Nutraceuticals as an Alternative Strategy for the use of Antimicrobials

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Take Home Messages

- Nutraceutical is a term derived from nutrition and pharmaceutical. There are many compounds that improve immune responses and reduce the risk of disease through different mechanisms of action.
- Prebiotics (biological modifying polysaccharides) are a group of indigestible carbohydrates that improve the growth of commensal bacteria. Some fractions (e.g., β-glucans and mannan-oligosaccharides) have direct immunomodulatory, gram-negative pathogen binding, or hydrophobic mycotoxin absorption capacities.
- Probiotics (direct-fed microbials) are viable microorganisms supplemented to an animal that offer potential health benefits to the animal. Probiotics are predominately supplemented to improve gastrointestinal health, rumen fermentation, or nutrient utilization.
- Phytonutrients are a group of compounds, isolated from plants, with potential therapeutic applications because of their intrinsic antioxidative, anti-inflammatory, and antimicrobial properties.

Introduction

Zoonotic multi-drug resistant bacterial strains and antibiotic resistance have encouraged changes to on-farm antimicrobial use. Veterinarians and producers are evaluating alternatives to the use of antimicrobials. Nutraceuticals, primarily derived from microbial and plant-based compounds, are receiving increased research and commercial attention. Nutraceuticals are a diverse group of compounds and microbes that offer some advantageous effects to health and productivity, including improved feed efficiency or reduced disease through either immune modulation or decreased infection. A more extensive review on the topic is available at Ballou et al. (2019). Nutraceuticals can be classified in many ways, with the most common based on the mechanism of action, chemical structure, or the source of the compounds. In this paper I will focus predominately on the mechanism of action and will discuss three broad classes of nutraceuticals: biological modifying polysaccharides (prebiotics), direct-fed microbials (probiotics), and phytonutrients. Nutraceuticals are not regulated by the Food and Drug Administration; therefore, statements regarding composition, dosage, effectiveness, and quality are not independently validated or standardized. This makes comparison and interpretation among extracts and commercial products difficult.

▪ Biological Modifying Polysaccharides

Indigestible carbohydrates, including oligosaccharides and fructans, can improve health through several mechanisms of action. One of these mechanisms is through a symbiotic or prebiotic effect, where these indigestible carbohydrates are an energy source for probiotic bacteria, and the health benefits are through improving the microbial ecology of the host gastro-intestinal tract. However, the focus of these indigestible carbohydrates in the current presentation will be on their immunomodulatory effects and ability to adsorb gram-negative bacteria as well as certain bacterial and fungal toxins.

Biological modifying polysaccharides are found in a variety of plants, milk, and the cell wall of fungi. I will focus on the polysaccharides extracted from cell walls of fungi, including mannan-oligosaccharides (MOS) and β-glucans (BG). The composition, availability, and physical chemistry of the extracts and carbohydrates influence their ability to improve the health of livestock. For example, a fungal extract from one fungus may behave very differently from another fungal extract. Further, many extracts are blended with other ingredients; therefore, one gram of Product A may have a different function than one gram of Product B. Unfortunately, the analytical chemistry to determine these structures and concentrations is complicated and expensive.

Type 1 fimbriae are mannose-specific filaments on the surface of pathogenic gram-negative bacteria. Ganner et al. (2013) conducted a study in which the fimbriae on gram-negative bacteria were adsorbed by yeast cell wall extracts, and the ability to adsorb both Salmonella species and E. coli were correlated with the concentration of MOS. The fimbriae adsorb to MOS and prevent the pathogenic bacteria from binding to the epithelium and colonizing the gastro-intestinal tract. Therefore, supplementing yeast extracts with greater quantities of MOS can be a useful prevention strategy for those animals with a high exposure to gram-negative pathogenic bacteria (Davis, 2018). The impacts of MOS on specific immune responses is not well understood. Further, most fungal extracts that contain MOS also contain BG, which are known to have immunomodulatory effects.

B-glucans from cell wall fractions from fungal sources have the potential for immunomodulatory effects. The β-1,3 glucans are able to ligate Dectin-1 receptors on monocytes, macrophages, neutrophils and to a lesser extent on dendritic cells and T cell surfaces (Taylor et al., 2002). Further, the size of the BG extract influences both the leukocyte type and the response that is impacted (Elder et al., 2017). Data indicate that smaller BG, which are more common on less virulent fungi, may limit inflammation, whereas large BG oligosaccharides may increase inflammation. Oral supplementation of BG may also impact systemic immune responses in addition to local gastro-intestinal immune responses. The systemic effects could be both direct and indirect. The direct systemic effect is thought to be mediated by M-cells, which are specialized cells that sample intestinal lumen contents, including BG. Preliminary data from our laboratory indicate that dairy calves supplemented with a BG extract had increased relative abundance of larger oligosaccharides, 7 and 8 oligosaccharides, in peripheral circulation when compared to calves not supplemented BG (Davis and Ballou, unpublished).

▪ Direct Fed Microbials

Direct-fed microbials, also known as probiotics, are live microorganisms that can improve the health and performance of livestock. Common commercially available microorganisms include Lactobacillus species and other lactic acid-producing bacteria, Bifidobacterium species, Bacillus species, and Saccharomyces cerevisiae. The dose is commonly reported as colony forming units supplemented per day or per kg of dry matter. Other important considerations when supplementing direct-fed microbials include the age or physiological state of the animal, infectious pressure, and the duration of supplementation. Oral supplementation of direct-fed microbials to impact gastro-intestinal health makes the most sense because the supplemented microorganisms target the microbial communities and cellular function within the gastro-intestinal tract.

The gastro-intestinal tract is a dynamic tissue that varies between animals, diets, age, environment, and management factors. To be considered a microorganism with probiotic effects, the microorganism should provide at least one of the following desirable outcomes:

- Regulate gastro-intestinal tract microbial communities
- Prevent adherence of potential pathogens in the gastro-intestinal tract
- Product anti-microbial or bactericidal molecules
- Improve gastro-intestinal tract integrity
- Improve mucosal adaptive immune responses
- Balance gastro-intestinal inflammation
- Improve fermentation and nutrient utilization

The application of direct-fed microbials in neonates is common. The gastro-intestinal tract of these animals is rapidly developing, and these animals are more susceptible to gastro-intestinal disease. Early in life the gastro-intestinal tract is colonized with facultative anaerobes (microorganisms that can survive with or without oxygen), which includes many bacteria from the environment, and then shifts more toward strict anaerobes (microorganisms that die in the presence of oxygen; Meale et al., 2017). Therefore, supplementing anaerobic lactic acid producing bacteria may speed up the microbial progression and reduce the risk for infection from environmental Enterobacteriaceae (Liang et al., 2020). The model of competitive exclusions has been around for a long time, where beneficial microorganisms take up space and use nutrients that are then less available for disease-causing microorganisms. Further, lactic acid producing bacteria can help lower pH in the lumen of the gastro-intestinal tract, which can help limit the establishment of pathogenic Enterobacteriaceae.

Another mechanism through which direct-fed microbials can improve gastro-intestinal health is by modulating the gut-associated mucosal tissue immune system. Many immune factors, including secretory IgA, antimicrobial peptides, and other regulatory leukocyte responses, concentrate themselves locally in the gastro-intestinal mucosa. The immune factors are important to maintain gastro-intestinal integrity and function, as well as balance the local inflammatory response. Liang et al. (2020) conducted a study with two groups of Jersey bull calves: one group supplemented with a blend of two strains of lactic acid producing bacteria and one group not supplemented. Both groups were then challenged with a moderate dose of Salmonella typhimurium. The calves that were supplemented with the direct-fed microbials had reduced systemic and local inflammation after they were infected with the Salmonella typhimurium. Localized inflammatory responses are often considered beneficial in most tissues; however, in the gastro-intestinal tract an excessive or prolonged inflammatory response can further exacerbate the pathogenesis of the disease because of impaired gastro-intestinal integrity.

Direct-fed microbials in adult livestock are also used to support gastro-intestinal health. However, in adult ruminants many of the direct-fed microbials are fed to target the rumen and improve nutrient digestibility and utilization. Although the main target is the rumen, some of the direct-fed microbials can make their way through the rumen and have similar impacts on intestinal health as noted above for young calves. In fact, supplementing direct-fed microbials to feedlot cattle is a common industry practice for preharvest food safety. Cattle supplemented with direct-fed microbials had decreased fecal shedding of pathogenic bacteria and decreased carcass contamination from the same bacteria (Brashears et al., 2003; Younts-Dahl et al., 2005; Peterson et al., 2007). In lactating dairy cows, most of the data focuses on production performance and milk quality. Fecal pathogen shedding or manure consistency are not often reported, but conceivably some of the performance benefits may be partially attributable to improvements in gastro-intestinal health. Further, the greatest health and economic benefits of supplementing direct-fed microbials are during stressful events, such as the transition period.

Phytonutrients

Phytonutrients are a broad group of compounds with potential therapeutic applications because they have antioxidative and anti-inflammatory properties. Plants synthesize polyphenols as a defense mechanism against both potential pathogens and ultraviolet irradiation. Various fruit and vegetable byproducts that are rich in phenolic compounds are available as feedstuffs for ruminants and may include citrus, grape, pomegranate, and green vegetable processing residues. Polyphenolic compounds can be absorbed in the small intestines and enter peripheral circulation where they can exert their bioactive effects on various tissues. The ruminal environment can modulate the activity of the dietary polyphenols. The rumen microbial communities can degrade polyphenols and decrease host availability. Therefore, the biological activity will depend on the structure in the diet as well as the concentration of the bioactive ingredients that bypass through the rumen.

Published reports on the immune effects of feeding flavonoid-rich products to ruminants are limited to predominately grape, pomegranate, and green tea derivatives. Supplementing grape polyphenols lowered oxidative damage in postpartum dairy cows (Colitti et al., 2006). Dairy calves supplemented with a pomegranate extract had increased measures of immune function including, in vitro secretion of interferon-γ and interleukin-4 as well as greater ovalbumin specific immunoglobulin G responses (Oliveira et al., 2010) Lastly, polyphenols from green tea extracts reduced the inflammation of small ruminants following a parasitic challenge (Zhong et al., 2014). These data suggest that the antioxidative and anti-inflammatory properties of these polyphenolic-rich compounds can play a role in improving the health of livestock.

Essential oils are another class of phytonutrients. In addition to immunomodulatory effects, some essential oils have antimicrobial activity against food borne pathogens and rumen microorganisms. The majority of research on the immunomodulatory effects of essential oils was conducted in monogastrics. Some of the mechanisms of action are through a direct receptor-mediated improvement in mucosal blood flow, altered cytokine and neuropeptide release, or modified leukocyte function. In ruminants the main essential oils investigated were carvacrol and thymol from oregano oil, garlic, and capsaicinoids, but due to ruminal degradation the impacts of some of these supplements in mature ruminants are not well understood. Supplementing milk-fed dairy calves with oregano oil reduced the incidence of scours, improved hematology, and increased immunoglobulin concentrations of the calves (Katsoulos et al., 2017; Seirafy and Sobhanirad, 2017; Ozkava et al., 2018). However, in lactating cows topical or intramammary administration of oregano failed to cure an experimentally-induced Streptococcus uberis infection. However, intra-abomasal infusion of garlic oil increased the neutrophil to lymphocyte ratio as well as increased the CD4 positive T cell population, and similarly, intra-abomasal infusion of capsaicinoids increased CD4 positive T cell proliferation (Oh et al., 2013). Lastly, capsaicinoids were able to reduce the acute phase response to an intravenous lipopolysaccharide challenge in mature dairy cows (Oh et al., 2015).

Summary

Nutraceuticals are a diverse group of compounds. To be considered a nutraceutical the oral supplementation must improve some aspect of animal health or production efficiency. There remains a lot of ambiguity regarding nutraceuticals because this is a rapidly evolving field without a lot of regulatory oversight. The concentration of bioactive ingredients or compounds is often not known or reported. Further, a lot of commercial products are extracts that can contain many different bioactive compounds that may work in a symbiotic or opposing manner. The presentation discussed nutraceuticals as biological modifying polysaccharides, direct-fed microbials, and phytonutrients. These compounds work through a variety of mechanisms including stabilizing microbial communities, improving mucosal responses and barrier function, adsorbing potential pathogens or toxins, improving antioxidant status, direct antimicrobial activity, and either increasing or decreasing systemic leukocyte responses.

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