Chapter

Bovine Respiratory Disease in Feedlot Cattle: Antimicrobial Resistance in Bovine Respiratory Bacterial Pathogens and Alternative Antimicrobial Approaches

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Abstract

Bovine respiratory disease (BRD) is the leading cause of morbidity and mortality in feedlot cattle in North America. The BRD is a complex multifactorial disease because its onset depends on the interaction between number of factors including host, environment, management and viral and bacterial infectious agents. The main bacterial pathogens associated with BRD are *Mannheimia haemolytica, Pasteurella multocida, Histophilus somni* and *Mycoplasma bovis.* Treatment and prevention of BRD in the feedlots are aimed mainly at bacterial pathogens through antimicrobial use. Although antimicrobial use has increased, the prevalence of BRD has also increased potentially due to the emergence of multidrug-resistant bacterial pathogens, which poses a serious threat to both animal and public health and necessitates the development of alternative antimicrobial approaches to mitigate BRD pathogens in feedlot cattle. The objective of this chapter is to provide a brief overview of pathogenesis of BRD, to review the current status of antimicrobial resistance in bacterial pathogens associated with BRD, and to discuss the potential antimicrobial alternative strategies, including probiotic and essential oil (EO) approaches, to mitigate bovine respiratory pathogens in feedlot cattle.

Keywords: bovine respiratory disease, bacterial pathogens, antimicrobial resistance, antimicrobial alternatives, feedlot cattle

1. Introduction

Cattle production is one of the important industries in North America, accounting for $78.2 billion (US) and $10.5 billion (Canada) in cash receipts during 2015. A substantial part of this economic benefit is derived from beef sector, where 10.6 and 2.5 million head of cattle and calves in the USA and Canada, respectively, were slaughtered for the beef market in 2015 [1, 2]. The number of beef cattle in the North American farms and ranches will continue to increase over the next decade

due to the growing red meat demand by an increasing world population, with an estimated increase from 7.6 billion people in 2017 to 8.6 billion people in 2030 [3].

Despite advances in veterinary medicine, animal husbandry and animal welfare, economic impacts of cattle disease on the beef cattle industry still remain significant, with BRD being the most significant health problem in modern feedlot industry in North America. Bovine respiratory disease is commonly associated with pneumonia in nursing beef calves and recently weaned feedlot cattle. Cattle are mostly affected by BRD within the first 45 days after feedlot placement [4, 5]. According to the Feedlot 2011 study conducted by the National Animal Health Monitoring System (NAHMS), 97% of feedlots across the USA reported having cattle with BRD, and 16.2% of the cattle in a feedlot were affected by BRD during the feeding period [6]. The annual financial loss attributed to BRD, including mortality, reduced feed efficiency and performance and treatment costs, has been estimated to be more than $4 billion to the US beef industry [7]. This loss surpasses the economic losses incurred by all other cattle diseases combined [8], given that BRD accounts for 70–80% of all morbidity and 40–50% of all mortality in the US feedlots [9].

Bovine respiratory disease is a complex disease with a multitude of stressors that predispose cattle to viral and bacterial infection. *Mannheimia haemolytica*, *Pasteurella multocida*, *Histophilus somni* and *Mycoplasma bovis* are the main bacterial pathogens involved in BRD and are, therefore, the main targets of antimicrobial treatments to control BRD [10]. In the North American feedlots, cattle considered at high risk for the development of clinical BRD signs are often given antimicrobial metaphylaxis upon feedlot arrival to prevent BRD [11]. However, recent studies have shown the emergence of BRD bacterial pathogens that are resistant to several classes of antibiotics used to both control and treat BRD [12–14]. The multidrug resistance in BRD pathogens towards particularly tilmicosin, tulathromycin and oxytetracycline has been increased in feedlot cattle in the last decade [15], and such increase may partially due to the increased use of these antibiotics as metaphylaxis. The continued rise in AMR in BRD bacterial pathogens necessitates the developing antimicrobial alternative approaches to mitigate bacterial pathogens associated with BRD in feedlot cattle. Recent research results suggest the potential use of probiotic and essential oil (EO) as antibiotic alternative approaches to mitigate bovine respiratory pathogens [16, 17]. The objective of this chapter is to provide a brief overview of pathogenesis of BRD, to review the current status of antimicrobial resistance in bacterial pathogens associated with BRD and to discuss the potential antimicrobial alternative strategies, including probiotic and EO approaches, to mitigate bovine respiratory pathogens in feedlot cattle.

2. Bovine respiratory disease (BRD)

2.1 Pathogenesis of BRD

2.1.1 Predisposing factors

Bovine respiratory disease, also known as a shipping fever, is a complex multifactorial disease because its onset depends on the interaction between number of factors including host, environment, management and viral and bacterial infectious agents (**Figure 1**) [18]. The host factors predisposing cattle to BRD include age, body weight, immune status and genetics [18]. The age and body weight of the calves entering the feedlot are, in most cases, inversely correlated with disease

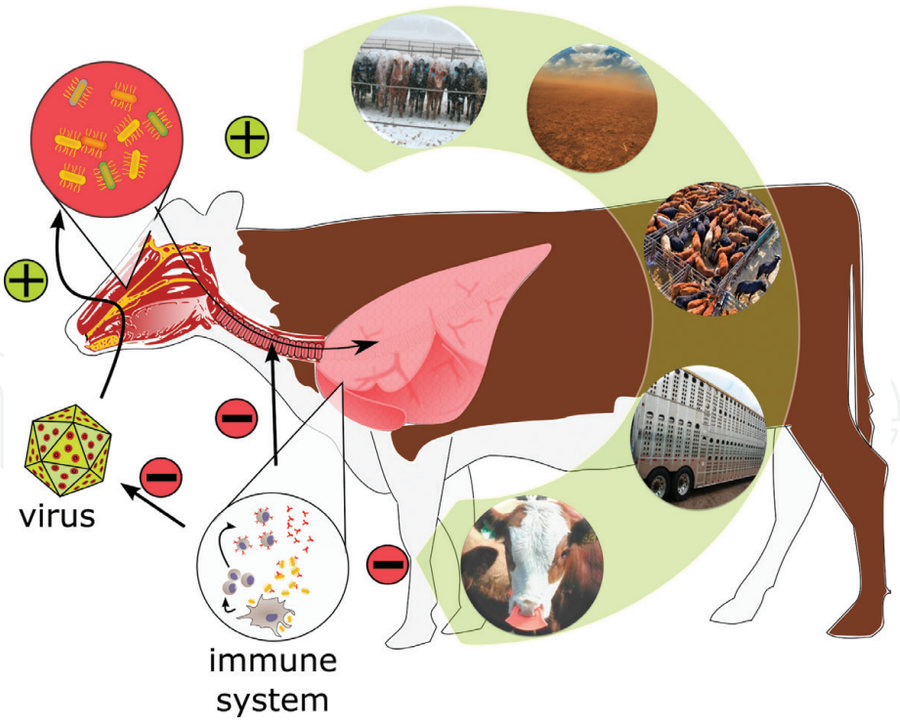

Figure 1.
Schematic overview of the pathogenesis of bovine respiratory disease in cattle.

susceptibility to BRD during the feeding phase [19, 20]. Shipping is the leading environmental risk factor for BRD due to the fact that almost all cattle placed in the feedlot are transported from elsewhere. Transportation distance has a negative impact on the animal resistance to the development of BRD owing to the stress and body weight loss that occur during the transportation [18]. In addition, commingling with other cattle in sale barns is an important management factor predisposing cattle to BRD. Because sale barn cattle have greater exposure to pathogens and stress as a result of mixing with cattle from multiple sources, feedlot cattle purchased from sale barn are often at greater risk for BRD compared to the ones purchased directly from the farm or ranch. Of note, the host, environment and management factors discussed above are necessary but not always sufficient to cause pneumonia, and thus, additional predisposing factors, such as viral infection, are often necessary to produce bacterial pneumonia [18].

2.1.2 Viral agents

The most common viral agents associated with BRD include bovine herpesvirus type 1 (BHV-1), parainfluenza-3 virus (PI3), bovine viral diarrhea virus (BVDV) and bovine respiratory syncytial virus (BRSV) [13]. These viral pathogens can induce primary infection with mild clinical signs of BRD and predispose cattle to bacterial infection [18, 21]. Viral infection can impair the mucosal barrier and respiratory pathogen clearance, damage the lung parenchyma and suppress immune responses in cattle. Combined, the effects of viral infection facilitate the proliferation of opportunistic bacterial pathogens in the upper respiratory tract and translocation of these pathogens into the lung and cause infections to the compromised lung [21]. A recent human study suggested that respiratory viruses can also affect the structure and composition of nasal microbiota, which may be another way through which virus weakens host resistance to bacterial pathogens [22].

2.1.3 Bacterial agents

The main bacterial pathogens associated with BRD are *M. haemolytica, P. multocida, H. somni* and *M. bovis* [10]. *M. haemolytica* is the principal bacterial agent of BRD and has a considerable economic impact on the North American feedlot industry. It is a small, Gram-negative and facultative anaerobic bacterium that commonly exists as a part of nasopharyngeal and tonsillar crypt microbiota in healthy cattle and sheep [23]. To date, 12 different (1, 2, 5–9, 12–14 and 16–17) capsular serotypes have been identified within *M. haemolytica* [23]. Among these serotypes, serotype 1 (S1), serotype 2 (S2) and serotype 6 (S6) are most frequently isolated from feedlot cattle, with the S1 and S6 being the most prevalent in bovine infection [24, 25]. *M. haemolytica* residing in the upper respiratory tract of healthy cattle maintains a commensal relationship with the host due to the containment by the local microbiota and host immunity [23]. However, when the local microbiota and host immunity get disrupted by stress and viral infections, this opportunistic bacterium proliferates in the upper respiratory tract and then translocates into the lung where it induces acute infection characteristics to fibrinous pneumonia [23]. *M. haemolytica*-induced pathogenesis is accomplished through a combination of virulence factors including outer membrane proteins, leukotoxin (Lkt), lipopolysaccharide (LPS) and lipoproteins [23]. The outer membrane proteins, such as adhesion protein, facilitate attachment and colonization of *M. haemolytica* to the bovine respiratory cells. The Lkt, being the most important virulence factor, attracts neutrophils and macrophages to the site of infection when it is present in low concentration. High levels of Lkt, however, induce cell death of leukocytes and phagocytes, allowing *M. haemolytica* to evade the detection and destruction by the host immune system. The other virulent factors, including LPS and lipoproteins, are involved in hemorrhage, edema, hypoxemia and acute inflammation [10]. The virulence factors of *M. haemolytica* differ among different serotypes, and such difference has been reported to attribute to the genetic differences among serotypes [25].

P. multocida and *H. somni* are also opportunistic BRD pathogens and are involved in the development of bronchopneumonia in cattle with clinical signs indistinguishable from pneumonia caused by *M. haemolytica*. The isolation rate of *P. multocida* and *H. somni* from clinically healthy cattle at feedlot entry is relatively high ranging from 15% up to 60% [10], suggesting they predominately exist as part of normal nasopharyngeal flora in healthy cattle. However, the isolation rate of these two pathogens is higher in the lower respiratory tract of feedlot cattle affected by BRD compared to healthy cattle [13]. The main virulence factors identified in *P. multocida* include a LPS, a cytotoxin, and iron acquisition proteins [10]. *H. somni* virulence factors include expression of immunoglobulin-binding proteins, survival in phagocytic cells, induction of apoptosis in endothelial cells, antigenic phase variation and endotoxic activity of the LPS and biofilm formation [10].

Compared to the other three BRD bacterial pathogens, *M. bovis* is the least characterized BRD pathogen. This bacterium lacks a cell wall and is fastidious, requiring specialized media and techniques for its isolation and culture. *M. bovis* is often associated with chronic pneumonia, and its mechanism of actions remains poorly understood [10].

2.2 Current prevention and control strategies for BRD in feedlots

Prevention and control of BRD in large commercial feedlots in North America are aimed mainly at bacterial pathogens, through the use of antimicrobials and vaccination programs. Cattle considered at high risk for the development of BRD are often given metaphylactic antimicrobials upon feedlot arrival [26]. Metaphylaxis

is defined as the mass treatment of an entire group or population of cattle with an antimicrobial to prevent and minimize an expected outbreak of disease [26]. Overall, 59.3% of feedlots in the USA with a capacity of >1000 head cattle use injective metaphylaxis, with approximately 21.3% of the cattle placed in the feedlot, receive metaphylactic antibiotics [6]. In Western Canada, more than 80% of the cattle in some feedlots receive injectable metaphylactic antibiotics on arrival to the feedlot (Personal communication with Dr. Steve Hendrick, Coaldale Vet Clinic, Alberta, Canada). The decision for metaphylactic intervention is primarily based on the nature of cattle population arriving at the feedlot. Cattle populations that are lighter body weight, multiple sources origin, and have poor health history and experienced long distance travel are often subjected to metaphylactic treatment at feedlot entry [26]. Metaphylactic treatment reduces BRD-associated morbidity and mortality by eradicating the already existing bacterial infections and preventing colonization and proliferation of pathogens in those immunosuppressed and vulnerable animals. Although efficacy of metaphylaxis to reduce BRD incidence in feedlots and subsequently improve cattle performance and carcass characteristics has been relatively well documented [26, 27], metaphylaxis is facing more and more public scrutiny due to the increased antimicrobial resistance in BRD pathogens, as well as increased public and scientific concerns regarding the overuse of antimicrobials in livestock production.

Bacterial vaccination is another common practice for the prevention of BRD in feedlot cattle in North America. There are a number of commercial vaccines available against *M. haemolytica*, *P. multocida*, *H. somni* and *M. bovis* [28]. These vaccines are made from bacterins or killed whole bacterium. Bacterial vaccines are less frequently used in feedlots compared to virus vaccines. This might be due to the controversial and limited efficacy of these vaccines against BRD bacterial pathogens [28].

2.3 Current challenges associated with BRD prevention: antimicrobial resistance

Despite advances in antimicrobials and vaccines, increased metaphylactic use and best management efforts to mitigate BRD, the prevalence of BRD in feedlot cattle continues to be increasing [9]. Although data are lacking, one contributor to increased BRD prevalence might be the development and spread of AMR in BRD pathogens. Recent studies have shown the emergence of BRD bacterial pathogens that are resistant to all classes of antibiotics used to treat BRD. For example, *P. multocida* strain isolated from a cow that died of BRD in Alberta has shown resistance up to five different antibiotics commonly used to control BRD (Alexander lab, unpublished data). *M. haemolytica* isolates isolated from Canadian and the US feedlots also exhibited resistance to more than three antibiotics [12, 13, 29]. Multidrug-resistant *H. somni* isolates have also been detected in Albertan feedlots [13].

The prevalence of multidrug-resistant BRD bacterial pathogens is relatively high and increasing in both Canadian and the US feedlots over the years [30]. A recent study conducted in commercial feedlots in Alberta, Canada, revealed that there were significantly high levels of resistance (>70%) against tulathromycin and oxytetracycline in *M. haemolytica* and *P. multocida* isolates and high levels of resistance against oxytetracycline (67%) and penicillin (52%) in *H. somni* isolates isolated from the lower respiratory tract of feedlot cattle with (n = 210) and without (n = 107) BRD [13]. Likewise, Anholt et al. [31] observed that 100% of the *M. haemolytica* (n = 233), *P. multocida* (n = 117) and *M. bovis* (n = 226) and 67% of the *H. somni* (n = 75) isolates isolated from both living and dead BRD-affected cattle, originated from 60 different commercial feedlots in southern Alberta, exhibited resistance towards at least one antimicrobial class. Over 90% of all isolates (n = 745) displayed resistance to macrolide antimicrobials, which are the class of antibiotics

commonly used as metaphylaxis. Furthermore, Snyder et al. [14] also reported that a significant increase (from 3.7 to 99.2%) in the prevalence of *M. haemolytica* isolates resistant to tulathromycin in newly received feedlot cattle (n = 169) within 2 weeks after tulathromycin was given as metaphylaxis.

Three or more resistant genes have been detected from *M. haemolytica* and *P. multocida* [15, 29]. These resistant genes are most likely occurring from *de novo* mutation or being acquired from other bacteria. It has been reported that some resistant genes present in BRD bacterial pathogens are being encoded in self-transmissible conjugative elements [15]. Klima et al. [29] identified *M. haemolytica, P. multocida* and *H. somni* isolates from the US and Albertan feedlots that contain integrative conjugative elements (ICE) that conferred resistance up to seven different antimicrobial classes. These ICE can be transferred not only from one BRD pathogens to another BRD pathogen but also to other non-BRD-related bacteria (e.g. *E. coli*) via conjugation [29].

The resistant BRD-related pathogens can not only cause substantial profitability losses to the beef industry and animal welfare issues due to the higher disease relapse and mortality rate but also pose potential threat to the public health given the possibility of these transferable elements carrying resistant genes transfer into zoonotic pathogens. Therefore, counteracting measurements to reduce the development and spread of AMR in BRD pathogens are urgently needed.

3. Alternative antimicrobial approaches to mitigate BRD bacterial pathogens

3.1 Probiotics

Probiotics are defined as "live microorganisms administered in adequate amounts that confer a beneficial health effect on the host" [32]. The scientific recognition of the health-promoting properties of live microbes began in the early 1900s when a Ukrainian scientist, Elias Metchnikoff, hypothesized that the beneficial microbes present in fermented milk could normalize bowel health and prolong life by inhibiting 'putrefactive' bacteria in the gut [32]. Then, lactic acid bacteria (LAB) strains isolated from fermented milk were commercialized with the intention to treat diarrhea in French children in 1906. The term probiotics has been used since 1962. In the past 2 decades, a significant research attention has been given to probiotics, and beneficial effects of probiotics for the mitigation of infections of oral cavity; respiratory, urogenital and gastrointestinal tract [33]; cancer [34] and obesity [35] have been identified.

Bacteria being used as probiotics today include LAB, non-pathogenic *Escherichia coli* and *Bacilli* [36]. The *Lactobacilli* and *Bifidobacteria* genera are the most commonly used as probiotics due to their specific health benefits, high safety profile, and stability [37, 38]. Probiotic bacterium possess unique genetic tools, special membrane structure and composition that allow them to survive under different environmental conditions after ingestion, adhere to the target niche, adapt to special nutrition conditions and integrate with the local microbiota [37].

3.1.1 Mechanisms of probiotic action

Probiotics deliver their beneficial effects to the host through direct inhibition against potential pathogenic bacteria, improving the epithelial barrier function, stimulating the host immune system and re-establishing the commensal microbial community [37]. Probiotic bacteria can directly inhibit pathogens by producing

antimicrobial compounds such as lactic acid and bacteriocins. They can also prevent adherence of pathogenic bacteria to the host cells via competitive exclusion, as probiotic strains use the same binding sites as the pathogenic bacteria or downregulate the expression of pathogen-binding sites [37]. Probiotic *Lactobacilli* have also been reported to preserve intestinal epithelial barrier function through stimulating mucin secretion, strengthening tight junction and preventing epithelial cell death and thereby inhibit pathogen translocation [37].

In addition, probiotics have the potential to boost host immune defenses against pathogens by modulating immune response [39]. Probiotics regulate innate and adaptive immune response by modulating immune cells and cytokine production via toll-like receptor-regulated signaling pathways [40]. Probiotic-induced alterations in the functions of dendritic cells, macrophages and T lymphocytes have been documented. For example, probiotic *Lactobacillus* strains modulated dendritic cells and thereby altered cell surface antigen expression and cytokine production in dendritic cells [37, 40]. Additionally, the impact of lactobacillus strains on macrophage function and its TNF-α production capacity has also been reported [41]. Probiotic bacteria *L. acidophilus* influenced the activity of regulatory T cells (Tregs) *in vitro* and *in vivo* in mice [42]. Tregs play a vital role in suppressing inflammation and maintaining immune tolerance.

Modulating the balance of pro- and anti-inflammatory cytokine production is one of the most important mechanisms through which probiotics protect the host from pathogen-induced injury and inflammation [43]. Probiotic bacteria have induced anti-inflammatory cytokine, IL-10, in dendritic and regulatory T cells [43]. IL-10, also known as the master regulator of immunity to infection, plays an essential role in facilitating the optimal pathogen clearance by inhibiting the activity of Th1 cells, NK cells and macrophages [44]. In addition, probiotics inhibit pro-inflammatory cytokine production and thereby prevent excessive inflammation. Probiotic strain *L. rhamnosus* GG inhibited the LPS-stimulated TNF-α production in murine macrophages [45]. Also, *L. rhamnosus* GR-1 strain has significantly or partially reduced LPS-induced number of proinflammatory cytokines including TNF, IFN-γ, IL-1β, IL-2 and IL-6 in human decidual cells [46]. Of note, the immune modulation properties of probiotics are species- and strain-specific, and therefore, different species or different strains within a species are expected to have different immunomodulation properties [37].

The role of probiotics on the local microbiota starts to be better understood due to the completion of the human genome project and the development of next generation DNA sequencing platforms that enabled a deeper understanding of the structure and composition of the host microbiome. Studies suggest that probiotics may re-establish the composition of the gut microbiota and confer beneficial effects on the gut microbial communities [47, 48]. However, there is limited information available with respect to the effects of probiotics on respiratory microbiota. A very recently published study showed that the oral probiotics alter respiratory microbiota of healthy cats [49]. The orally ingested probiotics were detected in the respiratory tract of the cat and were also associated with changes in richness and the overall composition of colonizing microbial populations of the respiratory tract. This observation points out that oral probiotics could alter the respiratory microbiota.

3.1.2 Using probiotics to mitigate BRD bacterial pathogens

Beneficial effects of probiotics in the prevention and control of human respiratory tract infections have been studied. For example, probiotic strain *Streptococcus salivarius* K12 can mitigate pharyngitis by inhibiting the colonization of pathogen

Streptococcus pyogenes and stimulating anti-inflammatory response in epithelial cells [50, 51]. A recent study revealed that the relative abundance of nasopharyngeal LAB in cattle entering the feedlot was significantly greater in animals that remained healthy compared with those that developed BRD [52], suggesting that a certain LAB are important to bovine respiratory mucosal health. Furthermore, an *in vitro* pilot study that we conducted to test antimicrobial properties of commercially available LAB strains (*Lactobacillus*) against *M. haemolytica* demonstrated the possibility of using probiotics to mitigate BRD pathogens [53]. The *Lactobacillus* strains isolated from the nasopharynx of healthy feedlot cattle displayed antimicrobial activity against the growth of *M. haemolytica in vitro* [54]. We also recently reported that the intranasal inoculation of *Lactobacillus* spp. strains inhibits the colonization of *M. haemolytica* S1 into the nasopharynx of dairy calves challenged with *M. haemolytica* S1 (Amat et al., unpublished data). These studies suggest the potential application of probiotics to mitigate BRD bacterial pathogens in feedlot cattle as an alternative to antimicrobial metaphylaxis.

3.2 Essential oils

Essential oils (EOs) from aromatic and medicinal plants are receiving increased scientific attention because of their long history of being sources of natural antimicrobial substances for the treatment of infectious diseases [55]. Thanks to their natural mixture of very complex chemical composition, EOs have shown a broad range of antimicrobial activities against both Gram-negative and Gram-positive bacterial pathogens and have long been used for respiratory tract infections (**Figure 2**) [56, 57]. For example, respiratory pathogens including *Streptococcus pyogenes*, *S. pneumonia* and *Escherichia coli* were effectively inhibited by EOs of cinnamon bark, thyme and spotted beebalm *in vitro* [58].

Interestingly, EOs exhibit minimal effects on LAB including *Lactobacilli* and *Bifidobacteria* that are commonly used as probiotics [59], suggesting EOs may have limited negative effects on beneficial bacteria within the host microbiota. The EOs showed higher minimal inhibition concentration (MIC) values for the probiotic bacteria, whereas it was effective in much lesser concentration against pathogenic bacteria in gastrointestinal tract [59]. Saguibo et al. [60] reported that some probiotic LAB have selective resistance against inhibitory effect of several plant extracts that displayed a strong inhibition on pathogenic bacteria. These evidences suggest the possible combination of the probiotics with EOs and combat with pathogenic bacteria. Probiotics accomplish their antimicrobial activities mainly through producing bacteriocin. In most cases, the probiotics inhibit proliferation of pathogens by generating acidic environment and thereby lower the chance of pathogens' survival. EOs exhibit their antibacterial effect by inducing morphological changes in the target bacterial cells as well as producing reactive oxygen species (ROS) within the bacterial culture [58]. The EOs can accomplish a complete killing of the pathogens even at a lower dosage as the pathogens are normally lack of counteracting mechanism against the effects of EOs [59]. Combining EOs with probiotics is expected to increase the efficacy of probiotics in controlling the bacterial pathogens owing to their synergistic effect which is normally higher than the two individual effects due to their complementary actions [61].

Immune stimulatory effects of EOs have also been well documented. EOs extracted from *Eucalyptus globules* stimulated the innate cell-mediated immune response [62]. Inhibition of cytokine production and arachidonic acid metabolism by a compound of eucalyptus EO has been observed in human blood monocytes *in vitro* [63]. The same authors also reported the anti-inflammatory effects of eucalyptus EO in bronchial asthma [64]. Likewise, vapors of EOs showed

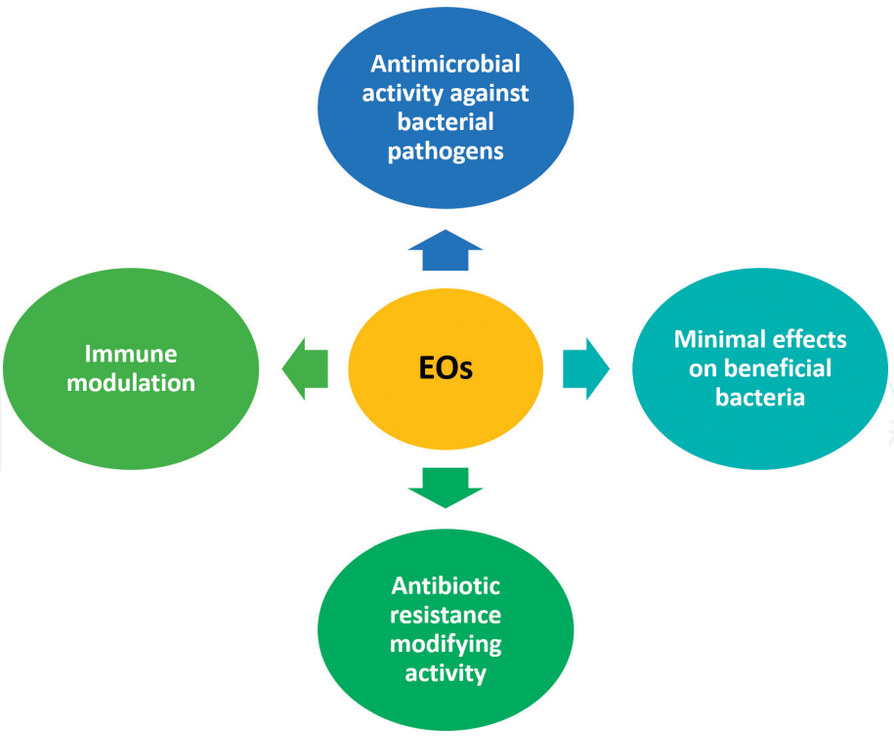

Figure 2.
The antibacterial properties of essential oils (EOs).

anti-inflammatory effect on the trachea and reduced asthma [65]. In addition to the antimicrobial and immune modulation properties, the antibiotic resistance modifying activity of EOs has recently been gaining research interest [66–68]. Some EOs and their major components, such as thymol and geraniol, have shown to improve the efficacy of antibiotics against multidrug-resistant bacterial pathogens and therefore have been suggested to be used as antibiotic adjuvants [67, 69, 70].

3.2.1 Using EOs to mitigate BRD bacterial pathogens

Although antimicrobial activity of EOs against human respiratory bacterial pathogens has been well documented, limited information is available with respect to the effects of EOs against bovine respiratory pathogens. We have recently published data showing that EOs inhibit the BRD bacterial pathogens *M. haemolytica*, *P. multocida* and *H. somni* [16]. The EOs of ajowan, thyme and cinnamon leaf completely or partially inhibited these BRD pathogens in both vapor and liquid phases [16, 17]. These EOs did not display any noticeable cytotoxicity to bovine turbinate cells of the upper respiratory tract [17] and also exhibited minimal antimicrobial activity on six commensal *Lactobacillus* strains that were isolated from the nasal pharynx of a healthy feedlot cattle [17]. This suggests that EOs will have limited negative effects on the commensal bacterial community within the bovine respiratory tract, when they are administered to target pathogens. In addition, Kissels et al. [71] evaluated four different EO components, including carvacrol, thymol, transanethole and 1,8-cineole, as antibacterial agents or as adjuvants for the antibiotics doxycycline and tilmicosin against *M. haemolytica* and *P. multocida*. Carvacrol and thymol inhibited the growth of both of these tested pathogens with MIC values ranged from 0.63 to 2.50 mM. These two EO compounds also displayed an additive effect when one of them was combined with tilmicosin. In addition, combination of thymol with dexycycline displayed synergetic effect against tested BRD pathogens. These studies demonstrated that EOs can be used to control bovine respiratory pathogens in feedlot cattle. Volatile nature of EO makes the EO more promising

therapy for the control of bovine respiratory pathogen in the upper respiratory tract as it makes suitable to intranasal administration via nasal spray [72]. However, further research in terms of the effect of EOs on the respiratory commensal microbiota of cattle and the cytotoxicity of EOs on lower respiratory tract is needed.

4. Conclusions

The economic impacts of cattle disease on the beef cattle industry still remain significant, with BRD being the most significant health problem in modern feedlot industry in North America. The BRD is commonly associated with pneumonia in nursing beef calves and recently weaned feedlot cattle and often occurs within the first 45 days after feedlot placement. The BRD is considered as one of the most significant health problems in the beef industry accounting for economic losses that surpass those incurred by all other diseases of cattle combined. Treatment and control of BRD in the beef sector are aimed mainly at bacterial pathogens through antimicrobial use (therapeutic and non-therapeutic administration) and vaccination programs. However, recent studies have shown the emergence of bacterial pathogens associated with BRD that are resistant to all classes of antibiotics used to treat BRD. The increase in the multidrug resistance towards these antimicrobials that are being used as metaphylaxis in feedlots necessitates the development of novel methods to mitigate bovine respiratory pathogens in feedlot cattle as alternatives to metaphylactic antimicrobial use. Probiotic and EOs, being two major natural antimicrobial sources, display the potential application of antimicrobial alternative agents against bovine respiratory bacterial pathogens. More research is needed to develop nasal-delivered probiotics or EOs that can inhibit pathogenic bacteria, with limited effects on commensals and respiratory tract, after intranasal administration.

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Conflict of interest

No conflict of interest.

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