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PROSPECTS OF ANTIQUORUM SUBSTANCES AS AN ALTERNATIVE TO ANTIBIOTIC THERAPY IN ANIMAL HUSBANDRY

(review)

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Abstract

Frequent and inappropriate use of antibiotics in animal husbandry threatens to expand the spectrum of antibiotic-resistant bacteria. Quorum sensing (QS) is one of the mechanisms responsible for this process. For its implementation, bacteria use autoinducers, the special signaling molecules for information exchange (A.A. Miller et al., 2011). The studies to give insight of this mechanism have shed light on the existence of substances that act as Quorum sensing inhibitors (quorum suppressors) (B. Remy et al., 2018), which made such studies even more relevant (J. Bzdreng et al., 2017). In our review, we have summarized the latest data on the search and development of the biologically active compounds that can become an alternative to antibiotic drugs used in animal husbandry. These include bacterial enzymes (AGL-lactonases, AGL-acylases, decarboxylases, and deaminases) that can degrade quorum sensing signal autoinducers (V.C. Kalia et al., 2011), as well as α-amylases, β-glucanases, lipases, and proteases involved in the destruction of biofilms (R. Sharma et al., 2001). The antimicrobial properties are also characteristic of animal enzymes acylase I (D. Paul et al., 2010), paraoxonase (J.F. Teiber et al., 2008), and lactonase, plant enzymes laccase (R. Al-Hussaini et al., 2009), alliinase, thiol-dependent enzyme and lactonase derived from garlic and medicinal plants (A. Adonizio et al., 2008), enzymes of marine organisms, particularly bromoperoxidase of the algae *Laminaria digitata*, alginate lyases from algae, invertebrates, and marine microorganisms, and halogenated furanones of *Delisea pulchra* (S.A. Borchardt et al., 2001; M. Manefield et al., 2000). In addition, we can distinguish antimicrobial digestive enzymes used as feed additives, e.g., phytase (O. Adeola et al., 2011), xylanase and lysozyme (G. Cheng et al., 2014). Studies of phytobiotics and essential oils as quorum sensing inhibitors are promising (V.I. Fisinin et al., 2018). Their inhibitory ability is shown due to the similarity of the chemical structures of some plant extracts to the structure of acyl-homoserine-lactone and inactivation of signaling molecules (R. Chevrot et al., 2006; F. Nazzaro et al., 2013). Another prospective alternative is the use of antimicrobial combinatins enabling a synergistic effect due to the variety of mechanisms of overcoming the recurrent bacterial communications and destroying persistent bacterial cells. These polypeptide cocktails may include the combination of antibiotics with natural compounds. The amtimicrobial efficacy has shown for combination of tobramycin and some plant extracts, partilularly cinnamaldehyde and baykalin hydrate against *Burkholderia cenocepacia* and *Pseudomonas aeruginos* (G. Brackman et al., 2011), a wide range of antibiotics, e.g., aminoglycosides (T.H. Jakobsen et al., 2012; M. Stenvang et al., 2016), quinolones (Q. Guo et al., 2016), polypeptide antibiotics (A. Furiga et al., 2016; Z.P. Bulman et al., 2017), cephalosporins and glycopeptides (D. Maura et al., 2017), and various quorum sensing inhibitors.

Keywords: quorum sensing, antibiotics, resistance, bacteria, plant extracts, enzymes

The discovery and use of antibiotics play an unprecedented role in solving many problems related to the prevention, control, and treatment of infectious diseases in animals [1]. In addition, the use of antibiotics in feed is an im-

portant factor in increasing its effectiveness, promoting growth, and improving the quality of animal products. However, despite all the advantages of using antibiotics, their excessive use has led to the emergence and increase in the number of resistant microorganisms [2, 3]. The use of antibiotics in agriculture not only causes resistance in animal microflora but also changes the composition and properties of microflora in natural habitats (soils, groundwater) in the direction of increasing the antibiotic resistance of the microbial community [4]. For this reason, in 1986, Sweden first introduced a ban on the use of certain antibiotics in animal feed [5]. In 2006, the countries of the European Union introduced a ban on antibiotics — the growth stimulants in accordance with the regulation of the European Parliament and the Council of the EU No. 1831/2003 of September 22, 2003. However, this caused negative consequences for livestock due to an increase in the incidence of infections. This led to the need not only to reuse antibiotics but also to increase the volume of their use [3, 6-8]. In the territory of Russia, there are no bans on the use of feed antibiotics, e.g., tetracyclines (biotin based on the producer of chlortetracycline), grisin, bacitracin (bihilicin), and tylosin are allowed. The only limitation is that antibiotics must be excluded from the diet 5 days to 3 weeks before slaughter [9]. The Russian government, in its order No. 604-r of March 30, 2019, approved an action plan for the implementation of the Strategies for preventing the spread of antimicrobial resistance.

Resistance in bacteria is controlled by a set of mechanisms to avoid exposure to antibiotics. It can be either congenital (the absence of a target for an antibiotic or its inaccessibility) [10] or acquired as a result of gene transfer from a neighboring organism [11-13], or it can arise due to an increased frequency of mutations [14-16], or manifest itself as an adaptive ecologically induced resistance [17]. Also, inactivation of an antibiotic can occur due to bacterial modification of the enzyme or with the participation of a degrading enzyme that changes the target of the antibiotic [18-22]. At the same time, bacteria can change the permeability of their cell wall for the outflow of antibiotics outside the cell using an efflux pump [23-25]. The clearance rate is usually higher than the drug penetration rate, thereby controlling the level of antibiotics in the cell [26, 27]. The American Society of Infectious Diseases has identified a group of microorganisms (*Staphylococcus aureus*, *Enterococcus faecium*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and *Enterobacter*) capable of "escaping" antibiotics with the described antibacterial mechanisms. These species represent a new paradigm of virulence, transmission, and antimicrobial resistance [28].

In addition, bacterial communities develop resistance through a process known as quorum sensing (QS), which will be considered as the main mechanism in this review. Its essence lies in the fact that microorganisms produce autoinducers, which act as intercellular signaling to control population density and coordinate its activities, including biofilm formation, virulence, reproduction, spore formation, and horizontal gene transfer [29]. Inside the biofilm, bacteria are approximately 1000 times more resistant to antibiotics than their planktonic precursors [8, 30].

The active substances that suppress QS are called quorum sensing inhibitors (QSIs). In contrast to the currently widely used antibiotics, these agents reduce the number of microbial infections by suppressing the induction of microbial QS, and, as a rule, they do not affect the growth of bacteria [31, 32]. Since QS induces various harmful traits, impairment of bacterial communication seems to be promising in many areas, especially in healthcare and agriculture [33, 34].

QS as a communication mechanism for bacteria. QS is a spe-

cial type of regulation of bacterial gene expression that functions under conditions of a critically high density of their population [35]. This molecular mechanism is required by microorganisms in order for them to collectively adapt their behavior in accordance with the density of the cell population and environmental conditions. This communication system allows bacteria to carry out processes that are costly and ineffective at low cell density, but become useful for the entire community at high cell density (virulence factor production, biofilm formation, and protease and siderophore synthesis) [36].

The QS system has been discovered and described in both gram-positive and gram-negative bacteria. In gram-positive microorganisms, autoinducing peptides (AIPs), autoinducer-2 (AI-2), and other signaling molecules such as quinolones, esters, and fatty acids that induce QS have been extensively studied. These peptides are species-specific and strain-specific and have been described in *Staphylococcus* spp., *Clostridium* spp., *Enterococcus* spp., and other strains [37].

In gram-negative bacteria such as *Pseudomonas* spp., *Acinetobacter* spp. and *Burkholderia* spp., another class of autoinducers, acyl-homoserine lactones (AHLs), has been described [38]. These compounds consist of a lactone ring and an aliphatic acyl chain of different lengths and with various modifications [38]. Most gram-negative bacteria combine several QS systems to integrate various signals or have a hierarchical system: for example, in *Pseudomonas aeruginosa*, it combines four QS systems (*las*, *rhl*, *iqs,* and *pqs*) acting in the network [39], while in the parallel hierarchical system *Vibrio harveyi*, three systems are integrated into one regulatory cascade [40].

Other types of signaling molecules have also been identified [41], including fatty acids used by *Xanthomonas* spp., *Burkholderia* spp., *Xylella* spp. [42], ketones in *Vibrio* spp., *Legionella* spp. [43], adrenaline, norepinephrine, AI-3 in enterohemorrhagic bacteria [44] and quinolones in *Pseudomonas aeruginosa* [45]. AI-2 (furanosyl borate diester) is used by both gram-negative and gram-positive bacteria [46].

Characterization of substances that suppress QS. The process that interferes with bacterial communication, known as quorum quenching (QQ), is of paramount importance to the problem of bacterial resistance. It was discovered as a natural phenomenon, first described in 2000, with the identification of the QQ enzyme capable of degrading AHL signals from *Erwinia carotovora* [47] during enzymatic hydrolysis.

In the QS system, the synthesis of signaling molecules plays a vital role in communication between cells [48]. Bacterial communication can be disrupted through several processes.

Suppressing the synthesis of signaling molecules by QSI is a direct way to disrupt QS. If no signaling molecules are produced, QS will not be felt. However, studies on inhibitors of signaling molecule synthesis are few and the data are very limited [49, 50].

The breakdown of signaling molecules is a more well-studied quenching process. It mainly involves enzymes produced by microorganisms or other organisms to destroy signaling molecules that perceive QS, which leads to a decrease in their concentration below the threshold value, as a result, pathogenic bacteria cannot express genes and produce pathogenic factors, losing the ability to infect the host [51 -54].

Inhibition of the conduction or binding of signaling molecules to receptors also plays an important role in reducing the pathogenicity of bacteria. Studies have shown that many organisms can secrete analogs of QS signals, compete with bacterial signal receptors, interfere with the regulation of the QS control system, and significantly reduce the pathogenicity of bacteria [55, 56].

Currently, all QSIs can be classified into several categories. According to their chemical structure, QSIs are classified into three groups: non-peptide small molecules, peptide and protein QSIs. Non-peptide QSIs include AHL analogs, ACP (acyl transfer protein) homologues, L/DS-adenosyl homocysteine and butyryl-S-adenosyl-L-methionine, peptide QSIs, mainly AIP homologues, and RNAIII inhibitory peptide (RIP) [57-59], interfering with the synthesis of QS signaling molecules or their binding to receptors. Protein QSIs include antibodies and enzymes [60], in particular, AHL acylase, lactonase, *Rhodococcus* oxidoreductase, and mammalian paraoxonase that destroy signaling molecules [61]. In addition, competing organisms are able to lyse signaling molecules for quenching QS [62]. For example, *Escherichia coli* is able to uptake AI-2, affecting QS in *Vibrio harveyi* [63].

QSI is divided into natural and synthetic. Among natural compounds, antagonist peptides designed to suppress gram-positive bacteria and QSIs aimed at QS of gram-negative bacteria and AI-2-mediated QS have been identified [64]. These include polyphenols isolated from tea or honey, ajoene from garlic, eugenol from cloves, and many compounds produced by marine organisms and fungi [65]. Among synthetic substances, fluorouracil (5-FU) and azithromycin can be distinguished [66, 67].

QSIs are likely to differ in mechanisms of action that are not always known [68]. Some molecules that inhibit QS, for example, azithromycin, are also considered antibiotics, since, starting at a certain concentration, they can inhibit bacterial growth [69]. Currently identified QQ enzymes mainly target AHL and AI-2-mediated QS: phosphotriesterase-like lactonases, lactonases, acylases, and oxidoreductases degrade AHL signals; the latter enzyme also targets AI-2 [70]. In this regard, a lot of research work has been done to find alternative approaches to prevent QS [71, 72].

Screening for natural antimicrobial agents. *Enzymes.* More than 2000 different enzymes are currently known. Enzymes are grouped into six classes: oxidoreductases, transferases, hydrolases, lyases (synthases), isomerases, and ligases [73].

There are several commercial hydrolase preparations effective against microbial biofilm: Spezyme GA300, Pandion, Resinase A2X, and Paradigm [74]. Substrates for hydrolases are peptidoglycans – components of the bacterial cell wall responsible for its rigidity. Degradation of the cell wall leads to cell lysis due to a violation of the internal osmotic pressure. Gram-negative bacteria are less sensitive to bacteriolytic enzymes than Gram-positive ones due to differences in the structure of the cell wall [73].

Proteases are enzymes that hydrolyze proteins; in particular, they include subtilisins, which are widely used to control biofilms under industrial conditions [75]. Lysostaphin is an endopeptidase that lyses the cell walls of staphylococci, including methicillin-resistant *Staphylococcus aureus* (MRSA), by cleaving pentaglycine cross-links of peptidoglycan [76]. Administration of lysostaphin in combination with oxacillin or vancomycin enhanced the antimicrobial effect [77].

Among the enzymes that hydrolyze polysaccharides, lysozyme, alginate lyase, dispersin B, and amylase have antimicrobial properties. Lysozyme immobilized in chitosan was effective in suppressing food spoilage by microorganisms [78]. Alpha-amylase hydrolyzes biofilms of *Staphylococcus aureus* [79]. The combination of proteases and amylases effectively removed *Pseudomonas fluorescens* biofilms [80].

Antimicrobial enzymes of bacteria. The enzymes that quench QS and are capable of degrading QS-signaling acylated homoserine-lactone au-

toinducers include AHL lactonases, AHL acylases, decarboxylases, and deaminases [62]. These enzymes are found in bacteria from different phyla — *Actinobacteria*, *Rhodococcus*, *Arthrobacter*, *Streptomyces*, *Firmicutes*, *Bacillus*, *Oceanobacillus*, *Anabaena*, *Cyanobacteria*, *Proteobacteria*, *Alteromonas*, *Comamonas*, *Halomonas*, *Hyphomonas*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Ralstonia*, and *Stappia* [81]. These bacteria have either AHL lactonases or AHL acylases; *Rhodococcus erythropolis* is the only known organism with two enzymes [82, 83]. Interestingly, *Bacillus thuringiensis* does not produce a QS signal, but produces AHL lactonase [84]. Microorganisms secreting bacteriolytic enzymes (for example, streptomycetes) usually express a complex of several enzymes with different specificities for cell wall degradation.

The use of lipase is considered an innovative and environmentally friendly approach for biofilm control due to the lytic and dispersing activity of this enzyme. Most of the lipases used in industry are of microbial origin. Lipases catalyze the hydrolysis of long-chain aliphatic acid esters. This enzyme is synthesized by eukarya, fungi, actinomycetes, yeast, bacteria, and archaea. Bacterial lipases are produced by representatives of the genera *Bacillus*, *Penicillium*, *Staphylococcus*, *Pseudomonas*, and *Aspergillus*. The properties of α-amylase, β-glucanase, lipase (EC 3.1.1.3), and protease, which destroy the flowing biofilms of *Pseudomonas fluorescens*, were also investigated. Four enzymes showed a moderate decrease in the number of colony-forming units in the biofilm [85, 86].

Antimicrobial enzymes of animals. Porcine kidney acylase I inactivated QS signals and prevented biofilm formation in *Pseudomonas putida* and *Aeromonas hydrophila* [87]. Mammalian paraoxonases have a hydrolytic effect on esters and lactones [88]. Mammalian lactonases differ from those isolated from bacteria in that the enzyme in mammals requires an active calcium ion [88]. Human epithelial cells are capable of inactivating the AHL autoinducer synthesized by *Pseudomonas aeruginosa* [89].

Pancreatic lipase catalyzes the synthesis of fatty acids in bacteria; therefore, it can serve as a potential antibacterial agent effective against many bacterial strains [86]. The mammalian enzymes paraoxonase and lactonase belong to the QSIs and can influence the development of infections caused by *Pseudomonas aeruginosa* [61].

Antimicrobial plant enzymes. Laccases, which are QSI enzymes, were found in extracts obtained from fruits, flowers, leaves, and bark of *Laurus nobilis, Combretum albiflorum,* and *Sonchus oleraceus;* analysis was performed using *Chromobacterium violaceum* [90]. Alliinase and a thiol-dependent enzyme isolated from garlic and medicinal plants act as a QSI for *Pseudomonas aeruginosa* [91]. Lactonase, which is present in clover, lotus, legumes, peas, sweet potatoes, and alfalfa, has shown the ability to degrade AHL in *Chromobacterium violaceum* CV12472 and CVO26 strains [92].

Enzymes of marine organisms. Algae, for example, *Laminaria digitata*, possess the enzyme haloperoxidase, which exhibits the ability to inhibit QS (QQ) through oxidation of the AHL signaling group [93]. Red algae *Delisea pulchra* contain halogenated furanones, which are structurally similar to bacterial AHL and can block receptors, interfering with the QS process [94, 95]. Alginate lyases (enzymes found in algae, invertebrates, and marine microorganisms) are used in combination with gentamicin against *Pseudomonas aeruginosa* in respiratory tract infections in patients with cystic fibrosis [96, 97].

Antimicrobial digestive enzymes. Digestive enzymes that supplement the diet to increase feed efficiency and stimulate nutrient absorption also affect the bacterial population in the digestive tract [98]. Several enzymes, such as phytases and carbohydrate-degrading enzymes, are marketed as feed additives

for monogastric animals [99]. Such additives increase the supply of nutrients to the intestinal flora, which allows it to better compete with pathogenic bacteria [98]. In broiler chickens, the addition of xylanase and lysozyme preparations to the diet minimized gastrointestinal damage by reducing the abundance of *Clostridium perfringens* in the ileum [100].

Limited information is available on the practical use of enzyme-based feed additives with antimicrobial properties. However, it is obvious that additives that inhibit QS are very promising and will be especially in demand in animal husbandry, given the current use of antibiotics in this industry. Unfortunately, the disadvantages of enzyme preparations – QS inhibitors – include the relatively high cost of their industrial production [101].

Plant extracts and essential oils (EOs). Plant substances known as phytobiotics are used in animal feeding as antioxidant, antimicrobial, anti-inflammatory, and antiparasitic agents [102, 103]. Many plants have beneficial multifunctional properties, and the bioactive substances obtained from them can have a beneficial effect on the animal's body. Plant extracts are generally considered safe, are effective against certain bacteria, are widely used in feed as growth stimulants and to protect animals, exhibiting antioxidant, antimicrobial, and immunostimulating effects [103, 104].

In pig breeding, the use of oregano, cinnamon, Mexican pepper, and thyme is recommended to suppress pathogenic microflora in the intestine [105-107], sangrovit and garlic extract containing allicin are able to increase live weight gain [108, 109], thyme, cloves, eugenol increase the productivity of pigs [110, 111]. The positive effect of phytogenic feed additives on the growth rates of poultry live weight has been reported [112].

Phytobiotic compounds are represented by phenols/polyphenols, alkaloids, terpenoids/EOs, and lectins/polypeptides [113]. Plant extracts have an *in vitro* antimicrobial effect at a minimum inhibitory concentration of 100-1000 μg/ml [114]. Some phytobiotics against pathogenic microorganisms exhibit QSI properties, since their chemical structure is similar to that of AHL [115]. In addition, gamma-aminobutyric acid, which is structurally similar to inducers of the *attKLM* operon, activates the expression of the AttM lactonase, which it calls, which, in turn, inactivates the QS signal [116]. The flavonoids kaempferol, naringenin, quercetin, and apigenin act as QSIs, inhibiting the HAI-1 or AI-2 QS-controlled bioluminescence autoinducers in *Vibrio harveyi* [117]. Catechins produced by tea plants can activate AHL-lactonase and suppress the transfer of the *Escherichia coli* conjugative R-plasmid, leading to its loss [118]. Furocoumarins and rosmarinic acid, present in grapefruit juice and sweet basil roots, disrupt biofilm formation in *Escherichia coli* and *Pseudomonas aeruginosa,* respectively [119]. Thymol is currently used in combination with vancomycin and ethylenediaminetetraacetic acid as an antimicrobial agent [120]. In addition, the combined action of the antibiotic tobramycin and some plant extracts (cinnamaldehyde and baicalin hydrate as QSI) was effective against *Burkholderia cenocepacia* and *Pseudomonas aeruginosa* [121-123]. The effect of herbal extracts *Artemisiae argyi*, *Cortex dictamni,* and *Solanum melongena on Pseudomonas aeruginosa* was studied [124]. It was also found that *Citrus sinensis* flavonoids were capable of inhibiting QS signals, which can significantly reduce the concentration of signaling molecules secreted by *Yersinia enterocolitica* and disrupt biofilm formation without affecting bacterial growth [125].

Quercus robur oak bark extract was widely used in animal husbandry, including for partial replacement of antibiotics. It inhibits the development of pathogenic microflora of the intestine of poultry on beef-extract agar due to anti-QS effects, which can be useful in the development of methods for controlling

bacterial infections [126].

Studies to assess the effectiveness of QSI in feeding poultry seem promising [127]. Seven components with anti-QS activity (in descending order) were found in the *Quercus cortex* extract: pyrogallol, propylresorcinol, coumarin, scopoletin, coniferyl alcohol, vanillin, antiarol [128]. The extract exhibits the most pronounced and stable anti-QS activity in the absence of obvious antibacterial substances in its composition [129]. This allows the use of QSIs isolated from oak bark as a feed additive for poultry, including in combination with other feed additives, among which probiotics and antibiotics in low doses can be distinguished [130]. It is also known that oak bark extract in the diet of cows increases the number of microorganisms that decompose cellulose and other polysaccharides, which stimulates the activity of various hydrolases in the rumen fluid [131].

The use of EOs is considered promising against epidemics caused by multidrug-resistant bacteria. EOs of lemon, white thyme, cinnamon, eucalyptus, and lemongrass have shown a high antibacterial effect against some resistant strains, in particular, representatives of the genera *Streptococcus*, *Candida*, and MRSA [132, 133]. A synergistic effect between EOs and antibiotics has been reported: the oils of *Mentha piperita*, *Thymus vulgaris*, and *Rosmarinus officinalis* in combination with ciprofloxacin exhibited a more pronounced antimicrobial effect [134]. Also, the anti-QS activity of essential oil or its components affects the expression of AI [135].

Analyzing the use of medicinal herbs and their extracts in animal husbandry, it should be noted that, due to their complex composition, their complex toxicological studies and safety assessment are difficult. It is necessary to identify biologically active components of additives based on plant raw materials and to quantify their effect on the efficiency of feed conversion, improvement of physiological parameters and the state of animal health. Currently, supplements in the market do not meet the principle of traceability and effectiveness. When used in large quantities (1-2%, sometimes up to 5% of the diet), they can negatively affect animals, in particular, digestion and absorption of nutrients. It is also important to consider the possible effects of phytogenic additives when combined with other feed additives. There is evidence of the adverse effects of the combined use of herbal preparations with enzymes [136] and with proteins, leading to their partial denaturation [100]. Although phytobiotics are a group of natural substances, more research is needed on their mechanisms of action, dietary compatibility, toxicity, and safety before they can be widely used in animal husbandry.

The combined effects of antimicrobial drugs. The combination of several drugs can provide a synergistic effect due to a variety of mechanisms required to overcome recurrent bacterial communication and kill persistent cells [73]. The composition of such multi-drug cocktails is not limited to antibiotics and may include combinations of antibiotics with natural compounds that have QQ properties and act as non-antibiotic adjuvants. The combined use enhances the antimicrobial effect and prevents the development of bacterial resistance [137], since the destruction of the biofilm makes bacteria more sensitive even to low doses of antibiotics. Combination of antibiotics and QSIs has been shown to be effective against resistant strains in staphylococcal infections, when the sensitivity of bacteria to commercial antibiotics was increased using the QS inhibitor — RNAIII-inhibiting peptide (RIP, YSPWTNF-NH_2) [138, 139]. QSIs such as furanone C30, patulin, penicillic acid, and garlic extract have been reported to increase the sensitivity of *Pseudomonas aeruginosa* to tobramycin and the phagocytic activity of leukocytes [8, 71]. Natural antimicrobial com-

pounds that can be used as adjuvants for antibiotics are of great interest to researchers [73].

Combination therapy with QQ in *Pseudomonas aeruginosa* infections has also been studied. The use of benzamide-benzimidazole inhibits the MvfR (PqsR) QS regulator, leads to a decrease in biofilm formation, and restores antibiotic susceptibility [140, 141]. Baicalin hydrate and hamamelitannin (respectively, AHL-oriented QSI and peptide QSI) enhance the destruction of biofilms in both gram-negative (*Pseudomonas aeruginosa* and *Burkholderia cepacia*) and gram-positive (*Staphylococcus aureus*) bacteria and show a synergistic effect *in vivo* and *in vitro* with tobramycin and clindamycin or vancomycin, respectively [121]. The effectiveness of a wide range of antibiotics, e.g., aminoglycosides [142, 143], quinolones [144], polypeptide antibiotics [145, 146], cephalosporins, and glycopeptides [141, 147], is enhanced by the addition of QSIs.

The results obtained show that QSIs are potential tools for increasing the sensitivity of microorganisms to antibiotics and, therefore, reducing the active doses of the latter. In addition, a similar trend and efficacy were noted for the combination of lactonase (QQ) and the antibiotic ciprofloxacin in experiments on mice [148]. The combination of antimicrobials and QQ has been shown to give promising results. Therefore, the use of QQ can be an effective strategy for reducing the applied doses of antibiotics, which is important for solving the problem of increasing resistance to them in farm animals.

Thus, substances acting as an alternative to antibiotics must meet a set of criteria: be non-toxic, have no side effects, be easily excreted from the body, do not stimulate bacterial resistance, persist stably in feed, do not decompose in the gastrointestinal tract, do not pollute the environment, do not affect the palatability, kill pathogenic microflora or suppress its growth, without affecting the normal flora, as well as improve the efficiency of nutrient assimilation of feed and the growth performance of animals. At present, there are no known compounds alternative to antibiotics that meet the listed requirements. Existing commercial enzyme preparations, as well as biofilm-inhibiting and quorum-suppressing enzyme preparations that are under development, are unstable and readily degraded in the digestive tract. In addition, the direct antimicrobial effect of antibiotics is higher than that of alternative compounds. Antibiotic drugs are made from one and relatively pure active substrate with high stability, their quality is ensured by long-term production practice. One recommendation is to use some of the natural antimicrobial compounds in combination with lower doses of antibiotics. Such combined use appears to be the most effective and fastest way to limit the adverse effects of antibiotic use and avoid the formation of bacterial resistance. This will minimize the economic losses caused by infections and maintain the high activity of antibiotics against pathogens if it is necessary to carry out effective antibiotic therapy.

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