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# Alternatives of Antibiotics in Animal Agriculture: One Health Perspective

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## Abstract

Due to the increasing trend of antimicrobial resistance bacteria and the increase of antimicrobial resistance genes, there is an urgent need to develop alternatives to antibiotics. This review evaluates the advances and perceptions of alternatives to antibiotics. The mode of action, application and perspective of alternatives such as clay minerals, probiotics, prebiotics, inhibitors such as quorum sensing inhibitors, biofilms inhibitors, bacterial virulence inhibitors, antimicrobial peptides, phytogenic compounds like organic acids, essential oil and herbs, bacteriophages, nanoparticles, vaccines, fecal microbiota transplant, immunity modulating stimulants and bacteriocins are discussed in this review. If used with proper strategies, these alternatives can replace antibiotics in livestock. These alternatives not only better cope with antimicrobial resistance but also can help in efficient animal growth, production and disease control. However, till now, none of the alternatives has been proven to efficiently replace antibiotics on a large scale, though, they appeared to be a partial replacement to antibiotics. These natural alternatives are promising to improve the overall health of the environment, animals and humans. Lastly, the idea of one health was adopted in recognition of the fact that animals and people share many infectious diseases and are connected in addition to existing in the same environment. Using one health concept, the World Health Organization (WHO), Food and Agriculture Organization (FAO), and World Organization for Animal Health (OIE) developed several action plans to tackle antibiotic resistance.

## Introduction

The complexity of the antimicrobial resistance problem appeared when researchers were working on the factors that will help reduce this problem [1]. The use of antibiotics for more than 70 years leads to antibiotic-resistant genes in human pathogens as well as in related bacteria. The spreading of these genes will occur in the environment by the water, air, wildlife, and humans. Therefore, there is a need for strategies for stopping the transfer of these resistant bacteria or genes from the "hot spot" of potential resistance area to the environment. Moreover, there exists a horizontal transfer of the highly resistant genes between the bacteria. The unnecessary use of antibiotics can be the reason for highly resistant genes; hence careful use of antibiotics can help in stopping the resistance to the spread of these genes [1]. Some novel genes can emerge due to selective pressure on the environmental and commensal bacteria. When comparing these genes to those that are resistant to environmental selection, we find that the former does not occur on mobile genetic elements (MGEs) and instead select onto MGEs through the use of integrons, transposons, and plasmids. After that, these genes become visible in human pathogens, such as the plasmid-borne CTX-M-5 extended-spectrum beta-lactamases that are found in Kluyvera ascorbata [2].

To support the health of food-producing animals, antibiotics have been used for a long time, but this practice is blocked by the United Nations. Multiple alternatives can be adopted including phage therapy, probiotics, prebiotics, bacteriocins, competitive exclusion of pathogens, phytogenic compounds, and organic acids. Phage therapy is considered one of the most valuable alternatives, as phages infect bacteria, so is used for the treatment of bacterial diseases. In Eastern Europe, many phage therapeutic products were sold, but in the United States, these products were made unavailable due to variable efficiency [3]. If we talk about the benefit of phage therapy, specificity (bacterium) and efficiency (topical or mucosal infection) are most important. Among the drawbacks is the emergence of resistance. Antibiotics are undoubtedly used to treat a variety of illnesses, but they are also frequently used to prevent illnesses. Almost half of the antibiotics used to treat pigs are done so to avoid disease [4]. The present understanding of animal husbandry's nutrition and sanitation practices has led to a decrease in the use of antibiotics to prevent infections in both people and animals. Furthermore, advancements in molecular science have been crucial in reducing both primary and secondary bacterial infections, including vaccinations.

There is another important alternative, the use of therapeutics in animal agriculture, which are molecules that will boost the immune system of the animals and will help in the prevention of diseases. One of the well-known immune-therapeutics used in animal agriculture is pegbovigrastim [5], a bovine G-CSF (granulocyte colony-stimulating factor), given to cattle to enhance the immune system by maintaining the number of neutrophils in the blood, as well as to minimize the cases of mastitis (Fig. 1). The benefits are enhancing the immune system, which will help in the prevention of disease, but there is a drawback also, about the delivery that should be precise, hence has become a challenging task when applied on-farm. The other effective alternative is the use of probiotics and prebiotics that will work by controlling the gut microbial community, involved in maintaining health [6]. If we talk about probiotics, these are living organisms, typically named good bacteria, introduced to improve the gut microbiota. If we see, prebiotics are molecular precursors that play a role in improving the existing gut microbiota, improving the health of the host.

Talking about other alternatives phytogenic chemicals are one of the safest and most effective antimicrobial agents that have the potential to replace antibiotics and thus help in coping with AMR. Phytogenic chemicals include plant-based derivatives like essential oils, organic acids, herbs and botanic. These compounds prove to be fruitful against pathogenic bacteria and provide health benefits to animals. Moreover, antimicrobial peptides, bacteriophages, and fecal microbiota transplant are all strategies that can be used combined with Antibiotic therapy to help overcome resistance and for the betterment of one health. When antibiotics are used in animal husbandry, they cause antibiotic resistance in food animals. When humans consume these food animals, will create antibiotic resistance in them. According to different research, ARGs present in food animals have reached the resistome of pathogens present in humans. One Health is associated with the integrative management approach that takes into account the environment, animal welfare, and human health in addition to the implementation of efficient public health laws. One health concern about public health aims to prevent and control infectious diseases. An international public health concern is antimicrobial resistance. Since several pathogenic bacteria and their resistance genes have

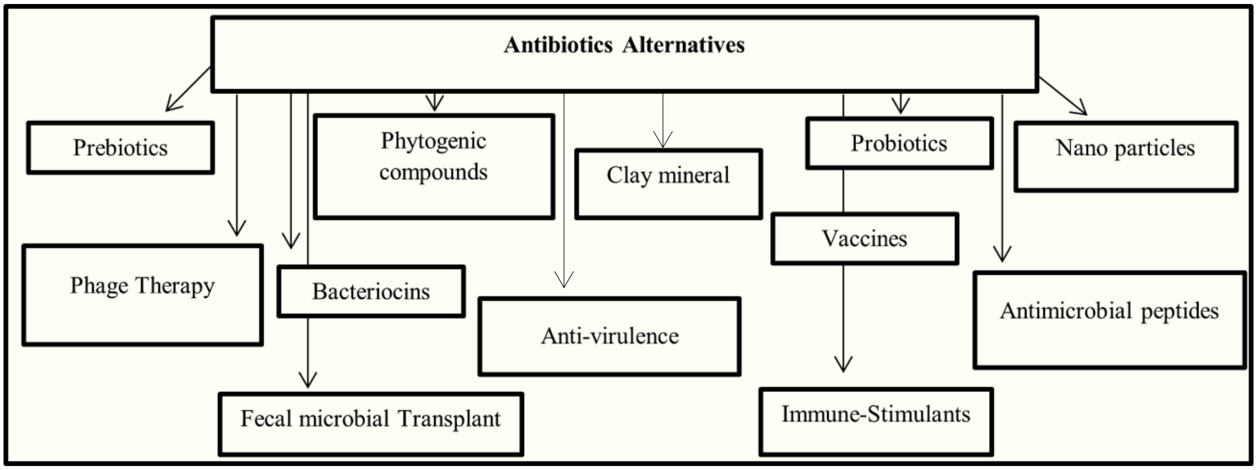


**Fig. 1** Alternatives for combating antibiotic resistance.

environmental origins, there is a general hope that the growth of comprehensive ecological studies will help in investigating the issue, followed by the understanding of the primarily connected consequences.

## Alternative to antibiotics

### Clay minerals

Silicon, aluminum, and oxygen molecules make up the stratified tetrahedral and octahedral layers that make up the composition of clay minerals [7]. Natural extracted clays (bentonites, zeolite, kaolin) are composed of a blend of different clays. The best clays are regarded as being clinoptilolite, montmorillonite, smectite, illite, kaolinite, and biotic [7]. Clay works by immobilizing harmful substances such as aflatoxins, plant metabolites, heavy metals, and poisons in the animal's digestive tract, which reduces their biological availability and toxicity [7]. It has been observed that clay has a significant impact on weaned pig diarrhea cases [7-9]. Since it binds to poisonous compounds, it is added to swine feed to protect the animals from the harmful effects of mycotoxins when fed to them. Although most studies have not accepted it as a practical substitute for antibiotics, it has shown promise in promoting the growth of younger pigs [8, 10-13].

### Probiotics

Probiotics have been defined by the World Health Organization as "microorganisms which, administered live and in adequate amounts, confer a benefit to the health of the host" (Fig. 2). Animal poisoning, allergies and diarrhea cases were reported after introducing probiotics into the feed fed by animals time to time. Lactobacilli and bifidobacteria were approved as safe for the probiotics [14]. The drawback is for the immunodeficient animals, as probiotics were seen as harmful to them [15]. It is seen that normal gut flora is disturbed by the use of probiotics, which can lead to urinary tract infections and other diseases, for example, dietary cider yeast, *Lactobacillus* and *Bacillus*. These abnormalities can be related to the given diet that will affect the endogenous microbiota [16]. The following challenges were faced when probiotics are practiced in animal feed:

1. The species that are considered safe as probiotics are less in number.
2. There exists deactivation of microbial preparations during the processing of feed, transport and storage procedures.
3. Low pH in the gastrointestinal tract and bile acids can deactivate probiotics.
4. High colonization of viable cells in the intestine cannot be achieved properly.

### Prebiotics

Prebiotics are known as food ingredients that cannot be digested by the host and produce useful effects by working in the intestinal tract through their selective metabolism [17]. We can use polysaccharides, oligosaccharides, natural plant extracts, polyols, etc. as prebiotics. We can see the way of working on prebiotics in the following flowchart (Fig. 3). The most commonly used prebiotics that showed encouraging results are oligosaccharides and acidifiers. If we talk about the benefits of prebiotics, these are stable compounds that leave no residue, there are no chances of induced resistance and there is a wide variety of sources. Unfortunately, many

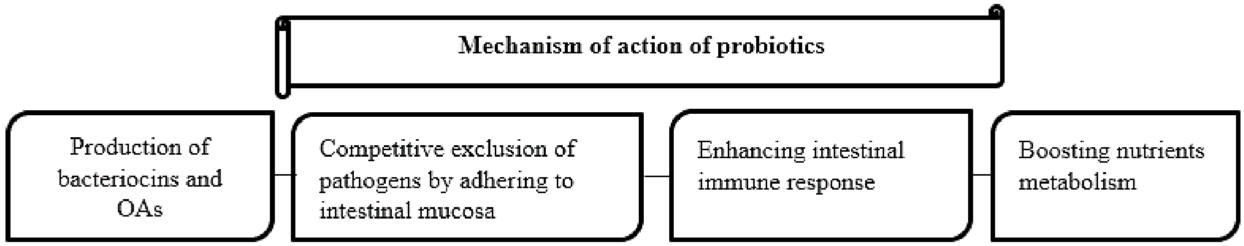


**Fig. 2** Mode of actions of probiotics.

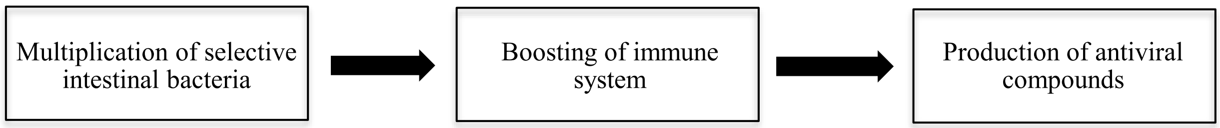


**Fig. 3** Mode of actions of prebiotics.

prebiotic products have been banned as feed additives under the Commission Regulation (EC) 1831/2003. There are a few disadvantages to using these products. These are unable to inhibit or kill pathogens so cannot be used for the treatment of bacterial infections. Many cases of bloating, diarrhea and other adverse reactions were seen, because of the fermentation in the gastrointestinal tract, when animals used an excess of prebiotics [18]. A study on mannose's prebiotic functions showed that its oligosaccharide structure was connected to mannose's prebiotic function [19]. Upon observation, B-galactomannan and MOS (mannan-oligosaccharides) were found to be involved in reducing the amount of IL6 and CXCL8 secreted by Salmonella-infected cells. However, the same outcomes were observed when cells were treated with a monosaccharide D-mannose. Although there is currently no solid evidence linking the structure and physiological function of prebiotics, research has shown that their effectiveness was correlated with various animal species, ages and physical conditions. Because prebiotics are expensive, their use in animal husbandry is restricted.

## Anti-virulence inhibitors

Quorum sensing is involved in the regulation and control of the pathogenicity of bacteria. If we focus on the components of the QS system, these are made up of self-induced signaling molecules (autoinducers, AIs), receptors and downstream regulatory proteins. Quorum-sensing inhibitors work by blocking the functions of the QS system. QS Inhibitors act as anti-virulence as they are involved in preventing bacterial virulence produced due to the QS system. So, by quorum sensing inhibitors (Table 1), we can prevent bacterial virulence. Biofilms are thin layers of polymer matrix attached to a solid surface where the community of bacteria is embedded in it. The matrix is composed of polysaccharides, proteins and DNA. The bacteria that form biofilms are highly resistant to antibiotics and disinfectants. They also have tolerance to resting phagocytes as well as other factors of the body's immune system. By using the biofilms forming inhibitors (Table 2), we can target the bacteria virulence by making them sensitive to antibiotics. We can also target bacterial virulence by blocking their virulence factors. Using the compounds that are involved in blocking the function and transmission of bacterial toxins can be proven very effective anti-infective strategy. There are several anthrax toxins, composed of lethal factor (LF), edema factor (EF), PA and other components. If we use anti-virulence inhibitors, that can block these factors, we can target bacterial virulence. Inhibiting bacterial virulence factors can also be proved successful alternative to combating antimicrobial resistance in the host. The development of compounds inhibiting the function and transmission of bacterial toxins is a novel anti-infective strategy.

## Bacteriocin

Bacteriocins are an additional class of antimicrobial peptides (AMPs). They are thought to be proteins or peptides that bacteria make and that have antibacterial properties (Table 3). Unlike antibiotics, which are byproducts of secondary metabolism, they are created in the late log growth phase and at the start of the stationary phase [36]. According to Schulze et al. [37], bacteria produce bacteriocins, which are tiny peptides with bactericidal or bacteriostatic properties

**Table 1** Quorum sensing inhibitors.

| Names | Examples | References |
|---|---|---|
| 1. Non-peptide small molecule- AHLs analogs | ACP homologs, L/D-S-adenosylhomocysteine and butyryl-S-adenosyl-L-methionine | [20] |
| 2. Peptide- AIPs homologs | AIP-II | [21] |
| 3. Proteins- QS quenching enzymes and QS quenching antibodies | AHL-acylase, lactonase, oxidoreductases from Rhodococous paraoxonase, paraoxonases 1, apolipoprotein B (ApoB) | [22] [23] |

**Table 2** Biofilm forming inhibitors.

| Names | Mechanisms | References |
|---|---|---|
| 1. Methane-thiosulfonate and mercurial p-hydroxymercuribenzoic acid | Their target is inhibiting the bacteria adhesion by acting on sortases. | [24] |
| 2. Polysaccharide hydrolases | Destroy the biofilm matrix. | [25] |
| 3. DNases, proteases, and alginate lyases] | Enhancing the effect of antibiotics on biofilm by making it more susceptible. | [26] [27] |
| 4. Urokinase or lumbrokinase | Stopping the formation of *P. aeruginosa* biofilms and making the biofilm more permeable for the entry of antibiotics. | [28] [29] |

**Table 3** Bacterial virulence inhibitors.

| Name | Mechanisms | References |
|---|---|---|
| 1. Hydroxamate (LFI) | Blocking the LF activation by binding with it, thus involved in stopping the anthrax infection. | [30] |
| 2. Cisplatin | Blocking the assembly of PA heptamer, thus stopping the toxicity of LF and EF. | [31] |
| 3. Cholestyramine | Weakening the toxicity caused by clostridial toxin | |
| 4. Pyridone | Preventing the adhesion of bacteria by blocking the blood clot formation and biofilm formation. | [32] |
| 5. Virstatin | Inhibiting the colonization of V. cholera in the gut. | [33] |
| 6. Acyl salicylaldehyde | Prevent the infection caused by *Yersinia pseudotuberculosis* by blocking the translocation of effector molecules and the invasion of Salmonella in the intestinal epithelium. | [34][35] |

that regulate bacterial ecosystems. They release bacterial strains that help stop infections from growing. In the food and medicine sectors, bacteriocins are useful antibiotics and preservatives Bacteriocins, according to Murugaiyan et al. [38], are less poisonous and stable to heat. They could therefore be used in place of or as a substitute for antibiotics. Bacteriocins are superior to antibiotics because they kill pathogenic bacteria specifically while sparing the surrounding microorganisms, hence changing the microbiota. The lack of consistency in the study, however, prevents us from fully understanding the role, potential, and thorough understanding of bacteriocins as an antibiotic replacement in animal production.

## Use of antimicrobial peptides

In recent years, antimicrobial peptides have gained much popularity because of their wide action against bacteria, fungi, viruses, and parasites. Antimicrobial peptides are a class of small peptides that synthesize naturally (as a natural defense of the immune system) and synthetically and have a great impact on pathogens [40] Because of the emergence of resistant bacteria, alternative strategies to combat bacterial infections are a major concern. Antimicrobial peptides as one of the effective candidates against broad spectrum resistant bacterium therefore, detailed studies are being done on AMPs. AMPs or heterogeneous cationic amphiphilic peptides are mostly produced when the protease enzyme cleaves proteins. To date, 5000 Amps have been discovered that have different ranges of actions and that is because of their nature; against Gram-negative and Gram-positive bacteria, fungi and viruses. Some AMPs target cell walls, some have actions on the plasma membrane and others affect DNA. Amps are considered bactericidal, so resistance against them is not a major concern [41]. Although AMPs are a better alternative to antibiotics, still studies are needed to overcome their limitations which are their hydrolysis, oxidation and photolysis. It may trigger chronic inflammation or may show cytotoxicity, in addition, a long R&D cycle and low investment return also hinder the use of AMPs [42] but for one-health betterment and animal improvement, AMPs could be a better alternative.

## Use of bacteriophages

Antibiotic resistance is a significant risk to humans.

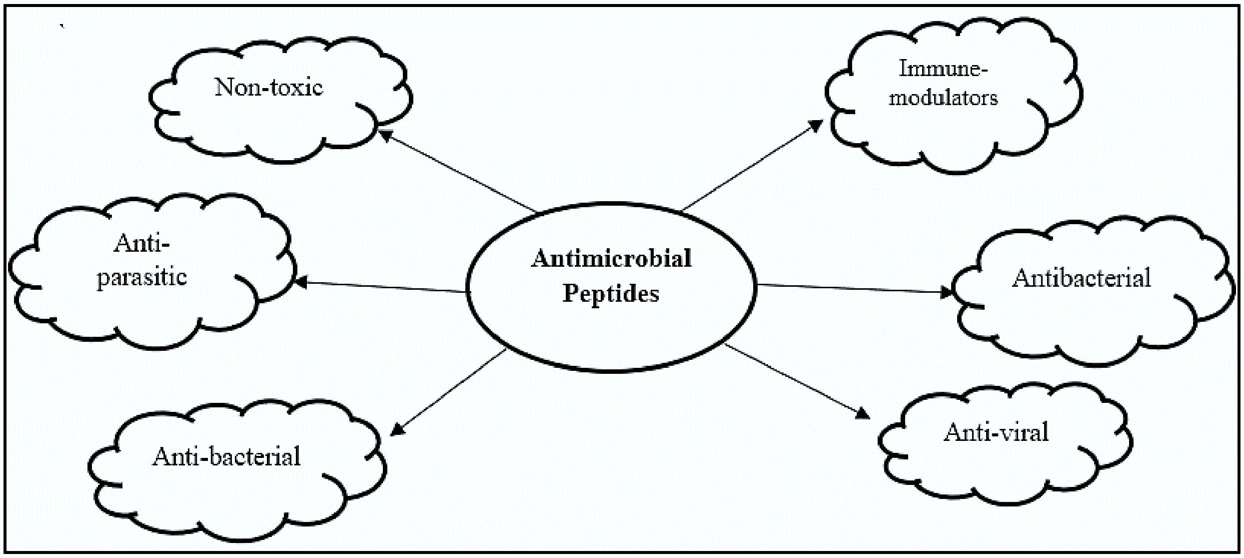


**Fig. 3** Actions of antimicrobial peptides

The scientific community is particularly concerned about finding alternatives because the rate at which new antibiotics are being discovered has decreased. Another substitute for antibiotics is Bacteriophages. Bacteriophages are viruses that infect bacteria with high specificity, kill bacteria without causing harm to animals and give relief from the disease. Despite being identified in the early 1900s, the growing problem of antibiotic resistance has recently sparked interest in bacteriophages again. They are especially helpful in animals because of their specificity and capacity for multiplication, which enable them to fight off numerous illnesses brought on by bacterial resistance. Antibiotics and phage therapy can be used in collaboration to promote phage production and bacterial cell elongation, which lowers the dosage and concentration of antibiotics required. Phage therapy serves as a proven alternative to antibiotics in animals, effectively combating health issues in animals, the environment and humans [44]. Replacing prophylactic antibiotics with this alternative can enhance overall health and help control the emergence of new diseases caused by resistant bacteria.

### Use of nanoparticles

Another advanced and effective method that can be used as an alternative to antibiotics is nanoparticles. Nanoparticles are biomaterials with sizes ranging from 1 and 100 nm [45]. Nanoparticles are advantageous as active antibacterial agents due to their larger surface area, therefore, despite the small dose, these particles exhibit greater activity and are used as viable alternatives against many bacterial infections [46]. If we take a look at the target of antibiotics then we have cell wall, DNA and essential protein synthesis as targets like in the case of beta-lactams, aminoglycosides and quinolones, etc. Bacteria survive the action of antibiotics by mutation and developing resisting mechanisms against these targets. But nanoparticles directly act on the cell wall, and penetrate cell membranes, and unlike target-specific antibiotics, they disrupt important molecular mechanisms, the release of free ions, and oxidative stress. Their actions vary according to NPs type [47]. Nanoparticles in synergy with antibiotic therapy have also been proven to prevent bacterial resistance. With the advancement, various NPs like copper, silver, selenium, nickel, gold and iron oxide have been studied for their antibacterial properties [46].

### Use of phytogenic compounds

Phytogenic compounds are bioactive compounds derived from plants and also referred to as plant secondary metabolites that include a variety of organic acids, essential oils, botanic, herbs and spices that have antimicrobial, antioxidant and anti-inflammatory properties [48]. With growing AMR such natural compounds gain popularity as they can be used as growth promoters and therapeutics (Table 4). Organic acids with general formula R-COOH, are carboxylic acids and are classified based on chain length. Short-chain fatty acids (SCFA), medium-chain fatty acids (MCFA) and long-chain fatty acids (LCFA) make up the organic acids (OA).

**Table 4** List of organic acids effective against microbes.

| Organic acid | Effective against | Reference |
|---|---|---|
| Propionic acid | *Staphylococcus aureus*, *Bacillus subtilis*, bacterium *Escherichia coli* and fungal strains, *Candida albicans* and *Aspergillus niger* | [52] |
| Formic acid | *Salmonella* spp. | [53] |
| Pelargonic acid | *Salmonella* spp. | [54] |
| Rosmarinic acid | *Staphylococcus aureus*, *E. coli*, *B. subtilis* and *Salmonella* | [55] |

**Table 5** List of plant extracts against a panel of microorganisms.

| Plant name | Part | Effective against | Reference |
|---|---|---|---|
| *Taraxacum officinale* | Root | *Staphylococcus aureus*, methicillin-resistant *S. aureus* and *Bacillus cereus* | [59] |
| *Momordica charantia* L. | Leaves | *Aeromonas hydrophila*, MRSA | [60, 61] |
| *Ocimum sanctum* | Leaves | *Staphylococcus aureus*, *Klebsiella pneumonia* | [62] |
| *Mentha piperita* L. | Leaves | *Staphylococcus epidermis* | [63] |
| *Melissa officinalis* | Leaves | *Pseudomonas oryzihabitans* | [63] |

The chemical makeup, shape, molecular weight, pKa value and targeted pathogen or microbe control all play a significant role in the OA's effectiveness [50]. These OAs are considered safe and used as feed additives in poultry for years to prevent microbial and fungal infections [50]. When OAs reach the gut, they alter the pH, increase the activity of gastric enzymes, decrease pathogenic bacteria and modulate gastrointestinal microbiota [51]. Organic acids cause the death of bacteria by entering the plasma membrane and by changing the pH to acidic which leads to alteration in the functioning of differing proteins. By disrupting metabolism, they effectively retard bacterial growth and cause the death of bacteria. Many resistant bacteria like *Clostridium perfringens* [50] become resistant to added antibiotics in feed so organic acid against *C. perfringens* has proven to be an alternative to this disease. The other phytogenic compounds that gained popularity for being effective against bacteria and can be used as a better substitute for antibiotics are essential oils (EO). The European Pharmacopoeia defines EO as an "Odorant product, generally of a complex composition, obtained from a botanically defined plant raw material, either by driving by the stream of water, either by dry distillation or by a suitable mechanical method without heating". They have been shown to possess the antibacterial, anti-parasitic, antiviral and regulatory properties of numerous metabolic processes [56]. Now AMR is one of the ten global health threats and essential oils are being studied extensively for their antibacterial properties [64]. Essential oils are extremely concentrated as they are formed by the steam distillation process and are highly volatile. The components comprised of two biosynthetically related groups namely terpenes and aromatic compounds [57]. The antimicrobial property of essential oil depends upon the type of compound it has, for example, clove has antimicrobial properties due to eugenol and a phenolic compound α-caryophyllene, which is present in trace amounts [57]. Both these compounds possess denatured proteins and react with cell membrane phospholipids and change their permeability resulting in the death of the bacterium [58]. Other EOs have different compounds that have different target sites and have been used for years as potent chemicals against different bacteria.

## Fecal microbial transplant as an alternative antimicrobial

Colonization of drug-resistant microorganisms in the gut is a major concern in livestock and humans. The scientific community is in search of an alternative to overcome resistant microbes. One of the advanced methods is fecal microbiota transplantation (FMT) which can reduce multiple drug-resistant microorganism colonization, but its mechanism is poorly understood [65]. Gut microbiota gives natural protection against resistant microbes by inhibiting their colonization. However, the use of excessive antibiotics affects the natural microflora of the gut leading to its destruction and subsequent colonization and dominance of AROs [66]. Different studies have been done in which patients subjected to fecal microbial transplants led to a decrease in ARO colonization and improved gut health.

## Use of vaccines

AMR is a major threat to animal agriculture. As an alternative, vaccines are the better source that not only combat the resistant microbes but also help lessen the use of antibiotics [67]. Antibiotics are now becoming a must as growth promoters and their prophylactic use results in increasing AMR. Vaccines have proven to be a promising source for decreasing the burden of disease caused by AROs and also prevent and control infections [68]. A variety of studies have been done to check the efficacy of vaccines against many bacterial and viral infections and reduce antibiotic usage in such populations. Many bacterial infections that become hard to treat with antibiotics are now being treated with vaccines. A popular example of vaccine use against bacterial infections is *Lawsonia intracellularis*, the causative agent of ileitis, in Danish pig herds that can reduce oxytetracycline consumption [68]. The infectious coryza vaccine is used to protect against infectious coryza (caused by *Haemophilus paragallinarum* or *Avibacterium paragallinarum*), a bacterial respiratory disease that affects poultry [69]. The use of vaccines is also beneficial because it reduces the cost of farming. Vaccines boost the natural immune system of animals and give longer protection against a disease. Although there are several vaccines available in the market for veterinary use but still a lot of work needs to be done to help build new and effective vaccines against new potential pathogens.

**Immune-stimulants**

Immune stimulants comprise a group of biological and synthetic compounds that enhance the non-specific cellular and humoral defense mechanism in animals [70]. With emerging AMR and AROs, the reliance on the immune-stimulants is under study. There are dozens of immune stimulants like nucleotides, thymosin, oregano oil, probiotics, herbs and their extracts used as immune stimulants and studied for their effectiveness against microbes [41]
It has been proven that adding immune stimulants to feed animals can improve innate immunity and provide defense against microbes. Also, immune-stimulant effects are different in different animal species. With the positive impact on the immune system, they could be detrimental as they can inhibit the positive aspects of the immune system [41]. There are also no uniform standards for evaluating their efficacy and safety. But overall immune-stimulants could be used as an alternative antimicrobial to cope with AMR.

## One-Health perspective

AMR is one of the growing global public health issues that is a threat to treating the infection caused by these invisible creatures. Many infections that were once treatable are now resistant to multiple drug classes. This resistance is continuously growing because of the unbothered use of antibiotics that persuades microorganisms to opt for strategies for resistance and survival. So, instead of inhibiting the antibiotic, bacteria grow their numbers by using that antibiotic or survive in the presence of that particular antibiotic. The environment is the major reservoir of these bacteria. Resistant genes and bacteria can move easily between human, veterinary and environmental pathogens reflecting microbial adaption across sectors. So, AMR is the concern of every sector as it is transferable from one sector to another. Strategies need to be opted to solve this growing concern to improve overall biome health. WHO Global Action Plan emphasizes the One-Health approach and includes five main objectives: (1) Awareness about AMR through effective communication, education and training; (2) strengthening knowledge by research and surveillance; (3) effective sanitation, hygiene and infection prevention measures to reduce the incidence of infection; (4) optimized use of antimicrobial medicine in human and animal; and (5) increase investment in new medicine, diagnostic tools, vaccines and other intervention to stop the growing resistance.

**Conclusions**

Antimicrobial resistance has become a global problem. To control this problem, we should move toward some alternatives. The use of prebiotics and probiotics has proved significant, but overuse can produce harmful effects on animals. Phage therapy is considered a successful strategy with fewer side effects. Antimicrobial peptides, phytogenic compounds like organic acids, essential oils and herbs, nanoparticles, vaccines, and fecal microbiota transplants all are strategies that if used with proper strategies can replace antibiotics in livestock. These alternatives not only better cope with AMR but also can help in efficient animal growth, production and disease control. But none of the alternatives has proven to be an efficient replacement for antibiotics on a large scale, they just to an extent can replace antibiotics. But these natural alternatives are promising to improve the overall health of the environment, animals and humans.

### Conflict of interest

The listed author(s) declares no conflicting interests.

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