Mannan-oligosaccharides and other Non-antibiotic Alternatives to the Management of Enteric Disease of Cattle

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Abstract

The relationship between nutrition, immunity and animal productivity has become more clear. Non-antibiotic feed additives are increasingly popular to maintain or stimulate intestinal and systemic immunity and maintain high levels of animal production. Yeast cell components, particularly mannan-oligosaccharides and β-glucan, have been evaluated as means of manipulating intestinal bacterial populations, stimulating immune response and promoting optimal production. To date, little published research exists in adult cattle regarding the use of either compound to improve milk production, intake or efficiency. It is still unclear whether either compound escapes ruminal degradation. However, some data, particularly with β-glucan, suggests that the compound has functional activity in adult ruminants. The objective of this presentation is to review some of the more recent data related to the use of yeast cell components in supporting optimal production in calves and cattle.

Introduction

Alternatives to antimicrobial growth promoters is a topic of intense interest in animal agriculture. Regulations in many parts of the world already restrict the use of antimicrobial growth promoters, and interest by consumers and retails for "antibiotic-free" foods are increasing. Therefore, methods of replacing these compounds with natural antimicrobial alternatives has been the subject of investigation by researchers in academia and industry for several years.

To achieve the goal of reducing enteric disease, any compound must possess several attributes:

- it must survive processing, storage and handling of animal feeds
- it must not be degraded by temperatures typical of storage and feeding
- it must survive the rumen and/or abomasum of the animal
- it must not be degraded by intestinal enzymes
- it must act while in the intestinal tract.

Mannan-oligosaccharides and β-glucans

Yeast is an excellent source of nutrients and has been used for hundreds of years as a source of nutrition for the animal. As a feed ingredient, whole yeast or yeast culture is a source of protein, carbohydrate, B-vitamins and compounds such as nucleotides (Table 1). Most yeast products used in animal agriculture are derived from *Saccharomyces cerevisiae*, the yeast used in the brewing and baking industries.

Yeast cell wall contains two types of carbohydrates that may have biological activity in the animal and, therefore, may provide some immune benefit to the animal. These two compounds are 1,3/1,6 β-glucan (BG) and mannan-oligosaccharide (MOS).

Cell Wall Structure and Composition

The cell wall of *S. cerevisiae* consists of three layers: an inner layer of alkali-insoluble β-glucan (30-35%), a middle layer of alkali-soluble BG (20%) and an outer layer of glycoprotein (30%) in which the carbohydrate is phosphorylated mannan (Table 2). The primary difference between soluble and insoluble BG is the number of β-(1→6)-linked glucose residues that are present in the long sequences of β-(1→3)-linked glucose chains.[24] The role of these polysaccharides is to provide structural integrity to the cell and to protect the cell from the outside environment.

Most yeast products are by-products from other industries, such as ethanol production. Some products

Table 1. Composition of yeast cells.

Item	Percent
Protein	50-52
True	42-46
Nucleic acid	6-8
Carbohydrate	30-37
Lipid	4-5
Ash	7-8

Adapted from: Reed and Nagodawithana, 1991.

available in animal agriculture are derived from yeast grown specifically for their purpose – especially in the case of glucan production. Also, most products are not purified MOS or BG but instead are combinations of the three layers of the cell wall. Some are simply cell walls produced as a by-product from the production of yeast extract, which is used as a flavor enhancer in human and pet foods, a dietary supplement and in industrial fermentations to promote microbial growth. Thammakiti *et al*[37] compared chemical composition of whole yeast cells, cell walls and four preparations of β-glucan (Table 3). The content of BG in the preparations ranged from 55 to 71%, indicating marked differences in BG (and MOS) content in commercial products.

Effect of Rumen Fermentation on Cell Wall Structure

The efficacy of yeast cell wall products containing BG and MOS depends upon these components surviving ruminal fermentation. There are few data to indicate that either component survives the rumen intact. The large population of ruminal microflora makes it likely that at least a portion of the yeast cell wall will be degraded by ruminal bacteria. Indeed, many researchers have documented changes in rumen fermentation when yeast or yeast components are fed to cattle.[4,36] Kung *et al*[23] reported that although viable *S. cerevisiae* did not reproduce in the rumen, cells that were added to rumen fluid remained viable for up to 48 hours. Others[11] have also suggested that yeast cells may remain viable through the rumen. However, this does not necessarily mean that cell wall fractions, including MOS and BG, will escape degraded in the rumen since lysis of the yeast cell wall would open the wall to degradation by rumen bacteria.[14] Further research is required to determine the survival of yeast cell wall products containing MOS and BG on survival through the rumen.

Table 2. Composition of yeast cell walls.

Item	Percent
Mannan	30-35
Glucan	30
Chitin	1-2
Lipids	10-12

Adapted from: Reed and Nagodawithana, 1991.

Role of MOS in Enteric Health

Oligosaccharides have been recognized as tools to manipulate intestinal microflora and gut immunity for many years. Oligosaccharides (including MOS) are a class of carbohydrates that are not absorbed or digested in the small intestine of man and animals and thus reach the colon unaltered. In the colon, oligosaccharides are readily fermented by the intestinal microflora. This may result in changes in the flora, thereby increasing the number of potentially beneficial microorganisms[15] while repressing the number of potentially harmful bacteria.[35] Changes in microbial populations may alter intestinal or systemic immune response.[6] Several classes of oligosaccharides are found in nature, including fructo-, mannan-, galacto-, gluco-oligosaccharides and others. Some have been produced chemically and are used as functional foods, or prebiotics. The term "prebiotic" has been coined to describe the effects of compounds like oligosaccharides in the gut. Products are available and have been tested in a wide number of animals species, including calves and cows.

Oligosaccharides have also been shown to reduce the binding of pathogens in the intestine of animals.[35] Certain bacteria attach to intestinal epithelium (cell surface) using mannose specific attachments called fimbriae.[42] Oligosaccharides resemble the fimbriae, which serves as a "decoy" attachment. Bacteria that attach to the oral oligosaccharide do not attach to the intestinal epithelium, thereby reducing the risk of infection.

In addition, production of VFA by bacteria fermenting oligosaccharides in animals may improve energy ef-

Table 3. Chemical composition of fractions of cell walls[1] of *S. cerevisiae*. From Thammakiti, *et al* (2004).

	CHO (%)	BG (%)	CP (%)	Ash (%)	Fat (%)
Whole cells	59.6[a]	23.6[a]	43.5[a]	10.3[a]	1.2[abc]
Cell walls	44.1[b]	21.3[b]	40.9[b]	4.7[b]	1.5[a]
β-glucan prep #1	65.2[c]	55.2[c]	6.5[c]	0.6[c]	0.2[bc]
β-glucan prep #2	71.8[d]	59.5[d]	4.4[c]	0.4[d]	0.3[ac]
Cell wall product #1	76.6[e]	71.2[e]	5.1[c]	6.8[e]	0.7[c]
Cell wall product #2	65.2[c]	57.9[cd]	7.2[c]	8.0[f]	0.6[ac]

[1]CHO = carbohydrate, BG = β-glucan, CP = crude protein.
[2]Carbohydrate as glucose.
[a,b,c,d,e,f]Mean values within the same column followed by a different superscript letters were significantly different ($P < 0.05$).

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ficiency and alter (improve) intestinal morphology. Several reviews have been published recently regarding the use of oligosaccharides in humans[7,34] and animals.[12,39]

There are relatively few published studies documenting the value of MOS (in contrast to complete yeast cells or yeast culture) in cattle. Most work with MOS has evaluated the role of MOS in intestinal health of young calves.

Heinrichs *et al*[16] recently compared the addition of MOS (4 g/d) added to calf milk replacer with antibiotic (400 and 200 g/ton or neomycin and oxytetracycline, respectively) or negative control for five weeks. Calves were fed milk replacer throughout the study and growth and health indices were recorded. Calves fed MOS consumed more calf starter than calves fed antibiotics (but not more than controls) and had improved fecal scores (Table 4). These data are consistent with other trials with oligosaccharide products in young milk-fed calves.[31]

Franklin *et al*[13] used Holstein cows (n = 50) that were fed 10 g/d of MOS during the last three weeks of the dry period. Cows were vaccinated against rotavirus at -4 and -2 weeks of parturition. Specific rotavirus titers in cows at calving was improved with the addition of MOS although colostrum rotavirus titers and Ig concentrations were unaffected by treatment. Calves from cows fed MOS tended to have greater serum rotavirus neutralization titers compared to cows fed control (Table 5), although colostral IgG and transfer of total IgG to serum of calves was unaffected by treatment. These data suggest that at least a portion of dietary MOS may escape ruminal fermentation and may exert some effect on immune response in cattle.

Role of BG in Enteric Health

The role of BG in enteric health appears to be mediated through the ability of BG to bind to and stimulate various components of the immune system. β-glucans have been shown to affect a number of different functions of macrophages, particularly the release of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6,[1] production of nitric oxide[26] and other cellular func-

Table 4. Least squares means of intake and performance of calves fed milk replacer containing antibiotic (AB), mannan oligosaccharide (MOS), or no additive (CON).

Item	CON	AB	MOS	SE
Body weight, kg				
Initial	54.1	51.5	51.4	1.1
Final	66.5	67.2	65.7	1.3
ADG, kg/d	0.36	0.38	0.34	0.03
Wither height, cm				
Initial	76.85	76.67	76.51	0.49
Final	84.51	83.84	83.98	0.49
ADG, cm/d	0.18	0.17	0.18	0.01
Grain intake, kg/d				
Week 1 to 5	0.130	0.117	0.137	0.012
Week 6	0.850[ab]	0.793[b]	0.944[a]	0.047

[a,b]Means within a row with different superscripts differ; $P < 0.05$.
Source: Heinrichs *et al*, 2003.

Table 5. Blood and colostrum parameters in cows at parturition and serum IgG in calves at 24 h of age from cows supplemented with 0 (CON) or 10 g/d of MOS from 4 wk before expected parturition through parturition.

Item	CON	MOS	SE	*P*
Cow serum titer[1]	3.37	3.45	0.10	0.04
Cow serum IgG, g/L	15.70	15.77	1.8	NS
Colostrum IgG, g/L	52.8	45.0	8.0	NS
Colostrum titer[1]	4.2	4.2	0.1	NS
Calf serum IgG, g/L	16.1	19.4	2.2	NS
Calf serum titer[1]	3.67	3.86	0.09	0.08

[1]Rotavirus titer: means of $\log_{10}$ of the reciprocals of the greatest dilution that provided for neutralization of rotavirus.
Source: Franklin *et al*, 2005.

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tions. Dectin-1, a pathogen-recognition receptor on macrophages, neutrophils and dendritic cells, recognizes BG.[33] More recent data also suggests effects on T and B-cells.[38]

Orally consumed BG is taken up by M cells in the intestine and phagocytosed by macrophages in the Peyer's Patches. Macrophages migrate to multiple sites, including thymus and bone marrow. Macrophages process the BG into components that are subsequently recognized by neutrophils. The net effect is to "prime" or educate the immune cells to more quickly respond to subsequent stimulation.

Effects of Processing of BG

Brown and Gordon[2] suggested that the size, structure and degree of processing of BG is fundamentally important to its ability to induce an immune response. Indeed, some of the responses reported in the literature, such as stimulation of macrophages to produce cytokines, have been contradicted by other studies using BG prepared in different ways. For example, Kataoka *et al*[21] reported that pretreatment of a linear (1→3)-β-D-glucan with sodium hydroxide to form single chain glucans increased immunogenicity of the molecules *in vitro*. Triple helix forms of the glucan were not immunostimulatory in the same system. Ohno *et al*[27] also reported that single strands of linear BG were more stimulatory that multiple helixes. These data would suggest that the method of processing may play a role in the effectiveness of products in animals. However, there is likely considerable rearrangement of BG as they travel throughout the digestive tract, so these *in vitro* studies may not accurately reflect the actual immunogenicity of BG in the animal. That suggests several more crude preparations of BG can affect immunity in calves, but different products appear to influence immunity differently.[5,9,10]

Role of beta-glucan on Immune Response

Oral BG may assist in prevention of economically important diseases in animals, including cattle. For example, Jung *et al*[20] reported that oral BG fed to pigs (50 mg/day) for three days prior to oral inoculation with 3 ml of tissue culture containing 2 X 10^6 $TCID_{50}$/ml of swine influenza virus had significantly less severe lung lesions compared to pigs challenged with SIV but without pre-treatment with oral BG. The authors also reported that concentrations of interferon-γ and nitric oxide in bronchoalveolar lavage fluid from pigs fed BG were greater than those fed control treatment at 5, 7 and 10 days post-infection.[20]

Hurnik *et al*[18] reported that addition of a commercial BG preparation (YBG-80, ImmuDyne Canada, Ltd.) and fed at 0, 40, 80 or 120 mg/kg of feed increased concentrations of neutrophils in blood of pigs fed the product for five weeks (Table 6). Similarly, Olson *et al*[28] reported that BG stimulated production of TNF-α by alveolar macrophages obtained from rabbits at concentrations up to 200 μg/ml, but inhibited TNF-α production at higher concentrations. At least part of the apparent inhibition of TNF-α may be associated with the ability of BG to bind TNF-α in the medium.[28] Indeed, the authors suggest that high doses of BG might be useful during periods of sepsis when over-production of TNF-α can lead to dramatic metabolic responses. Others[25] have also reported suppression of TNF-α expression by macrophages at high doses (500 μg/ml) of BG.

There are currently few data that have evaluated the potential immunological value in cattle. Several researchers have evaluated the use of BG in treating cows with clinical mastitis. Some have reported improvements in clinical signs associated with subcutaneous injection of purified BG,[3,19] while others[40] reported only small changes in parameters of udder health in cows infused in the mammary gland with BG at drying off followed by infection with *Staphylococcus aureus*. Others have used oral or injected BG as a means of reducing effects of shipping fever[29] and pneumonia in ruminants.

Pregnant mares (n = 6) received three intramuscular injections of BG (0.19 mg/kg of body weight). Mares were injected beginning 4 to 6 weeks prepartum and were injected once every seven days. On foaling, colostrum IgG concentration and foal IgG absorption were measured. In addition, ability of neutrophils to reduce nitrobluetetrazolium, phagocytic index and percent of killing neutrophils was determined prior to and after colostrum consumption.[22] Injection of BG into mares prepartum increased colostral IgG and IgM concentrations as well as total protein (Table 7). In addition, BG caused an increase in neutrophils activity in foals prior to colostrum consumption (Table 8).

Not all studies have shown positive responses to oral BG. For example, Hiss and Sauerwein[17] fed 75 weaned piglets (weaned at 28 d of age) oral BG (Antaferm MG, Dr. Eckel GmbH, Niederzissen, Germany) at 0, 0.015 or 0.03% of the ration for 28 d. The authors observed no effect on growth, efficiency or indi-

Table 6. Concentrations of neutrophils in blood of inblood of pigs fed oral β-glucan for five weeks.

Oral β-glucan (mg/kg feed)	Neutrophils 10^9/L blood
0	5.534
40	5.802
80	6.782
120	7.472

Source: Hurnik *et al*, 2004.
Linear increase with increasing BG.

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cators of immune response. However, intake tended ($P < 0.10$) to be greater in pigs fed 0.03% BG.

Role of BG on Mycotoxin Binding and Hemorrhagic Bowel Syndrome

Contamination of feed with various fungi may produce mycotoxins, which are produced during metabolism by fungi. High concentrations of mycotoxins can affect many different tissues in most classes of animals, including ruminants.[30] Lower concentrations still cause problems, including reduced growth rates of calves, impaired production and increased susceptibility to disease. There are more than 300 different mycotoxins recognized, although only a few are routinely identified.

Previous studies have shown that BG from the cell wall of *S. cerevisiae* adsorb mycotoxins such as zearalenone.[43] Other research[44] suggested that method of BG processing had an important effect on the ability of BG to adsorb zearalenone. Therefore, it is possible that BG (properly prepared) can play a role in reducing deleterious effects of mycotoxins in cattle. Indeed, many commercial mycotoxin binders in use today contain some component of yeast cell walls as a source of BG.

Table 7. Composition of colostrum in mares fed without or with added BG.

Item, g/L	Control	BG
IgG, g/L	61.6	143.1*
IgM, g/L	4.8	6.1*
IgA, g/L	9.2	8.2
Total protein, g/L	117.0	134.0*

From Krakowski *et al*, 1999.
*$P < 0.05$.

Table 8. Activity of neutrophils (reduction of NBT, phagocytic index and % killing) in foals from mares injected with 0 or 0.19 mg/kg of BG.

Item	Control	BG
NBT reduction		
0 h	2.0	4.2*
18 h	3.0	8.0*
Phagocytic index		
0 h	3.2	4.1*
18 h	3.8	4.8*
% killing cells		
0 h	45	55*
18 h	46	58*

From Krakowski *et al*, 1999. Data were estimated from graphs in manuscript.
*$P < 0.05$.

Hemorrhagic bowel syndrome or "dead gut" syndrome is considered to be a minor cause of death in adult cattle. Numerous causative agents have been proposed, including *Clostridium perfringens*[8] and immunosuppression with subsequent infection with *Aspergillus fumigatus* from moldy feed.

Researchers at Oregon have evaluated the role of BG as a means of reducing the effects of toxins from *A. fumigatus* as a potential causative agent in hemorrhagic bowel syndrome. Wang *et al*[41] fed sheep a commercial BG preparation (Omnigen-AF) in diets typical of dairy cattle for 28 days and treated groups with dexamethasone to suppress immune response. Production of L-selectin (a neutrophil adhesion molecule) and IL-1β from neutrophils were markedly reduced in dexamethasone-treated sheep. Addition of Omnigen-AF increased L-selectin concentration but had no effect on IL-1β. Addition of *A. fumigatus* and the BG product had greatest impact on innate immune response. These data suggests that at least some functional components of BG survive the rumen; that BG can interact with toxins in moldy feed to reduce immunosuppressive effects; and that addition of BG can partially improve immunosuppression caused by dexamethasone.

Conclusions

Yeast cell walls and cell wall components MOS and BG may play an important role in maintaining or promoting immunity in many classes of animals, including cattle. Recent research suggests that MOS plays a role in influencing intestinal microflora and volatile fatty acid production, and also may have a direct effect on the gut associated immune response. Similarly, BG is immunostimulatory and may play a role in overcoming immune suppression that occurs typically in production situations. A major limitation, however, is the lack of data on the role of processing on biological activity of both MOS and BG. Continued research in this important area will improve the consistency and effectiveness of yeast components in improving animal production.

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- Proven protection against BVD Type 1 and Type 2 Persistent Infection (PI)
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2008
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