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Strategies for Prevention and Control of Multidrug-resistant Bacteria in Ruminants

Gamil Sayed Gamil Zeedan, Abeer Mostafa Abdalhamed*, and Alaa Abdelmoneam Ghazy

Department of Parasitology and Animal Diseases (Infectious Diseases), National Research Centre, 33 Bohouth Street, Dokki, 12622, Giza, Egypt

*Corresponding author's Email: abeerg2007@yahoo.com

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ABSTRACT

Antibiotics are no longer effective in treating bacterial infections due to antimicrobial drug resistance. Therefore, various alternative strategies have been developed to combat multidrug-resistant (MDR) bacteria. The current review article aimed to shed light on strategies to prevent and control MDR bacteria in ruminants. Due to the development of new resistant bacteria, there is a need for effective treatments and prevention protocols in livestock and humans. With growing antibiotic-resistant organisms, a few antimicrobial medicines will be available to treat the infection when no new drugs are developed. This highlights the importance of looking for other strategies for combating antibiotic-resistant bacteria. In this regard, alternative strategies have been proposed to minimize antimicrobial drug overuse in ruminants. These alternative procedures include alternatives for growth promotion (such as in-feed enzymes, probiotics, prebiotics, synbiotics, and antimicrobial peptides), alternatives for disease prevention (such as vaccines, immune modulators, chicken egg yolk antibodies, farm management, and biosecurity), and alternatives for disease treatment such as plant extracts and phage-therapy to antibiotics. These alternative methods should be safe and efficient without inducing microbial resistance.

Keywords: Antibiotic, Bacteria, Multidrug-resistant, Medicine, Ruminants

INTRODUCTION

The increase in bacteria that are resistant to antibiotics increases the need for research to find alternative strategies to reduce the use of antibiotics in animals (Aizawa et al., 20016; Alfredo and Rodríguez-Hernández, 2017; Abdalhamed et al., 2018). Alternatives products with antibiotics activity should be non-toxic, easily eliminated from the body, stable through the gastrointestinal tract, easily decomposed, friendly to the environment, selectively active against pathogens with minimum effects on host gut flora, and also have a positive impact on feed efficiency and promote growth. In addition, be effective for prevention and treatment against multidrug-resistant (MDR) bacterial pathogens (Ali and Dixit, 2012)

Alternatives strategies for prevention and control of MDR bacteria in ruminants include antibiotics for growth promotion (such as in-feed enzymes, probiotics, prebiotics and synbiotics, and antimicrobial peptides), alternatives to antibiotics for disease prevention (such as vaccines, immune modulators, chicken egg yolk antibodies, farm management, and biosecurity), alternatives to antibiotics for disease treatment (such as phytochemicals plant extracts and phage-therapy), and other alternatives for disease prevention include Nanoparticles (NPs) (Alwhibi and Soliman, 2014). Alternative methods may reduce antibiotic resistance but could not be a substitution for antibiotics (Aizawa et al., 20016; Babutan et al., 2021).

Antimicrobial peptides are host defense peptides, abundantly distributed in nature, and used as alternatives to antibiotic therapy, as they have direct and indirect inhibitory effects on pathogenic bacteria (Alfredo and Rodríguez-Hernández, 2017). Using vaccines against infectious diseases as an alternative therapy has attracted much attention because no resistance occurred against vaccines (Alwhibi and Soliman, 2014; Ike et al., 2021). Hypericin, an anthraquinone, has antimicrobial activity against methicillin-resistant and methicillin-sensitive *Staphylococcus* spp. (Alwhibi and Soliman, 2014; Abdalhamed et al., 2021; Ike et al., 2021). Combinations between different plant extracts and purified plant derivative compounds could be effective against drug-resistant bacteria. Various plant compounds and antibiotic complexes could be effective against MDR bacteria (Anadón 2006, Abdalhamed et al., 2022).

Studies have revealed that about 70 species of bacteria, including methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus* spp., are susceptible to honey which has extreme antimicrobial activities (Atmaca, 2016; Ike et al., 2021). Bacteriophages (phages) are viral predators of bacteria and are evaluated as a potential alternative to antibiotics for treating antibiotic-resistant bacteria in human and veterinary medicine (Bai et al., 2018). Therefore, the current review article aimed to shed light on strategies to prevent and control MDR bacteria in ruminants.

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Alternatives to antibiotics for growth promotion

Probiotics, prebiotics, and synbiotic

Probiotics are live strains (yeast, fungi, and bacteria) of strictly selected microorganisms administered in adequate amounts to improve the balance of microbial activity in the gastrointestinal tract of ruminants. *Lactobacillus (L.)*spp., *Bacillus spp., Enterococcus spp., Bifidobacterium spp., Micrococcus spp., Pediococcus spp., Streptococcus spp., Propionibacterium spp., Saccharomyces spp., Aspergillus spp.* are the most common species that have been evaluated for their ability to replace with antibiotics for growth promotion and control enteric pathogens in dairy and beef cows (Baird et al., 2017; Razavi et al. 2019). An experiment that administered a probiotic mixture containing *Lactobacillus (L.) acidophilus, L. helveticus, L. bulgaricus, L. lactic, Streptococcus thermophiles,* and *Enterococcus faecium* to sheep experimentally infected with a Non-O157 Shiga toxin-producing *Escherichia coli* (*E. coli*) indicated a decreased fecal shedding of the pathogen (Baird et al., 2017). Probiotics are used as feed additives to improve animal health and productivity, stimulate intestinal microbial flora, improve digestion, enhance nutrient absorption and bioavailability, prevent enteric pathogens' colonization, stabilize pH, and increase mucosal immunity. They could act as an ideal candidate for enhancing the general health condition of ruminants. *Lactobacillus acidophilus* fecal isolate and *Bifidobacterium pseudo catenulatum* SPM1309 showed a strong growth inhibitory effect against MDR *pseudomonas aeruginosa* and MDR *acinetobacter baumannii* (Banai et al., 2002; Balakrishnan et al., 2017). The *L. fermentum* supernatant with bovine lactoferrin had synergistic inhibitory activities against methicillin-resistant *Staphylococcus aureus* (MRSA) strains (Barbu et al., 2016; Abdalhamed et al., 2021). The combinations of *L.casei* and *L. rhamnosus* with antibiotics amikacin and gentamycin (GEN) have synergistic activities on *P. aeruginosa* (Barthod et al., 2018).

Prebiotics are non-digestible dietary elements preferentially digested in gut microbes, resulting in increased immune response against antimicrobial activity and consequently improving host health. Carbohydrates, such as oligosaccharides, polysaccharides, polyols, and protein hydrolyses, are the most frequent prebiotics utilized in animal feed additives (Abd El-Moez et al., 2013). Fructo-oligosaccharide, spray-dried bovine serum, and oligosaccharides have specific health effects and decrease the incidence of enteric diseases. Manna-blocked pathogen colonization in the intestinal tract of calves that is by yeast fermentation such as yeast culture, cell walls, refined functional carbohydrates, and mannan-oligosaccharide (MOS) is used as prebiotics (Bechinger and Gorr, 2016). Mannan-oligosaccharide may act to inhibit bacterial and *cryptosporidium* attachment to the intestinal wall. Also, *Bacillus subtilis* alters the rumen microbiome and improves digestion at weaning. The administration of oligosaccharides promotes desirable intestinal microflora and improved growth performance in weaned calves. Commercial prebiotic celmanax prevents entero hemorrhagic *E. coli* colonization in the cattle gastrointestinal tract (Bhola and Bhadekar, 2019). Supplementing animal feed with probiotics increases lactate and antibody synthesis, reduces intestinal pH, inhibits intestinal microflora, and reduces pathogen bacteria in the stomach (Blair et al., 2015). Synbiotics are probiotics and prebiotics together. They are created to boost health benefits in a particular way. Continuous oral co-administration of synbiotics, such as the *Bifidobacterium breve strain Yakult* and galactooligosaccharides, enhanced survival rates and protected mice in an in-vivo investigation when they were challenged with MDR *Acinetobacter baumannii*. (Bricknell and Dalmo, 2005). Synbiotics are natural and safe, also supported by several research findings for possible application in food animals for preventing, supporting therapy, and safe alternative to current antibiotics for reducing antimicrobial usage (Chanda et al., 2011; Castillo and Gatlin 2015; Castelani et al., 2019).

Antimicrobial peptides

Antimicrobial peptides are host defense peptides, abundantly distributed in nature, and are used as alternatives to antibiotic therapy. They have direct and indirect inhibitory effects on pathogenic bacteria (Castillo and Gatlin, 2015). They are expected to be the next generation of alternatives to antibiotic therapy for preventing bacterial resistance (Chanda et al., 2011). Antimicrobial peptides (AMPs) have broad-spectrum antimicrobial activities and are amphipathic. They have hydrophobic/cationic properties which bind with the phospholipid bilayer of the bacterial cell wall, causing cell wall portion and resulting in cell death (Chusri et al., 2009; Cheng et al., 2014; Chanda et al., 2011). The AMPs enhance nutrient digestibility and benefit the growth performance of large and small ruminants (Cianciosi et al., 2018). They are formed by ribosomally synthesized bacteriocins and non-ribosomal bacitracin, gramicidin, and polymyxin (Cheng et al., 2014). The A3, P5, and cecropin AD are three synthetic AMPs that control animal growth by fostering a healthy gut microbiome (Cianciosi et al., 2018). Bacitracin zinc and methylene salicylic acid have been approved as feed additives in USA and China (Counoupas et al., 2018). SMAP-29, a cathelicidin-derived peptide isolated from sheep myeloid mRNA, induces antimicrobial activity against MRSA, vancomycin-resistant *E. faecium. faecium* and *Pseudomonas (P.) aeruginosa*. Antibacterial peptides isolated from *Enterococcus mundtii* (ST4V) have inhibitory effects against multidrug-resistant *Streptococcus* species, *P. aeruginosa, Klebsiella pneumonia, Streptococcus (S.) pneumonia* and *Staphylococcus* (Crisol-Martínez et al., 2017). Peptide AP-CECT7121 is an antimicrobial peptide produced by *Enterococcus faecalis* CECT7121, with bactericidal activity against Gram-positive bacteria, an attractive candidate for its use as a natural therapeutic tool for the treatment of infections produced by multi-resistant *Staph. aureus* and vancomycin-resistant *Ent. faecium* isolated from humans and animals (Delany et al., 2014; Delpech et al., 2017).

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Dewul (2014) suggests that AMP is used in feed additives for goats to improve rumen microbiota, and food efficiency, preventing ruminal fermentation and potentiating growth performance (Dhama et al., 2014). Dini et al. (2011) declared that the substitution and modification of peptide amino acids could enhance their antibacterial activity and be effective against all MDR bacteria spp.

Bacteriocin

Bacteriocins are ribosomal synthesized AMPs that destroy pathogenic bacteria cell walls. Bacteriocins are subdivided based on their modifications into class I (lantibiotics) and class II (heat-stable) peptides (Doolan et al., 2014; Dorneles et al., 2015). The *P. aeruginosa* is susceptible to the antibiotic actions of bacteriocins; in particular, pyocin S5 was effective at a concentration 100 times lower than tobramycin. Lactic acid (LAB) commonly secrete bacteriocins, while colicins and microcins are produced from *E. coli* (Eja et al., 2011). Probiotics using lactic acid bacteria (LAB) and bacteriocins like nisin are the most commonly explored (Giguère et al ., 2013). Founou et al. (2016) indicated that bacteriocins act on cell walls and inhibit protein expression genes. Commercially available bacteriocin products can treat superficial and systemic bacterial infections. They have several potential applications in veterinary medicine as nisin-based teat sanitizers, amrubisin, Wipe- Out® Dairy, Wipes, and Mast Out® are alternatives for antibiotics in treating mastitis. A teat dip containing lantibiotic available for therapeutic uses against staphylococcal infection. It has been demonstrated to be highly effective against *S. aureus and S. dysgalactiae* (Giguère et al., 2013). Founou et al. (2016) revealed that multidrug-resistant *Staphylococcus spp*., which causes mastitis, may be controlled by cationic nisin/dioctadecyl dimethyl ammonium bromide NPs.

In-feed enzymes

By acting on feed components in the animal's gastrointestinal tract, several enzymes are added to animal feed to improve digestion processes and nutritional bioavailability (Giguère et al., 2013). In-feed Enzymes are crucial components for minimizing drug misuse and are a stimulant for animals' immune and overall health. The most popular feed enzymes are glycanase and phytase, offered commercially as feed additives (Hamasalim, 2016). The advantages of feed enzymes are optimizing digestion and enhanced nutrient availability of high-fiber ration in the rumen of ruminants (Hambleton et al., 1988). The direct impact of feed enzymes is on animals' natural immunity; the *β-mannanase* enzyme is commercially available as β-mannanase (CTCzyme®); it could decrease the somatic cell counts in cow's milk (Hana et al., 2016). In light of these findings, in-feed enzymes could be an effective alternative to antibiotics in controlling Antimicrobial Resistance (AMR) bacteria in dairy cattle (Hazam et al., 2019).

Alternatives to antibiotics for disease prevention

Vaccines

Vaccination is an effective strategy for preventing and eradicating infectious diseases worldwide; it could be used against AMR bacteria in humans and animals. The application of vaccines as an alternative therapy to antibiotics has attracted much attention since there was no vaccination resistance (Hu et al., 2017). The common licensed veterinary vaccines include live-attenuated, inactivated, or killed vaccines and toxoids (Table 1). Veterinary vaccines are ideal candidates for preventing infections, reducing antibiotic consumption, enhancing productivity, and reducing antibiotic resistance (Jalilsood et al., 2015). Although vaccination has become a potent weapon against drug-resistant bacteria, some bacteria could evade the protection that vaccines are induced; hence, frequent vaccination updates are necessary (Jin et al., 2019). Vaccine development is crucial in the area where AMR bacteria are endemic (Jorge and Dellagostin, 2017).

Inactivated killed vaccines

The inactivated vaccine is produced *in-vitro* by inactivated bacterial cultures and adjuvant with oil-base to enhance immune responses. They are inexpensive in production and stable in storage. Oil adjuvant inactivated emulsion vaccine for Hemorrhagic septicemia (type B:6) is used for active immunization against hemorrhagic septicemia and pneumonic pasteurellosis for cattle, buffaloes, sheep, and goat vaccinations as shown in Table 1 (Jin et al., 2019). Currently, most bacterial vaccines include living attenuated and inactivated or killed microbial strains with varying degrees of efficacy; for example, *Brucella* (*B.) abortus* (RB51) is a vaccine used for brucellosis prevention in cattle (Jorge et al., 2016). Killed *S. aureus* vaccines are also developed for bovine mastitis (Jouda et al., 2016).

Live-attenuated vaccines

Live attenuated vaccines are prepared by the passage of bacteria in an unusual host or cell after several passages of the bacterial strain in different media (Kahn et al., 2019). Unlike the anti-viral vaccine, which is quite mature, the availability of antibacterial vaccines is still rare in the market (Jouda et al., 2016). However, *Brucella abortus* strain 19 and strain RB 51 vaccines, both live attenuated vaccines produced from *Brucella abortus*, are the most often utilized brucellosis vaccines in actual practice. The *Brucella abortus* strain 19 vaccination could provide longer-lasting protection for young calves than RB51. Furthermore, the RB51 vaccine aids in distinguishing between animals that have received the vaccination and those that have been infected by not interfering with serological diagnosis (Kar et al., 2016, Table 1).

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Table 1. Vaccination schedules for bacterial diseases in ruminants

Disease	Type	Time of vaccination	Immunity	Dose/ route	Indication
Black Quarter	Formal killed vaccine	Once a year, before the monsoon	One season	5 ml/ SC	Against Black Quarter in cattle and other ruminants.
`Brucellosis	*B. abortus* Strain 19 smooth (live) attenuated	About 6 months of age	3-4 calving	2 ml/ SC to female calves between 4 to 8 months old	Protection of cattle, buffaloes against Brucellosis
	RB51 Live attenuated vaccine of B. *abortus* rough strain RB51	1-2 years	animals vaccinated annually	2ml as one or 2 doses at 30-day interval	Protection cattle, buffaloes, and sheep against brucellosis by *B. abortus*
	Living attenuated *B. Melitensis* vaccine	3 to 8 months			lambs and kids
Hemorrhagic Septicemia (HS) Vaccine	Inactivated HS Oil Adjuvant Vaccine (type B:6)	Once a year, before monsoon	One season	2 ml in cattle 1 ml in sheep, IM	Protection of cattle and sheep against HS and pneumonic pasteurellosis
• Clostridial diseases • ULTRABAC® 7 • Covexin 8 • Cubolac 8 • Covaccin 10 • Polyvalient clostridia vaccine	ULTRABAC® 7 vaccine	First dose 6 Weed of age second dose 4-6 weeks later/ Annual revaccination with a single dose	One season	5 mL/ SC	Protection against clostridial diseases: • blackleg – *Clestrodium chauvoei* • malignant edema – *Clostridium septicum* • black disease – *Clostridium novyi* • gas-gangrene – *Clostridium sordellii* • enterotoxemia, enteritis – *Clostridium perfringens* types B, C, and D
	Covexin 8 Polyvalent formalized killed vaccine		6 months	2 ml - sheep 5 ml cattle IM	Protects cattle, sheep, and goat against clostridial diseases
Mixed Vaccine	Inactivated Bovine Rota, Corona Viruses, and *E. Coli* Vaccine	2 doses at least two weeks apart to pregnant cows, the second dose given 2-3 weeks before calving.	One year	4 ml in pregnant cow or buffalo	against diarrhea caused by Rota, Coronaviruses, and *E. Coli*
Tuberculosis	BCG	About 6 months of age			To be repeated every 2-3 years
Anthrax	Spore	Once a year, before monsoon	One season	1ml, SC	

B. abortus: *Brucella abortus*, RB51: *Brucella abortus* attenuated strain RB51 vaccine (RB51), BCG: Bacille Calmette-Guérin, SC: Subcutaneous, IM: Intramuscular, HS: Hemorrhagic septicemia, *E. Coli: Escherichia coli*

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Toxoids

Toxoid vaccines are bacterial toxins that physically or chemically have treated until they no longer produce disease but retain the capacity to induce immunity (Karuppiah and Rajaram, 2012). They are currently used commercially as single toxoid vaccines such as toxoid from *Corynebacterium pseudotuberculosis* causing *caseous Lymphadenitis*, and combined *Clostridium perfringens* Types C and D and tetanus (CD-T vaccine) for Sheep and goats (Karuppiah and Rajaram, 2012)

Recombinant vaccines

The DNA, subunit, and vector vaccinations are the three types of recombinant vaccines. Insertion cloning of a DNA segment into a vector is used to create recombinant vaccines. Recombinant DNA vaccines develop pathogenic agent-specific proteins, whereas subunit vaccines synthesize a recombinant protein in vitro and are injected into the host. Recombinant vector vaccines employ an attenuated bacterium to either proliferate and express the antigen within the host or multiply and express the antigen outside the host (Váradi et al., 2017). Advanced recombinant vaccines are unquestionably the future vaccines for animal disease prevention that develop safe, effective, and comprehensive protection against various infections. Before field trials, recombinant vaccinations must be safe for both the host and the environment (Kazemi et al., 2014). Recombinant *Bacillus* Calmette–Guérin (BCG) vaccine is vectored vaccine such as Ag85B antigen (a protein found on the bacterial surface) for cattle that showed protective immune responses against *Mycobacterium bovis* (Khulbe and Sati 2005). Various approaches have been investigated for vaccine development against *S. aureus* in bovine mastitis, including whole organism vaccines, live attenuated *S. aureus*, capsular-polysaccharide–protein conjugate vaccines, DNA vaccines encoding clumping factor A, and recombinant *S. aureus*-mutated enterotoxin type C (Kon and Rai 2012).

Immunostimulants

Immunostimulants are chemicals that activate phagocytes, and neutrophils and are the alternative complement system to lysozyme activity to boost the innate immune system of the hosts in a non-specific manner to promote resistance to the disease (Landers et al., 2012). By releasing cytokines and cytokine inhibitors, non-specific anti-inflammatory drugs (steroids), and changing a particular antigen-based response through interferons, immunostimulants regulate the immune response to pathogen assault (Langeveld et al., 2014). Some bacterial substances (-glucans) and different plant constituents could directly initiate innate defense mechanisms by expressing intracellular gene(s) and controlling antimicrobial compound production. Animals' natural immune protection against pathogenic bacterial assault might be improved by using immunostimulants as feed additives during stressful times (Liu et al., 2017; Lewis, 2018).

Chicken egg yolk antibodies

Chicken egg yolk antibodies (IgY) are immunoglobulin of birds, reptiles, and amphibians that transfer passive immunity to their embryos and offspring (Lubroth et al., 2007). Chicken IgY is used as an alternative to antibiotics for treating diarrhea in young calves (Figure 1). Also, IgY or hyperimmune egg products are commercially available worldwide to improve health and prevent enteric pathogens in young livestock. Now many companies are focusing on establishing and producing IgY for animal feed supplementation (Mabrouk, 2012). The oral administration of IgY to calves is commercially available against various intestinal pathogens, such as bovine enterotoxigenic *E. coli* and *Salmonella* spp. (Marquardt and Li, 2019). Data availability *in-vivo* about IgY in clinical trials indicates the possibility of using it as an alternative to current antibiotics (McCaughey et al., 2014).

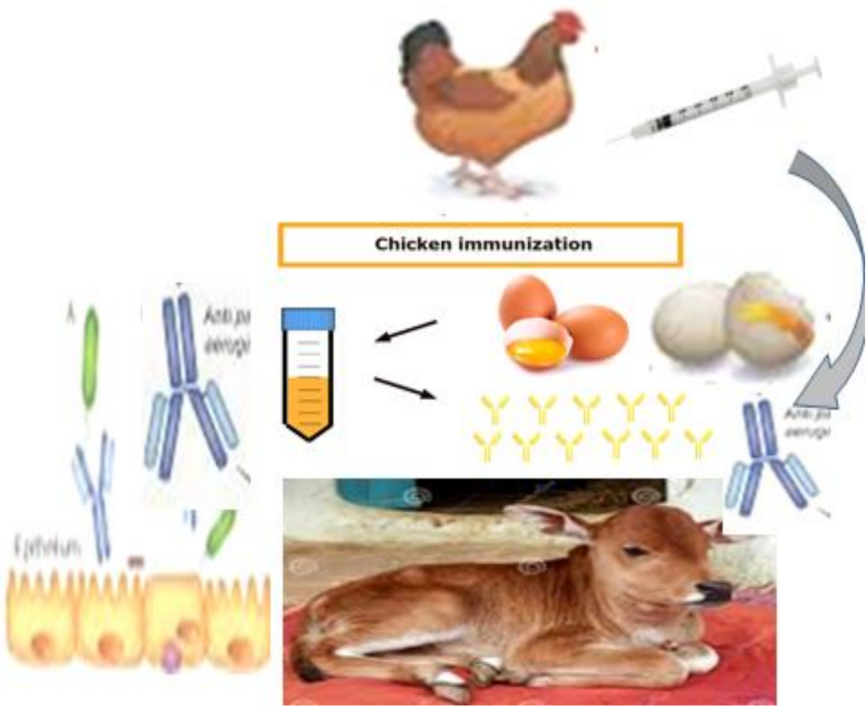

Figure 1. Hyperimmune egg-yolk antibodies as a prophylaxis and treatment of intestinal microbial diseases in livestock prepared in a dry form by spray- or freeze-drying and incorporated diet with egg yolk

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Alternatives to antibiotics for disease treatment

Plant-derived phytochemicals

Phytochemicals (phytobiotics or phytogenics) are natural bioactive compounds that originated from plants to treat MDR bacteria in ruminants or used as growth promoters (McCaughey et al., 2014; Marquardt and Li, 2018). Plant parts and extracts are mostly affordable, readily available, natural, and non-toxic. Quinones, alkaloids, flavonoids, phenols, terpenoids, essential oils, tannins, lignans, glucosinolates, and a few secondary metabolites are among the phytochemicals' bioactive constituents. Some antimicrobial agents of plants include peptides that possess antimicrobial activity against *P. aeruginosa* (Meeusen et al., 2019). Hypericin, an anthraquinone, had antimicrobial activity against methicillin-resistant and methicillin-sensitive *Staphylococcus* spp. An alkaloid called berberine has antibacterial properties against *S. Agalactiae*. Berberine, and its DNA-binding actions damage the bacterial cell membrane structure and cause cell death by making the membrane more permeable (Pliasas et al., 2022). A study showed the potent antibacterial properties of garlic against resistant bacterial strains, including *P. aeruginosa* (Molan and Rhodes, 2015). Methanol and chloroform extracts of Fenugreek (*Trigonella foenum-graecum)* inhibit *E. coli* (Mushtaq et al., 2016). *Thalictrum minus* extract showed antibacterial activities varied between the bacterial species, while 5-Hydroxy-thalidasine has good antibacterial activities in combination with ampicillin, chloramphenicol, and streptomycin against MDR. Anthraquinones and saponins in aloe vera have direct antibacterial effects (Okeke et al., 2011). Curcumin (CUR) and *Nigella sativa* have inhibitory effects against *S. cereus, and S. aureus* (Pachón-Ibanez et al., 2017). Egyptian honey, black cumin, and essential onion oils have an inhibitory effect against Gram-negative and positive AMR bacteria isolated from small ruminants with mastitis, with inhibitory zone diameter (IZD) of 13 mm to 28 mm and a minimum inhibitory concentration (MIC) of 3.25 to 25 mg/mL (Pariza and Cook, 2017). The IZD of *Comiphora (c.) molmol oils* extract against AMR *Pseudomonas spp.* isolated from dairy cows and buffaloes with mild mastitis varied from 3.25 and 6.25mg/mL (Payne, 2015). Peña-González et al. (2017) reported that the MIC of *C. molmol* methanolic extracts was 3.12 mg/mL for *E. coli*, *Klebsiella (K.) pneumoniae,* and *P.aeruginosa*. Meanwhile, it was 12.5 mg/mL for *A. baumannii*, and 6.25 mg/mL for *S. aureus*.

Combination therapy among herbal antimicrobials

Combinations between different plant extracts and purified plant derivative compounds synergize against drug-resistant bacteria (Purwanti and Yuwanta, 2014). The synergistic inhibitory effects of other fruits and leaves plant extracts (aqueous and ethanolic) of *Foeniculum vulgare, Priminellaanisum, Carumcarvi, Majorana hortensis, Mentha longifolia, and Salvia officinalis medicinal* plants reported on multi-drug-resistant *E. coli* O157:H7 isolated from human, cattle, and foods (Raguvaran et al., 2015). When tested individually, the aqueous extracts of *Foeniculum vulgare* had 1.4 cm (IZD) inhibition zone on E. coli O157:H7. Meanwhile, combining aqueous extracts of *Foeniculum vulgare, Priminellaanisum, and Carumcarvi* (1:1:1) had synergistic antibacterial effects against resistant *E. coli* with an inhibition zone of 4 cm . *Thymus vulgaris* combined with *Cinnamomum zeylonicum* essential oils have antibacterial activity against *E. coli* and *S. aureus*, which is indicated by the synergistic effect of the combination between *T. vulgaris*, *C. zeylonicum*on, and *S. aureus with* fractional inhibitory concentration (FIC) index of 0.26 (Ražná et al., 2020).

Combination between plant derivatives and antibiotics

The combination of plant compounds and antibiotics complexes synergizes against MDR bacteria. Synergistic effects were observed between tea extract and chloramphenicol against enteropathogens such as *Salmonella* (*Sa.) Typhimurium, Sa. Typhi, Sa. dysenteriae, Yersinia enterocolitica*, and *E. coli.* The synergistic inhibitory effects of chloramphenicol and tea extract against *S. Dysenteria were* 2.5 μg /mL (MIC 5 μg/mL) and 5.094 mg/ (MIC 9.089 mg/mL). The essential oil of *Helichrysum italicum* had inhibitory effects against *MDR E. coli* , *P. aeruginosa*, and *A. baumannii*, and when combined with beta-lactams, quinolones, and chloramphenicol increased their antimicrobial effects (Reinhardt, 2017). Mixing of ellagic and tannic acids enhanced the antibacterial activities of novobiocin, clorobiocin, rifampicin, and fusidic acid against *Acinetobacter baumannii* (Ren et al., 2019). A combination of ampicillin with *A. sativum* and, *Gongronema latifolium* extracts had additive effects and synergism against *S. aureus* (Rizzi et al., 2012). The synergistic activity between *Salvia officinalis* and *Cichorium intybus* extracts with amoxicillin and chloramphenicol against *S. aureus, E. coli, P. aeruginosa, B.subtilis, E.cloacae, K. pneumoniae, and P. mirabilis* has been noted (Rodriguez et al., 2002). The combination of *Coriandrum sativum* essential oil and gentamicin antibiotic has a synergistic effect. In contrast, the antagonistic effect was observed in the variety of *Coriandrum sativum* essential oil and erythromycin antibiotics on Gram-positive or Gram-negative bacteria (Salim et al., 2018).

Honey against multidrug-resistant bacteria

Honey has extreme antimicrobial activities. About 70 species of bacteria are susceptible to honey, including MRSA and vancomycin-resistant *Enterococcus spp.* (VRE). The antimicrobial effects of honey occur from different components, including flavonoids, phenols, high sugar concentration, acidity, and the production of hydrogen peroxide. Also, other types of honey have methylglyoxal, lysozyme, and defensin-1, which induce antibacterial activity (Ahmed and Ibrahim HM 2016). The Synergistic effect among all the bioactive components of honey is responsible for its intense antibacterial activity (Schatzschneider, 2019).

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Phage therapy

Bacteriophages (phages) are viral predators of bacteria, and they have the potential effect of being replaced with antibiotics for the treatment of antibiotic-resistant bacteria in humans and animals. Lytic phages *(Phagetherapy*) are used to treat MDR bacteria, while temperate phage is unsuitable. Bacteriophages integrate their genome into the bacterial host DNA and transfer virulence factors, including antibiotic resistance genes, to targeted pathogenic bacteria (Figures 2 and 3). However, it is challenging to discover lytic phages specific to all bacterial diseases in the cattle industry (Sharma et al., 2018). Phages can interact with bacterial-specific binding sites on specific pathogenic bacteria by tail fibers without harming beneficial microflora. Commercial phages were introduced by many companies in the USA and France (Sharma et al., 2017).

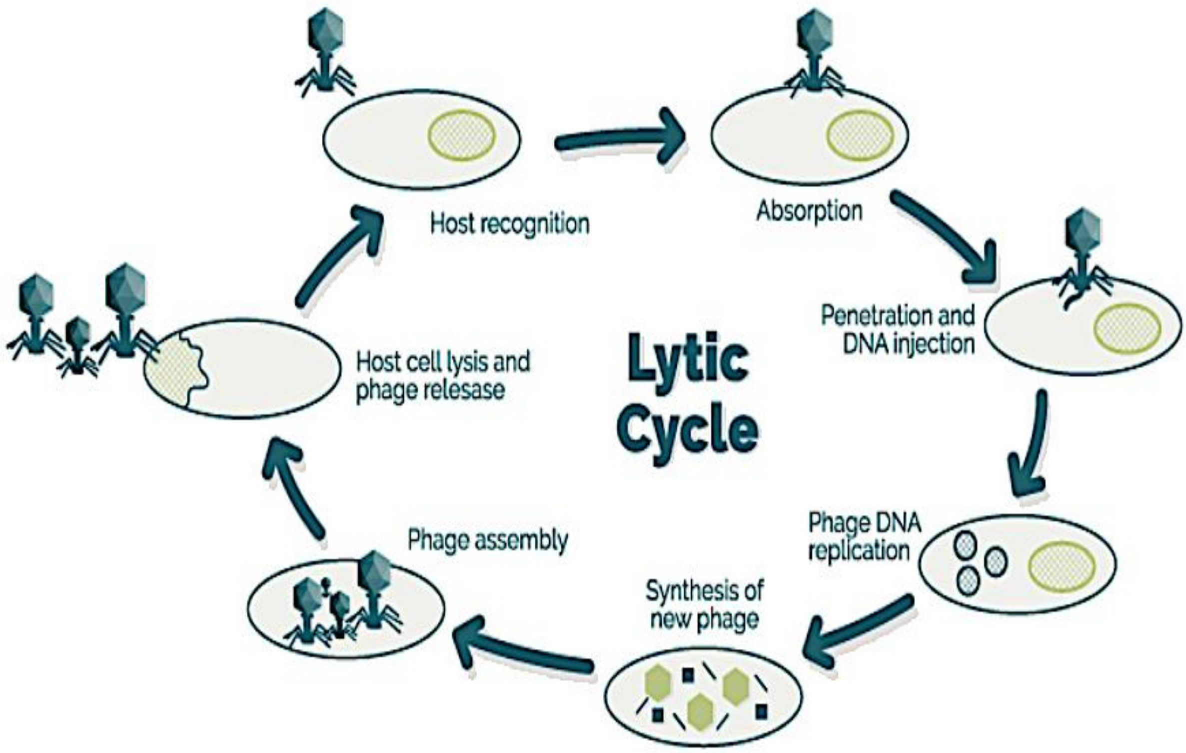

Figure 2. Differentiation between phages and lytic phages cycles (https://coliphages.com/index.php/reproduction/ with UploadWizard)

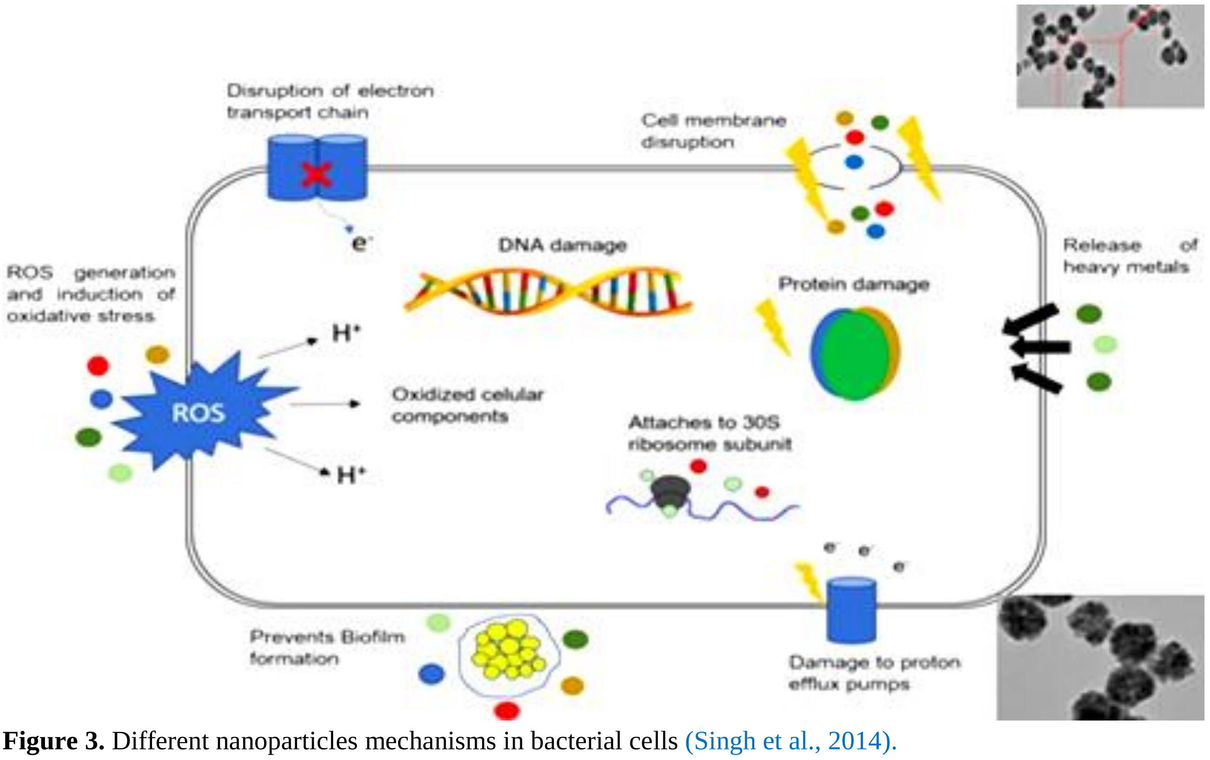

Figure 3. Different nanoparticles mechanisms in bacterial cells (Singh et al., 2014).

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Applications of nanoparticles for the prevention and treatment of multidrug-resistant bacteria

Nanotechnology has evolved into a novel, significant branch of science with broader applications in veterinary sciences, particularly against MDR bacteria (Tawfick and Gad, 2014; Suzuki et al., 2014; Siddiqi et al., 2018; Simons et al., 2020). Nanoparticles have antibacterial properties and include silver (Ag), iron oxide(Fe_3O_4), titanium oxide(TiO_2), copper oxide (CuO), gold (Au NPs), zinc oxide (ZnO), chitosan, carbon nanotubes. The antimicrobial mechanisms of NPs acted directly on the bacterial cell wall, preventing biofilm formation and triggering natural and acquired immune responses. They are produced by reactive oxygen species (ROS), which interact with DNA and proteins, as shown in the different bacterial mechanisms of NPs compared to standard antibiotics against MDR bacteria in Figure 3 (Varzakas et al., 2010; Vijayan et al., 2019).

The medicinal application of NPs for treating bovine mastitis is an important solution for treating MDR bacteria as an alternative to antibiotics against pathogenic bacteria. Wang et al. (2017) explored the synergistic activity of silver NPs and antibiotics by examining the antibacterial activity of AuNPs against *E. coli*, *Bacillus subtilis*, *S. aureus*, and *K. pneumonia* (Tiwari et al., 2005; Wittebole et al., 2014; Wang et al., 2017). They discovered that the MICs of AuNPs against the tested bacteria were 2.93 ug/ml, 7.56g/ml, 3.92 ug/ml, and 3.15 ug/ml, respectively. ZnONPs are used in animal health and production as an antibacterial, food preservative, and feed additive (Tiwari et al., 2005; Wittebole et al., 2014). Yew et al. (2016) reported that the different sizes of AuNPs successfully inhibited the growth of varying MDR bacteria, including MRSA. Zamek-Gliszczynski et al. (2018) mentioned that AgNPs and capsaicin have antibacterial characteristics and could effectively be used to inhibit the growth of MDR- extended-spectrum beta-lactamases (ESBL) producing *E. coli* of bovine origin (Thu et al., 2017; Zeedan et al., 2018). The AgNPS has a promising effect on AMR bacteria. AgNPs with an average size of 10 nm using biomolecule apigenin can inhibit cell viability and biofilm formation of MDR pathogenic bacteria such as *Prevotella Melaninogenica* and *Arcanobacterium pyogenes* isolated from uterine secretion (Zeedan et al., 2014).

Farm management and biosecurity control

Biosecurity is vital in controlling AMR bacteria and reducing antibiotic control of AMR bacteria in animals. It is defined as all actions to stop the spread of infectious diseases among people or animals on farms and in the surrounding environment. Biosecurity decreases the possibility of infectious agent spreading (Simons et al., 2020).

CONCLUSION

The rising antibiotic resistance and the lack of new antimicrobials have triggered scientists to develop an alternative for antimicrobial compounds to minimize antibiotics use. Some other options have been proposed to reduce antimicrobial drug overuse to overcome the increasing rate of MDR bacteria in ruminants. These alternative procedures include alternatives to antibiotics for growth promotion (such as in-feed enzymes, probiotics, prebiotics, synbiotics, and antimicrobial peptides), alternatives to antibiotics for disease prevention (such as vaccines, immune modulators, chicken egg yolk antibodies, farm management, and biosecurity), and alternatives to antibiotics for disease treatment such as plant extracts and phage-therapy. These alternative methods should be safe and efficient without inducing microbial resistance. These strategies reduce the need for antibiotics in animals and combat antibiotic-resistant bacteria. Besides, rapid and accurate diagnostic approaches which provide sufficient sensitivity and specificity are necessary for detecting resistance in bacterial pathogens to fight and solve this problem.

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Authors' contribution

Abeer M. Abdalhamed and Gamil SG Zeedan established the research idea and drafted the manuscript. Alaa A Ghazy shared in the conception of the research idea and helped in manuscript preparation.

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