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REVIEW ARTICLE

Antibiotic Resistance and Emerging Alternatives for Controlling Foodborne Pathogens

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A B S T R A C T

Antibiotic resistance in foodborne pathogens poses a significant challenge to public health and food safety. Major foodborne pathogens, such as *Salmonella*, Campylobacter, *Escherichia coli*, and *Listeria monocytogenes*, are commonly linked to contaminated meat, poultry, dairy products, and fresh produce, and their resistance to antibiotics is a growing concern. This resistance arises through genetic mechanisms like mutations and horizontal gene transfer, facilitated by resistance factors such as efflux pumps and biofilm formation. Geographical and temporal trends reveal disparities in resistance levels, with higher prevalence in low- and middle-income countries due to unregulated antibiotic use. Both agricultural and clinical antibiotic applications contribute to resistance, necessitating urgent intervention. Alternatives to antibiotics offer promising strategies to control foodborne pathogens. Bacteriophages, which target specific bacteria, are already applied in food safety but face limitations like phage resistance. Probiotics and prebiotics enhance gut health and inhibit pathogens, with effective combinations demonstrating synergistic effects. Antimicrobial peptides (AMPs) from natural and synthetic sources offer a broad spectrum of activity, while essential oils and plant extracts provide natural antimicrobial solutions in food preservation. Nano-based interventions, such as silver and chitosan nanoparticles, show potential but raise concerns about toxicity and environmental impacts. Vaccination strategies targeting livestock and humans offer a proactive approach but face challenges in development and implementation. CRISPR/CAS systems enable precise gene editing to eliminate resistance genes, while emerging solutions like lysozymes and competitive exclusion products further expand the toolkit. Applications of these alternatives span food processing, preservation, and animal agriculture, significantly reducing pathogen prevalence. Regulatory and policy frameworks must support their integration into food systems. Global collaborations and innovations are crucial for combating antibiotic resistance effectively, thereby ensuring safer food production and enhanced public health protection.

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INTRODUCTION

Foodborne pathogens include foodborne bacteria, viruses, and parasites that are capable of causing disease in humans. Such organisms are a global public health concern since they cause a significant level of morbidity and mortality as well as economic loss (Akinsemolu & Onyeaka, 2024). According to the World Health Organization (WHO), every year around 600 million people get sick due to foodborne diseases, resulting in around 420,000 deaths annually (Oduoye *et al.,* 2024). These foodborne pathogens can be transmitted to people through the ingestion of infected meat, milk, or eggs, and contamination from the environment, such as water runoff from farms (Gobena *et al.,* 2024; Yitbarek, 2024). These infections cut across all social groups but are most rife among children, pregnant women, the elderly, and immune-compromised individuals (Mfeka, 2021). Antibiotics have played a significant role in the control of foodborne illnesses caused by bacterial pathogens since the mid-20th century (Lawani-Luwaji, 2024). These drugs work by inhibiting or killing bacteria within the body, making the drugs effective against infections and alleviating the symptoms (Karunarathna *et al.,* 2024).

Antibiotics are widely used in both clinical and agricultural settings. Clinically, they are used to manage intensive bacterial infections, including those caused by foodborne pathogens, which include *Salmonella*, *E. coli*, *Campylobacter,* etc. In agriculture, antibiotics are also used to treat diseases in livestock, as a preventive measure as well as for growth stimulation. The use of antibiotics for agricultural purposes is one of the major factors contributing to antibiotic resistance and dissemination patterns (Yaqub *et al.,* 2024). Antibiotics are used not only to treat illnesses but also in healthy animals where they are used as prophylactic drugs or growth enhancers, and their usage is justified as they improve production. The non-therapeutic use of antibiotics fosters and selects for the survival and expansion of resistant bacteria.

Antibiotic resistance (AR) occurs when bacteria develop mechanisms that allow them to survive and proliferate despite the presence that would normally inhibit or kill them (Bai *et al.,* 2024). While there are serious illnesses for which antibiotics are irreplaceable, their extended and misused application in practice and agriculture has triggered a surge of AR. To address this challenge, a balanced and integrated strategy that optimizes the available treatment options and at the same time seeks to protect the antibiotic efficacy for the future is mandatory (Ahmed *et al.,* 2024; Legrand *et al.,* 2024). Antibiotic resistance in foodborne bacterial pathogens is not only widespread but also one of the most significant global health challenges, joined with climate change further complicates the control of infectious diseases, including those caused by foodborne pathogens. Shifts in temperature, extreme weather, and humidity can alter the survival, distribution, and transmission pattern of pathogenic microbes, potentially increase the risk of outbreaks and reducing the predictability of disease management strategies.

People can suffer severe and sometimes life-threatening infections due to pathogens that most of antibiotics cannot help in treating the diseases (Lewies *et al.,* 2015). Foodborne pathogens such as *Salmonella* spp., *E. coli*, *Campylobacter* spp., and *Listeria monocytogenes* have constantly developed resistance to numerous antibiotics, including those that are considered to be of utmost importance in modern medicine (Grudlewska-Buda *et al.,* 2023). Strains of these pathogens that are multidrug-resistant (MDR) have been isolated from foodstuffs, from agricultural and clinical settings, making treatment guidelines overly complex and leading to catastrophic health consequences (Alara & Alara, 2024). One of the chief determinants of AR in foodborne bacteria is the misuse of antibiotics in food-producing animals. The globalized nature of the supply chain of food has made it easy for antibiotic-resistant bacteria to be transmitted across nations, making AR a global phenomenon (Tang *et al.,* 2017; Sagar *et al.,* 2023).

When faced with the problem of antibiotic resistance, it is necessary to take multidisciplinary and cooperative action. Together, public health agencies, scientists, and politicians can strengthen surveillance systems, improve antibiotic practices, and come up with alternative means for pathogen eradication (Muteeb *et al.,* 2023). At the same time, awareness campaigns are useful to promote the most appropriate behavior of consumers and providers of healthcare services (Eruaga, 2024). The increased use of antibiotics has generated concern regarding the emergence of antibiotic-resistant pathogens, which necessitate the use of bacteriophages. These are viruses that invade bacterial cells, and bacteriophages have shown promise in the targeted approach to foodborne pathogens. Advisory bodies like the Food and Drug Administration (FDA) have approved the use of bacteriophage-based interventions (Qiao *et al.,* 2024).

Fermented products: containing essential oils or phenolic compounds have also been shown to possess some antimicrobial activity against foodborne pathogens. There has been an increased interest in these natural antimicrobials as additives in food preservatives and coatings for fresh-cut produce (Di Matteo *et al.,* 2024). Today, high-pressure or UV light treatment has been developed as a safe and effective method to reduce bacterial contamination. Other crucial aspects in the control of foodborne pathogens include proper biosecurity measures and hygiene practices in both agriculture and the food industry (Ndraha *et al.,* 2024). This review aims to highlight the major foodborne pathogens, their mechanisms of action, antimicrobial resistance, and alternatives to antibiotics for controlling foodborne pathogens.

Mechanism of antimicrobial resistance: This mechanism includes the production of enzymes like β-lactamases that degrade antibiotics, modification of antibiotic target sites (e.g., DNA Gyrase or mutation in ribosomal proteins), and activation of efflux pumps that expel antibiotics from the cell. Additionally, changes in membrane permeability reduce antibiotic uptake, and biofilm formation provides a physical barrier protecting bacteria from antimicrobial agents. Many of these resistance traits are carried on mobile genetic elements such as plasmids, transposons, and integrons, enabling rapid horizontal gene transfer within and between bacterial species (Fig. 1) (Table 1). The widespread use of antibiotics in food animals for growth promotion and disease prevention has accelerated the emergence and dissemination of these resistance mechanisms, posing a significant threat to food safety and public health.

Major foodborne pathogens: Foodborne pathogens pose major public health concerns worldwide and lead to millions of illnesses each year. These include bacteria,

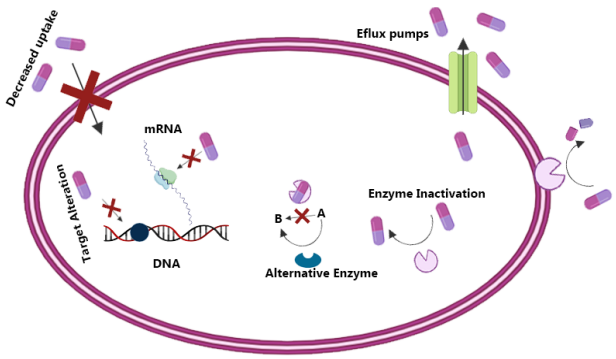

Fig. 1: Antibiotic efflux pump and enzymatic inactivation (Retrieved from biorender) (Kim & Ahn, 2022).

Table 1: Examples of significant mechanisms of antimicrobial resistance together with the corresponding bacteria and antimicrobials

Antibiotic resistance mechanism	Classical examples	Antibiotics affected	Examples of Bacteria utilizing this mechanism	References
Antibiotic destruction	β lactamases Penicillinases	Penicillin, narrow spectrum cephalosporins	*S. aureus* *N. Gonorrhoeae* *Haemophilus Influenzae* *Enterobacteriaceae*	(Vilvanathan, 2021)
	Extended- β Spectrum lactamases	Penicillin, first-, second, third-generation cephalosporins and aztreonam	*Enterobacteriaceae* *Pseudomonas aeruginosa*	(Mizrahi *et al.,* 2020)
	AmpC enzymes	Penicillin, first, second, third-generation cephalosporins, aztreonam, and cephamycins	*Enterobacteriaceae* *Acinetobacter* spp. *Pseudomonas* spp.	(Doern, 2021)
	Carbapenemases	Carbapenems and almost Hydrolysable β-lactams	*Enterobacteriaceae*	(Cooper *et al.,* 2021)
Antibiotic modification	Aminoglycoside Modifying Enzymes (AMEs)	Aminoglycosides	numerous bacteria	(Thacharodi & Lamont, 2022)
	Chloramphenicol acetyltransferases (CATs)	Chloramphenicol	numerous bacteria	(Biswas *et al.,* 2012)
Modifications of antibiotic-activating enzymes	Mutations in the nitroreductase genes *nfsA* and *nfsB*	Nitrofurantoin	*Enterobacteriaceae*	(Christaki *et al.,* 2020)
Target replacement or bypass	Penicillin-Binding Protein (PBP) replacement	β lactams	*Streptococcus pneumoniae*	(Fani *et al.,* 2012)
	Acquisition of a novel Penicillin-Binding Protein (PBP)	β lactams	*S. aureus*	(Wacnik *et al.,* 2022)
	Replacement of the terminal D-Alanine D-Alanine Moiety of the peptidoglycan precursors	Glycopeptides	*Enterococci* *S. aureus* (rarely)	(Wacnik *et al.,* 2022)
	Acquisition of a novel dihydrofolate reductase	Trimethoprim	Gram-negative bacteria *Staphylococci* *L. monocytogenes*	(Faltyn *et al.,* 2019)
	Acquisition of a novel dihydropteroate synthase	Sulfonamides	Gram-negative bacteria	(Gauba & Rahman, 2023)
	Utilization of folic exogenous acid	Trimethoprim Sulfonamides	*Enterococci*	(Fernández-Villa *et al.,* 2019)
Target site alteration (mutation or enzymatic alteration)	Mutations of the 23SrRNA	Linezolid	*Enterococci, S. aureus*	(Yang *et al.,* 2025)
		Macrolides Lincosamides Streptogramin B	numerous bacteria	(Petinaki & Papagiannitsis, 2019)
	Mutations in the bacterial Gyrase or Topoisomerase IV	Quinolones	numerous bacteria	(Badshah & Ullah, 2018)
	Mutations in the RNA Polymerase β subunit	Rifampicin	numerous bacteria	(Ning *et al.,* 2021)
	Mutational or Recombinational changes in the Dihydrofolate Reductase gene	Trimethoprim	numerous bacteria	(Sánchez-Osuna *et al.,* 2020)
	Mutational or recombinational changes in the dihydropteroate synthase gene	Sulfonamides	numerous bacteria	(Capasso & Supuran, 2019)
	Methylation of the 23SrRNA by erm genes	Macrolides Lincosamides Streptogramin B	numerous bacteria	(Cattoir & Leclercq, 2017)
	Methylation of the 23SrRNA by the cfr gene	Linezolid	*S. aureus*	(Yang *et al.,* 2025)
		Chloramphenicol Clindamycin	*Staphylococci*	(Vester, 2018)
Target site protection	Ribosomal Protection Proteins (RPPs)	Tetracyclines	numerous bacteria	(Yadav *et al.,* 2021)
	Qnr proteins	Quinolones	numerous bacteria	(Ruiz, 2019)
Target overproduction	Overproduction of Dihydrofolate Reductase	Trimethoprim	*E. coli*	(Yu, 2024)
Decreased permeability of the bacterial outer membrane	Mutations affecting the expression or function of porins	Hydrophilic antibiotics (e.g., β lactams, quinolones, tetracyclines, chloramphenicol)	Gram-negative bacteria	(Gauba & Rahman, 2023)
Antibiotic efflux	Multidrug efflux pumps	A wide range of antibiotics	numerous bacteria	(Blanco *et al.,* 2016)
	Substrate-specific efflux pumps	Tetracyclines	numerous bacteria	(Henderson *et al.,* 2021)
		Macrolides	*Streptococci* and other gram-positive organisms	(Lekshmi *et al.,* 2018)
		Chloramphenicol	numerous bacteria	(Seukep *et al.,* 2022)
Global cell adaptations	Mutations in genes implicated in phospholipid metabolism and those encoding regulatory mechanisms governing cell envelope homeostasis	Daptomycin	*Enterococci*	(Johnston, 2021)
	Gene mutations affecting important cell membrane processes and cell wall alterations	Daptomycin	*S. aureus*	(Poshvina *et al.,* 2023)
	Cell wall thickening is caused by mutations in genes that are components of regulatory mechanisms that regulate cell envelope homeostasis.	Intermediate susceptibility to glycopeptides	*S. aureus*	(Poshvina *et al.,* 2023)

viruses, parasites, and prions that, at one point or another during the production, processing, and preparation chain, contaminate foods (Pal & Ayele, 2020). Major foodborne pathogens such as *Salmonella*, *E. coli*, *L. monocytogenes*, *Campylobacter*, *Clostridium botulinum*, and Norovirus have been responsible for severe diseases, with some of them being fatal without timely intervention (Afreen & Bağdatlı, 2021). *Salmonella* is the major cause of bacterial foodborne illnesses worldwide. This pathogen is highly common in raw or undercooked poultry, eggs, and unpasteurized milk. Salmonellosis is caused by the ingestion of contaminated food and is manifested by diarrhea, abdominal cramps, fever, and vomiting. While the illness is usually self-limiting, severe infections may be present in immunocompromised individuals, children, and the elderly. Good hygiene practices and proper cooking of food are some of the necessary preventive measures (Ehuwa *et al.,* 2021).

Another major foodborne pathogen is *E. coli*, particularly the Shiga toxin-producing strain, O157:H7; this is normally associated with undercooked ground beef and raw vegetables, and also with contaminated water (Singha *et al.,* 2023). Symptoms also include severe diarrhea, with severe abdominal pain and vomiting, leading to serious complications such as hemolytic uremic syndrome. Kidney failures caused by Hemolytic Uremic Syndrome (HUS) may be manifested, which can affect children and older adults. Preventing *E. coli* contamination requires proper cooking to avoid cross-contamination by thoroughly washing produce (Possas & Pérez-Rodríguez, 2023).

L. monocytogenes is a kind of bacteria that can be particularly dangerous to pregnant women, newborn babies, and older adults. It can be found in refrigerated, ready-to-eat foods such as deli meats, soft cheeses, and smoked seafood. Infection with *Listeria* causes listeriosis, mostly leading to serious complications like meningitis, sepsis, and pregnancy complications, including miscarriage or stillbirth. Refrigeration does not kill this bacterium, so strict adherence to safe food storage and handling is very important (Wang *et al.,* 2021a). *Campylobacter* is a major cause of bacterial diarrhea worldwide and is commonly associated with raw or undercooked poultry, unpasteurized milk, and contaminated water (Rehman, 2022). The infection generally presents with diarrhea, abdominal pain, fever, and nausea. Infection is usually self-limiting, but complications include Guillain-Barré syndrome, a rare neurological condition. Proper cooking of poultry and prevention of cross-contamination during food preparation are important modes of prevention (Akinsemolu & Onyeaka, 2024).

C. botulinum produces a neurotoxin that is responsible for a rare but potentially lethal disease called botulism. It mostly occurs due to improperly canned or preserved foods. Symptoms include blurred vision, difficulty swallowing, muscle weakness, and, in severe cases, respiratory failure. Good food preservation practices and immediate disposal of damaged cans are very important safety considerations (Poulain & Popoff, 2019). Other leading contributors to foodborne illness are viruses. Norovirus is very contagious, acquired via food, water, or by touching any surface contaminated by an infected person. vomiting, diarrhea, nausea, and stomach cramps are the symptoms of Norovirus. It leads to outbreaks in group environments such as schools and cruise ships. Prevention includes good hand hygiene and cleaning of surfaces (Harris & Dabritz, 2024).

Other notable pathogens include *Staphylococcus aureus*, which elaborates heat-stable enterotoxins that can cause the rapid onset of food poisoning symptoms (Bao & Wu, 2024), and *C. perfringens*, whose outbreaks are commonly associated with improperly stored food (García *et al.,* 2019). *Bacillus cereus* is another cause of two notable types of illness: one causing diarrhea and the other causing emesis; these have been associated with rice dishes and improperly cooked foods (Rodrigo *et al.,* 2021). Among others, *Toxoplasma gondii* is a protozoan parasite found in undercooked meat that creates significant risks to pregnant women and people with immunocompromised conditions (Ducrocq *et al.,* 2021). Mild flu-like signs to severe neurological complications are included in the symptoms. *Cryptosporidium* and *Giardia lamblia* are transmitted through contaminated water and thus are also among the significant contributors to foodborne parasitic infections, causing protracted diarrhea (Rossi *et al.,* 2024).

Alternatives to antibiotics

Small Molecules (SMs): With drug-like qualities, SMs are non-peptide chemical compounds that may interact with biological molecules, such as proteins and nucleic acids, and change how they normally operate. Their strong hydrophilicity and low molecular weight (~200–500 Da) enable efficient absorption through both host and pathogen barriers. SMs can be altered to improve their mass applicability and antibacterial effectiveness. The creation of antibacterial medications and the discovery of SM candidates that prevent bacterial growth in whole-cell tests or the action of a primary bacterial enzyme or protein are two typical uses for high-throughput screening (HTS) (Alcalde-Rico *et al*., 2016). Targeting bacterial membranes, SMs have a minimal possibility for pathogens to acquire resistance, enhance the effectiveness of several antibiotics, and work well against biofilms and slow-growing bacteria. Plant pathogens such as Xanthomonas species, Erwinia tracheiphila, Acidovorax citrulli, and Salmonella infections have recently been treated using SMs (Deblais *et al*., 2019; Kathayat *et al*., 2020). The activity of SMs within the recipient's body, the possibility of binding to non-target molecules within the human body, and structural design limits are some of their functional limitations, despite their positive impacts. These drawbacks include the inability to precisely identify the modifying proteins that SMs should target, the difficulty of engineering SMs to target unstructured disordered polypeptides, and their poor affinity to bind or alter protein surface mediators (Gurevich & Gurevich, 2014).

Quorum-sensing/Antivirulence inhibitors: Bacterial cells use a technique known as quorum sensing (QS) to communicate with one another and adjust their density and activity in response to their surroundings (Gao *et al.,* 2023). Bacteria secrete extracellular signaling molecules known as autoinducers (AIs), which play a crucial role in regulating the production of virulence factors, enzymes, biofilm formation, stress adaptation, secondary metabolite

synthesis, and swarming motility. AIs are released into the environment by active transport or diffusion to facilitate effective bacterial cell-to-cell communication. AIs accumulate in the environment as the density of bacteria increases, and once this exceeds a specific threshold, bacteria employ them as extracellular signaling molecules to coordinate their gene expression and modify their density. Three basic ideas underlie QS systems: (1) the density of bacterial cells; (2) receptors produced in the cytoplasm or on the membrane; and (3) the recognition of AIs not only stimulates the expression of genes necessary for cooperative behaviors but also increases the bacterial synthesis of AIs. Bacterial QS systems are generally divided into three categories: (3) oligopeptide-two-component-type QS, (2) LuxI/LuxR-type QS, and (3) luxS-encoded autoinducer-2 (AI-2) QS (Dutta *et al.,* 2021). The AIs are divided into three categories: furanosyl borate diester, which is used by both Gram-positive and Gram-negative bacteria, oligopeptides, and acylated homoserine lactones (AHLs), which are used by Gram-negative bacteria (Koley *et al.,* 2023).

Bacterial biofilm development and pathogenicity are decreased when the connecting mechanism between bacterial cells is disrupted. As a result, several tactics have been created to break this link and manage bacterial infections that are dependent on QS. Low-mass substances with excellent selectivity for the QS regulator and no harmful side effects on the bacteria or a possible eukaryotic host are known as ideal QS inhibitors (QSIs). They also need to be very effective and chemically stable. QSIs work through a variety of mechanisms, including (1) inhibiting AI synthesis; (2) antagonistic interactions with AI receptors; (3) blocking targets downstream of receptor binding; (4) using antibodies to sequester AIs; (5) breaking down AI-catalytic antibodies (abzymes) or enzymes (such as lactonases, acylase, and oxidoreductase); (6) attenuating AI secretion/transport; and (7) competing with autoinducing signal molecules to bind to the transcriptional protein regulators of bacterial QS systems.

One of the key limitations of QSIs is the potential development of resistance, as bacteria possess multiple QS systems and may adapt mechanisms to bypass or resist QSI activity. . By acquiring mutations in the amino acid residue of the LuxR protein regulator, which codes for virulence factors, motility, biofilm formation, and the manufacture of antibiotics, gram-negative bacteria can avoid the effects of QSIs. (1) Indole signaling: In a nutrient-poor environment, *E. coli* and *Salmonella*'s QS systems react to indole by producing virulence factors, plasmid stability, adaptability, and antibiotic resistance (Escobar-Muciño *et al.,* 2022). Under these circumstances, indole and AIs compete for binding to the SdiA transcriptional regulator's AHL domain. (2) Disturbance of microbiota homeostasis: QSIs disrupt human microbiota homeostasis by influencing human microflora activities such as adhesion, biofilm formation, and the synthesis of antimicrobial metabolites, as well as by causing the dispersion of AI-2 signaling (Juszczuk-Kubiak, 2024).

Probiotics*:* When given in sufficient quantities, probiotic microorganisms that coexist in a symbiotic relationship with the host perform a number of biological tasks and offer health advantages (Ahire *et al.,* 2024). They fall into four groups: next-generation probiotics, viable and active probiotics, viable/non-active probiotics, and dead/nonviable probiotics (Silva *et al.,* 2020). Few studies have examined probiotics' antibacterial qualities as innovative antibiotic substitutes, despite a large body of research on their biological qualities. Viable and active probiotics benefit the host's health by increasing the concentration of hydrogen ions in the gut (Liu *et al.,* 2025), improving the synthesis of vital vitamins and enzymes, generating antimicrobial compounds, restoring intestinal microbiota following diarrhea, lowering serum cholesterol, strengthening the immune system, generating antioxidants, lowering food allergy sensitivities, and improving lactose and calcium absorption. Saliva enzymes, gastric fluid (acid and enzymes), bile salts, competitive gut bacteria, and inhibiting Gastrointestinal tract (GIT) conditions should all be avoided by them as they are moving from the mouth to the gut (Han *et al.,* 2021).

Postbiotics and parabiotics, often known as dead or nonviable probiotics, are viable probiotics that lack metabolic activity (Nataraj *et al.,* 2020). They are subjected to harmful stressors such as excessive O_2 supplementation, high osmotic pressure, temperature, and severe pH levels (Bustos *et al.,* 2025). As inactive viable probiotics, *Bacillus* species, including *B. coagulans*, *B. subtilis*, *B. clausii*, and *B. licheniformis* are utilized in human diets and to treat intestinal and urinary issues (Sadrimovahed & Ulusoy, 2024). Because *Bacillus* species generate bacteriocins that are efficient against both Gram-positive and Gram-negative bacteria and fungi present in food, they are frequently utilized as natural preservatives in the food business. Dead/nonviable probiotics can use dead/nonviable probiotic cells to defend the body against pathogenic microorganisms. To generate nonviable, inviable, inactivated, or dead probiotic cells, many methods are used, such as ionizing radiation (10 kGy), heat treatment at 121 °C for 560 minutes, and ultraviolet (UV) radiation exposure for 530 minutes (Helmy *et al.,* 2023). Among the structural and functional alterations linked to the inactivation process are protein denaturation, enzyme inactivation, nucleotide destruction, DNA breakage, and cell structural deformation. This is known as parabiotic/postbiotics, and it is seen as a new frontier in both the food business and microbial medicine (Piqué *et al.,* 2019).

By decreasing pathogenic cell adhesion and translocation into intestinal cells, heat-inactivated *L. plantarum* has reduced *S. enterica* infection in mice's liver, spleen, and blood, among other organs (Tao *et al.,* 2021). Heat-inactivated *Leuconostoc mesenteroides* cells inhibited the invasion of Caco-2 cells by L. monocytogenes by boosting the host immunological responses (Yap *et al.,* 2024). Yogurt that has been inactivated by heat kill prevents cytokines from rupturing the human intestinal epithelial cells' barrier. It has been discovered that inactivated *L. paracasei* and *L. rhamnosus* cells can prevent stomach and colon cancer by enhancing cancer cell apoptosis and decreasing proliferative activity. Gram-positive bacteria produce levochoic acid (LTA), a microbe-associated molecular pattern (MAMP) that is recognized by the Toll-like receptor 2 (TLR-2) on the surface of intestinal enterocytes (Frosali *et al.,* 2015). An inflammatory cytokine response is triggered when LTA

binds to TLR-2, starting cellular signaling. By preventing the production of new biofilms and eliminating existing ones, LTA produced from probiotic *Lactobacillus* strains has anti-biofilm characteristics against oral and enteric pathogens, including *S. mutans*, *S. aureus*, and *E. faecalis* (Giordani *et al.,* 2021). Compared to live probiotics, prebiotics, and postbiotics have a number of benefits, such as being simpler to produce and store, having unique mechanisms of action shown in Fig. 2, having better accessibility of MAMP when it comes into contact with pattern recognition receptors (PRR), and having a higher chance of triggering specific reactions through particular ligand–receptor interactions (Li and Wu, 2021).

Antimicrobial Peptides (AMPs): The innate immune systems of many different animals, plants, and microbes depend heavily on AMPs, which are spontaneously generated by immune cells (Li *et al.,* 2021). In addition to biological processes, including immunological regulation, angiogenesis, anticancer activity, and wound healing, they exhibit a broad range of antimicrobial action against bacteria, fungi, viruses, and parasites (Verhoef *et al.,* 2019). A component of the innate immune system, AMPs have several advantages over antibiotics, including the ability to act on multiple target sites on the intracellular targets and plasma membranes of pathogenic bacteria, have strong killing activity against drug-resistant bacteria, save time and energy compared to antibody synthesis via acquired immunity, and reach the target sites more quickly than immunoglobulin (Seixas *et al.,* 2022). Based on their protein structure, origins, net charge, and amino acid sequences, AMPs are divided into several classes. These subgroups include cationic α-helical AMPs, which are ≤40 amino acids long (50 percent hydrophobic) and have a charge of +2 to +9 with the C-terminus amidated, and anionic AMPs, which have 5–70 amino acid residues with a net charge range of −1 to −8. The stability of β-sheet AMP and biological processes depend heavily on cationic AMPs, which are peptides with 2–8 cysteine residues that form 1-4 pairs of intramolecular disulfide bonds (Koehbach & Craik, 2019).

Tryptophan, arginine, proline, histidine, and glycine are among the amino acids found in extended cationic AMPs, which are devoid of the typical secondary structures. The development of harmful bacteria and fungi is significantly impacted by fragments of antimicrobial proteins with a broad-spectrum bactericidal activity, including lysozyme (Starling, 2017). Numerous antimicrobial peptides that have been extracted from various sources have demonstrated efficacy against a broad range of harmful microorganisms described in Table 2. Both the kind and nature of AMPs and the bacterial infections they target are major determinants of their antibacterial action. AMPs have the ability to kill bacteria directly by disrupting their membranes, which ultimately results in the death of the bacterium, or indirectly by modifying the immune system (Erdem Büyükkiraz & Kesmen, 2022).

Nanoparticles (NPs): Because of their distinct chemical and physical properties, nanoparticles (NPs) as an antibiotic substitute for managing multidrug-resistant microbes. NPs are simple to interact with target organisms

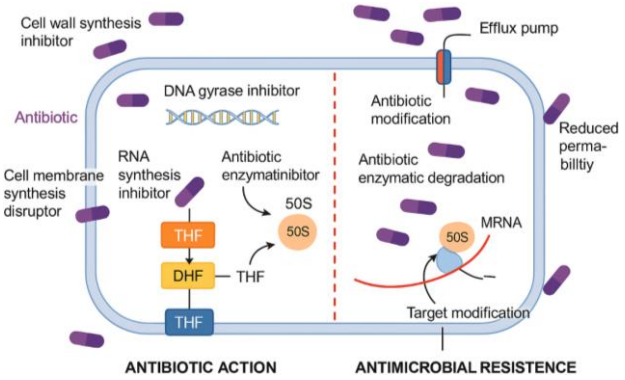

Fig. 2: Probiotics as an antibiotic.

Table 2: Antimicrobial peptides (AMPs), their sources, structures, and target pathogens.

AMP Name	Structure Type	Source	Target Microorganisms	Notable Features	References
Magainin-2	α-helix	Frog	*P. gingivalis, F. nucleatum, P. intermedia, E. coli, S. aureus*	Broad-spectrum activity	(Genco *et al.,* 2003)
Cecropin & P1	α-helix	Silk moth (Cecropin), Pig (P1)	*E. coli ML35p, S. aureus, B. subtilis, M. luteus, P. aeruginosa, S. Typhimurium, S. marcescens*	High efficacy against Gram-positive & Gram-negative bacteria	(Franco *et al.,* 2013)
Apo-lactoferrin	α-helix	Bovine & Human	*E. coli O157:H7*	Found in milk; strong anti-*E. coli* action	(Franco *et al.,* 2013)
Melittin	α-helix	Bee venom	*S. salivarius, S. mitis, S. mutans, S. sanguinis, S. sobrinus, L. casei, E. faecalis*	Potent oral pathogen inhibitor	(Leandro *et al.,* 2015)
Temporins A & L	Not specified	Frog	*MRSA, B. megaterium Bm11, S. aureus Cowan I, E. coli D21*	Effective against resistant strains	(Wang *et al.,* 2021b)
Buforin II	α-helix	Toad	*B. subtilis, S. aureus, E. coli, S. Typhimurium, E. coli ML35p, L. monocytogenes*	Penetrates bacterial cells	(Steinberg *et al.,* 1997).
Clavanin A	α-helix	*Styela clava* (tunicate)	Same as above (Buforin II)	Marine AMP with broad activity	(Steinberg *et al.,* 1997).
Protegrin-1	β-sheet	Pig & Human	*P. aeruginosa, MRSA*	β-sheet; strong pore-forming activity	(Han *et al.,* 2024)
Tachyplesin-I	β-sheet	Horseshoe crab	*S. Typhimurium*	Stable β-structure AMP	(Han *et al.,* 2024)
Hepcidin	β-structure	Human	*S. aureus, S. epidermidis, E. coli*	Iron-regulating hormone with AMP activity	(Michels *et al.,* 2015).
Daptomycin	Cyclic lipopeptide	*Streptomyces roseosporus*	*MRSA*	Clinical antibiotic	(Blaskovich *et al.,* 2018)
Nisin	Lantibiotic	*Lactococcus lactis*	*S. pneumoniae, Enterococci, C. difficile, MRSA*	Widely used food preservative and clinical interest	(Shin *et al.,* 2016)
Peptides P1–P3	Short peptides	*L. rhamnosus GG* (in Chicken)	*Avian pathogenic E. coli (APEC)*	Novel peptides with activity against poultry pathogens	(Kathayat *et al.,* 20 21)

because of their tiny size (1–100nm) and vast surface area. Their diverse chemical structures and ability to be produced from a variety of sources enable a range of functions. By focusing on important active areas in pathogens, NPs can partially or completely limit their antibacterial activity (Zaidi *et al.,* 2017). Metal and metal oxide are examples of inorganic NPs that have bactericidal action against bacteria through a variety of methods, earning them the moniker "nanobactericides." The structural elements and growth rate of bacterial cells determine their sensitivity to NPs. While non-porous cell walls function as barriers to penetration, gram-positive bacteria's permeable and negatively charged cell walls make them more vulnerable to NPs. Because fast-growing bacteria express distinct stress-response genes, slow-growing bacteria are more vulnerable to NPs (Khan & Al-Khedhairy, 2017).

Damage to the cell membrane, inhibition of electron transport and oxidative phosphorylation, modification of bacterial metabolism through disruption of enzymes, DNA, and ribosomes, inhibition of biofilm formation, oxidative stress, and elicitation of host immune responses are all part of NPs' deadly effects on microbial cells (Jagadeeshan & Parsanathan, 2019). The accumulation of silver nanoparticles (Ag) in human organs, oxidative damage caused by CuO, ZnO, or TiO2 NPs, accumulation of metallic NPs in tissues that may cause renal damage and liver or lung toxicity, the absence of a well-described standard technique that is not influenced by NP properties, and the possibility of bacterial resistance to NPs after exposure to metal NPs or metal-oxide NPs are some of the major limitations of NPs (Dianová *et al.,* 2022).

Essential Oils (EOs): EOs are intricate natural mixtures with anywhere from 20 and 60 different components in different ratios. Terpenes, terpenoids, and aromatic and aliphatic groups from various natural sources make up the majority of their constituents (85%) (Chouhan *et al.,* 2017: Şen & Gençer, 2023)). Many pathogens, including *P. aeruginosa*, *S. pyogenes*, *S. mutans*, *S. sanguis*, *S. salivarius*, and *E. feacalis*, have been demonstrated to be antagonistically affected by EOs. Extracted from different sources, thymol and carvacrol have demonstrated the ability to inhibit the growth of *S. aureus*, *C. hystoliticum, C. perfringens*, *E. coli* O157:H7, *S. Typhimurium*, *S. Enteritidis*, and *L. monocytogenes*. *P. aeruginosa*, *K. pneumoniae*, *E. coli* (DH5α), *E. coli* (MTCC 723), S. *Typhimurium*, *S. aureus*, *S. epidermidis*, and *S. mutans* have all been demonstrated to be inhibited by linalyl acetate, α-terpineol, nerol, and *G. citrata* Ehrh (Verma *et al.,* 2016; Bajer *et al.,* 2017).

Because of their hydrophobic properties, EOs and their constituents can interact with the lipids found in microbial cell membranes. Bacterial cell death, cytoplasmic membrane breakdown, and leakage of vital intracellular components can result from their ability to sensitize cells and seriously damage membranes. By binding to them, lowering virulence factors linked to cell walls, and translating certain target microorganism regulatory gene products, EOs can also directly target the production of biofilms. Because food ingredients contain a lot of fat, proteinaceous, and sugary substances that might interfere with their action, using EOs in food preparation decreases their availability as antimicrobial agents. Furthermore, EOs given to food have doses and concentrations that are 10–100 times lower than those seen in vitro, which reduces their effectiveness. Additionally, adding EOs to food products may alter their physical characteristics, including flavor and odor (Omonijo *et al.,* 2018).

Animal studies have shown that essential oils (EOs) are natural substitutes for antibiotics as part of livestock diets. Pan *et al.* (2023) discussed the biological effects of EOs, like antimicrobial, antioxidant, and anti-inflammatory activity, and pointed out their capability to enhance feed proficiency, boost immune functions, and decrease pathogenic burden in livestock, particularly in swine and poultry. Mo *et al.* (2022) showed that microencapsulated essential oils were superior to unencapsulated oils and antibiotics in weaning piglets. These benefits included better gut morphology, greater integrity of intestinal barrier function, and an improved gut microbiota status with more beneficial bacteria. In the same context, Giannenas *et al.* (2013) summarized a wide number of trials and found that EOs such as thymol, carvacrol, and cinnamaldehyde are responsible for improved growth performance, feed conversion, and microbial equilibrium in the poultry, pig, and ruminant gastrointestinal tract. Simitzis (2017) elaborated on this by highlighting the function of EOs in not only enhancing growth and immunity but also the quality of meat and products resulting from it, such as via increased oxidative stability and flavor. Lastly, Coles *et al.* (2023) conducted a review on several studies of broiler chickens and concluded that supplementation with essential oils in the diet markedly decreased the prevalence and severity of necrotic enteritis, a serious gut disease, by inhibiting Clostridium perfringens while enhancing gut health without impairing performance. Together, these studies prove that EOs can be a powerful and natural approach to replace antibiotics in animal feed to improve animal health, growth, and product quality and reduce the risk of antimicrobial resistance.

Bacteriophages: Bacteriophages, viruses that infect bacteria, have also been contemplated as specific biocontrol agents. They can substantially reduce bacterial populations without eliminating other useful microorganisms (Ke *et al.,* 2024). Since phages are very active against antibiotic-resistant bacteria, they have been exploited to control *L. monocytogenes* and *C. jejuni* in food products (Yang *et al.,* 2024). Phages can also be used for surface decontamination if applied at the time of food processing (Hill, 2019). Various Animal studies have shown the promise of bacteriophages as alternatives to antibiotics, especially against multidrug-resistant bacteria.

The research favors phage therapy as a specific and flexible method with limited effect on positive microbiota. Likewise, Joerger (2003) indicated that bacteriophages hold promise in poultry models by targeting *Salmonella* and *Campylobacter* effectively, which reduces colonization and enhances food safety, but without the downfalls of developing antibiotic resistance. In a systematic review by Taati Moghadam *et al.* (2020) reported evidence from various models of animals (mice, rabbits, and rats), demonstrating that phage therapy can effectively decrease the severity of wound infection, bacterial load, and inflammation triggered by multidrug-

resistant bacteria like *A. baumannii* and *K. pneumoniae*. Kutateladze and Adamia (2010) reporting on effective animal trials in which phage treatment precluded or cured infection by antibiotic-resistant strains with low toxicity and good tolerability. Plumet *et al.* (2022) surveyed several animal model studies of *S. aureus* infections, namely skin, bone, and systemic infections. The phage therapy in these models produced significant decreases in bacterial burden, enhanced healing rates, and, in a few instances, superior efficacy than conventional antibiotic regimens. Taken overall, these trials very clearly suggest that bacteriophages are a viable alternative or adjunct to antibiotics in veterinary medicine and could be an important weapon in the war against antibiotic resistance.

Organic Acids: Organic acids have also been widely investigated as possible natural alternatives to antibiotic growth promoters in agriculture. Saki *et al.* (2012) found that supplementing broiler diets with organic acids highly improved growth performance, intestinal integrity through the suppression of pathogenic bacteria like *E. coli*, and beneficial microorganisms like *Lactobacillus*, and enhanced immune function, thus suitable for organic poultry farming (Saki *et al.,* 2012). Khan *et al.* (2022) further proved that organic acids such as formic, propionic, lactic, and butyric acids lower gut pH, enhance nutrient digestibility, increase enzyme activity and gut morphology, and exhibit strong antimicrobial, antifungal, and immunomodulatory effects and thus can help in sustainable poultry production considering growing pressure on antibiotic usage (Khan *et al.,* 2022). Mroz (2005) showed that in pigs, organic acids enhance feed intake, protein digestion, daily gain, and feed efficiency, especially under unsatisfactory hygienic conditions, by lowering gastric pH and inhibiting pathogens such as *Salmonella* and *Clostridium*, as well as enhancing intestinal barrier functions and immune responses (Mroz, 2005).

Common organic acids (OAs) have a complex mode of action, which may be partly due to factors such as inhibiting the development of pathogenic microbes in the gastrointestinal tract by reducing gut pH, reducing gastric emptying rates, and maintaining endogenous enzyme secretion, mineral chelation and stimulation on intermediary metabolism, and facilitation of proper digestion due to lower gastric pH and enhanced pepsin secretion. Organic acids are weak acids that can easily diffuse across cell membranes, influencing cell metabolism and disrupting normal microbial cell functioning. They have a stronger effect on inhibiting gram-positive bacteria than gram-negative bacteria due to structural differences in the cell membrane described in Table 3 (Rathnayake *et al.,* 2021).

The application of organic acids as antibiotic alternatives has registered encouraging outcomes in various animal studies. By Long *et al.*'s (2018) study conducted a mixture of organic acids such as formic, lactic, and propionic acids considerably enhanced growth performance, strengthened serum immunity (especially IgG and IgA), and improved intestinal morphology and microbiota of weaned piglets. Acids increased villus height and enhanced the villus-to-crypt ratio, and also encouraged good bacteria such as Lactobacillus and inhibited bad *E. coli*. Likewise, Dibner and Buttin (2002) presented a critical review that showed that organic acids decrease the pH in the gastrointestinal tract to make it less favorable for pathogens such as *Salmonella* and *Clostridium*. They also reported that organic acids enhance nutrient digestion, activate the enzymes, and improve mineral absorption, all of which validate their effectiveness as good alternatives to antibiotics. Hassan *et al.* (2010) demonstrated in poultry that replacing antibiotic growth promoters with citric and propionic acids in broiler rations improved growth performance and modified gut microflora by suppressing

Table 3: Organic acids as an antibiotic alternative

Organic Acid	Dietary Dose	Observations	Reference
Formic Acid, Propionic Acid, Citric Acid	Not specifically quantified (inclusion in organic broiler diets)	Improved growth performance, gut health, and reduced pathogenic bacteria (*E. coli*).	(Saki *et al.,* 2012)
Formic, Acetic, Propionic, Butyric Acids	0.1–0.5% inclusion in broiler diets (variable)	Lowered gut pH, enhanced nutrient digestibility, and antimicrobial and immunomodulatory effects.	(Khan *et al.,* 2022)
Lactic Acid, Formic Acid, Fumaric Acid	1–2% in pig diets	Improved feed intake, feed efficiency, protein digestion, and reduced gastric pH.	(Mroz, 2005)
Oregano-derived organic acids (e.g., Carvacrol)	0.05–0.1% in pig diets	Enhanced intestinal health, increased villus height, and improved growth performance.	(Talavera *et al.,* 2020)
Water-soluble Organic Acids	0.2% in the weanling pig water supply	Improved growth rate and feed efficiency post-weaning.	(Nhara *et al.,* 2024)
Benzoic Acid	0.5–1.0% inclusion	Improved nutrient utilization, gut health, and performance similar to antibiotic growth promoters.	(Kiarie *et al.,* 2018)
Formic Acid, Lactic Acid, Essential Oils Combination	0.2–0.4% in piglet diets	Improved digestive enzyme activities, gut morphology, and intestinal health.	(Xu *et al.,* 2018)
Organic Acid Blend (Formic + Lactic + Propionic)	0.3–0.5% in nursery pig diets	Improved growth performance and gut microbial balance.	(Ferronato & Prandini, 2020)
Organic Acid Mixture (Orgacids™)	0.3% in growing pig diets	Decreased gut pH, improved gut microflora, reduced meat cholesterol.	(Tugnoli *et al.,* 2020)
Benzoic Acid + Essential Oils	0.5% total blend in piglet diets	Effective against *E. coli* F4 infection, improved intestinal health, and growth.	(Rodrigues *et al.,* 2020)
Citric Acid, Malic Acid, Tartaric Acid, Lactic Acid, Succinic Acid (in beverages/fruits study)	Analytical quantification, not feed-related	Detected and quantified via capillary electrophoresis; relevance for quality control.	(Liu *et al.,* 2020)
Organic Acids during Soy Sauce Fermentation	Not dietary; fermentation study	Organic acid profiles associated with bacterial community shifts during fermentation.	(Liu *et al.,* 2020)
Microencapsulated Organic Acids + Essential Oils	0.3% in piglet diets	Improved nutrient absorption, gut barrier function, and immunity under *E. coli* F4 challenge.	(Choi *et al.,* 2020)
Organic Acids as Feed Additives (Various types)	0.2–0.5% recommended	Potential replacements for antibiotic growth promoters; improve broiler health and performance.	(Dai *et al.,* 2021)

pathogenic bacteria and favoring the proliferation of beneficial bacteria. Moreover, Cai *et al.* (2024) researched that an organic acid mixture stimulated not only weaned piglet growth performance, but also improved their intestinal barrier function, antioxidant activity, and fecal microbial richness, indicating the multi-functionality of the compounds. Lastly, Dittoe *et al.* (2018) also pointed to the capacity of organic acids in positively modifying the avian gut with reduced pathogenic load and immune function support, hence offering a natural means of disease prevention and cure without antibiotics. In all, these studies suggest organic acids' capability to fully substitute for antibiotics in the production of livestock and poultry through enhancing gut health, immune function, and general performance.

The Minimum Inhibitory Concentration (MIC) is the lowest concentration of the antimicrobial agent, such as an antibiotic, antifungal, or antiseptic, which inhibits the visible growth of a microorganism after overnight incubation (Chen *et al.,* 2024). It's an important metric in microbiology that allows for the comparison of antimicrobial potency against specific pathogens shown in Table 4.

Phytochemicals: Phytochemicals, including essential oils, phenolics, and alkaloids, are strong antimicrobials. Eugenol, carvacrol, and thymol in plant essential oils such as oregano and clove act on a wide range of bacteria, viruses, and fungi described in Table 5. These natural antimicrobials disrupt microbial cell membranes and inhibit metabolic pathways; hence, they are promising food preservatives as shown in Fig 3 (Aljaafari *et al.,* 2021). AMPs are usually small peptides with broad-spectrum antimicrobial activity. They are found in various types of organisms, including humans and animals, and plants. For example, defensins and cathelicidins can disrupt microbial membranes, leading to their death (Li *et al.,* 2024). They work effectively against bacteria like *E. coli* and *Salmonella*, food-borne fungi, and viruses. The synthetic ones are under development with better stability and effectiveness (Liu *et al.,* 2020).

Physical alternatives: High-pressure processing (HPP) is a non-thermal technology that inactivates pathogens by applying high pressure (up to 600MPa) to food products (Akanni *et al.,* 2024). The process is very effective against bacteria, viruses, and fungi without compromising food quality. HPP is particularly effective against *Listeria* and *Norovirus* in ready-to-eat foods (Govaris & Pexara, 2021).

UV radiation, especially UV-C (wavelength 200-280 nm), has strong germicidal effects. It penetrates and damages microbial DNA, thus inhibiting replication and causing cell death (Alessio *et al.,* 2024). UV treatment is an accepted procedure in water purification; it has also been applied for the decontamination of food contact surfaces and packaging materials. It is efficient against bacteria such as Salmonella, viruses like Hepatitis A, and spoiling fungi (Jing *et al.,* 2022).

Pulsed Electric Fields (PEF) is a therapy that employs extremely short pulses of high voltage applied to food goods, producing electroporation of microbial cell membranes (Lytras *et al.,* 2024). The method has demonstrated efficacy against germs, viruses, and fungi while maintaining the food's nutritional value and flavor. PEF has the ability to significantly lower the levels of *Listeria* and *E. coli* in liquid foods like milk and juices (Martínez *et al.,* 2020).

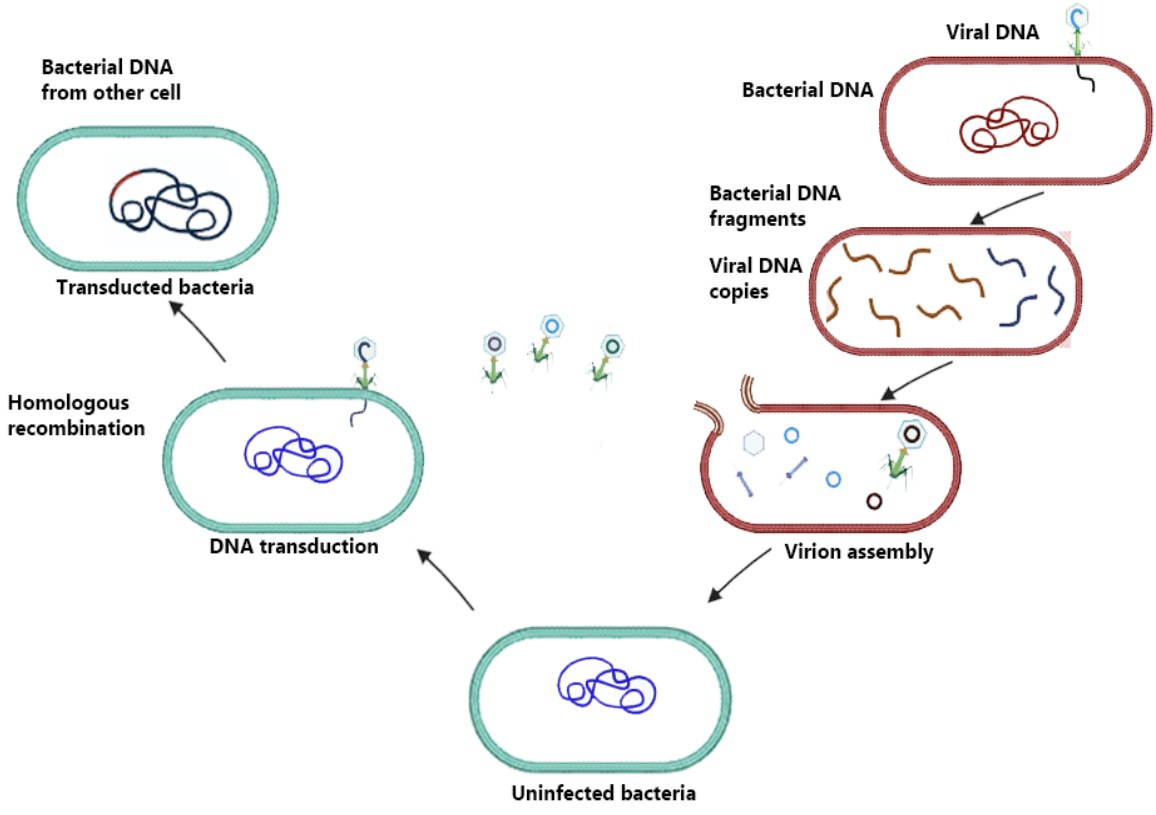

Fig. 3: Bacteriophage and Horizontal gene transfer.

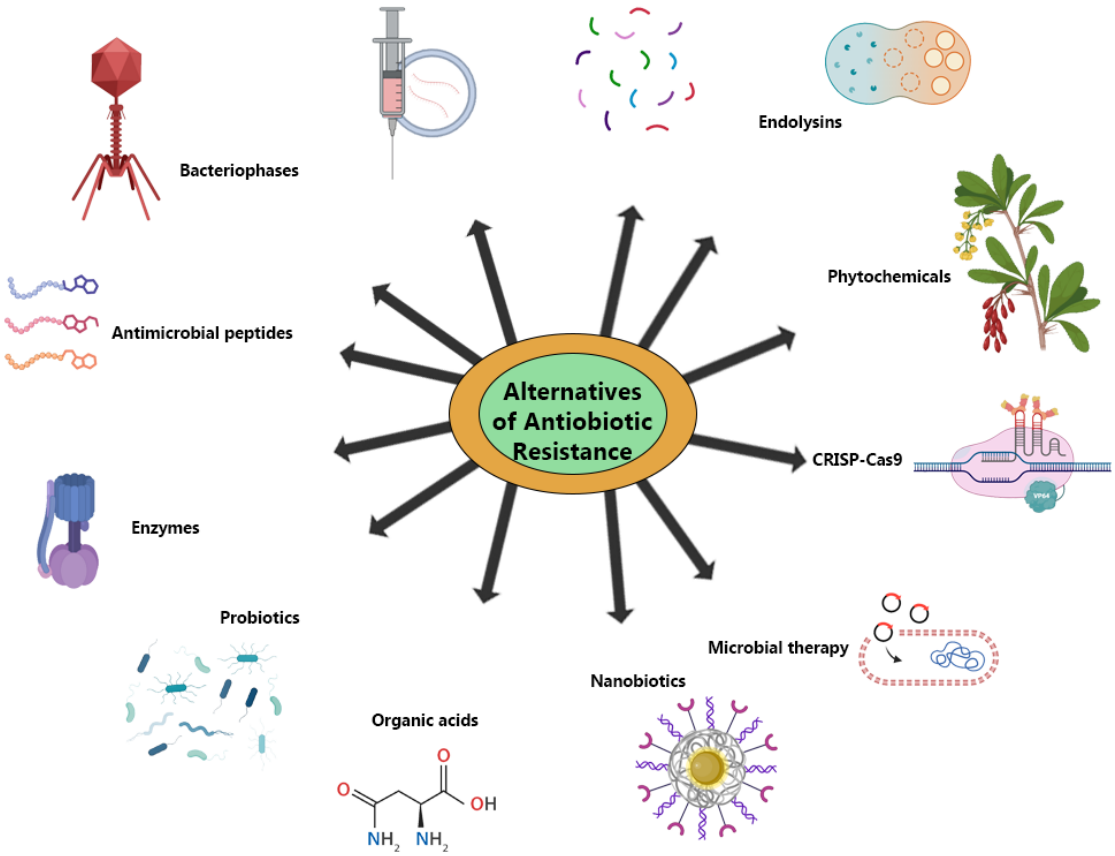

Fig. 4: Alternatives of Antibiotic resistance.

Table 4: The MIC value of different compounds obtained from plants against various foodborne microorganisms

Plant Derivatives	Plant Name	MIC Value	Bacterial sp.	References
Alkaloids, terpenoids, flavonoids, saponins, and tannins	*Anogeissusa cuminata*	0.29 mg/mL	*S. aureus*	(Mishra *et al.*, 2017)
		1.51 mg/mL	*A. baumannii*	
		3.41 mg/mL	*C. freundii*	
		3.41 mg/mL	*E. coli*	
		1.51 mg/mL	*K. oxytoca*	
		0.67 mg/mL	*K. pneumoniae*	
		0.67 mg/mL	*P. aeruginosa*	
Flavonoids and β-sitosterol	*Azadirachta indica*	3.41 mg/mL	*S. aureus*	(Mishra *et al.*, 2017, Cesa *et al.*, 2019)
		4.27 mg/mL	*A. baumannii*	
		3.41 mg/mL	*C. freundii*	
		4.27 mg/mL	*E. coli*	
		9.63 mg/mL	*K. oxytoca*	
		4.27 mg/mL	*K. pneumoniae*	
		9.63 mg/mL	*P. aeruginosa*	
		128 µg/mL	*H. pylori*	
Glucoside, tannins, saponins, terpenoids, flavonoids,	*Bauhinia variegata*	3.41 mg/mL	*S. aureus*	(Mishra *et al.*, 2017)
		9.63 mg/mL	*A. baumannii*	
		9.63 mg/mL	*C. freundii*	
		4.27 mg/mL	*E. coli*	
		9.63 mg/mL	*K. oxytoca*	
		4.27 mg/mL	*K. pneumoniae*	
		3.41 mg/mL	*P. aeruginosa*	
Flavonoids and β-sitosterol	*Boerhaavia diffusa*	4.27 mg/mL	*S. aureus*	(Mishra *et al.*, 2017)
		9.63 mg/mL	*A. baumannii*	
		9.63 mg/mL	*C. freundii*	
		NA	*E. coli*	
		9.63 mg/mL	*K. oxytoca*	
		9.63 mg/mL	*K. pneumoniae*	
		9.63 mg/mL	*P. aeruginosa*	
Punicalagin, ellagic acid, ellagitannin, and flavonoids	*Punica granatum*	0.29 mg/mL	*S. aureus*	(Mishra *et al.*, 2017)
		3.41 mg/mL	*A. baumannii*	
		0.67 mg/mL	*C. freundii*	
		0.67 mg/mL	*E. coli*	
		3.41 mg/mL	*K. oxytoca*	
		3.41 mg/mL	*K. pneumoniae*	
		0.67 mg/mL	*P. aeruginosa*	
Myricetin, luteolin 7-O-glucoside, methyl angolensate, flavonoids, and sitosterol	*Soymida febrifuga*	067 mg/mL	*S. aureus*	(Mishra *et al.*, 2017)
		1.51 mg/mL	*A. baumannii*	
		3.41 mg/mL	*C. freundii*	

		4.27 mg/mL	*E. coli*	
		3.41 mg/mL	*K. oxytoca*	
		3.41 mg/mL	*K. pneumoniae*	
		4.27 mg/mL	*P. aeruginosa*	
Alkaloids, terpenoids, flavonoids and flavins, tannins and their derivatives, glycosides, and steroids	*Terminalia chebula*	1.51 mg/mL	*S. aureus*	(Mishra *et al.,* 2017)
		9.63 mg/mL	*A. baumannii*	
		NA	*C. freundii*	
		9.63 mg/mL	*E. coli*	
		9.63 mg/mL	*K. oxytoca*	
		9.63 mg/mL	*K. pneumoniae*	
		9.63 mg/mL	*P. aeruginosa*	
Lactones, glycosides, steroids, phenolics, alkaloids, and terpenoids	*Tinospora cordifolia*	4.27 mg/mL	*S. aureus*	(Mishra *et al.,* 2017)
		NA	*A. baumannii*	
		9.63 mg/mL	*C. freundii*	
		4.27 mg/mL	*E. coli*	
		9.63 mg/mL	*K. oxytoca*	
		9.63 mg/mL	*K. pneumoniae*	
		4.27 mg/mL	*P. aeruginosa*	
Alkaloids, steroidal saponins, flavonoids, and flavonol glycosides	*Tribulus terrestris*	3.41 mg/mL	*S. aureus*	(Mishra *et al.,* 2017)
		9.63 mg/mL	*A. baumannii*	
		9.63 mg/mL	*C. freundii*	
		4.27 mg/mL	*E. coli*	
		4.27 mg/mL	*K. oxytoca*	
		9.63 mg/mL	*K. pneumoniae*	
		3.41 mg/mL	*P. aeruginosa*	
Coumarins, flavonoids, and phenolic	*Petroselinum crispum EO (Essential oil)*	22.68 µL/mL	*B. cereus*	(Semeniuc *et al.,* 2017)
		10.80 µL/mL	*S. aureus*	
		47.62 µL/mL	*P. aeruginosa*	
		10.80 µL/mL	*E. coli*	
		47.62 µL/mL	*S. typhimurium*	
Semantic anhydride, d-terpineol, terpenoids, n-butylidene phthalide, n-butyl phthalide, l, l phenolic,	*Levisticum officinale EO*	47.62 µL/mL	*B. cereus*	(Semeniuc *et al.,* 2017)
		2.45 µL/mL	*S. aureus*	
		22.68 µL/mL	*P. aeruginosa*	
		10.80 µL/mL	*E. coli*	
		47.62 µL/mL	*S. typhimurium*	
Terpenoid, phenol, and rosmarinic acid	*Occimomum basilicum EO*	10.80 µL/mL	*B. cereus*	(Semeniuc *et al.,* 2017)
		2.45 µL/mL	*S. aureus*	
		22.68 µL/mL	*P. aeruginosa*	
		10.80 µL/mL	*E. coli*	
		22.68 µL/mL	*S. typhimurium*	
Thymol, γ-terpinene, and p-cymene	*Thymus vulgare EO*	0.56 µL/mL	*B. cereus*	(Semeniuc *et al.,* 2017)
		0.06 µL/mL	*S. aureus*	
		0.56 µL/mL	*P. aeruginosa*	
		0.27 µL/mL	*E. coli*	
		0.56 µL/mL	*S. typhimurium*	
Flavonoids and phenol	*Cannabis sativa* L., *EO*	8 mg/mL	*S. aureus*	(Zengin *et al.,* 2018)
Flavonoids, phenol, and tannins of gallic and ellagic acids	*Acrosta phylosuvaursi*	90 µg/mL	*S. aureus*	(Ruiz, 2017)
Alkaloids and isoquinoline	*Coptis chinensis*	121 µg/mL		
α-pinene, p-cymene, and 1,8-cineole	*Eucalyptus globulus*	118 µg/mL		
Terpenoids, alkaloids, lignans, and flavonoids	*Larreatri dentata*	60 µg/mL		
Myrcene, limonene, and α-pinene	*Alpinia galanga*	3.12–25 mg/L	*Mycobacterium smegmatis* mc2 155	(Roy *et al.,* 2012)
Quercetin, kaempferol, and dioxyflavanol	*Ammannia* spp.	125 µg/mL	*E. coli*	(Dwivedi *et al.,* 2014)
Alkaloids, isoquinoline	*Berberis vulgaris*	250–1000 µg/mL	*P. aeruginosa*	(Aghayan *et al.,* 2017)
Tannins and flavonoids	*Acer saccharum*	5 and 10 mg/mL	*E. coli*	(Maisuria *et al.,* 2015)
			P. aeruginosa	
			P. mirabilis	
Terpenoid and limonene	*Catharanthus roseus*	25 mg/L	*P. aeruginosa*	(Dwivedi *et al.,* 2018)
Phytosterol, sitosterol, and triterpenoids	*Holarrhena antidysenterica*	20 mg/L	*P. aeruginosa*	(Siriyong *et al.,* 2017)
Steroids, alkaloids, phenols, flavonoids, glycosides, saponins, and tannins	*Cuminum cyminum*	5 mg/mL	*S. aureus*	(Kakarla *et al.,* 2017)
Rosemarinic acid, phenolics, and flavonoids	*Salvia fruticosa*	5 µl/mL	*S. epidermidis*	(Chovanová *et al.,* 2015)
Ascaridole, α-terpinene	*Chenopodium Ambrosioides*	170.6 µl/mL	*S. aureus*	(Limaverde *et al.,* 2017)
Gallic and ellagic acids	*Terminalia chebola*	12.1–97.5 µg/mL	*E. coli*	(Bag & Chattopadhyay, 2014)
Flavonoids,	*Persea lingue*	1.56 mg/L	*S. aureus*	(Holler *et al.,* 2012)
palbinium, palbine, palbidine, and ipomine	*Ipomoea muricata*	10 µg/mL	*E. coli*	(Maurya *et al.,* 2013)
essential oils, germacrene-D, α-pinene, β-ocimene, and β-caryophyllene	*Hypericum olympicum*	50 µM	*S. aureus*	(Shiu *et al.,* 2013)
There are three types of eudesmol: β-, α-, and γ-.	*Alkanna orientalis*	100 µM	*S. aureus*	(Bame *et al.,* 2013)
tannins, cardiac glycosides, steroids, flavonoids, and saponins	*Eucalyptus tereticornis*	25 and 50 µg/mL	*E. coli*	(Dwivedi *et al.,* 2014)
Terpenoids and phenols	*Salvia officinalis*	0.01 mg/mL	*E. cloacae*	(Mocan *et al.,* 2020)
		0.045 mg/mL	*E. coli*	
		0.045 mg/mL	*S. typhimurium*	
		0.045 mg/mL	*P. aeruginosa*	
		0.09 mg/mL	*B. cereus*	

Table 5: Plant-derived substances' (PDSs') mode of action against a variety of microorganisms

Phytochemicals	Extract	Mode of Action	Antimicrobial-Resistant Microbes	References
Flavonoids	Cranberry, or Vaccinium macrocarpon alt	alters the production of biofilms	*E. faecalis*, *E. coli*, *P. aeruginosa*	(Sun *et al.,* 2015; Wojnicz *et al.,* 2016)
	Epigallocatechin, myricetin, and robinetin	prevents the production of DNA in bacteria	*E. coli*	(Cushnie & Lamb, 2005)
	Quercetin	GrYB protein increases β-galactosidase and extracellular phosphatase while inhibiting ATPase activity.	*E. coli*, *S. aureus*	(Simões *et al.,* 2011)
Essential oils (EOs)	Thymus vulgaris, Levisticum officinale, Ocimum basilicum, and Petroselinum crispum essential oils, as well as Cannabis sativa L.	Cell permeability increases, cell components leak out, bacterial cell wall and membrane changes, ATP loss, protein synthesis inhibition, pH disruption, intracytoplasmic damage, DNA damage, and quorum sensing inhibition prevents the production of biofilms	*B. cereus*, *S. aureus*, *P. aeruginosa*, *E. coli*, *S. Typhimurium*, *S. aureus*	(Willers *et al.,* 2017; Mocan *et al.,* 2020)
Tea tree oil (TTO)	Terpenes, sesquiterpenes, and monoterpenes	causes cell death, destroys the cell membrane, interferes with cell development, and alters membrane permeability.	*E. coli*, *S. aureus*, *C. albicans*	(Carson *et al.,* 2006; Sharifi-Rad *et al.,* 2017)
Plant-derived peptides	*Moringa oleifera*	Membrane disruption	*E. coli*, *S. aureus*, *P. aeruginosa*, *S. Typhimurium*	(Suarez *et al.,* 2005)
Natural Efflux pump inhibitors (EPIs)	Carnosic acid, chalcones, curcumin, berberine, piperine, reserpine, and gallotannin	inhibit several bacterial efflux pumps (EtBr EP, MexAB-OprM)	MDR Uropathogenic *E. coli*, MDR, *P. aeruginosa* (clinical isolates)	(Sabatini *et al.,* 2017; Aghayan *et al.,* 2017; Willers *et al.,* 2017)

Challenges and future perspectives: For instance, bacteriophage resistance arises by mutations in the bacteria that prevent phage binding or through CRISPR/Cas-mediated immunity (Kadkhoda *et al.,* 2024). Similarly, biofilms may protect pathogens against AMPs and essential oils. Again, this illustrates the importance of multi-target strategies to minimize risks of resistance. The cost of developing, producing, and deploying such alternatives like CRISPR/Cas systems, nano-based antimicrobials, and bacteriophages is inhibitive (Ahmed *et al.,* 2024). Most technologies are yet to overcome scaling challenges for application in agricultural and food processing systems.

Antibiotic resistance in foodborne pathogens is a very complex global issue. This requires creative solution strategies, harmonization of responses, and the future perspective must point toward multi-strategy approaches, advanced research and technology, and well-developed cohesive global policies (Jia *et al.,* 2024). Precision microbiology, synthetic biology, and AI are the grounds for the new generation of technologies facing the resistance management challenge. Under precision microbiology, the analysis of pathogen genomes will make way for effective targeted interventions for highly targeted antimicrobials (Branda & Scarpa, 2024). Utilizing the CRISPR/Cas system, new approaches have been developed that are capable of knocking out resistant genes selectively without affecting useful bacteria. In this respect, government-industry-academia collaborations may be useful in promoting research funding, sharing of data, and harmonized regulatory environments (Purnell, 2024). Such actions would specifically serve to support LMICs, which are relatively speaking more challenged in taking full approaches to resistance. Any future effort at ensuring innovation, collaboration, and sustainable practices can potentially serve in prevention to protect the world's food systems from antimicrobial resistance towards foodborne pathogens.

Conclusions: The emergence and increase of antibiotic resistance among foodborne pathogens including *Salmonella*, *Campylobacter*, *E. coli*, and *L. monocytogenes* are an immense risk to public health and food safety on a worldwide basis, even further increased due to the use of antibiotics under non-regulated manners in farming and clinical fields, notably within low- and middle-income economies. This review highlights, the latest research and developments have brought forward a large range of physical, chemical, and natural substitutes to reduce antibiotic use without impairing effective control of pathogens. Natural substitutes such as bacteriophages, probiotics, antimicrobial peptides (AMPs), and essential oils have demonstrated promising results in the inhibition of pathogenic bacteria and food preservation and safety. Physical means, such as nano-based systems and CRISPR/Cas systems, present very effective and targeted means of managing bacterial populations with minimal reliance on conventional antibiotics. Chemical means, such as the creation of novel food-grade preservatives and the application of nanoparticles, provide other means of managing microbial development and increasing the shelf life of foods. Together, these options hold great promise to upgrade food processing, preservation, and animal husbandry operations into sustainable and health-friendly systems. To move from promise to practice, global efforts must prioritize; Research investment, policy and regulation, capacity building, and public-private collaboration. For their effective inclusion in conventional food production, there needs to be intense global coordination, the setup of effective regulatory systems, and ongoing oversight to ensure the safe, efficient, and sustainable utilization of these advanced solutions.

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REFERENCES

Afreen M and Bağdatlı İ, 2021. Food-borne pathogens in seafood. Eurasian J Agri Res 5(1):44-58.

Aghayan SS, Mogadam HK and Fazli M, *et al.,* 2017. The effects of berberine and palmatine on efflux pumps inhibition with different gene patterns in *Pseudomonas aeruginosa* isolated from burn infections. Avicenna J Med Biotechnol 9(1):2.

Ahire JJ, Rohilla A and Kumar V, *et al.,* 2024. Quality management of probiotics: Ensuring safety and maximizing health benefits. Current Microbiol 81(1):1.

Ahmed MM, Kayode HH and Okesanya OJ, *et al.,* 2024. CRISPR-Cas Systems in the fight against antimicrobial resistance: Current status, potentials, and future directions. Infec Drug Resis 17:5229-5245.

Akanni SF, Oke MO and Olatunde SJ, 2024. Non-thermal food processing technologies for reducing microbial loads. Engine Sci Lett 3(03):117-121.

Akinsemolu AA and Onyeaka HN, 2024. Microorganisms associated with food spoilage and foodborne diseases. Food Saf Qual Global South edn: Springer 489-531.

Alara JA and Alara OR, 2024. An overview of the global alarming increase of multiple drug resistant: a major challenge in clinical diagnosis. Infec Disor Drug Targets 24(3):26.

Alcalde-Rico M, Hernando-Amado S and Blanco P, *et al.,* 2016. Multidrug efflux pumps at the crossroad between antibiotic resistance and bacterial virulence. Front Microbio 7:1483.

Alessio N, Ambrosino A and Boggi A, *et al.,* 2024. Germicidal lamps using UV-C radiation may pose health safety issues: a biomolecular analysis of their effects on apoptosis and senescence. Aging (Albany NY)16(9):751.

Aljaafari MN, AlAli AO and Baqais L, *et al.,* 2021. An overview of the potential therapeutic applications of essential oils. Molecules 26(3):628.

Badshah SL and Ullah A, 2018. New developments in non-quinolone-based antibiotics for the inhibiton of bacterial gyrase and topoisomerase IV. Europ J Medici Chem 152:393-400.

Bag A and Chattopadhyay RR, 2014. Efflux-pump inhibitory activity of a gallotannin from *Terminalia chebula* fruit against multidrug-resistant uropathogenic *Escherichia coli*. Natural Prod Res 28(16):1280-1283.

Bai C, Cai Y and Sun T, *et al.,* 2024. Mechanism of antibiotic resistance spread during sub-lethal ozonation of antibiotic-resistant bacteria with different resistance targets. Water Res 259:121837.

Bajer T, Šilha D and Ventura K, *et al.,* 2017. Composition and antimicrobial activity of the essential oil, distilled aromatic water and herbal infusion from Epilobium parviflorum Schreb. Ind Crop prod 100:95-105.

Bame JR, Graf TN and Junio HA, 2013. Sarothrin from Alkanna orientalis is an antimicrobial agent and efflux pump inhibitor. Planta Medica 79(05):327-329.

Bao X and Wu J, 2024. Natural anti-adhesive components against pathogenic bacterial adhesion and infection in gastrointestinal tract: case studies of Helicobacter pylori, Salmonella enterica, Clostridium difficile, and diarrheagenic *Escherichia coli*. Crit Rev Food Sci Nutr 1-46.

Biswas T, Houghton JL and Garneau-Tsodikova S, *et al.,* 2012. The structural basis for substrate versatility of chloramphenicol acetyltransferase CATI. Protein Sci 21(4):520-530.

Blanco P, Hernando-Amado S and Reales-Calderon JA, *et al.,* 2016. Bacterial multidrug efflux pumps: much more than antibiotic resistance determinants. Microorganisms 4(1):14.

Blaskovich MAT, Hansford KA and Gong Y, *et al.,* 2018. Protein-inspired antibiotics active against vancomycin- and daptomycin-resistant bacteria. Nat Commun 9:22.

Branda F and Scarpa F, 2024. Implications of artificial intelligence in addressing antimicrobial resistance: Innovations, global challenges, and healthcare's future. Antibiotics13(6):502.

Bustos AY, Taranto MP and Gerez CL, *et al.,* 2025. Recent advances in the understanding of stress resistance mechanisms in probiotics: Relevance for the design of functional food systems. Probio Antimicrob Protein 17:138-158.

Cai L, Zhao Y and Chen W, *et al.,* 2024. Effect of an organic acid blend as an antibiotic alternative on growth performance, antioxidant capacity, intestinal barrier function, and fecal microbiota in weaned piglets. J Animal Sci 102:149.

Capasso C and Supuran CT, 2019. Dihydropteroate synthase (sulfonamides) and dihydrofolate reductase inhibitors. Bacter Resis Antibiot 163-172.

Carson CF, Hammer KA and Riley TV, 2006. *Melaleuca alternifolia* (tea tree) oil: a review of antimicrobial and other medicinal properties. Clinic Microbiol Rev 19(1):50-62.

Cattoir V and Leclercq R, 2017. Resistance to macrolides, lincosamides, and streptogramins. *AMR:* Mechan Drug Resis 1:269-280.

Cesa S, Sisto F and Zengin G, *et al.,* 2019. Phytochemical analyses and pharmacological screening of Neem oil. S Afr j Bot 120:331-337.

Chen S, Li Z and Chitrakar B, *et al.,* 2024. Minimum inhibitory concentration (MIC) of essential Oils against microorganisms: Methods, function, accuracy factors and application. Food Rev Inter 40(10):3445-3470.

Choi J, Wang L and Liu S, *et al.,* 2020. Effects of a microencapsulated formula of organic acids and essential oils on nutrient absorption, immunity, gut barrier function, and abundance of enterotoxigenic *Escherichia coli* F4 in weaned piglets challenged with *E. coli* F4. J Anim Sci 98(9):259.

Chouhan S, Sharma K and Guleria S, 2017. Antimicrobial activity of some essential oils-present status and future perspectives. Medicines 4: 58.

Chovanová R, Mezovská J and Vaverková Š, *et al.,* 2015. The inhibition the Tet (K) efflux pump of tetracycline resistant *Staphylococcus epidermidis* by essential oils from three Salvia species. Lett Appl Microbiol 61(1):58-62.

Christaki E, Marcou M and Tofarides A, 2020. Antimicrobial resistance in bacteria: mechanisms, evolution, and persistence. J Mol Evolu 88(1):26-40.

Coles ME, Graham BD and Latorre JD, *et al.,* 2023. Essential oils as an alternative to antibiotics to reduce the incidence and severity of necrotic enteritis in broiler chickens: a short review. Food Nutri Sci 14(3):233-57.

Cooper AL, Carter C and McLeod H, *et al.,* 2021. Detection of carbapenem-resistance genes in bacteria isolated from wastewater in Ontario. Facets 6(1):569-591.

Cushnie TT and Lamb AJ, 2005. Antimicrobial activity of flavonoids. Inter J Antimicro Agents 26(5):343-356.

Dai D, Qiu K and Zhang H-j, *et al.,* 2021. Organic acids as alternatives for antibiotic growth promoters alter the intestinal structure and microbiota and improve the growth performance in broilers. Front Microbiol 11:618144.

Deblais L, Vrisman C and Kathayat D, *et al.,* 2019. Imidazole and methoxybenzylamine growth inhibitors reduce *Salmonella* persistence in tomato plant tissues. J Food Protect 82(6):997-1006.

Di Matteo A, Lavorgna M and Russo C, *et al.,* 2024. Natural plant-derived terpenes: antioxidant activity and antibacterial properties against foodborne pathogens, food spoilage and lactic acid bacteria. App Food Res 4(2):100528.

Dianová L, Tirpák F and Halo M, *et al.,* 2022. Effects of selected metal nanoparticles (Ag, ZnO, TiO2) on the structure and function of reproductive organs. Toxics 10(8):459.

Dibner JJ and Buttin P, 2002. Use of organic acids as a model to study the impact of gut microflora on nutrition and metabolism. J Appl Poult Res 1(4):453-63.

Dittoe DK, Ricke SC and Kiess AS, 2018. Organic acids and potential for modifying the avian gastrointestinal tract and reducing pathogens and disease. Front Vet Sci 5:216.

Doern CD, 2021. Review of AmpC Beta-Lactamases in the Enterobacterales-answers to common questions. Clin Microbiol Newslet 43(10):81-86.

Ducrocq J, Simon A and Lemire M, *et al.,* 2021. Exposure to *Toxoplasma gondii* through consumption of raw or undercooked meat: a systematic review and meta-analysis. Vector-Borne Zoo Dis 21(1):40-49.

Dutta B, Lahiri D and Nag M, *et al.,* 2021. Introduction to bacterial biofilm and acute infections. Biofilm Mediat Dis 1-20.

Dwivedi GR, Tyagi R and Sanchita N, *et al.,* 2018. Antibiotics potentiating potential of catharanthine against superbug *Pseudomonas aeruginosa*. J Biomol Struct Dyn 36(16):4270-4284.

Dwivedi GR, Upadhyay HC and Yadav DK, *et al.,* 2014. 4-Hydroxy-α-Tetralone and its derivative as drug resistance reversal agents in multidrug-resistant *Escherichia coli*. Chem Biol Drug Desi 83(4):482-492.

Ehuwa O, Jaiswal AK and Jaiswal S, 2021. *Salmonella*, food safety and food handling practices. Foods 10(5):907.

Erdem Büyükkiraz M, and Kesmen Z, 2022. Antimicrobial peptides (AMPs): A promising class of antimicrobial compounds. J Appl Microbiol 132:1573-1596.

Eruaga MA, 2024. Assessing the role of public education in enhancing food safety practices among consumers. Int J Sci Technol Res 4:022-031.

Escobar-Muciño E, Arenas-Hernández MM, and Luna-Guevara ML, 2022. Mechanisms of inhibition of quorum sensing as an alternative for the control of *E. coli* and *Salmonella*. Microorganisms 10(5):884.

Faltyn M, Alcock B and McArthur A, 2019. Evolution and nomenclature of the trimethoprim resistant dihydrofolate (dfr) reductases. Preprints.

Fani F, Leprohon P and Légaré D, *et al.,* 2012. Whole genome sequencing of penicillin-resistant *Streptococcus pneumoniae* reveals mutations in penicillin-binding proteins and in a putative iron permease. Geno Biol 12:1-12.

Fernández-Villa D, Aguilar MR and Rojo L, 2019. Folic acid antagonists: antimicrobial and immunomodulating mechanisms and applications. Int J Mol Sci 20(20):4996.

Ferronato G and Prandini A, 2020. Dietary supplementation of inorganic, organic, and fatty acids in pig: A review. Animals 10(10):1740.

Franco I, Pérez MD and Castillo E, *et al.,* 2013. Effect of high pressure on the structure and antibacterial activity of bovine lactoferrin treated in different media. J Dairy Res 80(3):283-90.

Frosali S, Pagliari D and Gambassi G, *et al.,* 2015. How the intricate interaction among toll-like receptors, microbiota, and intestinal immunity can influence gastrointestinal pathology. J Immunol Res 1:489821.

Gao X, Li C and He R, *et al.,* 2023. Research advances on biogenic amines in traditional fermented foods: Emphasis on formation mechanism, detection and control methods. Food Chem 405:13491.

García S, Vidal JE and Heredia N, *et al.,* 2019. *Clostridium perfringens*. Food Microbiol Funda front 513-540.

Gauba A and Rahman KM, 2023. Evaluation of antibiotic resistance mechanisms in gram-negative bacteria. Antibiotics 12(11):1590.

Genco CA, Maloy WL and Kari UP, *et al.,* 2003. Antimicrobial activity of magainin analogues against anaerobic oral pathogens. Inter J Antimicrob Agent 21(1):75-8.

Giannenas I, Bonos E and Christaki E, *et al.,* 2013. Essential oils and their applications in animal nutrition. Med Aromat Plants 2(140):2167-0412.

Giordani B, Parolin C and Vitali B, 2021. Lactobacilli as anti-biofilm strategy in oral infectious diseases: a mini-review. Front Med Techno 3:769172.

Gobena T, Belina D and Kebede A, *et al.,* 2024. Foodborne bacterial pathogens in animal, food, and environmental samples collected from the physical exposure of children with diarrhea in Ethiopia: a one health approach. Environ Health Insights 18: 11786302241288167.

Govaris A and Pexara A, 2021. Inactivation of foodborne viruses by high-pressure processing (HPP). Foods 10(2):215.

Grudlewska-Buda K, Bauza-Kaszewska J and Wiktorczyk-Kapischke N, *et al.,* 2023. Antibiotic Resistance in selected emerging bacterial foodborne Pathogens-An issue of concern? Antibiotics 12(5):880.

Gurevich EV and Gurevich VV, 2014. Therapeutic potential of small molecules and engineered proteins. Arrestins Pharmacol Ther Pot 1-2.

Han L, Sun D and Huang M, *et al.,* 2024. Impact of tyrosine substitution on tachyplesin I: Development and characterization of the antimicrobial peptide TP I-Y4. LWT 213:17059.

Harris RA and Dabritz HA, 2024. Infant botulism: in search of *Clostridium botulinum* spores. Curr Microbiol 81(10):306.

Hassan HM, Mohamed MA and Youssef Aw *et al.,* 2010. Effect of using organic acids to substitute antibiotic growth promoters on performance and intestinal microflora of broilers. Asian-Austra J Animal Sci 23(10):1348-53.

Han S, Lu Y and Xie J, *et al.,* 2021. Probiotic gastrointestinal transit and colonization after oral administration: A long journey. Front Cellular Infect Microbio 11: 609722.

Helmy YA, Taha-Abdelaziz K and Hawwas HA, *et al.,* 2023. Antimicrobial resistance and recent alternatives to antibiotics for the control of bacterial pathogens with an emphasis on foodborne pathogens. Antibiotics 12(2):274.

Henderson PJ, Maher C and Elbourne LD, *et al.,* 2021. Physiological functions of bacterial "multidrug" efflux pumps. Chemical Rev 121(9):5417-5478.

Hill C, 2019- Bacteriophages: Viruses that infect bacteria. Front Young Minds 7.

Holler JG, Christensen SB and Slotved H-C, *et al.,* 2012. Novel inhibitory activity of the *Staphylococcus aureus* NorA efflux pump by a kaempferol rhamnoside isolated from Persea lingue Nees. J Antimicrob Chemother 67(5):1138-1144.

Jagadeeshan S and Parsanathan R, 2019. Nano-metal oxides for antibacterial activity. Adv nanostruct mater environm remedi 59-90.

Jia T, Fan C and Li Q, *et al.,* 2024. A brain-inspired harmonized learning with concurrent arbitration for enhancing motion planning in fuzzy environments. IEEE Transact Fuzzy Sys 33(2):631-643.

Jing Z, Lu Z and Santoro D, *et al.,* 2022. Which UV wavelength is the most effective for chlorine-resistant bacteria in terms of the impact of activity, cell membrane and DNA? Chemi Engine J 447:137584.

Joerger RD, 2003. Alternatives to antibiotics: bacteriocins, antimicrobial peptides and bacteriophages. Poult Sci 82(4): 640-647.

Johnston RD, 2021. Perturbing fatty acid metabolism in *Enterococcus faecalis* disrupts responses to exogenous fatty acids and the antibiotic daptomycin. PhD diss., University of Tennessee.

Kadkhoda H, Gholizadeh P and Kafil HS, *et al.,* 2024. Role of CRISPR-Cas systems and anti-CRISPR proteins in bacterial antibiotic resistance. Heliyon 10(14):e34692.

Kakarla P, Floyd J and Mukherjee M, *et al.,* 2017. Inhibition of the multidrug efflux pump LmrS from *Staphylococcus aureus* by cumin spice Cuminum cyminum. Arch Microbiol 199:465-474.

Karunarathna I, Gunasena P and Gunathilake S, *et al.,* 2024. Antibiotic resistance and gentamicin: Current trends and clinical implications. Curr Trends Clin Implicat 152-163.

Kathayat D, Antony L and Deblais L, *et al.,* 2020. Small molecule adjuvants potentiate colistin activity and attenuate resistance development in Escherichia coli by affecting pmr AB system. Infec Drug Resis 10:2205-22.

Kathayat D, Closs Jr G and Helmy YA, *et al.,* 2021. Peptides affecting the outer membrane lipid asymmetry system (MlaA-OmpC/F) reduce avian pathogenic *Escherichia coli* (APEC) colonization in chickens. Appl Environ Microbio 87(17): e00567-21.

Ke D, Luo J and Liu P, *et al.,* 2024. Advancements in bacteriophages for the fire blight pathogen erwinia amylovora. Viruses 16(10):1619.

Khan RU, Naz S and Raziq F, *et al.,* 2022. Prospects of organic acids as safe alternative to antibiotics in broiler chickens diet. Environ Sci Pollut Res 29(22):32594-32604.

Khan ST and Al-Khedhairy AA, 2017. Metals and metal oxides: important nanomaterials with antimicrobial activity. Antimicro Nanoarch 1:196-215.

Kiarie E, Voth C and Wey D, *et al.,* 2018. Comparative efficacy of antibiotic growth promoter and benzoic acid on growth performance, nutrient utilization, and indices of gut health in nursery pigs fed corn–soybean meal diet. Can J Anim Sci 98(4):868-874.

Kim J and Ahn J, 2022. Emergence and spread of antibiotic-resistant foodborne pathogens from farm to table. Food Sci Biotech 31(12):1481-1499.

Koehbach J and Craik DJ, 2019. The vast structural diversity of antimicrobial peptides. Trends Pharmacol Sci 40(7):517-28.

Koley S, Bose A, and Mukherjee M, 2023. Quorum Sensing in Gram-negative bacteria. Nat Prod 25-61. CRC Press.

Kutateladze M and Adamia R, 2010. Bacteriophages as potential new therapeutics to replace or supplement antibiotics. Trends Biotech 28(12):591-595.

Lawani-Luwaji E, 2024. The antibiotic era: A golden age and Its challenges. British J Multidis Adva Stud 5(2):57-68.

Leandro LF, Mendes CA and Casemiro LA, *et al.,* 2015. Antimicrobial activity of apitoxin, melittin and phospholipase A2 of honey bee (Apis mellifera) venom against oral pathogens. An Acad Bras Ciênc 87(1):147-55.

Legrand W, Kuokkanen H and Marucco F, *et al.,* 2024. Survival of the fittest? A call for hospitality to incorporate ecology into business practice and education. Corn Hosp Quart 65(1):68-87.

Lekshmi M, Ammini P and Adjei J, *et al.,* 2018. Modulation of antimicrobial efflux pumps of the major facilitator superfamily in *Staphylococcus aureus*. AIMS Microbio 4(1):1.

Lewies A, Wentzel JF and Jacobs G, *et al.,* 2015- The potential use of natural and structural analogues of antimicrobial peptides in the fight against neglected tropical diseases. Molecules 20(8):15392-15433.

Li T, Ren X and Luo X, *et al.,* 2024. A foundation model identifies broad-Spectrum antimicrobial peptides against drug-resistant bacterial infection. Nat Commun15(1):7538.

Li D and Wu M, 2021. Pattern recognition receptors in health and diseases. Signal Transduct Target Ther 6:291.

Li J, Hu S and Jian W, *et al.,* 2021. Plant antimicrobial peptides: structures, functions, and applications. Botanical Stud 62(1):5.

Limaverde PW, Campina FF and da Cunha FA, *et al.,* 2017. Inhibition of the TetK efflux-pump by the essential oil of *Chenopodium ambrosioides L.* and α-terpinene against *Staphylococcus aureus* IS-58. Food Chemi Toxicol 109:957-961.

Liu S, Brul S and Zaat SA, 2020. Bacterial persister-cells and spores in the food chain: Their potential inactivation by antimicrobial peptides (AMPs). Int J Mol Sci 21(23):8967.

Liu X, Mao B and Tang X, *et al.,* 2025. Bacterial viability retention in probiotic foods: a review. Critic Rev Food Sci Nutrit 1-23.

Long SF, Xu YT and Pan L, *et al.,* 2018. Mixed organic acids as antibiotic substitutes improve performance, serum immunity, intestinal morphology and microbiota for weaned piglets. Anim Feed Sci Technol 235:23-32.

Lytras F, Psakis G and Gatt R, *et al.,* 2024. Exploring the efficacy of pulsed electric fields (PEF) in microbial inactivation during food processing: A deep dive into the microbial cellular and molecular mechanisms. Innova Food Sci Emerg Technol 95:103732.

Maisuria VB, Hosseinidoust Z and Tufenkji N, 2015. Polyphenolic extract from maple syrup potentiates antibiotic susceptibility and reduces biofilm formation of pathogenic bacteria. Appl Environ Microbiol 81(11):3782-3792.

Martínez JM, Delso C and Álvarez I, Raso J, 2020. Pulsed electric field-assisted extraction of valuable compounds from microorganisms. Compr Rev Food Sci Food Saf 19(2):530-552.

Maurya A, Dwivedi GR and Darokar MP, *et al.,* 2013, Antibacterial and synergy of clavine alkaloid lysergol and its derivatives against nalidixic acid-resistant *E. coli*. Chemi Biol Drug Des 81(4):484-490.

Mfeka SM, 2021. Identification and analysis of cryptosporidium glutathione transferase. University of KwaZulu-Natal, Pietermaritzburg 467102217.

Michels K, Nemeth E and Ganz T, *et al.,* 2015. Hepcidin and host defense against infectious diseases. PLoS Pathog 11(8):e1004998.

Mishra MP, Rath S and Swain SS, 2017. In vitro antibacterial activity of crude extracts of 9 selected medicinal plants against UTI causing MDR bacteria. J King Saud Uni Sci 29(1):84-95.

Mizrahi A, Delerue T and Morel H, *et al.,* 2020. Infections caused by naturally AmpC-producing Enterobacteriaceae: Can we use third-generation cephalosporins? A narrative review. Int J Antimicrob Agents 55(2):105834.

Mo K, Li J and Liu F, *et al.,* 2022. Superiority of microencapsulated essential oils compared with common essential oils and antibiotics: effects on the intestinal health and gut microbiota of weaning piglet. Front Nutrit 8:808106.

Mocan A, Babotă M, and Pop A, *et al.,* 2020. Chemical constituents and biologic activities of sage species: A comparison between Salvia officinalis L., S. glutinosa L. and S. transsylvanica (schur ex griseb. & schenk) schur. Antioxid 9(6):480.

Mroz Z, 2005. Organic acids as potential alternatives to antibiotic growth promoters for pigs. Advan Pork Produc 16(1):169-182.

Muteeb G, Rehman MT and Shahwan M, *et al.,* 2023 Origin of antibiotics and antibiotic resistance, and their impacts on drug development: A narrative review. Pharmaceuticals 16(11):1615.

Nataraj BH, Ali SA and Behare PV, *et al.,* 2020. Postbiotics-parabiotics: The new horizons in microbial biotherapy and functional foods. Microb Cell Factor 19-1-22.

Ndraha N, Lin HY and Hsiao HI, *et al.,* 2024. Managing the microbiological safety of tilapia from farm to consumer. CRFSFS 23(5):e70023.

Nhara RB, Marume U and Nantapo CWT, 2024. Potential of organic acids, essential oils and their blends in pig diets as alternatives to antibiotic growth promoters. Animals14(5):762.

Ning Q, Wang D and Cheng F, *et al.,* 2021. Predicting rifampicin resistance mutations in bacterial RNA polymerase subunit beta based on majority consensus. BMC Bioinformatics 22:1-16.

Oduoye MO, Akilimali A, Karim KA, *et al.,* 2024. Diseases Transmitted to Humans through Foodborne Microbes in the Global South. Food Saf Qual Glob South. edn.: Springer 561-597.

Omonijo FA, Ni L and Gong J, *et al.,* 2018. Essential oils as alternatives to antibiotics in swine production. Anim Nutri 4(2):126-36.

Pal M and Ayele Y, 2020. Emerging role of foodborne viruses in public health. Biomed Res Int 5:1-4.

Pan J, Zhu Y and Abdel-Samie MA, *et al.,* 2023. Biological properties of essential oil emphasized on the feasibility as antibiotic substitute in feedstuff. Grain & Oil Sci Techno 6(1):10-23.

Petinaki E and Papagiannitsis C, 2019. Resistance of *Staphylococci* to Macrolides-Lincosamides-Streptogramins B (MLS): Epidemiology. *Staph aureus* 117.

Piqué i Clusella N, Berlanga Herranz M and Miñana i Galbis D, 2019. Health benefits of heat-killed (Tyndallized) probiotics: An overview. Inter J Molecul Sci 10:2534.

Plumet L, Ahmad-Mansour N and Dunyach-Remy C, *et al.,* 2022. Bacteriophage therapy for *Staphylococcus aureus* infections: a review of animal models, treatments, and clinical trials. Front Cellu Infec Microbio12:907314.

Poshvina DV, Dilbaryan DS and Vasilchenko AS, 2023. Gausemycin A-resistant *Staphylococcus aureus* demonstrates affected cell membrane and cell wall homeostasis. Microorganisms 11(5):1330.

Possas A and Pérez-Rodríguez F, 2023. New insights into cross-contamination of fresh-produce. Cur Opin Food Sci 49:100954.

Poulain B and Popoff MR, 2019. Why are botulinum neurotoxin-producing bacteria so diverse and botulinum neurotoxins so toxic? Toxins 11(1):34.

Purnell PJ, 2024. Transdisciplinary research: How much is academia heeding the call to work more closely with societal stakeholders such as industry, government, and nonprofits? arXiv preprint arXiv:240814024.

Qiao D, Fatima N and Ahmad U, 2024. Current Advancements in applications of bacteriophages in food microbiology: A review. Food Sci App Microbiol Repo 3(1):45-50.

Rathnayake D, Mun HS and Dilawar MA, *et al.,* 2021. Time for a paradigm shift in animal nutrition metabolic pathway: Dietary inclusion of organic acids on the production parameters, nutrient digestibility, and meat quality traits of swine and broilers. Life 11(6):476.

Rehman SU, 2022. Campylobacter: A brief review of its causes, diagnostic approaches and prevention. Nation J Biol Sci 3(2):38-66.

Rodrigues LM, Neto TodAL and Garbossa CAP, *et al.,* 2020. Benzoic acid combined with essential oils can be an alternative to the use of antibiotic growth promoters for piglets challenged with *E. coli* F4. Animals 10(11):1978.

Rodrigo D, Rosell CM and Martinez A, 2021. Risk of *Bacillus cereus* in relation to rice and derivatives. Foods 10(2):302.

Rossi F, Santonicola S and Amadoro C, *et al.,* 2024. Food and drinking water as sources of pathogenic protozoans: An update. Appl Sci 14(12):5339.

Roy SK, Pahwa S and Nandanwar H, Jachak SM, 2012. Phenylpropanoids of *Alpinia galanga* as efflux pump inhibitors in *Mycobacterium smegmatis* mc2 155. Fitoterapia 83(7):1248-1255.

Ruiz G, 2017. Bacterial development of resistance to botanical antimicrobials. J Evolut Health 2(2): 2334-3591.

Ruiz J, 2019. Transferable mechanisms of quinolone resistance from 1998 onward. Clin Microbiol Rev 32(4):10-1128.

Sabatini S, Piccioni M and Felicetti T, *et al.,* 2017. Investigation on the effect of known potent *S. aureus* NorA efflux pump inhibitors on the staphylococcal biofilm formation. RSC Advance 7(59):37007-37014.

Sadrimovahed M and Ulusoy BH, 2024. *Bacillus clausii*: a review into story of its probiotic success and potential food applications. Fermentation 10:522.

Sagar P, Aseem A and Banjara SK, *et al.,* 2023. The role of food chain in antimicrobial resistance spread and One Health approach to reduce risks. Int J Food Microbiol 391:110148.

Sánchez-Osuna M, Cortés P and Llagostera M, *et al.,* 2020. Exploration into the origins and mobilization of di-hydrofolate reductase genes and the emergence of clinical resistance to trimethoprim. Microb Genom 6(11):e000440.

Seixas AM, Sousa SA and Leitão JH, 2022. Antibody-based immunotherapies as a tool for tackling multidrug-resistant bacterial infections. Vaccines 10(11):1789.

Semeniuc CA, Pop CR and Rotar AM, 2017. Antibacterial activity and interactions of plant essential oil combinations against Gram-positive and Gram-negative bacteria. J Food Drug Analy 25(2):403-408.

Şen E, and Gençer NS, 2023. Toxic effects of essential oils against *Bemisia tabaci* (Gennadius, 1889)(Hemiptera: Aleyrodidae) and its certain important natural enemies. Pak J Agric Sci 1:60(1).

Seukep AJ, Mbuntcha HG and Kuete V, *et al.,* 2022. What approaches to thwart bacterial efflux pumps-mediated resistance? Antibiotics 11(10):1287.

Sharifi-Rad J, Salehi B and Varoni EM, 2017. Plants of the Melaleuca genus as antimicrobial agents: From farm to pharmacy. Phytoth Res 31(10):1475-1494.

Shin JM, Gwak JW and Kamarajan P, *et al.,* 2016. Biomedical applications of nisin. J Appl Microbiol 120(6):1449-65.

Shiu WK, Malkinson JP and Rahman MM, *et al., 2013*. A new plant-derived antibacterial is an inhibitor of efflux pumps in *Staphylococcus aureus*. Inter J Antimicro Agents 42(6):513-518.

Silva DR, Sardi JD and de Souza Pitangui N, *et al.,* 2020. Probiotics as an alternative antimicrobial therapy: Current reality and future directions. J Funct Food 73:104080.

Simitzis PE, 2017. Enrichment of animal diets with essential oils—a great perspective on improving animal performance and quality characteristics of the derived products. Medicines 4(2):35.

Simões LC, Lemos M and Pereira AM, *et al.,* 2011. Persister cells in a biofilm treated with a biocide. Biofouling 27(4):403-411.

Singha S, Thomas R and Viswakarma JN, *et al.,* 2023. Foodborne illnesses of Escherichia coli O157origin and its control measures. J Food Sci Technol 60(4):1274-1283.

Siriyong T, Srimanote P and Chusri S, *et al.,* 2017. Conessine as a novel inhibitor of multidrug efflux pump systems in *Pseudomonas aeruginosa*. BMC Complement Altern Med 17:1-7.

Starling S. 2017. Innate immunity: A new way out for lysozyme. Nat Rev Gastroenterol Hepatol 14:567.

Steinberg DA, Hurst MA and Fujii CA, *et al.,* 1997. Protegrin-1: a broad-spectrum, rapidly microbicidal peptide with in vivo activity. Antimicrob Agents Chemother 41(8):1738-42.

Suarez M, Haenni M and Canarelli S, 2005. Structure-function characterization and optimization of a plant-derived antibacterial peptide. Antimicrob Agents Chemother 49(9):3847-3857.

Sun J, Marais JPand Khoo C, *et al.,* 2015. Cranberry (Vaccinium macrocarpon) oligosaccharides decrease biofilm formation by uropathogenic Escherichia coli. J Funct Foods 17:235-242.

Taati Moghadam M, Khoshbayan A and Chegini Z *et al.,* 2020. Bacteriophages, a new therapeutic solution for inhibiting multidrug-resistant bacteria causing wound infection: lesson from animal models and clinical trials. Drug Des Dev Ther 15:1867-83.

Talavera K, Startek JB and Alvarez-Collazo J, *et al.,* 2020. Mammalian transient receptor potential TRPA1 channels: from structure to disease. Physiol Rev 100(2): 725-803.

Tang KL, Caffrey NP and Nóbrega DB, *et al.,* 2017. Restricting the use of antibiotics in food-producing animals and its associations with antibiotic resistance in food-producing animals and human beings: a systematic review and meta-analysis. Lancet Plan Health 1(8):e316-e327.

Tao X, Tian L and Zhan H *et al.,* 2021. In vitro and in vivo assessments of *Artemisia argyi* fermented with Lactobacillus plantarum WLPL01 as an alternative anti-*Salmonella* agent. Food Control 126:108079.

Thacharodi A and Lamont IL 2022. Aminoglycoside-modifying enzymes are sufficient to make *Pseudomonas aeruginosa* clinically resistant to key antibiotics. Antibiotics 11(7):884.

Tugnoli B, Giovagnoni G and Piva A, *et al.,* 2020. From acidifiers to intestinal health enhancers: how organic acids can improve growth efficiency of pigs. Animals 10(1):134.

Verhoef J, van Kessel K and Snippe H, 2019. Immune response in human pathology: infections caused by bacteria, viruses, fungi, and parasites. InNijkamp Parnham's Princip Immunopharmaco 165-178. Cham: Springer International Publishing.

Verma SK, Goswami P and Verma RS, *et al.,* 2016. Chemical composition and antimicrobial activity of bergamot-mint (Mentha citrata Ehrh.) essential oils isolated from the herbage and aqueous distillate using different methods. Indus Crops Products 91:152-60.

Vester B, 2018. The cfr and cfr-like multiple resistance genes. Res Microbiol 169(2):61-66.

Vilvanathan S, 2021. Penicillins, Cephalosporins, and other β-Lactam antibiotics. Intro Basics Pharmacol Toxicol 821-834.

Wacnik K, Rao VA, and Chen X, *et al.,* 2022. Penicillin-binding protein 1 (PBP1) of *Staphylococcus aureus* has multiple essential functions in cell division. MBio 13(4):e00669-00622.

Wang Z, Tao X and Liu S, *et al.,* 2021a. An update review on Listeria infection in pregnancy. Infec Drug Res 1967-1978.

Wang W, Yang W and Du S, *et al.,* 2021b.Bioevaluation and targeted modification of temporin-FL from the skin secretion of dark-spotted frog (Pelophylax nigromaculatus). Front Molecul Biosci 8:707013.

Willers C, Wentzel JF and Du Plessis LH, *et al.,* 2017. Efflux as a mechanism of antimicrobial drug resistance in clinical relevant microorganisms: the role of efflux inhibitors. Expert Opin Ther Target 21(1):23-36.

Wojnicz D, Tichaczek-Goska D and Korzekwa K, *et al.,* 2016, Study of the impact of cranberry extract on the virulence factors and biofilm formation by *Enterococcus faecalis* strains isolated from urinary tract infections. Inter J Food Sci Nutri 67(8):1005-1016.

Xu Y, Liu L and Long S, *et al.,* 2018. Effect of organic acids and essential oils on performance, intestinal health and digestive enzyme activities of weaned pigs. Anim Feed Sci Technol 235:110-119.

Yadav K, Garoff L and Huseby DL, *et al.,* 2021. Phenotypic and genetic barriers to establishment of horizontally transferred genes encoding ribosomal protection proteins. J Antimicrob Chemother 76(6):1441-1447.

Yang J, Zhu X and Xu X, *et al.,* 2024. Recent knowledge in phages, phage-encoded endolysin, and phage encapsulation against foodborne pathogens. Critic Rev Food Sci Nutrit 64(32):12040-12060.

Yang W, Chen T and Zhou Q, *et al.,* 2025. Resistance to linezolid in *Staphylococcus aureus* by mutation, modification, and acquisition of genes. J Antibiotics 78(1):4-13.

Yap PC, Chai LC and Lee HY, 2024. Antilisterial potential of bacteriocinogenic Lactobacillus plantarum L001 and *Enterococcus faecium* L103 isolated from fermented foods. Inter Food Res J 31(5).

Yaqub MO, Joseph CE and Jain A, *et al.,* 2024. Resistome mapping in foodborne pathogens: Understanding role in the transmission dynamics of resistance genes. App Microbiol 4(4):1476-1492.

Yitbarek T, 2024. Review on rational use of veterinary drugs and Its status in Ethiopia. J Vet Sci Med 12(1):1.

Yu LW, 2024. The prevalence of trimethoprim-resistance-conferring dihydrofolate reductase genes in multidrug resistant bacteria from clinical isolates in Malaysia. UTAR.

Zaidi S, Misba L and Khan AU, 2017. Nano-therapeutics: A revolution in infection control in post antibiotic era. Nanomedicine: NBM 13(7):2281-301.

Zengin G, Menghini L and Di Sotto A, *et al.,* 2018. Chromatographic analyses, in vitro biological activities, and cytotoxicity of *Cannabis sativa L.* essential oil: A multidisciplinary study. Molecules 23(12):3266.