.* **2006**, *149*, 551–559. [CrossRef]

95. Sheremet, A.B.; Zigangirova, N.A.; Zayakin, E.S.; Luyksaar, S.I.; Kapotina, L.N.; Nesterenko, L.N.; Kobets, N.V.; Gintsburg, A.L. Small molecule inhibitor of type three secretion system belonging to a class 2, 4-disubstituted-4H-[1,3,4]-thiadiazine-5-ones improves survival and decreases bacterial loads in an airway *Pseudomonas aeruginosa* infection in mice. *Biomed. Res. Int.* **2018**, *2018*, 5810767. [CrossRef]

96. Nesterenko, L.N.; Zigangirova, N.A.; Zayakin, E.S.; Luyksaar, S.I.; Kobets, N.V.; Balunets, D.V.; Shabalina, L.A.; Bolshakova, T.N.; Dobrynina, O.Y.; Gintsburg, A.L. A small-molecule compound belonging to a class of 2, 4-disubstituted 1, 3, 4-thiadiazine-5-ones suppresses Salmonella infection in vivo. *J. Antibiot.* **2016**, *69*, 422–427. [CrossRef] [PubMed]

97. Thakral, D.; Tae, H.S. Discovery of a Structurally Unique Small Molecule that Inhibits Protein Synthesis. *Yale J. Biol. Med.* **2017**, *90*, 35–43. [PubMed]

98. Stokes, N.R.; Baker, N.; Bennett, J.M.; Berry, J.; Collins, I.; Czaplewski, L.G.; Logan, A.; Macdonald, R.; MacLeod, L.; Peasley, H. An improved small-molecule inhibitor of FtsZ with superior in vitro potency, drug-like properties, and in vivo efficacy. *Antimicrob. Agents Chemother.* **2013**, *57*, 317–325. [CrossRef] [PubMed]

99. Yu, J.; Rao, L.; Zhan, L.; Zhou, Y.; Guo, Y.; Wu, X.; Song, Z.; Yu, F. Antibiofilm Activity of Small-Molecule ZY-214-4 Against *Staphylococcus aureus*. *Front. Microbiol.* **2021**, *12*, 618922. [CrossRef] [PubMed]

100. Soehnlen, M.K.; Tran, M.A.; Lysczek, H.R.; Wolfgang, D.R.; Jayarao, B.M. Identification of novel small molecule antimicrobials targeting Mycoplasma bovis. *J. Antimicrob. Chemother.* **2011**, *66*, 574–577. [CrossRef]

101. Johnson, J.G.; Yuhas, C.; McQuade, T.J.; Larsen, M.J.; DiRita, V.J. Narrow-Spectrum Inhibitors of *Campylobacter jejuni* Flagellar Expression and Growth. *Antimicrob. Agents Chemother.* **2015**, *59*, 3880–3886. [CrossRef]

102. Deblais, L.; Helmy, Y.A.; Kumar, A.; Antwi, J.; Kathayat, D.; Acuna, U.M.; Huang, H.-C.; de Blanco, E.C.; Fuchs, J.R.; Rajashekara, G. Novel narrow spectrum benzyl thiophene sulfonamide derivatives to control Campylobacter. *J. Antibiot.* **2019**, *72*, 555–565. [CrossRef]

103. Dombach, J.L.; Quintana, J.L.; Nagy, T.A.; Wan, C.; Crooks, A.L.; Yu, H.; Su, C.-C.; Yu, E.W.; Shen, J.; Detweiler, C.S. A small molecule that mitigates bacterial infection disrupts Gram-negative cell membranes and is inhibited by cholesterol and neutral lipids. *PLoS Pathog.* **2020**, *16*, e1009119. [CrossRef]

104. Deblais, L.; Helmy, Y.A.; Kathayat, D.; Huang, H.-c.; Miller, S.A.; Rajashekara, G. Novel Imidazole and Methoxybenzylamine Growth Inhibitors Affecting Salmonella Cell Envelope Integrity and its Persistence in Chickens. *Sci. Rep.* **2018**, *8*, 13381. [CrossRef]

105. Kathayat, D.; Helmy, Y.A.; Deblais, L.; Rajashekara, G. Novel small molecules affecting cell membrane as potential therapeutics for avian pathogenic Escherichia coli. *Sci. Rep.* **2018**, *8*, 15329. [CrossRef]

106. Kathayat, D.; Helmy, Y.A.; Deblais, L.; Srivastava, V.; Closs, G., Jr.; Khupse, R.; Rajashekara, G. Novel Small Molecule Growth Inhibitor Affecting Bacterial Outer Membrane Reduces Extraintestinal Pathogenic Escherichia coli (ExPEC) Infection in Avian Model. *Microbiol. Spectr.* **2021**, *9*, e0000621. [CrossRef]

107. Helmy, Y.A.; Deblais, L.; Kassem, I.I.; Kathayat, D.; Rajashekara, G. Novel small molecule modulators of quorum sensing in avian pathogenic Escherichia coli (APEC). *Virulence* **2018**, *9*, 1640–1657. [CrossRef]

108. Helmy, Y.A.; Kathayat, D.; Deblais, L.; Srivastava, V.; Closs, G., Jr.; Tokarski, R.J., 2nd; Ayinde, O.; Fuchs, J.R.; Rajashekara, G. Evaluation of Novel Quorum Sensing Inhibitors Targeting Auto-Inducer 2 (AI-2) for the Control of Avian Pathogenic Escherichia coli Infections in Chickens. *Microbiol. Spectr.* **2022**, *10*, e0028622. [CrossRef]

109. Ashraf, K.; Yasrebi, K.; Hertlein, T.; Ohlsen, K.; Lalk, M.; Hilgeroth, A. Novel Effective Small-Molecule Antibacterials against Enterococcus Strains. *Molecules* **2017**, *22*, 2193. [CrossRef]

110. Thanissery, R.; Zeng, D.; Doyle, R.G.; Theriot, C.M. A Small Molecule-Screening Pipeline to Evaluate the Therapeutic Potential of 2-Aminoimidazole Molecules Against Clostridium difficile. *Front. Microbiol.* **2018**, *9*, 1206. [CrossRef]

111. Muschiol, S.; Normark, S.; Henriques-Normark, B.; Subtil, A. Small molecule inhibitors of the Yersinia type III secretion system impair the development of Chlamydia after entry into host cells. *BMC Microbiol.* **2009**, *9*, 75. [CrossRef]

112. Pang, Y.-P.; Davis, J.; Wang, S.; Park, J.G.; Nambiar, M.P.; Schmidt, J.J.; Millard, C.B. Small molecules showing significant protection of mice against botulinum neurotoxin serotype A. *PLoS ONE* **2010**, *5*, e10129. [CrossRef]

113. Lieberman, L.A.; Higgins, D.E. A small-molecule screen identifies the antipsychotic drug pimozide as an inhibitor of Listeria monocytogenes infection. *Antimicrob. Agents Chemother.* **2009**, *53*, 756–764. [CrossRef]

114. Akgul, A.; Al-Janabi, N.; Das, B.; Lawrence, M.; Karsi, A. Small molecules targeting LapB protein prevent Listeria attachment to catfish muscle. *PLoS ONE* **2017**, *12*, e0189809. [CrossRef]

115. Greenberg, M.; Kuo, D.; Jankowsky, E.; Long, L.; Hager, C.; Bandi, K.; Ma, D.; Manoharan, D.; Shoham, Y.; Harte, W.; et al. Small-molecule AgrA inhibitors F12 and F19 act as antivirulence agents against Gram-positive pathogens. *Sci. Rep.* **2018**, *8*, 14578. [CrossRef]

116. Gao, X.; Li, C.; He, R.; Zhang, Y.; Wang, B.; Zhang, Z.-H.; Ho, C.-T. Research advances on biogenic amines in traditional fermented foods: Emphasis on formation mechanism, detection and control methods. *Food Chem.* **2023**, *405*, 134911. [CrossRef]

117. Miller, M.B.; Bassler, B.L. Quorum sensing in bacteria. *Annu. Rev. Microbiol.* **2001**, *55*, 165–199. [CrossRef]

118. Preda, V.G.; Săndulescu, O. Communication is the key: Biofilms, quorum sensing, formation and prevention. *Discoveries* **2019**, *7*, e100. [CrossRef]

119. Kose-Mutlu, B.; Ergon-Can, T.; Koyuncu, I.; Lee, C.-H. Quorum quenching for effective control of biofouling in membrane bioreactor: A comprehensive review of approaches, applications, and challenges. *Environ. Eng. Res.* **2019**, *24*, 543–558. [CrossRef]

120. Williams, P.; Cámara, M. Quorum sensing and environmental adaptation in *Pseudomonas aeruginosa*: A tale of regulatory networks and multifunctional signal molecules. *Curr. Opin. Microbiol.* **2009**, *12*, 182–191. [CrossRef]

121. Kaplan, H.B.; Greenberg, E.P. Diffusion of autoinducer is involved in regulation of the Vibrio fischeri luminescence system. *J. Bacteriol.* **1985**, *163*, 1210–1214. [CrossRef]

122. Seed, P.C.; Passador, L.; Iglewski, B.H. Activation of the *Pseudomonas aeruginosa* lasI gene by LasR and the Pseudomonas autoinducer PAI: An autoinduction regulatory hierarchy. *J. Bacteriol.* **1995**, *177*, 654–659. [CrossRef]

123. Fuqua, C.; Greenberg, E.P. Listening in on bacteria: Acyl-homoserine lactone signalling. *Nat. Rev. Mol. Cell Biol.* **2002**, *3*, 685–695. [CrossRef]

124. Papenfort, K.; Bassler, B.L. Quorum sensing signal-response systems in Gram-negative bacteria. *Nat. Rev. Microbiol.* **2016**, *14*, 576–588. [CrossRef]

125. Chan, W.C.; Coyle, B.J.; Williams, P. Virulence Regulation and Quorum Sensing in Staphylococcal Infections: Competitive AgrC Antagonists as Quorum Sensing Inhibitors. *J. Med. Chem.* **2004**, *47*, 4633–4641. [CrossRef]

126. Singh, V.K.; Kavita, K.; Prabhakaran, R.; Jha, B. Cis-9-octadecenoic acid from the rhizospheric bacterium Stenotrophomonas maltophilia BJ01 shows quorum quenching and anti-biofilm activities. *Biofouling* **2013**, *29*, 855–867. [CrossRef]

127. Asfour, H.Z. Anti-Quorum Sensing Natural Compounds. *J. Microsc. Ultrastruct.* **2018**, *6*, 1–10. [CrossRef]

128. Sheng, L.; Olsen, S.A.; Hu, J.; Yue, W.; Means, W.J.; Zhu, M.J. Inhibitory effects of grape seed extract on growth, quorum sensing, and virulence factors of CDC "top-six" non-O157 Shiga toxin producing *E. coli. Int. J. Food Microbiol.* **2016**, *229*, 24–32. [CrossRef]

129. Ravichandiran, V.; Shanmugam, K.; Solomon, A.P. Screening of SdiA inhibitors from Melia dubia seeds extracts towards the hold back of uropathogenic E.coli quorum sensing-regulated factors. *Med. Chem.* **2013**, *9*, 819–827. [CrossRef]

130. Escobar-Muciño, E.; Arenas-Hernández, M.M.P.; Luna-Guevara, M.L. Mechanisms of Inhibition of Quorum Sensing as an Alternative for the Control of *E. coli* and *Salmonella. Microorganisms* **2022**, *10*, 884. [CrossRef]

131. Utari, P.D.; Vogel, J.; Quax, W.J. Deciphering Physiological Functions of AHL Quorum Quenching Acylases. *Front. Microbiol.* **2017**, *8*, 1123. [CrossRef]

132. Chen, F.; Gao, Y.; Chen, X.; Yu, Z.; Li, X. Quorum quenching enzymes and their application in degrading signal molecules to block quorum sensing-dependent infection. *Int. J. Mol. Sci.* **2013**, *14*, 17477–17500. [CrossRef]

133. Park, S.Y.; Kang, H.O.; Jang, H.S.; Lee, J.K.; Koo, B.T.; Yum, D.Y. Identification of extracellular N-acylhomoserine lactone acylase from a Streptomyces sp. and its application to quorum quenching. *Appl. Environ. Microbiol.* **2005**, *71*, 2632–2641. [CrossRef]

134. Ha, J.H.; Eo, Y.; Grishaev, A.; Guo, M.; Smith, J.A.; Sintim, H.O.; Kim, E.H.; Cheong, H.K.; Bentley, W.E.; Ryu, K.S. Crystal structures of the LsrR proteins complexed with phospho-AI-2 and two signal-interrupting analogues reveal distinct mechanisms for ligand recognition. *J. Am. Chem. Soc.* **2013**, *135*, 15526–15535. [CrossRef]

135. Rasmussen, T.B.; Givskov, M. Quorum-sensing inhibitors as anti-pathogenic drugs. *Int. J. Med. Microbiol.* **2006**, *296*, 149–161. [CrossRef]

136. De Lamo Marin, S.; Xu, Y.; Meijler, M.M.; Janda, K.D. Antibody catalyzed hydrolysis of a quorum sensing signal found in Gram-negative bacteria. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1549–1552. [CrossRef] [PubMed]

137. Hentzer, M.; Wu, H.; Andersen, J.B.; Riedel, K.; Rasmussen, T.B.; Bagge, N.; Kumar, N.; Schembri, M.A.; Song, Z.; Kristoffersen, P.; et al. Attenuation of *Pseudomonas aeruginosa* virulence by quorum sensing inhibitors. *EMBO J.* **2003**, *22*, 3803–3815. [CrossRef]

138. Gohil, N.; Ramírez-García, R.; Panchasara, H.; Patel, S.; Bhattacharjee, G.; Singh, V. Book Review: Quorum Sensing vs. Quorum Quenching: A Battle With No End in Sight. *Front. Cell Infect. Microbiol.* **2018**, *8*, 106. [CrossRef]

139. Lee, J.H.; Wood, T.K.; Lee, J. Roles of indole as an interspecies and interkingdom signaling molecule. *Trends Microbiol.* **2015**, *23*, 707–718. [CrossRef] [PubMed]

140. DeLisa, M.P.; Wu, C.F.; Wang, L.; Valdes, J.J.; Bentley, W.E. DNA microarray-based identification of genes controlled by autoinducer 2-stimulated quorum sensing in Escherichia coli. *J. Bacteriol.* **2001**, *183*, 5239–5247. [CrossRef] [PubMed]

141. Sully, E.K.; Malachowa, N.; Elmore, B.O.; Alexander, S.M.; Femling, J.K.; Gray, B.M.; DeLeo, F.R.; Otto, M.; Cheung, A.L.; Edwards, B.S. Selective chemical inhibition of agr quorum sensing in *Staphylococcus aureus* promotes host defense with minimal impact on resistance. *PLoS Pathog.* **2014**, *10*, e1004174. [CrossRef]

142. Curtis, M.M.; Russell, R.; Moreira, C.G.; Adebesin, A.M.; Wang, C.; Williams, N.S.; Taussig, R.; Stewart, D.; Zimmern, P.; Lu, B. QseC inhibitors as an antivirulence approach for Gram-negative pathogens. *MBio* **2014**, *5*, e02165-14. [CrossRef]

143. Peterson, M.M.; Mack, J.L.; Hall, P.R.; Alsup, A.A.; Alexander, S.M.; Sully, E.K.; Sawires, Y.S.; Cheung, A.L.; Otto, M.; Gresham, H.D. Apolipoprotein B is an innate barrier against invasive *Staphylococcus aureus* infection. *Cell Host Microbe* **2008**, *4*, 555–566. [CrossRef]

144. Wang, W.; Li, D.; Huang, X.; Yang, H.; Qiu, Z.; Zou, L.; Liang, Q.; Shi, Y.; Wu, Y.; Wu, S.; et al. Study on Antibacterial and Quorum-Sensing Inhibition Activities of Cinnamomum camphora Leaf Essential Oil. *Molecules* **2019**, *24*, 3792. [CrossRef]

145. Rasko, D.A.; Moreira, C.G.; Li, D.R.; Reading, N.C.; Ritchie, J.M.; Waldor, M.K.; Williams, N.; Taussig, R.; Wei, S.; Roth, M.; et al. Targeting QseC signaling and virulence for antibiotic development. *Science* **2008**, *321*, 1078–1080. [CrossRef]

146. Witsø, I.L.; Valen Rukke, H.; Benneche, T.; Aamdal Scheie, A. Thiophenone Attenuates Enteropathogenic Escherichia coli O103:H2 Virulence by Interfering with AI-2 Signaling. *PLoS ONE* **2016**, *11*, e0157334. [CrossRef] [PubMed]

147. Cáceres, M.; Hidalgo, W.; Stashenko, E.; Torres, R.; Ortiz, C. Essential Oils of Aromatic Plants with Antibacterial, Anti-Biofilm and Anti-Quorum Sensing Activities against Pathogenic Bacteria. *Antibiotics* **2020**, *9*, 147. [CrossRef] [PubMed]

148. Girennavar, B.; Cepeda, M.L.; Soni, K.A.; Vikram, A.; Jesudhasan, P.; Jayaprakasha, G.K.; Pillai, S.D.; Patil, B.S. Grapefruit juice and its furocoumarins inhibits autoinducer signaling and biofilm formation in bacteria. *Int. J. Food Microbiol.* **2008**, *125*, 204–208. [CrossRef] [PubMed]

149. Truchado, P.; Larrosa, M.; Castro-Ibáñez, I.; Allende, A. Plant food extracts and phytochemicals: Their role as Quorum Sensing Inhibitors. *Trends Food Sci. Technol.* **2015**, *43*, 189–204. [CrossRef]

150. Almasoud, A.; Hettiarachchy, N.; Rayaprolu, S.; Babu, D.; Kwon, Y.M.; Mauromoustakos, A. Inhibitory effects of lactic and malic organic acids on autoinducer type 2 (AI-2) quorum sensing of Escherichia coli O157:H7 and Salmonella Typhimurium. *LWT-Food Sci. Technol.* **2016**, *66*, 560–564. [CrossRef]

151. Rahman, M.R.; Lou, Z.; Zhang, J.; Yu, F.; Timilsena, Y.P.; Zhang, C.; Zhang, Y.; Bakry, A.M. Star Anise (Illicium verum Hook. f.) as Quorum Sensing and Biofilm Formation Inhibitor on Foodborne Bacteria: Study in Milk. *J. Food Prot.* **2017**, *80*, 645–653. [CrossRef]

152. Rubini, D.; Banu, S.F.; Subramani, P.; Hari, B.N.V.; Gowrishankar, S.; Pandian, S.K.; Wilson, A.; Nithyanand, P. Extracted chitosan disrupts quorum sensing mediated virulence factors in Urinary tract infection causing pathogens. *Pathog. Dis.* **2019**, *77*, ftz009. [CrossRef]

153. Pan, J.; Xie, X.; Tian, W.; Bahar, A.A.; Lin, N.; Song, F.; An, J.; Ren, D. (Z)-4-bromo-5-(bromomethylene)-3-methylfuran-2(5H)-one sensitizes Escherichia coli persister cells to antibiotics. *Appl. Microbiol. Biotechnol.* **2013**, *97*, 9145–9154. [CrossRef]

154. Li, G.; Yan, C.; Xu, Y.; Feng, Y.; Wu, Q.; Lv, X.; Yang, B.; Wang, X.; Xia, X. Punicalagin inhibits Salmonella virulence factors and has anti-quorum-sensing potential. *Appl. Environ. Microbiol.* **2014**, *80*, 6204–6211. [CrossRef]

155. Maskey, R.P.; Asolkar, R.N.; Kapaun, E.; Wagner-Döbler, I.; Laatsch, H. Phytotoxic arylethylamides from limnic bacteria using a screening with microalgae. *J. Antibiot.* **2002**, *55*, 643–649. [CrossRef]

156. Teasdale, M.E.; Liu, J.; Wallace, J.; Akhlaghi, F.; Rowley, D.C. Secondary metabolites produced by the marine bacterium Halobacillus salinus that inhibit quorum sensing-controlled phenotypes in gram-negative bacteria. *Appl. Environ. Microbiol.* **2009**, *75*, 567–572. [CrossRef] [PubMed]

157. Tommonaro, G.; Abbamondi, G.R.; Iodice, C.; Tait, K.; De Rosa, S. Diketopiperazines produced by the halophilic archaeon, Haloterrigena hispanica, activate AHL bioreporters. *Microb. Ecol.* **2012**, *63*, 490–495. [CrossRef] [PubMed]

158. Abed, R.M.; Dobretsov, S.; Al-Fori, M.; Gunasekera, S.P.; Sudesh, K.; Paul, V.J. Quorum-sensing inhibitory compounds from extremophilic microorganisms isolated from a hypersaline cyanobacterial mat. *J. Ind. Microbiol. Biotechnol.* **2013**, *40*, 759–772. [CrossRef] [PubMed]

159. Li, X.; Jeong, J.H.; Lee, K.T.; Rho, J.R.; Choi, H.D.; Kang, J.S.; Son, B.W. γ-Pyrone derivatives, kojic acid methyl ethers from a marine-derived fungusaltenaria sp. *Arch. Pharmacal Res.* **2003**, *26*, 532–534. [CrossRef]

160. Tan, L.Y.; Yin, W.-F.; Chan, K.-G. Silencing quorum sensing through extracts of Melicope lunu-ankenda. *Sensors* **2012**, *12*, 4339–4351. [CrossRef]

161. Chatterjee, M.; D'morris, S.; Paul, V.; Warrier, S.; Vasudevan, A.K.; Vanuopadath, M.; Nair, S.S.; Paul-Prasanth, B.; Mohan, C.G.; Biswas, R. Mechanistic understanding of Phenyllactic acid mediated inhibition of quorum sensing and biofilm development in *Pseudomonas aeruginosa*. *Appl. Microbiol. Biotechnol.* **2017**, *101*, 8223–8236. [CrossRef]

162. Krishnan, T.; Yin, W.-F.; Chan, K.-G. Inhibition of quorum sensing-controlled virulence factor production in *Pseudomonas aeruginosa* PAO1 by Ayurveda spice clove (Syzygium aromaticum) bud extract. *Sensors* **2012**, *12*, 4016–4030. [CrossRef]

163. Vinothkannan, R.; Tamizh, M.M.; Raj, C.D.; Princy, S.A. Fructose furoic acid ester: An effective quorum sensing inhibitor against uropathogenic *Escherichia coli*. *Bioorg. Chem.* **2018**, *79*, 310–318. [CrossRef]

164. Tello, E.; Castellanos, L.; Arévalo-Ferro, C.; Duque, C. Disruption in quorum-sensing systems and bacterial biofilm inhibition by cembranoid diterpenes isolated from the octocoral Eunicea knighti. *J. Nat. Prod.* **2012**, *75*, 1637–1642. [CrossRef]

165. Sun, J.; Wu, J.; An, B.; de Voogd, N.J.; Cheng, W.; Lin, W. Bromopyrrole alkaloids with the inhibitory effects against the biofilm formation of Gram negative bacteria. *Mar. Drugs* **2018**, *16*, 9. [CrossRef]

166. Silva, D.R.; de Cássia Orlandi Sardi, J.; de Souza Pitangui, N.; Roque, S.M.; da Silva, A.C.B.; Rosalen, P.L. Probiotics as an alternative antimicrobial therapy: Current reality and future directions. *J. Funct. Foods* **2020**, *73*, 104080. [CrossRef]

167. de Melo Pereira, G.V.; de Oliveira Coelho, B.; Júnior, A.I.M.; Thomaz-Soccol, V.; Soccol, C.R. How to select a probiotic? A review and update of methods and criteria. *Biotechnol. Adv.* **2018**, *36*, 2060–2076. [CrossRef]

168. Tharmaraj, N.; Shah, N.P. Antimicrobial effects of probiotics against selected pathogenic and spoilage bacteria in cheese-based dips. *Int. Food Res. J.* **2009**, *16*, 261–276.

169. Parente, E.; Brienza, C.; Moles, M.; Ricciardi, A. A comparison of methods for the measurement of bacteriocin activity. *J. Microbiol. Methods* **1995**, *22*, 95–108. [CrossRef]

170. Adimpong, D.B.; Nielsen, D.S.; Sørensen, K.I.; Derkx, P.M.; Jespersen, L. Genotypic characterization and safety assessment of lactic acid bacteria from indigenous African fermented food products. *BMC Microbiol.* **2012**, *12*, 75. [CrossRef] [PubMed]

171. Flemming, H.-C.; Wingender, J.; Szewzyk, U.; Steinberg, P.; Rice, S.A.; Kjelleberg, S. Biofilms: An emergent form of bacterial life. *Nat. Rev. Microbiol.* **2016**, *14*, 563–575. [CrossRef]

172. Helmy, Y.A.; Closs, G., Jr.; Jung, K.; Kathayat, D.; Vlasova, A.; Rajashekara, G. Effect of Probiotic *E. coli* Nissle 1917 Supplementation on the Growth Performance, Immune Responses, Intestinal Morphology, and Gut Microbes of *Campylobacter jejuni* Infected Chickens. *Infect. Immun.* **2022**, *90*, e0033722. [CrossRef] [PubMed]

173. Helmy, Y.A.; Kassem, I.I.; Rajashekara, G. Immuno-modulatory effect of probiotic *E. coli* Nissle 1917 in polarized human colonic cells against *Campylobacter jejuni* infection. *Gut Microbes* **2021**, *13*, 1–16. [CrossRef]

174. Helmy, Y.A.; Kassem, I.I.; Kumar, A.; Rajashekara, G. In vitro evaluation of the impact of the probiotic E. coli Nissle 1917 on *Campylobacter jejuni*'s invasion and intracellular survival in human colonic cells. *Front. Microbiol.* **2017**, *8*, 1588. [CrossRef]

175. Kechagia, M.; Basoulis, D.; Konstantopoulou, S.; Dimitriadi, D.; Gyftopoulou, K.; Skarmoutsou, N.; Fakiri, E.M. Health benefits of probiotics: A review. *Int. Sch. Res. Not.* **2013**, *2013*, 481651. [CrossRef]

176. Zendeboodi, F.; Khorshidian, N.; Mortazavian, A.M.; da Cruz, A.G. Probiotic: Conceptualization from a new approach. *Curr. Opin. Food Sci.* **2020**, *32*, 103–123. [CrossRef]

177. Saarela, M.H. Safety aspects of next generation probiotics. *Curr. Opin. Food Sci.* **2019**, *30*, 8–13. [CrossRef]

178. Blagodatskaya, E.; Kuzyakov, Y. Active microorganisms in soil: Critical review of estimation criteria and approaches. *Soil Biol. Biochem.* **2013**, *67*, 192–211. [CrossRef]

179. Kumar, Y.; Singh, L. Health benefits of fermented and functional foods. *J. Plant Dev. Sci.* **2009**, *1*, 151–155.

180. Holzapfel, W.H.; Schillinger, U. Introduction to pre-and probiotics. *Food Res. Int.* **2002**, *35*, 109–116. [CrossRef]

181. Holzapfel, W.H.; Haberer, P.; Snel, J.; Schillinger, U.; in't Veld, J.H.H. Overview of gut flora and probiotics. *Int. J. Food Microbiol.* **1998**, *41*, 85–101. [CrossRef] [PubMed]

182. Lahtinen, S.J.; Gueimonde, M.; Ouwehand, A.C.; Reinikainen, J.P.; Salminen, S.J. Comparison of four methods to enumerate probiotic bifidobacteria in a fermented food product. *Food Microbiol.* **2006**, *23*, 571–577. [CrossRef] [PubMed]

183. Blinkova, L.; Martirosyan, D.M.; Pakhomov, Y.; Dmitrieva, O.; Vaughan, R.; Altshuler, M. Nonculturable forms of bacteria in lyophilized probiotic preparations. *Funct. Foods Health Dis.* **2014**, *4*, 66–76. [CrossRef]

184. Elshaghabee, F.M.; Rokana, N.; Gulhane, R.D.; Sharma, C.; Panwar, H. Bacillus as potential probiotics: Status, concerns, and future perspectives. *Front. Microbiol.* **2017**, *8*, 1490. [CrossRef]

185. Abriouel, H.; Franz, C.M.; Omar, N.B.; Gálvez, A. Diversity and applications of Bacillus bacteriocins. *FEMS Microbiol. Rev.* **2011**, *35*, 201–232. [CrossRef]

186. Cutting, S.M. Bacillus probiotics. *Food Microbiol.* **2011**, *28*, 214–220. [CrossRef]

187. Nataraj, B.H.; Ali, S.A.; Behare, P.V.; Yadav, H. Postbiotics-parabiotics: The new horizons in microbial biotherapy and functional foods. *Microb. Cell Factories* **2020**, *19*, 168. [CrossRef] [PubMed]

188. Ishikawa, H.; Kutsukake, E.; Fukui, T.; Sato, I.; Shirai, T.; Kurihara, T.; Okada, N.; Danbara, H.; Toba, M.; Kohda, N. Oral administration of heat-killed Lactobacillus plantarum strain b240 protected mice against Salmonella enterica Serovar Typhimurium. *Biosci. Biotechnol. Biochem.* **2010**, *74*, 1338–1342. [CrossRef]

189. Nakamura, S.; Kuda, T.; An, C.; Kanno, T.; Takahashi, H.; Kimura, B. Inhibitory effects of Leuconostoc mesenteroides 1RM3 isolated from narezushi, a fermented fish with rice, on Listeria monocytogenes infection to Caco-2 cells and A/J mice. *Anaerobe* **2012**, *18*, 19–24. [CrossRef] [PubMed]

190. Zeng, J.; Jiang, J.; Zhu, W.; Chu, Y. Heat-killed yogurt-containing lactic acid bacteria prevent cytokine-induced barrier disruption in human intestinal Caco-2 cells. *Ann. Microbiol.* **2016**, *66*, 171–178. [CrossRef]

191. Orlando, A.; Refolo, M.; Messa, C.; Amati, L.; Lavermicocca, P.; Guerra, V.; Russo, F. Antiproliferative and proapoptotic effects of viable or heat-killed Lactobacillus paracasei IMPC2. 1 and Lactobacillus rhamnosus GG in HGC-27 gastric and DLD-1 colon cell lines. *Nutr. Cancer* **2012**, *64*, 1103–1111. [CrossRef]

192. Peng, G.C.; Hsu, C.H. The efficacy and safety of heat-killed Lactobacillus paracasei for treatment of perennial allergic rhinitis induced by house-dust mite. *Pediatr. Allergy Immunol.* **2005**, *16*, 433–438. [CrossRef] [PubMed]

193. Zhu, L.; Shimada, T.; Chen, R.; Lu, M.; Zhang, Q.; Lu, W.; Yin, M.; Enomoto, T.; Cheng, L. Effects of lysed Enterococcus faecalis FK-23 on experimental allergic rhinitis in a murine model. *J. Biomed. Res.* **2012**, *26*, 226–234. [CrossRef]

194. Tareb, R.; Bernardeau, M.; Gueguen, M.; Vernoux, J.-P. In vitro characterization of aggregation and adhesion properties of viable and heat-killed forms of two probiotic Lactobacillus strains and interaction with foodborne zoonotic bacteria, especially *Campylobacter jejuni*. *J. Med. Microbiol.* **2013**, *62*, 637–649. [CrossRef] [PubMed]

195. Segawa, S.; Wakita, Y.; Hirata, H.; Watari, J. Oral administration of heat-killed Lactobacillus brevis SBC8803 ameliorates alcoholic liver disease in ethanol-containing diet-fed C57BL/6N mice. *Int. J. Food Microbiol.* **2008**, *128*, 371–377. [CrossRef]

196. Hiippala, K. Epithelial Interactions of Gram-Negative Commensals in Human Gastrointestinal Tract. Ph.D. Thesis, University of Helsinki, Helsinki, Finland, 2020.

197. Foligné, B.; Daniel, C.; Pot, B. Probiotics from research to market: The possibilities, risks and challenges. *Curr. Opin. Microbiol.* **2013**, *16*, 284–292. [CrossRef]
198. Howard, F.; Bradley, J.; Flynn, D.; Noone, P.; Szawatkowski, M. Outbreak of necrotising enterocolitis caused by Clostridium butyricum. *Lancet* **1977**, *310*, 1099–1102. [CrossRef] [PubMed]
199. Cassir, N.; Benamar, S.; La Scola, B. Clostridium butyricum: From beneficial to a new emerging pathogen. *Clin. Microbiol. Infect.* **2016**, *22*, 37–45. [CrossRef]
200. Martín, R.; Miquel, S.; Benevides, L.; Bridonneau, C.; Robert, V.; Hudault, S.; Chain, F.; Berteau, O.; Azevedo, V.; Chatel, J.M.; et al. Functional characterization of novel Faecalibacterium prausnitzii strains isolated from healthy volunteers: A step forward in the use of F. prausnitzii as a next-generation probiotic. *Front. Microbiol.* **2017**, *8*, 1226. [CrossRef]
201. Zhang, M.; Qiu, X.; Zhang, H.; Yang, X.; Hong, N.; Yang, Y.; Chen, H.; Yu, C. Faecalibacterium prausnitzii inhibits interleukin-17 to ameliorate colorectal colitis in rats. *PLoS ONE* **2014**, *9*, e109146. [CrossRef]
202. Foditsch, C.; Pereira, R.V.V.; Ganda, E.K.; Gomez, M.S.; Marques, E.C.; Santin, T.; Bicalho, R.C. Oral administration of Faecalibacterium prausnitzii decreased the incidence of severe diarrhea and related mortality rate and increased weight gain in preweaned dairy heifers. *PLoS ONE* **2015**, *10*, e0145485. [CrossRef] [PubMed]
203. Watson, R.R.; Preedy, V.R. *Bioactive Foods in Promoting Health: Probiotics and Prebiotics*; Academic Press: Cambridge, MA, USA, 2010.
204. Kumar, M.; Nagpal, R.; Verma, V.; Kumar, A.; Kaur, N.; Hemalatha, R.; Gautam, S.K.; Singh, B. Probiotic metabolites as epigenetic targets in the prevention of colon cancer. *Nutr. Rev.* **2013**, *71*, 23–34. [CrossRef] [PubMed]
205. Chenoll, E.; Moreno, I.; Sánchez, M.; Garcia-Grau, I.; Silva, Á.; González-Monfort, M.; Genovés, S.; Vilella, F.; Seco-Durban, C.; Simón, C. Selection of new probiotics for endometrial health. *Front. Cell. Infect. Microbiol.* **2019**, *9*, 114. [CrossRef]
206. Plaza-Diaz, J.; Ruiz-Ojeda, F.J.; Gil-Campos, M.; Gil, A. Mechanisms of action of probiotics. *Adv. Nutr.* **2019**, *10*, S49–S66. [CrossRef]
207. Skonieczna-Żydecka, K.; Kaczmarczyk, M.; Łoniewski, I.; Lara, L.F.; Koulaouzidis, A.; Misera, A.; Maciejewska, D.; Marlicz, W. A systematic review, meta-analysis, and meta-regression evaluating the efficacy and mechanisms of action of probiotics and synbiotics in the prevention of surgical site infections and surgery-related complications. *J. Clin. Med.* **2018**, *7*, 556. [CrossRef]
208. Liu, D.; Jiang, X.-Y.; Zhou, L.-S.; Song, J.-H.; Zhang, X. Effects of Probiotics on Intestinal Mucosa Barrier in Patients With Colorectal Cancer after Operation: Meta-Analysis of Randomized Controlled Trials. *Medicine* **2016**, *95*, e3342. [CrossRef] [PubMed]
209. Kumar, A.; Helmy, Y.A.; Fritts, Z.; Vlasova, A.; Saif, L.J.; Rajashekara, G. Anti-rotavirus Properties and Mechanisms of Selected Gram-Positive and Gram-Negative Probiotics on Polarized Human Colonic (HT-29) Cells. *Probiotics Antimicrob. Proteins* **2022**, *15*, 107–128. [CrossRef] [PubMed]
210. Dawood, M.A.O.; Koshio, S.; Esteban, M.Á. Beneficial roles of feed additives as immunostimulants in aquaculture: A review. *Rev. Aquac.* **2018**, *10*, 950–974. [CrossRef]
211. Wan, M.L.Y.; Forsythe, S.J.; El-Nezami, H. Probiotics interaction with foodborne pathogens: A potential alternative to antibiotics and future challenges. *Crit. Rev. Food Sci. Nutr.* **2019**, *59*, 3320–3333. [CrossRef]
212. Mingmongkolchai, S.; Panbangred, W. Bacillus probiotics: An alternative to antibiotics for livestock production. *J. Appl. Microbiol.* **2018**, *124*, 1334–1346. [CrossRef]
213. Apetroaie-Constantin, C.; Mikkola, R.; Andersson, M.A.; Teplova, V.; Suominen, I.; Johansson, T.; Salkinoja-Salonen, M. Bacillus subtilis and B. mojavensis strains connected to food poisoning produce the heat stable toxin amylosin. *J. Appl. Microbiol.* **2009**, *106*, 1976–1985. [CrossRef]
214. Mawad, A.; Helmy, Y.A.; Shalkami, A.-G.; Kathayat, D.; Rajashekara, G.E. coli Nissle microencapsulation in alginate-chitosan nanoparticles and its effect on *Campylobacter jejuni* in vitro. *Appl. Microbiol. Biotechnol.* **2018**, *102*, 10675–10690. [CrossRef]
215. Arena, M.P.; Silvain, A.; Normanno, G.; Grieco, F.; Drider, D.; Spano, G.; Fiocco, D. Use of Lactobacillus plantarum strains as a bio-control strategy against food-borne pathogenic microorganisms. *Front. Microbiol.* **2016**, *7*, 464. [CrossRef]
216. Di Lena, M.; Quero, G.M.; Santovito, E.; Verran, J.; De Angelis, M.; Fusco, V. A selective medium for isolation and accurate enumeration of Lactobacillus casei-group members in probiotic milks and dairy products. *Int. Dairy J.* **2015**, *47*, 27–36. [CrossRef]
217. de Matos, F.E.; Santos, T.T.; Burns, P.G.; Reinheimer, J.A.; Vinderola, C.G.; Trindade, C.S.F. Evaluation of lactobacillus paracasei LP11 and lactobacillus rhamnosus 64 potential as candidates for use as probiotics in functional foods. *J. Microbiol. Biotechnol. Food Sci.* **2020**, *9*, 1126–1133.
218. Bian, X.; Evivie, S.E.; Muhammad, Z.; Luo, G.-W.; Liang, H.-Z.; Wang, N.-N.; Huo, G.-C. In vitro assessment of the antimicrobial potentials of Lactobacillus helveticus strains isolated from traditional cheese in Sinkiang China against food-borne pathogens. *Food Funct.* **2016**, *7*, 789–797. [CrossRef] [PubMed]
219. Johnson-Henry, K.C.; Hagen, K.E.; Gordonpour, M.; Tompkins, T.A.; Sherman, P.M. Surface-layer protein extracts from Lactobacillus helveticus inhibit enterohaemorrhagic Escherichia coli O157: H7 adhesion to epithelial cells. *Cell. Microbiol.* **2007**, *9*, 356–367. [CrossRef] [PubMed]
220. Singh, T.P.; Kaur, G.; Kapila, S.; Malik, R.K. Antagonistic activity of Lactobacillus reuteri strains on the adhesion characteristics of selected pathogens. *Front. Microbiol.* **2017**, *8*, 486. [CrossRef] [PubMed]
221. Lin, Y.P.; Thibodeaux, C.H.; Peña, J.A.; Ferry, G.D.; Versalovic, J. Probiotic Lactobacillus reuteri suppress proinflammatory cytokines via c-Jun. *Inflamm. Bowel Dis.* **2008**, *14*, 1068–1083. [CrossRef]

222. Dinev, T.; Beev, G.; Denev, S.; Dermendzhieva, D.; Tzanova, M.; Valkova, E. Antimicrobial activity of Lactobacillus acidophilus against pathogenic and food spoilage microorganisms: A review. *Agric. Sci. Technol.* **2017**, *9*, 3–9. [CrossRef]

223. Kathayat, D.; Closs, G., Jr.; Helmy, Y.A.; Deblais, L.; Srivastava, V.; Rajashekara, G. In Vitro and In Vivo Evaluation of Lacticaseibacillus rhamnosus GG and Bifidobacterium lactis Bb12 Against Avian Pathogenic Escherichia coli and Identification of Novel Probiotic-Derived Bioactive Peptides. *Probiotics Antimicrob. Proteins* **2022**, *14*, 1012–1028. [CrossRef]

224. Evivie, S.E.; Abdelazez, A.; Li, B.; Lu, S.; Liu, F.; Huo, G. *Lactobacillus delbrueckii* subsp. bulgaricus KLDS 1.0207 exerts antimicrobial and cytotoxic effects in vitro and improves blood biochemical parameters in vivo against notable foodborne pathogens. *Front. Microbiol.* **2020**, *11*, 583070. [CrossRef]

225. O'Mahony, D.; Murphy, S.; Boileau, T.; Park, J.; O'Brien, F.; Groeger, D.; Konieczna, P.; Ziegler, M.; Scully, P.; Shanahan, F.; et al. Bifidobacterium animalis AHC7 protects against pathogen-induced NF-κB activation in vivo. *BMC Immunol.* **2010**, *11*, 63.

226. Lim, H.J.; Shin, H.S. Antimicrobial and immunomodulatory effects of bifidobacterium strains: A review. *J. Microbiol. Biotechnol.* **2020**, *30*, 1793–1800. [CrossRef]

227. Rahimifard, N.; Naseri, M. Evaluation and comparison of three antimicrobial activity methods using Bifidobacteriabifidum and Bifidobacteria infantis as probiotic bacteria against Salmonella enterica serotype Enteritidis. *J. Bacteriol. Mycol.* **2016**, *2*, 24.

228. Ruiz, P.A.; Hoffmann, M.; Szcesny, S.; Blaut, M.; Haller, D. Innate mechanisms for Bifidobacterium lactis to activate transient proinflammatory host responses in intestinal epithelial cells after the colonization of germ-free rats. *Immunology* **2005**, *115*, 441–450. [CrossRef] [PubMed]

229. Nair, D.V.; Kollanoor Johny, A. Characterizing the antimicrobial function of a dairy-originated probiotic, Propionibacterium freudenreichii, against multidrug-resistant Salmonella enterica serovar Heidelberg in turkey poults. *Front. Microbiol.* **2018**, *9*, 1475. [CrossRef] [PubMed]

230. Prete, R.; Garcia-Gonzalez, N.; Battista, N.; Corsetti, A. Interaction of food-associated Lactobacillus plantarum with human derived intestinal epithelial cells. In Proceedings of the 12th International Scientific Conference on Probiotics, Prebiotics, Gut Microbiota and Health-IPC2018, Budapest, Hungary, 18–21 June 2018; pp. 47–48.

231. Abbasiliasi, S.; Tan, J.S.; Bashokouh, F.; Ibrahim, T.A.T.; Mustafa, S.; Vakhshiteh, F.; Sivasamboo, S.; Ariff, A.B. In vitro assessment of Pediococcus acidilactici Kp10 for its potential use in the food industry. *BMC Microbiol.* **2017**, *17*, 121. [CrossRef]

232. Benmechernene, Z.; Chentouf, H.F.; Yahia, B.; Fatima, G.; Quintela-Baluja, M.; Calo-Mata, P.; Barros-Velázquez, J. Technological aptitude and applications of Leuconostoc mesenteroides bioactive strains isolated from Algerian raw camel milk. *Biomed. Res. Int.* **2013**, *2013*, 418132. [CrossRef] [PubMed]

233. Wu, Y.; Zhen, W.; Geng, Y.; Wang, Z.; Guo, Y. Pretreatment with probiotic *Enterococcus faecium* NCIMB 11181 ameliorates necrotic enteritis-induced intestinal barrier injury in broiler chickens. *Sci. Rep.* **2019**, *9*, 10256. [CrossRef]

234. Stašková, A.; Sondorová, M.; Nemcová, R.; Kačírová, J.; Maďar, M. Antimicrobial and Antibiofilm Activity of the Probiotic Strain Streptococcus salivarius K12 against Oral Potential Pathogens. *Antibiotics* **2021**, *10*, 793. [CrossRef]

235. Evivie, S.E.; Ogwu, M.C.; Abdelazez, A.; Bian, X.; Liu, F.; Li, B.; Huo, G. Suppressive effects of Streptococcus thermophilus KLDS 3.1003 on some foodborne pathogens revealed through in vitro, in vivo and genomic insights. *Food Funct.* **2020**, *11*, 6573–6587. [CrossRef]

236. Masumuzzaman, M.; Evivie, S.E.; Ogwu, M.C.; Li, B.; Du, J.; Li, W.; Huo, G.; Liu, F.; Wang, S. Genomic and in vitro properties of the dairy Streptococcus thermophilus SMQ-301 strain against selected pathogens. *Food Funct.* **2021**, *12*, 7017–7028. [CrossRef]

237. Jensen, G.S.; Cash, H.A.; Farmer, S.; Keller, D. Inactivated probiotic Bacillus coagulans GBI-30 induces complex immune activating, anti-inflammatory, and regenerative markers in vitro. *J. Inflamm. Res.* **2017**, *10*, 107. [CrossRef]

238. Dalmasso, G.; Cottrez, F.; Imbert, V.; Lagadec, P.; Peyron, J.-F.; Rampal, P.; Czerucka, D.; Groux, H. Saccharomyces boulardii inhibits inflammatory bowel disease by trapping T cells in mesenteric lymph nodes. *Gastroenterology* **2006**, *131*, 1812–1825. [CrossRef]

239. Vandenplas, Y.; Brunser, O.; Szajewska, H. Saccharomyces boulardii in childhood. *Eur. J. Pediatr.* **2009**, *168*, 253–265. [CrossRef] [PubMed]

240. Czerucka, D.; Rampal, P. Diversity of Saccharomyces boulardii CNCM I-745 mechanisms of action against intestinal infections. *World J. Gastroenterol.* **2019**, *25*, 2188. [CrossRef] [PubMed]

241. Takahashi, M.; Taguchi, H.; Yamaguchi, H.; Osaki, T.; Komatsu, A.; Kamiya, S. The effect of probiotic treatment with Clostridium butyricum on enterohemorrhagic Escherichia coli O157: H7 infection in mice. *FEMS Immunol. Med. Microbiol.* **2004**, *41*, 219–226. [CrossRef]

242. Seo, M.; Inoue, I.; Tanaka, M.; Matsuda, N.; Nakano, T.; Awata, T.; Katayama, S.; Alpers, D.H.; Komoda, T. Clostridium butyricum MIYAIRI 588 improves high-fat diet-induced non-alcoholic fatty liver disease in rats. *Dig. Dis. Sci.* **2013**, *58*, 3534–3544. [CrossRef] [PubMed]

243. Taha-Abdelaziz, K.; Astill, J.; Kulkarni, R.R.; Read, L.R.; Najarian, A.; Farber, J.M.; Sharif, S. In vitro assessment of immunomodulatory and anti-Campylobacter activities of probiotic lactobacilli. *Sci. Rep.* **2019**, *9*, 17903. [CrossRef]

244. Ty, M.; Taha-Abdelaziz, K.; Demey, V.; Castex, M.; Sharif, S.; Parkinson, J. Performance of distinct microbial based solutions in a Campylobacter infection challenge model in poultry. *Anim. Microbiome* **2022**, *4*, 2. [CrossRef]

245. Shojadoost, B.; Alizadeh, M.; Boodhoo, N.; Astill, J.; Karimi, S.H.; Shoja Doost, J.; Taha-Abdelaziz, K.; Kulkarni, R.; Sharif, S. Effects of Treatment with Lactobacilli on Necrotic Enteritis in Broiler Chickens. *Probiotics Antimicrob. Proteins* **2022**, *14*, 1110–1129. [CrossRef]

246. Gibson, G.R.; Hutkins, R.; Sanders, M.E.; Prescott, S.L.; Reimer, R.A.; Salminen, S.J.; Scott, K.; Stanton, C.; Swanson, K.S.; Cani, P.D.; et al. Expert consensus document: The International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of prebiotics. *Nat. Rev. Gastroenterol. Hepatol.* **2017**, *14*, 491–502. [CrossRef]

247. Manning, T.S.; Gibson, G.R. Prebiotics. *Best Pract. Res. Clin. Gastroenterol.* **2004**, *18*, 287–298. [CrossRef]

248. Mohanty, D.; Misra, S.; Mohapatra, S.; Sahu, P.S. Prebiotics and synbiotics: Recent concepts in nutrition. *Food Biosci.* **2018**, *26*, 152–160. [CrossRef]

249. Davani-Davari, D.; Negahdaripour, M.; Karimzadeh, I.; Seifan, M.; Mohkam, M.; Masoumi, S.J.; Berenjian, A.; Ghasemi, Y. Prebiotics: Definition, Types, Sources, Mechanisms, and Clinical Applications. *Foods* **2019**, *8*, 92. [CrossRef] [PubMed]

250. Sarangi, N.R.; Babu, L.K.; Kumar, A.; Pradhan, C.R.; Pati, P.K.; Mishra, J.P. Effect of dietary supplementation of prebiotic, probiotic, and synbiotic on growth performance and carcass characteristics of broiler chickens. *Vet. World* **2016**, *9*, 313–319. [CrossRef] [PubMed]

251. Pourabedin, M.; Zhao, X. Prebiotics and gut microbiota in chickens. *FEMS Microbiol. Lett.* **2015**, *362*, fnv122. [CrossRef] [PubMed]

252. Solis-Cruz, B.; Hernandez-Patlan, D.; Hargis, B.M.; Tellez, G. Use of prebiotics as an alternative to antibiotic growth promoters in the poultry industry. In *Prebiotics and Probiotics-Potential Benefits in Nutrition and Health*; IntechOpen: London, UK, 2019.

253. Rajendran, S.R.C.K.; Okolie, C.L.; Udenigwe, C.C.; Mason, B. Structural features underlying prebiotic activity of conventional and potential prebiotic oligosaccharides in food and health. *J. Food Biochem.* **2017**, *41*, e12389. [CrossRef]

254. Cunningham, M.; Azcarate-Peril, M.A.; Barnard, A.; Benoit, V.; Grimaldi, R.; Guyonnet, D.; Holscher, H.D.; Hunter, K.; Manurung, S.; Obis, D.; et al. Shaping the Future of Probiotics and Prebiotics. *Trends Microbiol.* **2021**, *29*, 667–685. [CrossRef]

255. Connolly, M.L.; Lovegrove, J.A.; Tuohy, K.M. Konjac glucomannan hydrolysate beneficially modulates bacterial composition and activity within the faecal microbiota. *J. Funct. Foods* **2010**, *2*, 219–224. [CrossRef]

256. So, D.; Whelan, K.; Rossi, M.; Morrison, M.; Holtmann, G.; Kelly, J.T.; Shanahan, E.R.; Staudacher, H.M.; Campbell, K.L. Dietary fiber intervention on gut microbiota composition in healthy adults: A systematic review and meta-analysis. *Am. J. Clin. Nutr.* **2018**, *107*, 965–983. [CrossRef]

257. Wilson, B.; Whelan, K. Prebiotic inulin-type fructans and galacto-oligosaccharides: Definition, specificity, function, and application in gastrointestinal disorders. *J. Gastroenterol. Hepatol.* **2017**, *32*, 64–68. [CrossRef]

258. Micciche, A.C.; Foley, S.L.; Pavlidis, H.O.; McIntyre, D.R.; Ricke, S.C. A Review of Prebiotics Against Salmonella in Poultry: Current and Future Potential for Microbiome Research Applications. *Front. Vet. Sci.* **2018**, *5*, 191. [CrossRef]

259. Kim, S.A.; Jang, M.J.; Kim, S.Y.; Yang, Y.; Pavlidis, H.O.; Ricke, S.C. Potential for Prebiotics as Feed Additives to Limit Foodborne Campylobacter Establishment in the Poultry Gastrointestinal Tract. *Front. Microbiol.* **2019**, *10*, 91. [CrossRef]

260. Elshaghabee, F.M.F.; Rokana, N. Mitigation of antibiotic resistance using probiotics, prebiotics and synbiotics. A review. *Environ. Chem. Lett.* **2022**, *20*, 1295–1308. [CrossRef]

261. Kondepudi, K.K.; Ambalam, P.; Nilsson, I.; Wadström, T.; Ljungh, A. Prebiotic-non-digestible oligosaccharides preference of probiotic bifidobacteria and antimicrobial activity against Clostridium difficile. *Anaerobe* **2012**, *18*, 489–497. [CrossRef] [PubMed]

262. Koruri, S.S.; Chowdhury, R.; Bhattacharya, P. Potentiation of functional and antimicrobial activities through synergistic growth of probiotic Pediococcus acidilactici with natural prebiotics (garlic, basil). In *Microbes in the Spotlight: Recent Progress in the Understanding of Beneficial and Harmful Microorganisms*; Brown Walker Press: Irvine, CA, USA, 2016; pp. 219–224.

263. Bomba, A.; Nemcová, R.; Gancarcíková, S.; Herich, R.; Guba, P.; Mudroňová, D. Improvement of the probiotic effect of micro-organisms by their combination with maltodextrins, fructo-oligosaccharides and polyunsaturated fatty acids. *Br. J. Nutr.* **2002**, *88*, S95–S99. [CrossRef] [PubMed]

264. Lewis, S.; Burmeister, S.; Brazier, J. Effect of the prebiotic oligofructose on relapse of Clostridium difficile-associated diarrhea: A randomized, controlled study. *Clin. Gastroenterol. Hepatol.* **2005**, *3*, 442–448. [CrossRef] [PubMed]

265. Teng, P.-Y.; Kim, W.K. Review: Roles of Prebiotics in Intestinal Ecosystem of Broilers. *Front. Vet. Sci.* **2018**, *5*, 245. [CrossRef]

266. Ricke, S.C. Impact of Prebiotics on Poultry Production and Food Safety. *Yale J. Biol. Med.* **2018**, *91*, 151–159.

267. Abd El-Hack, M.E.; El-Saadony, M.T.; Salem, H.M.; El-Tahan, A.M.; Soliman, M.M.; Youssef, G.B.A.; Taha, A.E.; Soliman, S.M.; Ahmed, A.E.; El-kott, A.F.; et al. Alternatives to antibiotics for organic poultry production: Types, modes of action and impacts on bird's health and production. *Poult. Sci.* **2022**, *101*, 101696. [CrossRef]

268. Svensson, U.; Håkansson, J. Safety of food and beverages: Safety of probiotics and prebiotics. *Encycl. Food Saf.* **2014**, *3*, 441–446.

269. Zhang, Q.-Y.; Yan, Z.-B.; Meng, Y.-M.; Hong, X.-Y.; Shao, G.; Ma, J.-J.; Cheng, X.-R.; Liu, J.; Kang, J.; Fu, C.-Y. Antimicrobial peptides: Mechanism of action, activity and clinical potential. *Mil. Med. Res.* **2021**, *8*, 48. [CrossRef]

270. Lei, J.; Sun, L.; Huang, S.; Zhu, C.; Li, P.; He, J.; Mackey, V.; Coy, D.H.; He, Q. The antimicrobial peptides and their potential clinical applications. *Am. J. Transl. Res.* **2019**, *11*, 3919–3931.

271. Mookherjee, N.; Anderson, M.A.; Haagsman, H.P.; Davidson, D.J. Antimicrobial host defence peptides: Functions and clinical potential. *Nat. Rev. Drug Discov.* **2020**, *19*, 311–332. [CrossRef] [PubMed]

272. Pfalzgraff, A.; Brandenburg, K.; Weindl, G. Antimicrobial Peptides and Their Therapeutic Potential for Bacterial Skin Infections and Wounds. *Front. Pharmacol.* **2018**, *9*, 281. [CrossRef] [PubMed]

273. Mwangi, J.; Hao, X.; Lai, R.; Zhang, Z.-Y. Antimicrobial peptides: New hope in the war against multidrug resistance. *Zool. Res.* **2019**, *40*, 488–505. [CrossRef] [PubMed]

274. Di Somma, A.; Moretta, A.; Canè, C.; Cirillo, A.; Duilio, A. Antimicrobial and Antibiofilm Peptides. *Biomolecules* **2020**, *10*, 652. [CrossRef]

275. Dennison, S.R.; Harris, F.; Mura, M.; Phoenix, D.A. An Atlas of Anionic Antimicrobial Peptides from Amphibians. *Curr. Protein Pept. Sci.* **2018**, *19*, 823–838. [CrossRef]

276. Almarwani, B.; Phambu, N.; Hamada, Y.Z.; Sunda-Meya, A. Interactions of an Anionic Antimicrobial Peptide with Zinc(II): Application to Bacterial Mimetic Membranes. *Langmuir* **2020**, *36*, 14554–14562. [CrossRef]

277. Teixeira, V.; Feio, M.J.; Bastos, M. Role of lipids in the interaction of antimicrobial peptides with membranes. *Prog. Lipid Res.* **2012**, *51*, 149–177. [CrossRef]

278. Gennaro, R.; Zanetti, M. Structural features and biological activities of the cathelicidin-derived antimicrobial peptides. *Biopolymers* **2000**, *55*, 31–49. [CrossRef]

279. Lewies, A.; Wentzel, J.F.; Jacobs, G.; Du Plessis, L.H. The Potential Use of Natural and Structural Analogues of Antimicrobial Peptides in the Fight against Neglected Tropical Diseases. *Molecules* **2015**, *20*, 15392–15433. [CrossRef]

280. Koehbach, J.; Craik, D.J. The Vast Structural Diversity of Antimicrobial Peptides. *Trends Pharmacol. Sci.* **2019**, *40*, 517–528. [CrossRef]

281. Starling, S. Innate immunity: A new way out for lysozyme. *Nat. Rev. Gastroenterol. Hepatol.* **2017**, *14*, 567. [CrossRef] [PubMed]

282. Ibrahim, H.R.; Thomas, U.; Pellegrini, A. A helix-loop-helix peptide at the upper lip of the active site cleft of lysozyme confers potent antimicrobial activity with membrane permeabilization action. *J. Biol. Chem.* **2001**, *276*, 43767–43774. [CrossRef]

283. Genco, C.A.; Maloy, W.L.; Kari, U.P.; Motley, M. Antimicrobial activity of magainin analogues against anaerobic oral pathogens. *Int. J. Antimicrob. Agents* **2003**, *21*, 75–78. [CrossRef] [PubMed]

284. Silvestro, L.; Weiser, J.N.; Axelsen, P.H. Antibacterial and antimembrane activities of cecropin A in *Escherichia coli*. *Antimicrob. Agents Chemother.* **2000**, *44*, 602–607. [CrossRef] [PubMed]

285. Pillai, A.; Ueno, S.; Zhang, H.; Lee, J.M.; Kato, Y. Cecropin P1 and novel nematode cecropins: A bacteria-inducible antimicrobial peptide family in the nematode Ascaris suum. *Biochem. J.* **2005**, *390*, 207–214. [CrossRef]

286. Franco, I.; Pérez, M.D.; Castillo, E.; Calvo, M.; Sánchez, L. Effect of high pressure on the structure and antibacterial activity of bovine lactoferrin treated in different media. *J. Dairy Res.* **2013**, *80*, 283–290. [CrossRef]

287. Leandro, L.F.; Mendes, C.A.; Casemiro, L.A.; Vinholis, A.H.; Cunha, W.R.; de Almeida, R.; Martins, C.H. Antimicrobial activity of apitoxin, melittin and phospholipase A$_2$ of honey bee (Apis mellifera) venom against oral pathogens. *An. Acad. Bras. Cienc.* **2015**, *87*, 147–155. [CrossRef]

288. Wang, W.; Yang, W.; Du, S.; Xi, X.; Ma, C.; Wang, L.; Zhou, M.; Chen, T. Bioevaluation and Targeted Modification of Temporin-FL From the Skin Secretion of Dark-Spotted Frog (*Pelophylax nigromaculatus*). *Front. Mol. Biosci.* **2021**, *8*, 707013. [CrossRef]

289. Brancaccio, D.; Pizzo, E.; Cafaro, V.; Notomista, E.; De Lise, F.; Bosso, A.; Gaglione, R.; Merlino, F.; Novellino, E.; Ungaro, F.; et al. Antimicrobial peptide Temporin-L complexed with anionic cyclodextrins results in a potent and safe agent against sessile bacteria. *Int. J. Pharm.* **2020**, *584*, 119437. [CrossRef]

290. Park, C.B.; Yi, K.S.; Matsuzaki, K.; Kim, M.S.; Kim, S.C. Structure-activity analysis of buforin II, a histone H2A-derived antimicrobial peptide: The proline hinge is responsible for the cell-penetrating ability of buforin II. *Proc. Natl. Acad. Sci. USA* **2000**, *97*, 8245–8250. [CrossRef]

291. Lee, I.H.; Cho, Y.; Lehrer, R.I. Effects of pH and salinity on the antimicrobial properties of clavanins. *Infect. Immun.* **1997**, *65*, 2898–2903. [CrossRef]

292. Steinberg, D.A.; Hurst, M.A.; Fujii, C.A.; Kung, A.H.; Ho, J.F.; Cheng, F.C.; Loury, D.J.; Fiddes, J.C. Protegrin-1: A broad-spectrum, rapidly microbicidal peptide with in vivo activity. *Antimicrob. Agents Chemother.* **1997**, *41*, 1738–1742. [CrossRef] [PubMed]

293. Dai, J.G.; Xie, H.W.; Jin, G.; Wang, W.G.; Zhang, Y.; Guo, Y. Preliminary study on high-level expression of tandem-arranged tachyplesin-encoding gene in Bacillus subtilis Wb800 and its antibacterial activity. *Mar. Biotechnol.* **2009**, *11*, 109–117. [CrossRef] [PubMed]

294. Michels, K.; Nemeth, E.; Ganz, T.; Mehrad, B. Hepcidin and Host Defense against Infectious Diseases. *PLoS Pathog.* **2015**, *11*, e1004998. [CrossRef] [PubMed]

295. Blaskovich, M.A.T.; Hansford, K.A.; Gong, Y.; Butler, M.S.; Muldoon, C.; Huang, J.X.; Ramu, S.; Silva, A.B.; Cheng, M.; Kavanagh, A.M.; et al. Protein-inspired antibiotics active against vancomycin- and daptomycin-resistant bacteria. *Nat. Commun.* **2018**, *9*, 22. [CrossRef] [PubMed]

296. Shin, J.M.; Gwak, J.W.; Kamarajan, P.; Fenno, J.C.; Rickard, A.H.; Kapila, Y.L. Biomedical applications of nisin. *J. Appl. Microbiol.* **2016**, *120*, 1449–1465. [CrossRef]

297. Kathayat, D.; Closs, G.; Helmy Yosra, A.; Lokesh, D.; Ranjit, S.; Rajashekara, G. Peptides Affecting the Outer Membrane Lipid Asymmetry System (MlaA-OmpC/F) Reduce Avian Pathogenic *Escherichia coli* (APEC) Colonization in Chickens. *Appl. Environ. Microbiol.* **2021**, *87*, e00567-21. [CrossRef]

298. Kumar, P.; Kizhakkedathu, J.N.; Straus, S.K. Antimicrobial Peptides: Diversity, Mechanism of Action and Strategies to Improve the Activity and Biocompatibility In Vivo. *Biomolecules* **2018**, *8*, 4. [CrossRef]

299. Zhang, J.; Sun, Y.; Kang, Y.; Shang, D. Antimicrobial peptide temporin-1CEa isolated from frog skin secretions inhibits the proinflammatory response in lipopolysaccharide-stimulated RAW264.7 murine macrophages through the MyD88-dependent signaling pathway. *Mol. Immunol.* **2021**, *132*, 227–235. [CrossRef]

300. Lee, T.H.; Hall, K.N.; Aguilar, M.I. Antimicrobial Peptide Structure and Mechanism of Action: A Focus on the Role of Membrane Structure. *Curr. Top. Med. Chem.* **2016**, *16*, 25–39. [CrossRef]

301. Mandal, S.M.; Khan, J.; Mahata, D.; Saha, S.; Sengupta, J.; Silva, O.N.; Das, S.; Mandal, M.; Franco, O.L. A self-assembled clavanin A-coated amniotic membrane scaffold for the prevention of biofilm formation by ocular surface fungal pathogens. *Biofouling* **2017**, *33*, 881–891. [CrossRef] [PubMed]

302. Zhang, Y.; Liu, S.; Li, S.; Cheng, Y.; Nie, L.; Wang, G.; Lv, C.; Wei, W.; Cheng, C.; Hou, F.; et al. Novel short antimicrobial peptide isolated from Xenopus laevis skin. *J. Pept. Sci.* **2017**, *23*, 403–409. [CrossRef] [PubMed]

303. Cardoso, M.H.; Meneguetti, B.T.; Costa, B.O.; Buccini, D.F.; Oshiro, K.G.N.; Preza, S.L.E.; Carvalho, C.M.E.; Migliolo, L.; Franco, O.L. Non-Lytic Antibacterial Peptides That Translocate Through Bacterial Membranes to Act on Intracellular Targets. *Int. J. Mol. Sci.* **2019**, *20*, 4877. [CrossRef] [PubMed]

304. Mardirossian, M.; Barrière, Q.; Timchenko, T.; Müller, C.; Pacor, S.; Mergaert, P.; Scocchi, M.; Wilson, D.N. Fragments of the Nonlytic Proline-Rich Antimicrobial Peptide Bac5 Kill Escherichia coli Cells by Inhibiting Protein Synthesis. *Antimicrob. Agents Chemother.* **2018**, *62*, e00534-18. [CrossRef] [PubMed]

305. Yang, H.; Fu, J.; Zhao, Y.; Shi, H.; Hu, H.; Wang, H. Escherichia coli PagP Enzyme-Based De Novo Design and In Vitro Activity of Antibacterial Peptide LL-37. *Med. Sci. Monit.* **2017**, *23*, 2558–2564. [CrossRef]

306. Braffman, N.R.; Piscotta, F.J.; Hauver, J.; Campbell, E.A.; Link, A.J.; Darst, S.A. Structural mechanism of transcription inhibition by lasso peptides microcin J25 and capistruin. *Proc. Natl. Acad. Sci. USA* **2019**, *116*, 1273–1278. [CrossRef]

307. Kurpe, S.R.; Grishin, S.Y.; Surin, A.K.; Panfilov, A.V.; Slizen, M.V.; Chowdhury, S.D.; Galzitskaya, O.V. Antimicrobial and Amyloidogenic Activity of Peptides. Can Antimicrobial Peptides Be Used against SARS-CoV-2? *Int. J. Mol. Sci.* **2020**, *21*, 9552. [CrossRef]

308. Andersson, D.I.; Hughes, D.; Kubicek-Sutherland, J.Z. Mechanisms and consequences of bacterial resistance to antimicrobial peptides. *Drug Resist. Updates* **2016**, *26*, 43–57. [CrossRef]

309. Haney, E.F.; Hancock, R.E. Peptide design for antimicrobial and immunomodulatory applications. *Biopolymers* **2013**, *100*, 572–583. [CrossRef]

310. Engelkirk, P.G.; Duben-Engelkirk, J.; Fader, R.C. *Burton's Microbiology for the Health Sciences*; Jones & Bartlett Publishers: Burlington, MA, USA, 2020.

311. Sabour, P.M.; Griffiths, M.W. *Bacteriophages in the Control of Food-and Waterborne Pathogens*; American Society for Microbiology Press: Washington, DC, USA, 2010.

312. Romero-Calle, D.; Guimarães Benevides, R.; Góes-Neto, A.; Billington, C. Bacteriophages as alternatives to antibiotics in clinical care. *Antibiotics* **2019**, *8*, 138. [CrossRef]

313. Golkar, Z.; Bagasra, O.; Pace, D.G. Bacteriophage therapy: A potential solution for the antibiotic resistance crisis. *J. Infect. Dev. Ctries.* **2014**, *8*, 129–136. [CrossRef] [PubMed]

314. Wittebole, X.; De Roock, S.; Opal, S.M. A historical overview of bacteriophage therapy as an alternative to antibiotics for the treatment of bacterial pathogens. *Virulence* **2014**, *5*, 226–235. [CrossRef] [PubMed]

315. Azeredo, J.; Sutherland, I.W. The use of phages for the removal of infectious biofilms. *Curr. Pharm. Biotechnol.* **2008**, *9*, 261–266. [CrossRef] [PubMed]

316. Ligonenko, O.V.; Borysenko, M.; Digtyar, I.; Ivashchenko, D.; Zubakha, A.; Chorna, I.; Shumeyko, I.; Storozhenko, O.; Gorb, L.; Ligonenko, O.O. Application of bacteriophages in complex of treatment of a shot-gun wounds of soft tissues in the patients, suffering multiple allergy for antibiotics. *Klin. Khirurhiia* **2015**, *10*, 65–66.

317. El-Shibiny, A.; El-Sahhar, S. Bacteriophages: The possible solution to treat infections caused by pathogenic bacteria. *Can. J. Microbiol.* **2017**, *63*, 865–879. [CrossRef]

318. Kashoma, I.P.; Srivastava, V.; Rajashekara, G. Advances in Vaccines for Controlling Campylobacter in Poultry. In *Food Safety in Poultry Meat Production*; Venkitanarayanan, K., Thakur, S., Ricke, S.C., Eds.; Springer International Publishing: Cham, Switzerland, 2019; pp. 191–210.

319. Abubakar, S.; Suleiman, B.H.; Abbagana, B.A.; Mustafa, I.A.; Musa, I.A. Novel uses of bacteriophages in the treatment of human infections and antibiotic resistance. *Am. J. Biosci.* **2016**, *4*, 34. [CrossRef]

320. Dufour, N.; Delattre, R.; Ricard, J.-D.; Debarbieux, L. The lysis of pathogenic Escherichia coli by bacteriophages releases less endotoxin than by β-lactams. *Clin. Infect. Dis.* **2017**, *64*, 1582–1588. [CrossRef]

321. Majewska, J.; Beta, W.; Lecion, D.; Hodyra-Stefaniak, K.; Kłopot, A.; Kaźmierczak, Z.; Miernikiewicz, P.; Piotrowicz, A.; Ciekot, J.; Owczarek, B. Oral application of T4 phage induces weak antibody production in the gut and in the blood. *Viruses* **2015**, *7*, 4783–4799. [CrossRef]

322. Love, M.J.; Bhandari, D.; Dobson, R.C.; Billington, C. Potential for bacteriophage endolysins to supplement or replace antibiotics in food production and clinical care. *Antibiotics* **2018**, *7*, 17. [CrossRef]

323. Kucharewicz-Krukowska, A.; Slopek, S. Immunogenic effect of bacteriophage in patients subjected to phage therapy. *Arch. Immunol. Ther. Exp.* **1987**, *35*, 553–561.

324. Jault, P.; Leclerc, T.; Jennes, S.; Pirnay, J.P.; Que, Y.-A.; Resch, G.; Rousseau, A.F.; Ravat, F.; Carsin, H.; Le Floch, R. Efficacy and tolerability of a cocktail of bacteriophages to treat burn wounds infected by *Pseudomonas aeruginosa* (PhagoBurn): A randomised, controlled, double-blind phase 1/2 trial. *Lancet Infect. Dis.* **2019**, *19*, 35–45. [CrossRef] [PubMed]

325. Speck, P.; Smithyman, A. Safety and efficacy of phage therapy via the intravenous route. *FEMS Microbiol. Lett.* **2016**, *363*, fnv242. [CrossRef] [PubMed]

326. Dedrick, R.M.; Guerrero-Bustamante, C.A.; Garlena, R.A.; Russell, D.A.; Ford, K.; Harris, K.; Gilmour, K.C.; Soothill, J.; Jacobs-Sera, D.; Schooley, R.T.; et al. Engineered bacteriophages for treatment of a patient with a disseminated drug-resistant Mycobacterium abscessus. *Nat. Med.* **2019**, *25*, 730–733. [CrossRef] [PubMed]

327. Pabary, R.; Singh, C.; Morales, S.; Bush, A.; Alshafi, K.; Bilton, D.; Alton, E.W.; Smithyman, A.; Davies, J.C. Antipseudomonal bacteriophage reduces infective burden and inflammatory response in murine lung. *Antimicrob. Agents Chemother.* **2016**, *60*, 744–751. [CrossRef]

328. Wang, Y.; Mi, Z.; Niu, W.; An, X.; Yuan, X.; Liu, H.; Li, P.; Liu, Y.; Feng, Y.; Huang, Y. Intranasal treatment with bacteriophage rescues mice from Acinetobacter baumannii-mediated pneumonia. *Future Microbiol.* **2016**, *11*, 631–641. [CrossRef]

329. Ujmajuridze, A.; Chanishvili, N.; Goderdzishvili, M.; Leitner, L.; Mehnert, U.; Chkhotua, A.; Kessler, T.M.; Sybesma, W. Adapted bacteriophages for treating urinary tract infections. *Front. Microbiol.* **2018**, *9*, 1832. [CrossRef]

330. Sarker, S.A.; Brüssow, H. From bench to bed and back again: Phage therapy of childhood Escherichia coli diarrhea. *Ann. N. Y. Acad. Sci.* **2016**, *1372*, 42–52. [CrossRef]

331. Rhoads, D.; Wolcott, R.; Kuskowski, M.; Wolcott, B.; Ward, L.; Sulakvelidze, A. Bacteriophage therapy of venous leg ulcers in humans: Results of a phase I safety trial. *J. Wound Care* **2009**, *18*, 237–243. [CrossRef]

332. Rose, T.; Verbeken, G.; De Vos, D.; Merabishvili, M.; Vaneechoutte, M.; Lavigne, R.; Jennes, S.; Zizi, M.; Pirnay, J.-P. Experimental phage therapy of burn wound infection: Difficult first steps. *Int. J. Burn. Trauma* **2014**, *4*, 66.

333. Yoichi, M.; Abe, M.; Miyanaga, K.; Unno, H.; Tanji, Y. Alteration of tail fiber protein gp38 enables T2 phage to infect Escherichia coli O157: H7. *J. Biotechnol.* **2005**, *115*, 101–107. [CrossRef]

334. Vander Elst, N.; Linden, S.B.; Lavigne, R.; Meyer, E.; Briers, Y.; Nelson, D.C. Characterization of the Bacteriophage-Derived Endolysins PlySs2 and PlySs9 with In Vitro Lytic Activity against Bovine Mastitis Streptococcus uberis. *Antibiotics* **2020**, *9*, 621. [CrossRef] [PubMed]

335. Gilmer, D.B.; Schmitz, J.E.; Euler, C.W.; Fischetti, V.A. Novel bacteriophage lysin with broad lytic activity protects against mixed infection by Streptococcus pyogenes and methicillin-resistant *Staphylococcus aureus*. *Antimicrob. Agents Chemother.* **2013**, *57*, 2743–2750. [CrossRef]

336. D'Angelantonio, D.; Scattolini, S.; Boni, A.; Neri, D.; Di Serafino, G.; Connerton, P.; Connerton, I.; Pomilio, F.; Di Giannatale, E.; Migliorati, G.; et al. Bacteriophage Therapy to Reduce Colonization of *Campylobacter jejuni* in Broiler Chickens before Slaughter. *Viruses* **2021**, *13*, 1428. [CrossRef] [PubMed]

337. O'Flynn, G.; Ross, R.P.; Fitzgerald, G.F.; Coffey, A. Evaluation of a cocktail of three bacteriophages for biocontrol of Escherichia coli O157:H7. *Appl. Environ. Microbiol.* **2004**, *70*, 3417–3424. [CrossRef] [PubMed]

338. Bigwood, T.; Hudson, J.A.; Billington, C. Influence of host and bacteriophage concentrations on the inactivation of food-borne pathogenic bacteria by two phages. *FEMS Microbiol. Lett.* **2009**, *291*, 59–64. [CrossRef] [PubMed]

339. Wagenaar, J.A.; Van Bergen, M.A.; Mueller, M.A.; Wassenaar, T.M.; Carlton, R.M. Phage therapy reduces *Campylobacter jejuni* colonization in broilers. *Vet. Microbiol.* **2005**, *109*, 275–283. [CrossRef] [PubMed]

340. Modi, R.; Hirvi, Y.; Hill, A.; Griffiths, M.W. Effect of phage on survival of Salmonella enteritidis during manufacture and storage of cheddar cheese made from raw and pasteurized milk. *J. Food Prot.* **2001**, *64*, 927–933. [CrossRef]

341. Bigot, B.; Lee, W.J.; McIntyre, L.; Wilson, T.; Hudson, J.A.; Billington, C.; Heinemann, J.A. Control of Listeria monocytogenes growth in a ready-to-eat poultry product using a bacteriophage. *Food Microbiol.* **2011**, *28*, 1448–1452. [CrossRef]

342. Bueno, E.; García, P.; Martínez, B.; Rodríguez, A. Phage inactivation of *Staphylococcus aureus* in fresh and hard-type cheeses. *Int. J. Food Microbiol.* **2012**, *158*, 23–27. [CrossRef]

343. Lee, N.-Y.; Ko, W.-C.; Hsueh, P.-R. Nanoparticles in the treatment of infections caused by multidrug-resistant organisms. *Front. Pharmacol.* **2019**, *10*, 1153. [CrossRef]

344. Hemeg, H.A. Nanomaterials for alternative antibacterial therapy. *Int. J. Nanomed.* **2017**, *12*, 8211. [CrossRef] [PubMed]

345. World Health Organization. *Antimicrobial Resistance: Global Report on Surveillance*; World Health Organization: Geneva, Switzerland, 2014.

346. Slavin, Y.N.; Asnis, J.; Häfeli, U.O.; Bach, H. Metal nanoparticles: Understanding the mechanisms behind antibacterial activity. *J. Nanobiotechnol.* **2017**, *15*, 65. [CrossRef] [PubMed]

347. Li, H.; Chen, Q.; Zhao, J.; Urmila, K. Enhancing the antimicrobial activity of natural extraction using the synthetic ultrasmall metal nanoparticles. *Sci. Rep.* **2015**, *5*, 11033. [CrossRef]

348. Armentano, I.; Arciola, C.R.; Fortunati, E.; Ferrari, D.; Mattioli, S.; Amoroso, C.F.; Rizzo, J.; Kenny, J.M.; Imbriani, M.; Visai, L. The interaction of bacteria with engineered nanostructured polymeric materials: A review. *Sci. World J.* **2014**, *2014*, 410423. [CrossRef]

349. Gao, W.; Thamphiwatana, S.; Angsantikul, P.; Zhang, L. Nanoparticle approaches against bacterial infections. *Wiley Interdiscip. Rev. Nanomed. Nanobiotechnol.* **2014**, *6*, 532–547. [CrossRef] [PubMed]

350. Khan, S.T.; Musarrat, J.; Al-Khedhairy, A.A. Countering drug resistance, infectious diseases, and sepsis using metal and metal oxides nanoparticles: Current status. *Colloids Surf. B Biointerfaces* **2016**, *146*, 70–83. [CrossRef]

351. Zaidi, S.; Misba, L.; Khan, A.U. Nano-therapeutics: A revolution in infection control in post antibiotic era. *Nanomedicine* **2017**, *13*, 2281–2301. [CrossRef]

352. Dizaj, S.M.; Lotfipour, F.; Barzegar-Jalali, M.; Zarrintan, M.H.; Adibkia, K. Antimicrobial activity of the metals and metal oxide nanoparticles. *Mater. Sci. Eng. C* **2014**, *44*, 278–284. [CrossRef]

353. Yang, W.; Shen, C.; Ji, Q.; An, H.; Wang, J.; Liu, Q.; Zhang, Z. Food storage material silver nanoparticles interfere with DNA replication fidelity and bind with DNA. *Nanotechnology* **2009**, *20*, 085102. [CrossRef]

354. Beyth, N.; Houri-Haddad, Y.; Domb, A.; Khan, W.; Hazan, R. Alternative antimicrobial approach: Nano-antimicrobial materials. *Evid. -Based Complement. Altern. Med.* **2015**, *2015*, 246012. [CrossRef]

355. Roy, A.; Bulut, O.; Some, S.; Mandal, A.K.; Yilmaz, M.D. Green synthesis of silver nanoparticles: Biomolecule-nanoparticle organizations targeting antimicrobial activity. *RSC Adv* **2019**, *9*, 2673–2702. [CrossRef] [PubMed]

356. Ansari, M.; Khan, H.; Khan, A.; Cameotra, S.S.; Saquib, Q.; Musarrat, J. Interaction of A l2 O 3 nanoparticles with E scherichia coli and their cell envelope biomolecules. *J. Appl. Microbiol.* **2014**, *116*, 772–783. [CrossRef] [PubMed]

357. Baptista, P.V.; McCusker, M.P.; Carvalho, A.; Ferreira, D.A.; Mohan, N.M.; Martins, M.; Fernandes, A.R. Nano-strategies to fight multidrug resistant bacteria—"A Battle of the Titans". *Front. Microbiol.* **2018**, *9*, 1441. [CrossRef]

358. Wei, L.; Lu, J.; Xu, H.; Patel, A.; Chen, Z.-S.; Chen, G. Silver nanoparticles: Synthesis, properties, and therapeutic applications. *Drug Discov. Today* **2015**, *20*, 595–601. [CrossRef]

359. Zhao, Y.; Jiang, X. Multiple strategies to activate gold nanoparticles as antibiotics. *Nanoscale* **2013**, *5*, 8340–8350. [CrossRef] [PubMed]

360. Finley, P.J.; Norton, R.; Austin, C.; Mitchell, A.; Zank, S.; Durham, P. Unprecedented silver resistance in clinically isolated Enterobacteriaceae: Major implications for burn and wound management. *Antimicrob. Agents Chemother.* **2015**, *59*, 4734–4741. [CrossRef]

361. Barros, C.H.; Fulaz, S.; Stanisic, D.; Tasic, L. Biogenic nanosilver against multidrug-resistant bacteria (MDRB). *Antibiotics* **2018**, *7*, 69. [CrossRef]

362. Wu, B.; Huang, R.; Sahu, M.; Feng, X.; Biswas, P.; Tang, Y.J. Bacterial responses to Cu-doped TiO_2 nanoparticles. *Sci. Total Environ.* **2010**, *408*, 1755–1758. [CrossRef]

363. Cavassin, E.D.; de Figueiredo, L.F.P.; Otoch, J.P.; Seckler, M.M.; de Oliveira, R.A.; Franco, F.F.; Marangoni, V.S.; Zucolotto, V.; Levin, A.S.S.; Costa, S.F. Comparison of methods to detect the in vitro activity of silver nanoparticles (AgNP) against multidrug resistant bacteria. *J. Nanobiotechnol.* **2015**, *13*, 64. [CrossRef]

364. Chatterjee, A.K.; Chakraborty, R.; Basu, T. Mechanism of antibacterial activity of copper nanoparticles. *Nanotechnology* **2014**, *25*, 135101. [CrossRef]

365. Vandebriel, R.J.; De Jong, W.H. A review of mammalian toxicity of ZnO nanoparticles. *Nanotechnol. Sci. Appl.* **2012**, *5*, 61. [CrossRef] [PubMed]

366. Dittoe, D.K.; Ricke, S.C.; Kiess, A.S. Organic Acids and Potential for Modifying the Avian Gastrointestinal Tract and Reducing Pathogens and Disease. *Front. Vet. Sci.* **2018**, *5*, 216. [CrossRef] [PubMed]

367. Coban, H.B. Organic acids as antimicrobial food agents: Applications and microbial productions. *Bioprocess Biosyst. Eng.* **2020**, *43*, 569–591. [CrossRef]

368. Davidson, P.M.; Sofos, J.N.; Branen, A.L. *Antimicrobials in Food*; CRC Press: Boca Raton, FL, USA, 2005.

369. Polen, T.; Spelberg, M.; Bott, M. Toward biotechnological production of adipic acid and precursors from biorenewables. *J. Biotechnol.* **2013**, *167*, 75–84. [CrossRef]

370. Blach, P.; Böstrom, Z.; Franceschi-Messant, S.; Lattes, A.; Perez, E.; Rico-Lattes, I. Recyclable process for sustainable adipic acid production in microemulsions. *Tetrahedron* **2010**, *66*, 7124–7128. [CrossRef]

371. Ciriminna, R.; Meneguzzo, F.; Delisi, R.; Pagliaro, M. Citric acid: Emerging applications of key biotechnology industrial product. *Chem. Cent. J.* **2017**, *11*, 22. [CrossRef]

372. Abdel-Rahman, M.A.; Tashiro, Y.; Sonomoto, K. Lactic acid production from lignocellulose-derived sugars using lactic acid bacteria: Overview and limits. *J. Biotechnol.* **2011**, *156*, 286–301. [CrossRef]

373. Marques, C.; Sotiles, A.R.; Farias, F.O.; Oliveira, G.; Mitterer-Daltoé, M.L.; Masson, M.L. Full physicochemical characterization of malic acid: Emphasis in the potential as food ingredient and application in pectin gels. *Arab. J. Chem.* **2020**, *13*, 9118–9129. [CrossRef]

374. Rodríguez-Pazo, N.; Salgado, J.M.; Cortés-Diéguez, S.; Domínguez, J.M. Biotechnological production of phenyllactic acid and biosurfactants from trimming vine shoot hydrolyzates by microbial coculture fermentation. *Appl. Biochem. Biotechnol.* **2013**, *169*, 2175–2188. [CrossRef]

375. Hashemi, S.M.B.; Roohi, R. Kinetic models for production of propionic acid by Propionibacter freudenrechii subsp. shermanii and Propionibacterium freudenreichii subsp. freudenreichii in date syrup during sonication treatments. *Biocatal. Agric. Biotechnol.* **2019**, *17*, 613–619. [CrossRef]

376. Galli, G.M.; Aniecevski, E.; Petrolli, T.G.; da Rosa, G.; Boiago, M.M.; Simões, C.A.D.P.; Wagner, R.; Copetti, P.M.; Morsch, V.M.; Araujo, D.N.; et al. Growth performance and meat quality of broilers fed with microencapsulated organic acids. *Anim. Feed. Sci. Technol.* **2021**, *271*, 114706. [CrossRef]

377. Kuenz, A.; Hoffmann, L.; Goy, K.; Bromann, S.; Prüße, U. High-level production of succinic acid from crude glycerol by a wild type organism. *Catalysts* **2020**, *10*, 470. [CrossRef]

378. Brul, S.; Coote, P. Preservative agents in foods. Mode of action and microbial resistance mechanisms. *Int. J. Food Microbiol.* **1999**, *50*, 1–17. [CrossRef] [PubMed]

379. Theron, M.M.; Lues, J.F.R. Organic Acids and Meat Preservation: A Review. *Food Rev. Int.* **2007**, *23*, 141–158. [CrossRef]

380. Stratford, M.; Anslow, P.A. Evidence that sorbic acid does not inhibit yeast as a classic 'weak acid preservative'. *Lett. Appl. Microbiol.* **1998**, *27*, 203–206. [CrossRef]

381. Kundukad, B.; Udayakumar, G.; Grela, E.; Kaur, D.; Rice, S.A.; Kjelleberg, S.; Doyle, P.S. Weak acids as an alternative anti-microbial therapy. *Biofilm* **2020**, *2*, 100019. [CrossRef]

382. Ben Braïek, O.; Smaoui, S. Chemistry, Safety, and Challenges of the Use of Organic Acids and Their Derivative Salts in Meat Preservation. *J. Food Qual.* **2021**, *2021*, 6653190. [CrossRef]

383. Mani-López, E.; García, H.S.; López-Malo, A. Organic acids as antimicrobials to control Salmonella in meat and poultry products. *Food Res. Int.* **2012**, *45*, 713–721. [CrossRef]

384. Hauser, C.; Thielmann, J.; Muranyi, P. Chapter 46—Organic Acids: Usage and Potential in Antimicrobial Packaging. In *Antimicrobial Food Packaging*; Barros-Velázquez, J., Ed.; Academic Press: San Diego, CA, USA, 2016; pp. 563–580.

385. Hajati, H. Application of organic acids in poultry nutrition. *Int. J. Avian Wildl. Biol.* **2018**, *3*, 324–329. [CrossRef]

386. Flors, V.; Miralles, M.C.; Varas, E.; Company, P.; González-Bosch, C.; García-Agustín, P. Effect of analogues of plant growth regulators on in vitro growth of eukaryotic plant pathogens. *Plant Pathol.* **2004**, *53*, 58–64. [CrossRef]

387. Fernández-Rubio, C.; Ordóñez, C.; Abad-González, J.; Garcia-Gallego, A.; Honrubia, M.P.; Mallo, J.J.; Balaña-Fouce, R. Butyric acid-based feed additives help protect broiler chickens from Salmonella Enteritidis infection. *Poult. Sci.* **2009**, *88*, 943–948. [CrossRef] [PubMed]

388. Timbermont, L.; Lanckriet, A.; Dewulf, J.; Nollet, N.; Schwarzer, K.; Haesebrouck, F.; Ducatelle, R.; Van Immerseel, F. Control of Clostridium perfringens-induced necrotic enteritis in broilers by target-released butyric acid, fatty acids and essential oils. *Avian Pathol.* **2010**, *39*, 117–121. [CrossRef] [PubMed]

389. Rambabu, K.; Bharath, G.; Banat, F.; Show, P.L.; Cocoletzi, H.H. Mango leaf extract incorporated chitosan antioxidant film for active food packaging. *Int. J. Biol. Macromol.* **2019**, *126*, 1234–1243. [CrossRef]

390. Show, P.L.; Oladele, K.O.; Siew, Q.Y.; Aziz Zakry, F.A.; Lan, J.C.-W.; Ling, T.C. Overview of citric acid production from Aspergillus niger. *Front. Life Sci.* **2015**, *8*, 271–283. [CrossRef]

391. Laury, A.M.; Alvarado, M.V.; Nace, G.; Alvarado, C.Z.; Brooks, J.C.; Echeverry, A.; Brashears, M.M. Validation of a lactic acid- and citric acid-based antimicrobial product for the reduction of Escherichia coli O157: H7 and Salmonella on beef tips and whole chicken carcasses. *J. Food Prot.* **2009**, *72*, 2208–2211. [CrossRef]

392. Beuchat, L.R. Influence of organic acids on heat resistance characteristics of Talaromyces flavus ascospores. *Int. J. Food Microbiol.* **1988**, *6*, 97–105. [CrossRef]

393. Zhang, S.; Farber, J.M. The effects of various disinfectants againstListeria monocytogeneson fresh-cut vegetables. *Food Microbiol.* **1996**, *13*, 311–321. [CrossRef]

394. Zou, X.; Zhou, Y.; Yang, S.T. Production of polymalic acid and malic acid by Aureobasidium pullulans fermentation and acid hydrolysis. *Biotechnol. Bioeng.* **2013**, *110*, 2105–2113. [CrossRef]

395. Beauprez, J.J.; De Mey, M.; Soetaert, W.K. Microbial succinic acid production: Natural versus metabolic engineered producers. *Process Biochem.* **2010**, *45*, 1103–1114. [CrossRef]

396. Li, C.; Yang, X.; Gao, S.; Chuh, A.H.; Lin, C.S.K. Hydrolysis of fruit and vegetable waste for efficient succinic acid production with engineered *Yarrowia lipolytica*. *J. Clean. Prod.* **2018**, *179*, 151–159. [CrossRef]

397. Over, K.F.; Hettiarachchy, N.; Johnson, M.G.; Davis, B. Effect of organic acids and plant extracts on *Escherichia coli* O157:H7, Listeria monocytogenes, and Salmonella Typhimurium in broth culture model and chicken meat systems. *J. Food Sci.* **2009**, *74*, M515–M521. [CrossRef] [PubMed]

398. Kovanda, L.; Zhang, W.; Wei, X.; Luo, J.; Wu, X.; Atwill, E.R.; Vaessen, S.; Li, X.; Liu, Y. In vitro antimicrobial activities of organic acids and their derivatives on several species of gram-negative and gram-positive bacteria. *Molecules* **2019**, *24*, 3770. [CrossRef] [PubMed]

399. Brenes, A.; Roura, E. Essential oils in poultry nutrition: Main effects and modes of action. *Anim. Feed. Sci. Technol.* **2010**, *158*, 1–14. [CrossRef]

400. Stefanakis, M.K.; Touloupakis, E.; Anastasopoulos, E.; Ghanotakis, D.; Katerinopoulos, H.E.; Makridis, P. Antibacterial activity of essential oils from plants of the genus Origanum. *Food Control* **2013**, *34*, 539–546. [CrossRef]

401. Djilani, A.; Dicko, A.J.N. The therapeutic benefits of essential oils. *Nutr. Well-Being Health* **2012**, *7*, 155–179.

402. Chouhan, S.; Sharma, K.; Guleria, S. Antimicrobial Activity of Some Essential Oils-Present Status and Future Perspectives. *Medicines* **2017**, *4*, 58. [CrossRef]

403. Shaaban, H.A.E.; El-Ghorab, A.H.; Shibamoto, T. Bioactivity of essential oils and their volatile aroma components: Review. *J. Essent. Oil Res.* **2012**, *24*, 203–212. [CrossRef]

404. Nikolić, M.; Jovanović, K.K.; Marković, T.; Marković, D.; Gligorijević, N.; Radulović, S.; Soković, M. Chemical composition, antimicrobial, and cytotoxic properties of five Lamiaceae essential oils. *Ind. Crops Prod.* **2014**, *61*, 225–232. [CrossRef]

405. Kachur, K.; Suntres, Z. The antibacterial properties of phenolic isomers, carvacrol and thymol. *Crit. Rev. Food Sci. Nutr.* **2020**, *60*, 3042–3053. [CrossRef]

406. Verma, S.K.; Goswami, P.; Verma, R.S.; Padalia, R.C.; Chauhan, A.; Singh, V.R.; Darokar, M.P. Chemical composition and antimicrobial activity of bergamot-mint (*Mentha citrata* Ehrh.) essential oils isolated from the herbage and aqueous distillate using different methods. *Ind. Crops Prod.* **2016**, *91*, 152–160. [CrossRef]

407. Radaelli, M.; da Silva, B.P.; Weidlich, L.; Hoehne, L.; Flach, A.; da Costa, L.A.; Ethur, E.M. Antimicrobial activities of six essential oils commonly used as condiments in Brazil against Clostridium perfringens. *Braz. J. Microbiol.* **2016**, *47*, 424–430. [CrossRef] [PubMed]

408. Bajer, T.; Šilha, D.; Ventura, K.; Bajerová, P. Composition and antimicrobial activity of the essential oil, distilled aromatic water and herbal infusion from *Epilobium parviflorum* Schreb. *Ind. Crops Prod.* **2017**, *100*, 95–105. [CrossRef]

409. Zhang, Y.; Liu, X.; Wang, Y.; Jiang, P.; Quek, S. Antibacterial activity and mechanism of cinnamon essential oil against Escherichia coli and *Staphylococcus aureus*. *Food Control* **2016**, *59*, 282–289. [CrossRef]

410. El Kolli, M.; Laouer, H.; El Kolli, H.; Akkal, S.; Sahli, F. Chemical analysis, antimicrobial and anti-oxidative properties of Daucus gracilis essential oil and its mechanism of action. *Asian Pac. J. Trop. Biomed.* **2016**, *6*, 8–15. [CrossRef]

411. Churklam, W.; Chaturongakul, S.; Ngamwongsatit, B.; Aunpad, R. The mechanisms of action of carvacrol and its synergism with nisin against *Listeria monocytogenes* on sliced bologna sausage. *Food Control* **2020**, *108*, 106864. [CrossRef]

412. Tariq, S.; Wani, S.; Rasool, W.; Shafi, K.; Bhat, M.A.; Prabhakar, A.; Shalla, A.H.; Rather, M.A. A comprehensive review of the antibacterial, antifungal and antiviral potential of essential oils and their chemical constituents against drug-resistant microbial pathogens. *Microb. Pathog.* **2019**, *134*, 103580. [CrossRef]

413. Omonijo, F.A.; Ni, L.; Gong, J.; Wang, Q.; Lahaye, L.; Yang, C. Essential oils as alternatives to antibiotics in swine production. *Anim. Nutr.* **2018**, *4*, 126–136. [CrossRef]

414. Hyldgaard, M.; Mygind, T.; Meyer, R.L. Essential oils in food preservation: Mode of action, synergies, and interactions with food matrix components. *Front. Microbiol.* **2012**, *3*, 12. [CrossRef]

415. da Silva, B.D.; Bernardes, P.C.; Pinheiro, P.F.; Fantuzzi, E.; Roberto, C.D. Chemical composition, extraction sources and action mechanisms of essential oils: Natural preservative and limitations of use in meat products. *Meat Sci.* **2021**, *176*, 108463. [CrossRef]

416. Ait-Ouazzou, A.; Cherrat, L.; Espina, L.; Lorán, S.; Rota, C.; Pagán, R. The antimicrobial activity of hydrophobic essential oil constituents acting alone or in combined processes of food preservation. *Innov. Food Sci. Emerg. Technol.* **2011**, *12*, 320–329. [CrossRef]

417. Gupta, S.; Allen-Vercoe, E.; Petrof, E.O. Fecal microbiota transplantation: In perspective. *Ther. Adv. Gastroenterol.* **2016**, *9*, 229–239. [CrossRef] [PubMed]

418. Chauhan, A.; Kumar, R.; Sharma, S.; Mahanta, M.; Vayuuru, S.K.; Nayak, B.; Kumar, S. Fecal microbiota transplantation in Hepatitis B e antigen-positive chronic Hepatitis B patients: A pilot study. *Dig. Dis. Sci.* **2021**, *66*, 873–880. [CrossRef] [PubMed]

419. Ueckermann, V.; Hoosien, E.; De Villiers, N.; Geldenhuys, J. Fecal microbial transplantation for the treatment of persistent multidrug-resistant *Klebsiella pneumoniae* infection in a critically ill patient. *Case Rep. Infect. Dis.* **2020**, *2020*, 8462659. [CrossRef] [PubMed]

420. Hourigan, S.K.; Ahn, M.; Gibson, K.M.; Pérez-Losada, M.; Felix, G.; Weidner, M.; Leibowitz, I.; Niederhuber, J.E.; Sears, C.L.; Crandall, K.A. Fecal transplant in children with *Clostridioides difficile* gives sustained reduction in antimicrobial resistance and potential pathogen burden. *Open Forum Infect. Dis.* **2019**, *6*, ofz379. [CrossRef] [PubMed]

421. Wang, X.; Xing, Y.; Ji, Y.; Xi, H.; Liu, X.; Yang, L.; Lei, L.; Han, W.; Gu, J. The Combination of Phages and Faecal Microbiota Transplantation Can Effectively Treat Mouse Colitis Caused by *Salmonella enterica* Serovar Typhimurium. *Front. Microbiol.* **2022**, *13*, 944495. [CrossRef] [PubMed]

422. Wei, Y.; Gong, J.; Zhu, W.; Guo, D.; Gu, L.; Li, N.; Li, J. Fecal microbiota transplantation restores dysbiosis in patients with methicillin resistant *Staphylococcus aureus* enterocolitis. *BMC Infect. Dis.* **2015**, *15*, 265. [CrossRef]

423. Singh, R.; de Groot, P.F.; Geerlings, S.E.; Hodiamont, C.J.; Belzer, C.; Berge, I.; de Vos, W.M.; Bemelman, F.J.; Nieuwdorp, M. Fecal microbiota transplantation against intestinal colonization by extended spectrum beta-lactamase producing Enterobacteriaceae: A proof of principle study. *BMC Res Notes* **2018**, *11*, 190. [CrossRef]

424. Mańkowska-Wierzbicka, D.; Stelmach-Mardas, M.; Gabryel, M.; Tomczak, H.; Skrzypczak-Zielińska, M.; Zakerska-Banaszak, O.; Sowińska, A.; Mahadea, D.; Baturo, A.; Wolko, Ł. The effectiveness of multi-session FMT treatment in active ulcerative colitis patients: A pilot study. *Biomedicines* **2020**, *8*, 268. [CrossRef]

425. Paramsothy, S.; Paramsothy, R.; Rubin, D.T.; Kamm, M.A.; Kaakoush, N.O.; Mitchell, H.M.; Castaño-Rodríguez, N. Faecal microbiota transplantation for inflammatory bowel disease: A systematic review and meta-analysis. *J. Crohn's Colitis* **2017**, *11*, 1180–1199. [CrossRef]

426. Zhang, Z.; Mocanu, V.; Cai, C.; Dang, J.; Slater, L.; Deehan, E.C.; Walter, J.; Madsen, K.L. Impact of fecal microbiota transplantation on obesity and metabolic syndrome—A systematic review. *Nutrients* **2019**, *11*, 2291. [CrossRef]

427. Kragsnaes, M.S.; Kjeldsen, J.; Horn, H.C.; Munk, H.L.; Pedersen, F.M.; Holt, H.M.; Pedersen, J.K.; Holm, D.K.; Glerup, H.; Andersen, V. Efficacy and safety of faecal microbiota transplantation in patients with psoriatic arthritis: Protocol for a 6-month, double-blind, randomised, placebo-controlled trial. *BMJ Open* **2018**, *8*, e019231. [CrossRef] [PubMed]

428. Xiao, Y.; Angulo, M.T.; Lao, S.; Weiss, S.T.; Liu, Y.-Y. An ecological framework to understand the efficacy of fecal microbiota transplantation. *Nat. Commun.* **2020**, *11*, 3329. [CrossRef] [PubMed]

429. Guo, W.; Ren, K.; Ning, R.; Li, C.; Zhang, H.; Li, D.; Xu, L.; Sun, F.; Dai, M. Fecal microbiota transplantation provides new insight into wildlife conservation. *Glob. Ecol. Conserv.* **2020**, *24*, e01234. [CrossRef]

430. Khoruts, A.; Sadowsky, M.J. Understanding the mechanisms of faecal microbiota transplantation. *Nat. Rev. Gastroenterol. Hepatol.* **2016**, *13*, 508–516. [CrossRef] [PubMed]

431. Brandt, L.J.; Aroniadis, O.C.; Mellow, M.; Kanatzar, A.; Kelly, C.; Park, T.; Stollman, N.; Rohlke, F.; Surawicz, C. Long-Term Follow-Up of Colonoscopic Fecal Microbiota Transplant for RecurrentClostridium difficileInfection. *Off. J. Am. Coll. Gastroenterol. ACG* **2012**, *107*, 1079–1087. [CrossRef] [PubMed]

432. Leshem, A.; Horesh, N.; Elinav, E. Fecal microbial transplantation and its potential application in cardiometabolic syndrome. *Front. Immunol.* **2019**, *10*, 1341. [CrossRef]

433. Li, S.S.; Zhu, A.; Benes, V.; Costea, P.I.; Hercog, R.; Hildebrand, F.; Huerta-Cepas, J.; Nieuwdorp, M.; Salojärvi, J.; Voigt, A.Y. Durable coexistence of donor and recipient strains after fecal microbiota transplantation. *Science* **2016**, *352*, 586–589. [CrossRef]

434. Li, N.; Tian, H.; Ma, C.; Ding, C.; Ge, X.; Gu, L.; Zhang, X.; Yang, B.; Hua, Y.; Zhu, Y. Efficacy analysis of fecal microbiota transplantation in the treatment of 406 cases with gastrointestinal disorders. *Zhonghua Wei Chang. Wai Ke Za Zhi Chin. J. Gastrointest. Surg.* **2017**, *20*, 40–46.

435. Gweon, T.-G.; Na, S.-Y. Next generation fecal microbiota transplantation. *Clin. Endosc.* **2021**, *54*, 152. [CrossRef]

436. Allegretti, J.R.; Elliott, R.J.; Ladha, A.; Njenga, M.; Warren, K.; O'Brien, K.; Budree, S.; Osman, M.; Fischer, M.; Kelly, C.R. Stool processing speed and storage duration do not impact the clinical effectiveness of fecal microbiota transplantation. *Gut Microbes* **2020**, *11*, 1806–1808. [CrossRef]

437. Greenwood, B. The contribution of vaccination to global health: Past, present and future. *Philos. Trans. R. Soc. B-Biol. Sci.* **2014**, *369*, 20130433. [CrossRef] [PubMed]

438. Elaish, M.; Ngunjiri, J.M.; Ali, A.; Xia, M.; Ibrahim, M.; Jang, H.; Hiremath, J.; Dhakal, S.; Helmy, Y.A.; Jiang, X.; et al. Supplementation of inactivated influenza vaccine with norovirus P particle-M2e chimeric vaccine enhances protection against heterologous virus challenge in chickens. *PLoS ONE* **2017**, *12*, e0171174. [CrossRef] [PubMed]

439. Fawzy, M.; Helmy, Y.A. The One Health Approach is Necessary for the Control of Rift Valley Fever Infections in Egypt: A Comprehensive Review. *Viruses* **2019**, *11*, 139. [CrossRef]

440. Hoelzer, K.; Bielke, L.; Blake, D.P.; Cox, E.; Cutting, S.M.; Devriendt, B.; Erlacher-Vindel, E.; Goossens, E.; Karaca, K.; Lemiere, S.; et al. Vaccines as alternatives to antibiotics for food producing animals. Part 2: New approaches and potential solutions. *Vet. Res.* **2018**, *49*, 70. [CrossRef] [PubMed]

441. Klugman, K.P.; Black, S. Impact of existing vaccines in reducing antibiotic resistance: Primary and secondary effects. *Proc. Natl. Acad. Sci. USA* **2018**, *115*, 12896–12901. [CrossRef] [PubMed]

442. Micoli, F.; Bagnoli, F.; Rappuoli, R.; Serruto, D. The role of vaccines in combatting antimicrobial resistance. *Nat. Rev. Microbiol.* **2021**, *19*, 287–302. [CrossRef]

443. Kennedy, D.A.; Read, A.F. Why does drug resistance readily evolve but vaccine resistance does not? *Proc. Biol. Sci.* **2017**, *284*, 20162562. [CrossRef]

444. Sihvonen, R.; Siira, L.; Toropainen, M.; Kuusela, P.; Patari-Sampo, A. Streptococcus pneumoniae antimicrobial resistance decreased in the Helsinki Metropolitan Area after routine 10-valent pneumococcal conjugate vaccination of infants in Finland. *Eur. J. Clin. Microbiol. Infect. Dis.* **2017**, *36*, 2109–2116. [CrossRef]

445. Klugman, K.P.; Madhi, S.A.; Huebner, R.E.; Kohberger, R.; Mbelle, N.; Pierce, N.; Grp, V.T. A trial of a 9-valent pneumococcal conjugate vaccine in children with and those without HIV infection. *N. Engl. J. Med.* **2003**, *349*, 1341–1348. [CrossRef]

446. WHO. *Pakistan First Country to Introduce New Typhoid Vaccine into Routine Immunization Programme*; WHO: Geneva, Switzerland, 2019.

447. Kaufhold, S.; Yaesoubi, R.; Pitzer, V.E. Predicting the Impact of Typhoid Conjugate Vaccines on Antimicrobial Resistance. *Clin. Infect. Dis.* **2019**, *68*, S96–S104. [CrossRef]

448. House, J.K.; Ontiveros, M.M.; Blackmer, N.M.; Dueger, E.L.; Fitchhorn, J.B.; McArthur, G.R.; Smith, B.P. Evaluation of an autogenous Salmonella bacterin and a modified live Salmonella serotype Choleraesuis vaccine on a commercial dairy farm. *Am. J. Vet. Res.* **2001**, *62*, 1897–1902. [CrossRef] [PubMed]

449. Harvey, R.R.; Friedman, C.R.; Crim, S.M.; Judd, M.; Barrett, K.A.; Tolar, B.; Folster, J.P.; Griffin, P.M.; Brown, A.C. Epidemiology of *Salmonella enterica* Serotype Dublin Infections among Humans, United States, 1968–2013. *Emerg. Infect. Dis.* **2017**, *23*, 1493–1501. [CrossRef] [PubMed]

450. Nair, D.V.T.; Venkitanarayanan, K.; Kollanoor, J.A. Antibiotic-Resistant Salmonella in the Food Supply and the Potential Role of Antibiotic Alternatives for Control. *Foods* **2018**, *7*, 167. [CrossRef] [PubMed]

451. Cummings, K.J.; Rodriguez-Rivera, L.D.; Capel, M.B.; Rankin, S.C.; Nydam, D.V. Short communication: Oral and intranasal administration of a modified-live Salmonella Dublin vaccine in dairy calves: Clinical efficacy and serologic response. *J. Dairy Sci.* **2019**, *102*, 3474–3479. [CrossRef]

452. Hosomi, K.; Hinenoya, A.; Suzuki, H.; Nagatake, T.; Nishino, T.; Tojima, Y.; Hirata, S.-I.; Matsunaga, A.; Kondoh, M.; Yamasaki, S.; et al. Development of a bivalent food poisoning vaccine: Augmented antigenicity of the C-terminus of *Clostridium perfringens* enterotoxin by fusion with the B subunit of *Escherichia coli* Shiga toxin 2. *Int. Immunol.* **2019**, *31*, 91–100. [CrossRef]

453. Taha-Abdelaziz, K.; Alkie, T.N.; Hodgins, D.C.; Yitbarek, A.; Shojadoost, B.; Sharif, S. Gene expression profiling of chicken cecal tonsils and ileum following oral exposure to soluble and PLGA-encapsulated CpG ODN, and lysate of *Campylobacter jejuni*. *Vet. Microbiol.* **2017**, *212*, 67–74. [CrossRef]

454. Taha-Abdelaziz, K.; Yitbarek, A.; Alkie, T.N.; Hodgins, D.C.; Read, L.R.; Weese, J.S.; Sharif, S. PLGA-encapsulated CpG ODN and *Campylobacter jejuni* lysate modulate cecal microbiota composition in broiler chickens experimentally challenged with *C. jejuni*. *Sci. Rep.* **2018**, *8*, 12076. [CrossRef]

455. Alizadeh, M.; Shojadoost, B.; Boodhoo, N.; Astill, J.; Taha-Abdelaziz, K.; Hodgins, D.C.; Kulkarni, R.R.; Sharif, S. Necrotic enteritis in chickens: A review of pathogenesis, immune responses and prevention, focusing on probiotics and vaccination. *Anim. Health Res. Rev.* **2021**, *22*, 147–162. [CrossRef]

456. Taha-Abdelaziz, K.; Hodgins, D.C.; Alkie, T.N.; Quinteiro-Filho, W.; Yitbarek, A.; Astill, J.; Sharif, S. Oral administration of PLGA-encapsulated CpG ODN and *Campylobacter jejuni* lysate reduces cecal colonization by *Campylobacter jejuni* in chickens. *Vaccine* **2018**, *36*, 388–394. [CrossRef]

457. Taha-Abdelaziz, K.; Singh, M.; Sharif, S.; Sharma, S.; Kulkarni, R.R.; Alizadeh, M.; Yitbarek, A.; Helmy, Y.A. Intervention Strategies to Control Campylobacter at Different Stages of the Food Chain. *Microorganisms* **2023**, *11*, 113. [CrossRef]

458. Nothaft, H.; Perez-Muñoz, M.E.; Gouveia, G.J.; Duar, R.M.; Wanford, J.J.; Lango-Scholey, L.; Panagos, C.G.; Srithayakumar, V.; Plastow, G.S.; Coros, C.; et al. Coadministration of the *Campylobacter jejuni* N-Glycan-Based Vaccine with Probiotics Improves Vaccine Performance in Broiler Chickens. *Appl. Environ. Microbiol.* **2017**, *83*, e01523-17. [CrossRef] [PubMed]

459. Buchy, P.; Ascioglu, S.; Buisson, Y.; Datta, S.; Nissen, M.; Tambyah, P.A.; Vong, S. Impact of vaccines on antimicrobial resistance. *Int. J. Infect. Dis.* **2020**, *90*, 188–196. [CrossRef]

460. Mishra, R.P.; Oviedo-Orta, E.; Prachi, P.; Rappuoli, R.; Bagnoli, F. Vaccines and antibiotic resistance. *Curr. Opin. Microbiol.* **2012**, *15*, 596–602. [CrossRef] [PubMed]

461. Poolman, J.T. Expanding the role of bacterial vaccines into life-course vaccination strategies and prevention of antimicrobial-resistant infections. *NPJ Vaccines* **2020**, *5*, 84. [CrossRef] [PubMed]

462. Tekle, Y.I.; Nielsen, K.M.; Liu, J.; Pettigrew, M.M.; Meyers, L.A.; Galvani, A.P.; Townsend, J.P. Controlling antimicrobial resistance through targeted, vaccine-induced replacement of strains. *PLoS ONE* **2012**, *7*, e50688. [CrossRef]

463. Yadav, D.K.; Yadav, N.; Khurana, S.M.P. Vaccines. In *Animal Biotechnology*; Elsevier: Amsterdam, The Netherlands, 2014; pp. 491–508.

464. Mak, T.; Saunders, M.; Jett, B. Vaccination. In *Primer to the Immune Response*; Elsevier: Amsterdam, The Netherlands, 2014; pp. 333–375.

465. Parham, P.; Janeway, C. *The Immune System*, 4th ed.; Garland Science, Taylor & Francis Group: New York, NY, USA, 2015; p. 1.

466. Lidder, P.; Sonnino, A. Biotechnologies for the Management of Genetic Resources for Food and Agriculture. In *Advances in Genetics*; Elsevier: Amsterdam, The Netherlands, 2012; Volume 78, pp. 1–167.

467. Micoli, F.; MacLennan, C.A. Outer membrane vesicle vaccines. *Semin. Immunol.* **2020**, *50*, 101433. [CrossRef]

468. Rappuoli, R. Glycoconjugate vaccines: Principles and mechanisms. *Sci. Transl. Med.* **2018**, *10*, eaat4615. [CrossRef]

469. Ura, T.; Okuda, K.; Shimada, M. Developments in Viral Vector-Based Vaccines. *Vaccines* **2014**, *2*, 624–641. [CrossRef]

470. Gheibi Hayat, S.M.; Darroudi, M. Nanovaccine: A novel approach in immunization. *J. Cell. Physiol.* **2019**, *234*, 12530–12536. [CrossRef]

471. Lyon, C.E.; Sadigh, K.S.; Carmolli, M.P.; Harro, C.; Sheldon, E.; Lindow, J.C.; Larsson, C.J.; Martinez, T.; Feller, A.; Ventrone, C.H.; et al. In a randomized, double-blinded, placebo-controlled trial, the single oral dose typhoid vaccine, M01ZH09, is safe and immunogenic at doses up to 1.7×1010 colony-forming units. *Vaccine* **2010**, *28*, 3602–3608. [CrossRef]

472. Schukken, Y.H.; Bronzo, V.; Locatelli, C.; Pollera, C.; Rota, N.; Casula, A.; Testa, F.; Scaccabarozzi, L.; March, R.; Zalduendo, D.; et al. Efficacy of vaccination on *Staphylococcus aureus* and coagulase-negative staphylococci intramammary infection dynamics in 2 dairy herds. *J. Dairy Sci.* **2014**, *97*, 5250–5264. [CrossRef] [PubMed]

473. Middleton, J.R.; Ma, J.; Rinehart, C.L.; Taylor, V.N.; Luby, C.D.; Steevens, B.J. Efficacy of different Lysigin™ formulations in the prevention of *Staphylococcus aureus* intramammary infection in dairy heifers. *J. Dairy Res.* **2006**, *73*, 10–19. [CrossRef] [PubMed]

474. Smith, G.W.; Smith, F.; Zuidhof, S.; Foster, D.M. Short communication: Characterization of the serologic response induced by vaccination of late-gestation cows with a Salmonella Dublin vaccine. *J. Dairy Sci.* **2015**, *98*, 2529–2532. [CrossRef] [PubMed]

475. Crouch, C.F.; Withanage, G.S.K.; de Haas, V.; Etore, F.; Francis, M.J. Safety and efficacy of a maternal vaccine for the passive protection of broiler chicks against necrotic enteritis. *Avian Pathol.* **2010**, *39*, 489–497. [CrossRef] [PubMed]

476. Huberman, Y.D.; Velilla, A.V.; Terzolo, H.R. Evaluation of different live Salmonella enteritidis vaccine schedules administered during layer hen rearing to reduce excretion, organ colonization, and egg contamination. *Poult. Sci.* **2019**, *98*, 2422–2431. [CrossRef]

477. Pollard, A.J.; Bijker, E.M. A guide to vaccinology: From basic principles to new developments. *Nat. Rev. Immunol.* **2021**, *21*, 83–100. [CrossRef]

478. Wiedermann, U.; Garner-Spitzer, E.; Wagner, A. Primary vaccine failure to routine vaccines: Why and what to do? *Hum. Vaccines Immunother.* **2016**, *12*, 239–243. [CrossRef]

479. Moyle, P.M.; Toth, I. Modern Subunit Vaccines: Development, Components, and Research Opportunities. *ChemMedChem* **2013**, *8*, 360–376. [CrossRef]

480. Deng, F. Advances and challenges in enveloped virus-like particle (VLP)-based vaccines. *J. Immunol. Sci.* **2018**, *2*, 36–41. [CrossRef]

481. Rossi, O.; Citiulo, F.; Mancini, F. Outer membrane vesicles: Moving within the intricate labyrinth of assays that can predict risks of reactogenicity in humans. *Hum. Vaccines Immunother.* **2021**, *17*, 601–613. [CrossRef]

482. Mettu, R.; Chen, C.-Y.; Wu, C.-Y. Synthetic carbohydrate-based vaccines: Challenges and opportunities. *J. Biomed. Sci.* **2020**, *27*, 9. [CrossRef] [PubMed]

483. Singh, A.; Chaudhary, S.; Agarwal, A.; Verma, A.S. Antibodies. In *Animal Biotechnology*; Elsevier: Amsterdam, The Netherlands, 2014; pp. 265–287.

484. Liddell, E. Antibodies. In *The Immunoassay Handbook*; Elsevier: Amsterdam, The Netherlands, 2013; pp. 245–265.

485. van Erp, E.A.; Luytjes, W.; Ferwerda, G.; van Kasteren, P.B. Fc-Mediated Antibody Effector Functions During Respiratory Syncytial Virus Infection and Disease. *Front. Immunol.* **2019**, *10*, 548. [CrossRef] [PubMed]

486. DiGiandomenico, A.; Sellman, B.R. Antibacterial monoclonal antibodies: The next generation? *Curr. Opin. Microbiol.* **2015**, *27*, 78–85. [CrossRef] [PubMed]

487. McConnell, M.J. Where are we with monoclonal antibodies for multidrug-resistant infections? *Drug Discov. Today* **2019**, *24*, 1132–1138. [CrossRef] [PubMed]

488. Cavaco, M.; Castanho, M.A.R.B.; Neves, V. The Use of Antibody-Antibiotic Conjugates to Fight Bacterial Infections. *Front. Microbiol.* **2022**, *13*, 835677. [CrossRef] [PubMed]

489. Yamada, T. Therapeutic monoclonal antibodies. *Keio J. Med.* **2011**, *60*, 37–46. [CrossRef]

490. Reichert, J.M.; Dewitz, M.C. Ooutlook—Anti-infective monoclonal antibodies: Perils and promise of development. *Nat. Rev. Drug Discov.* **2006**, *5*, 191–195. [CrossRef]

491. Chan, C.E.Z.; Chan, A.H.Y.; Hanson, B.J.; Ooi, E.E. The use of antibodies in the treatment of infectious diseases. *Singap. Med. J.* **2009**, *50*, 663–672.

492. Kohler, G.; Milstein, C. Continuous cultures of fused cells secreting antibody of predefined specificity (Reprinted from Nature, vol 256, 1975). *J. Immunol.* **2005**, *174*, 2453–2455.

493. Pelfrene, E.; Mura, M.; Cavaleiro Sanches, A.; Cavaleri, M. Monoclonal antibodies as anti-infective products: A promising future? *Clin. Microbiol. Infect.* **2019**, *25*, 60–64. [CrossRef]

494. Zurawski, D.V.; McLendon, M.K. Monoclonal Antibodies as an Antibacterial Approach Against Bacterial Pathogens. *Antibiotics* **2020**, *9*, 155. [CrossRef] [PubMed]

495. Nagy, E.; Nagy, G.; Power, C.A.; Badarau, A.; Szijarto, V. Anti-bacterial Monoclonal Antibodies. *Recomb. Antibodies Infect. Dis.* **2017**, *1053*, 119–153.

496. Lu, L.L.; Suscovich, T.J.; Fortune, S.M.; Alter, G. Beyond binding: Antibody effector functions in infectious diseases. *Nat. Rev. Immunol.* **2018**, *18*, 46–61. [CrossRef] [PubMed]

497. Peck, M.; Rothenberg, M.E.; Deng, R.; Lewin-Koh, N.; She, G.; Kamath, A.V.; Carrasco-Triguero, M.; Saad, O.; Castro, A.; Teufel, L.; et al. A Phase 1, Randomized, Single-Ascending-Dose Study To Investigate the Safety, Tolerability, and Pharmacokinetics of DSTA4637S, an Anti-*Staphylococcus aureus* Thiomab Antibody-Antibiotic Conjugate, in Healthy Volunteers. *Antimicrob. Agents Chemother.* **2019**, *63*, e02588-18. [CrossRef]

498. Guptill, J.T.; Raja, S.M.; Juel, V.C.; Walter, E.B.; Cohen-Wolkowiez, M.; Hill, H.; Sendra, E.; Hauser, B.; Jackson, P.; Swamy, G.K. Safety, Tolerability, and Pharmacokinetics of NTM-1632, a Novel Mixture of Three Monoclonal Antibodies against Botulinum Toxin B. *Antimicrob. Agents Chemother.* **2021**, *65*, e02329-20. [CrossRef] [PubMed]

499. Greig, S.L. Obiltoxaximab: First Global Approval. *Drugs* **2016**, *76*, 823–830. [CrossRef]

500. Mazumdar, S. Raxibacumab. *mAbs* **2009**, *1*, 531–538. [CrossRef]

501. Weisman, L.E.; Thackray, H.M.; Garcia-Prats, J.A.; Nesin, M.; Schneider, J.H.; Fretz, J.; Kokai-Kun, J.F.; Mond, J.J.; Kramer, W.G.; Fischer, G.W. Phase 1/2 Double-Blind, Placebo-Controlled, Dose Escalation, Safety, and Pharmacokinetic Study of Pagibaximab (BSYX-A110), an Antistaphylococcal Monoclonal Antibody for the Prevention of Staphylococcal Bloodstream Infections, in Very-Low-Birth-Weight Neonates. *Antimicrob. Agents Chemother.* **2009**, *53*, 2879–2886. [CrossRef]

502. Soon, T.L. *Recombinant Antibodies for Infectious Diseases*; Springer Berlin Heidelberg: New York, NY, USA, 2018.

503. Merakou, C.; Schaefers, M.M.; Priebe, G.P. Progress Toward the Elusive *Pseudomonas aeruginosa* Vaccine. *Surg. Infect.* **2018**, *19*, 757–768. [CrossRef]

504. Sousa, S.A.; Seixas, A.M.M.; Marques, J.M.M.; Leitão, J.H. Immunization and Immunotherapy Approaches against *Pseudomonas aeruginosa* and *Burkholderia cepacia* Complex Infections. *Vaccines* **2021**, *9*, 670. [CrossRef]

505. Chames, P.; Van Regenmortel, M.; Weiss, E.; Baty, D. Therapeutic antibodies: Successes, limitations and hopes for the future: Therapeutic antibodies: An update. *Br. J. Pharmacol.* **2009**, *157*, 220–233. [CrossRef] [PubMed]

506. Spadiut, O.; Capone, S.; Krainer, F.; Glieder, A.; Herwig, C. Microbials for the production of monoclonal antibodies and antibody fragments. *Trends Biotechnol.* **2014**, *32*, 54–60. [CrossRef] [PubMed]

507. Samaranayake, H.; Wirth, T.; Schenkwein, D.; Räty, J.K.; Ylä-Herttuala, S. Challenges in monoclonal antibody-based therapies. *Ann. Med.* **2009**, *41*, 322–331. [CrossRef] [PubMed]

508. Liu, J.K.H. The history of monoclonal antibody development—Progress, remaining challenges and future innovations. *Ann. Med. Surg.* **2014**, *3*, 113–116. [CrossRef]

509. Iannello, A.; Ahmad, A. Role of antibody-dependent cell-mediated cytotoxicity in the efficacy of therapeutic anti-cancer monoclonal antibodies. *Cancer Metastasis Rev.* **2005**, *24*, 487–499. [CrossRef] [PubMed]