International Journal of Research in Engineering and Science (IJRES)
ISSN (Online): 2320-9364, ISSN (Print): 2320-9356
www.ijres.org Volume 4 Issue 8 ǁ Aug. 2016 ǁ PP. 114-120

Antibiotic Alternatives: The Substitution of Antibiotics in Animal Husbandry

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ABSTRACT
The emergence and spread of antibiotic resistance have created a growing global threat. Because the use of antibiotics in any setting drives resistance expansion everywhere, it is important to minimize the use of these drugs - a goal that depends on eliminating inappropriate uses and finding other means of preventing infections. Within the meantime, concerns over the increasing emergence of antibiotic-resistant bacteria thanks to the unreasonable use of antibiotics and an appearance of less novelty antibiotics have prompted efforts to develop so-called alternatives to antibiotics. Whether or not the alternatives could really replace antibiotics remains a controversial issue. This review summarizes recent development and perspectives of alternatives to antibiotics. The mechanism of actions, applications, and prospectives of the alternatives like immunity modulating agents, bacteriophages and their lysins, antimicrobial peptides, pro-, pre- and synbiotics, plant extracts, inhibitors targeting pathogenicity (bacterial quorum sensing, biofilm, and virulence), and feeding enzymes are thoroughly discussed. Lastly, the feasibility of alternatives to antibiotics is deeply analyzed. It's hard to conclude that the alternatives might substitute antibiotics in medicine within the foreseeable future. At this time, prudent use of antibiotics and therefore the establishment of scientific monitoring systems are the simplest and fastest thanks to limit the adverse effects of the abuse of antibiotics and to make sure the security of animal-derived food and environment.
KEYWORDS: *Antibiotics, antibiotic alternatives, application, plant extracts, prospective..*

I. INTRODUCTION

Since the invention and application of penicillin in 1940s, antibiotics have played unparalleled roles within the prevention, control, and treatment of infectious diseases for humans and animals. It's also proved that the utilization of antibiotics in animal feeds is a crucial thanks to enhance feed efficiency, to market animal growth, and to enhance the standard of the animal products. Recent studies showed that the growth-promoting effect of antibiotics was correlated with the decreased activity of salt hydrolase, an intestinal bacteria-produced enzyme that exerts negative impact on host fat digestion and utilization. Therefore, antibiotics are effective tools for ensuring the event of intensive and large-scale farming industry. However, the unreasonable use of antibiotics has given rise to a fear of the event of resistant bacteriawhich will cause the transfer of resistant bacteria and its resistant factors from animals to humans (Stanton, 2013). Non-therapeutic antimicrobial uses also are linked to the propagation of multidrug resistance (MDR), including resistance against drugs that were never used on the farm (Marshall and Levy, 2011). Thanks to this concern, Sweden firstly prohibited the utilization of a number of the antibiotics in animal feeds in 1986, and European Union (EU) member nations banned all antibiotic growth promoters in 2006 consistent with European Parliament and Council Regulation EC No. 1831/2003.

To overcome the increased rate of mortality and morbidity thanks to the ban of in-feed antibiotics, variety of alternatives/replacements are proposed (Seal et al., 2013). they're antibacterial vaccines, immunomodulatory agents, bacteriophages and their lysins, antimicrobial peptides (AMPs), pro-, pre-, and synbiotics, plant extracts, inhibitors for bacterial quorum sensing (QS), biofilm and virulence, and feed enzymes, etc. (Millet and Maertens, 2011). Are these antibiotic alternatives really as effective as antibiotics to regulate the diseases in animals? The event and application of the alternatives to antibiotic was reviewed, and therefore the possibility of the alternatives to antibiotics was discussed during this paper.

II. IMMUNITY MODULATING AGENTS

The development of an infection is that the interaction between the pathogen and therefore the system of the host. The system protects the body against the disease by recognizing and neutralizing the pathogen. The innate immune reaction includes both humoral and cellular defense like the complement system and therefore the processes played by granulocytes and macrophages. Immunity modulating agents (immune modulators) are used for immunotherapy, which is defined as treatment of disease by inducing, enhancing, or suppressing an

immune reaction. Vaccine is one among the foremost important immune modulators, and a few pharmaceutical agents could even be used as immune modulators.

III. ANTIBACTERIAL VACCINES

Traditional vaccines are generally classified into live-attenuated and inactivated/killed vaccines. Bacterin may be a suspension of killed or weakened bacteria used as a vaccine. Live-attenuated bacteria, replicating transiently within the host, are capable of expressing a full repertoire of antigens. Take Salmonella vaccine for an example. Many live Salmonella vaccine strains are tested with varying degrees of efficacies (Desin et al., 2013). However, the main drawbacks of the live strains is that they continue the animal body for extended time and have a high risk of reverting to full virulence. Although various Salmonella live-attenuated vaccines are reported, not all of them are tested under field conditions. Additionally, they are doing not induce sufficient cross protection against other non-host-adapted serotypes.

With the increasing use of bacterins, there are concerns that this might cause the increasing virulence of bacteria. As an alternate, subunit vaccine consists of either one antigen or multiple defined antigens (predominantly proteins). This type of vaccines lack the regulatory and biological complications related to the living organisms. On the opposite hand, subunit vaccines are usually poorly immunogenic, requiring formulation with appropriate adjuvant(s). Although Salmonella subunit vaccines are under development, it's hard to conclude that one class of vaccines is more efficacious than another. Besides, the utilization of oral subunit vaccines in large animals remains problematic thanks to the degradation of the antigens and poor absorption in guts.

Last but not least, the event of a vaccine that's both practical and cheap in order that it are often affordable to be used in poor countries remains a key problem (Zhang and Sack, 2012). As for poultry vaccines, the foremost important challenge for mass immunization is that the cost of vaccine also because the ability in most cases. While vaccines may lessen our reliance on the utilization of antibiotics, they're complementary instead of a replacement.

IV. OTHER IMMUNE MODULATORS

Immune modulators, mainly immune stimulants, are ready to non-specifically enhance the innate immune function and to enhance the host's resistance to diseases. the utilization of immunotherapy in infectious diseases may leading to modulating the immune reaction to a microbe (e.g., by using cytokines and cytokine inhibitors), modifying a selected antigen-based response (e.g., using interferons) and minimizing end-organ damage using non-specific anti-inflammatory agents. ß-Glucans, bacterial products, and plant constituents could directly initiate activation of innate defense mechanisms working on receptors and triggering intracellular gene(s) which will end in the assembly of antimicrobial molecules.

There is a spread of immune stimulants, no but a dozen categories with many varieties (Table1). Since 1990s, nucleotides, thymosin, and oregano oil have mainly been used as immune stimulants. Later, probiotics, herbs and their extracts have also become subjects to immune stimulant studies. Studies in animals exhibit significant health benefits by using ß-1,3/1,6-glucan (from yeast cell walls) as a feed ingredient to guard animals against microorganisms (Williams et al., 1996). It's suggested that the utilization of immune stimulants as feed additives can improve the innate defense of animals, providing resistance against pathogens during times of high stress, like grading, reproduction, transfer, and vaccination (Bricknell and Dalmo, 2005).

Table 1 : Classification of immunostimulants.

Category	Variety
Mineral substances	Selenium, zinc, etc.
Vitamins	Vitamin A, vitamin E, vitamin C, etc.
Amino acids	Arginine, leucine, ubenimex, etc.
Chinese herbal medicines	*Astragalus*, *Echinacea*, etc.
Plant polysaccharides	*Astragalus* polysaccharide, lentinan, algal polysaccharides, ganoderan, *Polyporus* polysaccharide, chitosan, etc.
Oligosaccharides	Mannan-oligosaccharides, fructooligosaccharide, etc.
Microbial preparations	BCG vaccine, corynebacterium seedlings, *Lactobacillus*, cholera toxin B subunit, *Mycobacterium phlei*, muroetasin, prodigiosin, etc.
Immunologic adjuvants	Aluminum adjuvant, propolis, liposome, Freund's adjuvant, etc.
Hormones and hormone-like substances	Growth hormone, thymosin, metallothionein, thymopentin, etc.
Nucleic acid preparations	Polynucleotide, immune ribonucleic acid, etc.

Category	Variety
Anthelmintics	Levomisole, metronidazole, etc.
Chemical synthetics	Levomisole, cimetidine, sodium houttuyfonate, imiquimod, pidotimod, ubenimex, tilorone, polyinosinic acid, etc.
Bacterial extracts	β-Glucan, peptidoglycan, lipopolysaccharide, etc.
Biological (cytokines)	Interferon, transfer factor, interleukin, immune globulin, etc.
Others	Bee pollen, bursa extracts, gamma globulin, heat shock protein, poly IC, glycyrrhizin, etc.

Many factors affect the efficacy of immune stimulants. Immune stimulants exhibit different effects in several animal species. They are doing not reveal a linear relationship between dose and effect, usually more efficient during or before infection. Besides the beneficial effects, immune stimulants have so broad effects among which they inhibit the protective aspects of the host system (Thacker, 2010). When immunogenic stimulation persists or autoregulatory immune mechanisms cease, adaptive immunologic events may result in immune-mediated processes detrimental to systemic or organ-specific homeostasis (Moore, 2004). It's been proposed in larval fish aquaculture that the delivery of immune stimulants as a feed additive might be of considerable benefit in boosting the animals' innate defense with little detriment to the developing of fishes. Conversely, immune modulating a neotenous animal before its system is fully formed may adversely affect the event of a traditional immune reaction (Bricknell and Dalmo, 2005). Importantly, most immune modulators just enhance the system of animals, instead of directly kill the bacteria.

V. BACTERIOPHAGES

Bacteriophages are viruses that are parasitic on bacteria, and that they are considered together of the kinds of agents to treat bacterial infections for an extended time (Wittebole et al., 2014). They were first discovered by Frederick Twort in UK in 1915 and by Félix d'Herell in France in 1917. The primary study on the clinical use of phage was published in Belgium in 1921 by Bruynoghe and Maisin who injected staphylococcus-specific phage near the bottom of the cutaneous boils to treat cutaneous furuncles and carbuncles. The commercial phages was introduced by two companies within the USA and France in 1940s. Recent animal studies show that phage therapy is worth of recognition. It's reported that phages has certain preventive effects on pathogens as E. coli O157:H7, Salmonella and Campylobacter. In 2006, a phage cocktail designated LMP-102TM containing six sorts of pure bacteriophages was approved by US-FDA as a food additives for prevention of meat contamination with Listeria. In 2007, USA Department of Agriculture (USDA) approved another phage product to be used for disinfection of E. coli in hidden parts of cattle. Nonetheless, most of the bacteriophage products so far are still within the research stage.

VI. ENDOLYSINS

Endolysins, including glucosidase, amidase, endopeptidase, and transglycosylase, are generated at the late phage lytic cycle, degrading bacterial peptidoglycan to facilitate the discharge of latest phages from the infected bacteria. Endolysins were first discovered within the 1950s (Ralston et al., 1955), and revealed antibacterial activity against Staphylococcus, Bacillus anthracis, L. monocytogenes, and Clostridium butyricum within the 1990s. Endolysins can treat sepsis and a couple of Gram-positive bacteria infections, like Enterococcus faecalis, C. perfringens, and B Streptococcus (Fenton et al., 2010). Endolysin PAL is in a position to kill A Streptococcus which cause tonsillitis and other infections. Amidase PAL and endopeptidase Cpl-1 from phage Cpl-1 is capable of synergistically reducing the incidence of local and systemic pneumococcal disease (Loeffler et al., 2003; Fischetti, 2005). Endolysins LysK from phage K could kill nine Staphylococcus, including methicillin-resistant S. aureus. Endolysins PlyV12 shows an honest lytic activity against Enterococci, vancomycin-resistant E. faecalis and E. faecium. Endolysins isolated from phage phi3626 can treat Clostridium infections.

VII. ANTIMICROBIAL PEPTIDES

There are many reports on the protective effect of AMPs on humansand animals. Here, bacteriocins which are produced by bacteria are taken as an example. Bacteriocins are defined into four classes as lantibiotics, the tiny heat-stable peptides (SHSPs), the massive heat-labile proteins (LHLPs), and undefined mixture proteins with lipids and carbohydrates (Bierbaum and Sahl, 2009). Bacteriocins also can be subdivided on the idea of their modifications into class I (modified) and sophistication II (unmodified or circular; Cotter et al., 2013). There are many identified bacteriocins like nisin, lactacin, lactocin, helveticin, fermenticin, sakacin, lacticin, plantacin, subticin, etc. In vitro tests show that bacteriocins have strong killing and suppressive effects on a spread of pathogens, including resistant pathogens. In 1988, nisin received the US-FDA approval as

artificial additive for the primary time. Pediocin PA-1 from Pediococcus is on the market now. However, pure bacteriocins have thus far only few and limited authorized uses in foods.

VIII. PROBIOTICS

Probiotics are defined by the planet Health Organization as "microorganisms which, administered live and in adequate amounts, confer a benefit to the health of the host." Probiotics are considered to be ready to destroy pathogenic microorganisms by producing antimicrobial compounds like bacteriocins and organic acids, improve gastrointestinal microbial environment by adherence to intestinal mucosa thereby preventing attachment of pathogens and competing with pathogens for nutrients, stimulate the intestinal immune responses and improve the digestion and absorption of nutrients. The commonly used probiotics include Bacillus, Lactobacillus, Lactococcus, Streptococcus, Enterococcus, Pediococcus, Bifidobacterium, Bacteroides, Pseudomonas, yeast, Aspergillus, and Trichoderma, etc. Microbiological feed additives utilized in EU mainly include Bacillus (B. cereus var. toyoi, B. licheniformis, B. subtilis), Enterococcus (E. faecium), Lactobacillus (L. acidophilus, L. casei, L. farciminis, L. plantarum, L. rhamnosus), Pediococcus (P. acidilactici), Streptococcus (S. infantarius), and a few fungi like baker's yeast and kluyveromyces (Anadon et al., 2006). Japan started using probiotics in 1960s, and China began the appliance of probiotics in 1980s. US-FDA approved 42 probiotics till 1989. In 2000, the entire sale of feed probiotics worldwide was $186 million.

IX. PREBIOTICS

Prebiotics are non-digestible (by the host) food ingredients that have a beneficial effect through their selective metabolism within the intestinal tract (Gibson et al., 2004). Prebiotics include oligosaccharides, polysaccharides, natural plant extracts, protein hydrolysates, polyols, etc. Prebiotics can selectively proliferate intestinal bacteria, promote immune functions and show anti-viral activity. A number of them are ready to promote mineral absorption and regulate metabolism. The applications of prebiotics as feed additives began within the late 1980s. China began to use them within the late 1990s. Currently, the foremost promising prebiotics are multifunctional oligosaccharides and acidifiers.

X. SYNBIOTICS

Synbiotics are the joint preparations of probiotics and prebiotics, and thus have the twin role of them (Andersson et al., 2001). There are some reports on the effect of synbiotics on the physiological and biochemical indexes of piglets including the enhancement of immune function in piglets, the development of average daily gain and digestibility, the reduction of diarrhea morbidity and mortality, the convenience of weaning stress response, and therefore the significant promotion of piglet performance. However, the reports of the beneficial effects of synbiotics on swine production are still limited. The blending proportions of probiotics/prebiotics for the bulk of synbiotics are inadequate, thus leading to a non-synergistic effect. So far, synergy mechanism of probiotics and prebiotics has not been thoroughly understood; hence, the extensive application of synbiotics features a great distance to travel.

XI. PLANT EXTRACTS

Plant materials are used widely in traditional systems of drugs (Savoia, 2012). Plant extracts, also referred to as phytobiotics, are exploited in animal nutrition, particularly for his or her antimicrobial, anti-inflammatory, anti-oxidative, and anti-parasitic activities. Many plants have beneficial multifunctional properties derived from their specific bioactive components. Biologically active constituents of plants are mostly secondary metabolites, like terpenoids (mono- and sesquiterpenes, steroids, etc.), phenolics (tannins), glycosides, and alkaloids (present as alcohols, aldehydes, ketones, esters, ethers, lactones, etc.). Among 109 new antibacterial drugs, approved within the period of 1981~2006, 69% originated from natural products, and 21% of the antifungal drugs were natural derivatives or compounds mimicking natural products.

XII. QUORUM SENSING INHIBITORS

Bacterial pathogenicity is, in part, under the regulation and control of QS system (Swift et al., 2001). QS system consists of self-induced signaling molecules (autoinducers, AIs), receptors, and downstream regulatory proteins. AIs are N-acyl homoserine lactones (AHLs) secreted by Gram-negative bacteria, autoinducing peptide (AIPs) secreted by Gram-positive bacteria, autoinducer-2 (AI-2), and other signaling molecules like quinolones, esters, and fatty acids.

Inhibitors targeting QS can block the functions of QS system and thus prevent bacterial virulence regulated by QS system. QS inhibitors (QSIs) are classified into three groups including non-peptide small molecule, peptide (mainly AIPs homologs), and protein QSIs. Non-peptide QSIs mainly include AHLs analogs, like ACP homologs, l/d-S-adenosyl homocysteine and butyryl-S-adenosyl-l-methionine (Parsek et al., 1999), which may interfere with the synthesis of QS signal molecules or the binding to the receptors. Mice treated with

synthetic AIP-II had resistance to S. aureus infection (Mayville et al., 1999) and treated with furanone observed the decrease of virulence of P. aeruginosa (Hentzer et al., 2003). QS quenching enzymes and QS quenching antibodies are proteinaceous QSIs (Amara et al., 2011). The previous, like AHL-acylase, lactonase, oxidoreductases from Rhodococcus and paraoxonase from mammals, degrade signaling molecules. Human and murine paraoxonases1 show the host modulators of P. aeruginosa QS (Ozer et al., 2005). Additionally, competitive organisms are ready to clear the signal molecule to quench QS (Kalia and Purohit, 2011). As an example, E. coli ingest AI-2s to influence the QS of Vibrio harveyi (Xavier and Bassler, 2005). Bacteria with AHL-degrading activity protect Artemia spp., rotifers and larvae of turbot or prawn from infection (Nhan et al., 2010). In animal serum, apolipoprotein B (ApoB) bind with AIP1 molecules of S. aureus, effectively reducing its QS (Peterson et al., 2008).

XIII. BIOFILM INHIBITORS

Biofilms are structured consortium of bacteria embedded during a self-produced polymer matrix consisting of polysaccharide, protein and DNA. Biofilm-forming bacteria may cause chronic infections because they show increased tolerance to antibiotics and disinfectant chemicals also as resisting phagocytosis and other components of the body's defence system (Hoiby et al., 2010). As for treating staphylococcal biofilm, protein synthesis inhibitors (e.g., oxazolidinones and tetracyclines), cell wall and wall-active antibiotics (e.g., lipopeptides and glycopeptides) and inhibitors for DNA and RNA synthesis (e.g., rifampin) are often used (Kiedrowski and Horswill, 2011). Methane-thiosulfonate and mercurial p-hydroxymercuribenzoic acid could target sortases, a membrane enzyme catalyzing the covalent anchoring of surface proteins to peptidoglycans, which are involved in bacteria adhesion (Chen and Wen, 2011).

The way from molecular mechanisms of biofilm formation to anti-biofilm products is promising, but still an extended one. Although biofilm inhibitors can inhibit biofilm formation, they are doing not inhibit bacterial growth or kill bacteria. Hence, when biofilm inhibitor use is discontinued, bacteria will produce biofilm again to guard themselves against the adverse environmental conditions.

XIV. BACTERIAL VIRULENCE INHIBITORS

An important emerging strategy to combat bacteria seeks to dam the power of bacteria to harm the host by inhibiting bacterial virulence factors. Development of compounds inhibiting the function and transmission of bacterial toxins may be a novel anti-infective strategy. The protein complex of anthrax toxin contains lethal factor (LF), edema factor (EF), PA, and other components. Single component is non-toxic, but the mixture of LF or EF with PA will cause a pathological effect (Young and Collier, 2007). alittle molecular, hydroxamate (LFI), can bind to the site of LF, inhibiting the activation of LF and preventing anthrax infection (Shoop et al., 2005). Cisplatin shows inhibitory effect to PA heptamer assembly, thus blocks the toxicity of LF and EF. However, only simultaneous feeding of cisplatin and a lethal amount of anthrax toxin features a protective effect on rodents, while delayed feeding of cisplatin would have resulted during a failure (Moayeri et al., 2006). Cholestyramine can bind with clostridial toxin to stop its adsorption to intestinal epithelial cells, thus weakening the toxicity cause by the toxin.

XV. FEED ENZYMES

The nutrients for the multiplication and growth of bacteria within the intestinal tract are derived largely from dietary components, which are either not digested by digestive enzymes or absorbed so slowly that bacteria in host guts compete for them. Exogenous enzymes not only influence the absorption of nutrients but also produce nutrients for specific populations of bacteria through their action (Bedford and Cowieson, 2012). Therefore, their use features a direct impact on the microfloral populations (Apajalahti et al., 2004).

XVI. PERSPECTIVES

Ideal alternatives to antibiotics should: (i) have non-toxic or no side effects on animals, (ii) be easy to eliminate from the body or contains short term of residues, (iii) not induce bacterial resistance, (iv) be stable within the feed and animal alimentary canal , (v) be easily decomposed and not affect the environment, (vi) not affect palatability, (vii) not destroy the traditional microorganism of animals, (viii) kill or inhibit the expansion of pathogenic bacteria, (ix) enhance the body resistance to the disease, (x) improve feed efficiency and promote animal growth, and (xi) have good compatibility. In fact, there are not any alternatives to antibiotic that currently meet all the above mentioned requirements.

The efficacy of traditional antibiotics can still be improved. Some "old" antibiotics can find new bacterial targets and reinforce the anti-infectious therapy toward some MDR bacteria. It's been demonstrated that in many cases, there are non-carbapenem alternatives for the treatment of extended-spectrum-ß-lactamase-producing E. coli (ESBL-Ec) infections (Fournier et al., 2013). Besides, new formulations can allow targeted drug delivery via nanoparticles and therefore the association of molecules can reinforce the antimicrobial effect

of antibiotics (Bourlioux, 2013). Furthermore, in empirical therapy, use of broad-spectrum bactericidal agents which will eradicate the presumed infective microorganism(s), which potentially might be MDR, should be preferred. Once an infection is in check and therefore the culture and susceptibility results are reported, it's important to modify to the foremost suitable narrow-spectrum agent thus decreasing the potential of adverse drug effects and therefore the risk of development of antibiotic-induced resistance (Lynch, 2012).

XVII. CONCLUSION

In summary, reasonable use of antibiotics and continuous development of alternatives to antibiotics are needed to make sure the long-term sustainable development of farming. We must strictly define the target animals, duration of the treatment and therefore the withdrawal period, for prudent use of antibiotics also as regulation/policy making regarding their use. At an equivalent time, we must strengthen the supervision and enforcement of laws so as to regulate antibiotic resistance and residues from the organic phenomenon within established safe levels. The research of antibiotics alternatives are going to be an extended process. additionally to research and development of latest efficient and safe alternatives, we should always strengthen the study concerning the consequences of combined use of antibiotics and their alternatives aimed toward maintaining a healthy agricultural economy and preservation of potent antibiotics for efficacious therapy in humans.

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