Effects of *Saccharomyces cerevisiae boulardii* (CNCM I-1079) on feed intake, blood parameters, and production during early lactation

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ABSTRACT

The periparturient period is a metabolically demanding time for dairy animals because of increased nutrient requirements for milk yield. The objective of this study was to investigate the effect of feeding *Saccharomyces cerevisiae boulardii* (CNCM I-1079), a commercial active dry yeast (ADY), in dairy cows on productive and metabolic measures during the periparturient period. Primiparous (n = 33) and multiparous (n = 35) cows were fed a close-up total mixed ration (TMR) before calving and a lactation TMR postpartum. Three weeks before expected calving time, animals were blocked by parity and body weight and then randomly assigned to either control group (control; n = 34) or treatment (ADY; n = 34). All animals were housed in a tie-stall barn with individual feed bunks; the ADY animals received supplementary *Saccharomyces cerevisiae boulardii* (CNCM I-1079), top dressed daily at a predicted dosage of 1.0 × 1010 cfu (12.5 g) per head. Blood samples were collected weekly along with milk yield and milk composition data; feed intake data were collected daily. Serum samples were analyzed for glucose, nonesterified fatty acid, β-hydroxybutyrate, haptoglobin (Hp), and the cytokines tumor necrosis factor-α, IL-6, and IL-18. Colostrum samples collected within the first 6 to 10 h were analyzed for somatic cell score and IgG, IgA, and IgM concentrations. Data were analyzed using PROC GLIMMIX in SAS with time as a repeated measure; model included time, parity, treatment, and their interactions. The ADY groups had greater milk yield (39.0 ± 2.4 vs. 36.7 ± 2.3 kg/d) and tended to produce more energy-corrected milk with better feed efficiency. There was no difference in plasma glucose, serum nonesterified fatty acid, serum β-hydroxybutyrate, Hp, IL-6, or IL-18 due to ADY treatment. The tumor necrosis factor-α increased in ADY-supplemented animals (1.17 ± 0.69 vs. 4.96 ± 7.7 ng/mL), though week, parity, and their interactions had no effect. Serum amyloid A tended to increase in ADY-supplemented animals when compared to control animals and was additionally affected by week and parity; there were no significant interactions. No difference in colostrum IgG, IgA, and IgM was observed between treatments. Supplementing transition cow TMR with ADY (CNCM I-1079) improved milk production and tended to improve efficiency in early lactation; markers of inflammation were also influenced by ADY treatment, though the immunological effect was inconsistent.

Key words: periparturient cow, energy metabolites, immune response markers, *Saccharomyces cerevisiae boulardii* (CNCM I-1079)

INTRODUCTION

During the transition period, beginning 3 wk before parturition, drastic metabolic and immunological changes occur in the dairy cow (LeBlanc, 2010). Due to the high energy demand of lactation and inability of DMI to keep pace, cows enter negative energy balance associated with body condition score loss, risk of metabolic disorders, and immune function changes. In cattle, parturition induces an acute phase response, which is also linked to energy balance (Tóthová et al., 2014). Further, negative energy balance is linked to decreased neutrophil function and uterine disease (Hammon et al., 2006). Overall, the parturition transition creates great metabolic and immunological stress that must be mitigated to optimize cattle health.

Direct-fed microbial products such as bacteria and fungi are one possible avenue to improve animal health during the parturition transition. A subset of direct-fed microbials, active dry yeasts (ADY), which commonly include *Saccharomyces cerevisiae*, are a supplement group of particular interest. Active dry yeasts have been found to act as a growth promoter (McAllister et al., 2011), influence the immune system in several
species (Sanchez et al., 2021), and improve milk production in dairy cows (Schlabitz et al., 2022). To our knowledge, the impact of ADY on transition cows is poorly understood. One S. cerevisiae strain decreased HSP-70 and increased lymphocyte proliferative response (Nasiri et al., 2019). Additionally, yeast cultures or hydrolyzed yeast mixtures increased milk production (Faccio-Demarco et al., 2019), fecal IgA concentrations, and tended to increase bacteria-killing abilities of whole blood (Yuan et al., 2015). Together, these studies suggest a possible immunological response of dairy cows to ADY supplementation.

Mechanisms of action for ADY are wide and varied. Active dry yeasts have been shown to affect lactate and lactic acid production, increase feed digestibility and efficiency, and decrease oxygen and improve fermentation and feed breakdown dynamics in the rumen (Seo et al., 2010). In beef steers, ADY have been shown to improve immune response via increased TLR-4 expression (Lopreiato et al., 2020). In the lower gut, ADY may inhibit growth of pathogens, stimulate an immune response, and balance microbial growth (Seo et al., 2010). The positive effects of ADY supplementation are dependent on the diet, formulation, and amount of supplementation and therefore can vary from farm to farm (Elghandour et al., 2015). Results on ADY have been inconsistent across a range of studies with a wide variety of variables examined (Lynch and Martin, 2002; Sanchez et al., 2010; Sanchez et al., 2021), likely due to the variability in efficacy among different strains of the same species.

Yeast phenotypes in S. cerevisiae alone are diverse, encompassing at least 74 phenotypes grouped into 10 categories including environmental condition sensitivity, lipid and carbohydrate metabolism defects, carbon catabolite repression, and nitrogen utilization defects (Hampsey, 1998). Whether S. boulardii is a strain of S. cerevisiae or a separate species entirely is still unsettled (Pais et al., 2020). *Saccharomyces cerevisiae boulardii* (SCB) is known to impact intestinal mucosa, modulating immune response, gene expression, and protein synthesis (Buts and DeKeyser, 2006). In ruminants, different S. cerevisiae strains can change rumen fermentation profile to a more acidic and gluconic state (Chung et al., 2011) or impact fiber digestion (Newbold et al., 1995). Among 7 strains of S. cerevisiae, there exists considerable strain-to-strain variation between in vitro rumen ammonia production and fiber degradation (Chaucheyras-Durand et al., 2008). Beyond S. cerevisiae, other yeast species such as *Kluyveromyces marxianus, Candida tropicalis,* and *Candida utilis* (Shurson, 2018) have shown positive impacts on rumen fermentation (Wang et al., 2016) and fiber digestion (Jiao et al., 2018). Additionally, neurological, immunological, and endocrinological effects, as well as bioactives production, are currently understood to be highly strain-dependent (Hill et al., 2014). Due to the known strain-to-strain variation, it is important to distinguish the strains used in studies so that findings for 1 strain are not confounded with findings from other strains or isolates.

One strain of ADY holding considerable promise is SCB, of which, a strain (CNCM I-1079) is known to affect the small intestine and colon of calves. Specifically, SCB has been found to decrease crypt depth and width in dairy calves, increase goblet cell number in pre- and postweaned calves (Fomenky et al., 2017), and increase growth in postweaned dairy calves (Renaud et al., 2019). Protective effects on the small intestine in calves show promise in reducing inflammation and immune response by reducing pathogen load (Ma et al., 2018). Currently, the effects of SCB (CNCM I-1079) on health and productivity in the dairy cow parturition transition is unknown. The objectives of this study were to examine the effects of SCB (CNCM I-1079) on individual DMI, milk production, and markers of immune response and inflammation during the transition period and into early lactation. We hypothesized that SCB supplementation would improve milk production in early lactation and improve immune response of transition and early lactation dairy cattle.

**MATERIALS AND METHODS**

**Animal Management**

This study was approved by the Institutional Animal Care and Use Committee at the University of Idaho (AUP# IACUC-2017-63). Dairy heifers (n = 34) and multiparous dairy cows (n = 38 total; n = 19 for second lactation, and n = 16 for third lactation) from the University of Idaho Dairy Center were moved into individual stalls at University of Idaho Research Barn and assigned to either control (CTRL; n = 36) or a top-dressed, direct-fed microbial SCB (CNCM I-1079; ADY; n = 36) at 12.5 g/d, predicted dosage of 1.0 × 10^10 cfu. Treatment assignments were balanced for BW, parity, and previous lactation milk yield (multiparous cows only) with cows blocked by seasonal calving dates. Figure 1 depicts a visual representation of the experimental design. The experimental unit was the cow. Two animals (one from the group CTRL-P, primiparous control animals; and one from the group CTRL-M, multiparous control animals) were removed from the study within 2 d for failure to adapt to the tie-stall research barn; any data obtained from these 2 animals were not used in this study. Two additional animals were removed from the study due to left-displaced ab-
 omasum (CTRL-M) and recurring mastitis (ADY-M). Thus, the final animal numbers per treatment were CTRL-P (n = 16), ADY-P (n = 17), CTRL-M (n = 17), and ADY-M (n = 18).

Dose of ADY was based upon manufacturer recommendations; no vehicle or flavoring was used as the ADY was top dressed and mixed directly into the top 6 inches of the TMR in each individual bunk. Treatments were consumed within the first 30 min after feeding. Cows were fed a TMR daily at 0700 and 1700 h. The ADY treatment was top dressed in morning feeding, and as such, the yeast was given as a pulse dose each morning. Diets were fed to target 5 to 10% orts daily. Actual orts were 4.9 ± 4.5 kg/cow per d or 11.9 ± 10.3% of the total amount fed. For approximately 3 wk before the expected calving date (18.5 ± 6.3 d), cows were housed in the tie-stall research barn and were fed a TMR with (multiparous) or without (primiparous) anionic salts with a 90:10 forage:concentrate ratio (Table 1). At calving, all cows were moved to maternity pens where they were fed alfalfa hay and water free choice. After 24 h, they were moved to a bedded pack barn for up to 48 h to ensure adequate movement and successful expulsion of placenta. Cows were then returned to the tie-stall research barn and were fed a lactation diet with a forage:concentrate ratio of 45:55 (Table 1). From wk 1 to 4 postcalving, cows were milked 4 times per d at 0700 h, 1100 h, 2000 h, and 0000 h. From wk 5 to 9, cows were milked 2 times per d at 0700 h and 2000 h. Table 2 provides information on the nutritional analysis of the close-up and lactation diets; Table 3 displays main effect and interaction P-values for all data analyzed.

**Sampling**

Blood and feed were sampled weekly, and cows were weighed between morning and evening feedings on an in-ground livestock scale. Blood samples were taken on the same day weekly until calving, at which point a sample was taken within 24 h of calving (wk 0). Then cows were assigned to 1 of 3 sampling groups according to the day of the week in which they calved. For example, a cow that calved on a Monday would have her blood sampled for 7 DIM the following Monday, along with all other Sunday and Monday calvers. Tuesday, Wednesday, and Thursday calvers would be sampled on Wednesdays, and Friday and Saturday calvers would be sampled on Fridays. This ensured that all cows were sampled ± 2 d from each other for each weekly sample.

Milk production and DMI was averaged weekly; milk was sampled twice weekly and DMI thrice weekly. Samples from all milkings were pooled together and DMI were averaged for the week. Feed samples were...
taken from the whole TMR (not individual feed bunks), dried, ground through a 2-mm screen, sent to a commercial laboratory (Dairy One Labs), and analyzed via established wet chemistry techniques for DM (AOAC International, 2012), CP (AOAC International, 2012), soluble protein (Licita et al., 1996), aNDF (Van Soest et al., 1991), ADF (AOAC International, 2012), lignin (AOAC International, 2012), starch (AOAC International, 2012), crude fat (AOAC International, 2012), and ash (AOAC International, 2012). Calculations of NFC and TDN were carried out according to NRC (2001).

Postcalving, milk composite samples were taken weekly with equal amounts from all milkings and analyzed for milk components using wet chemistry at Dairy One Labs. Colostrum was sampled at first milking after calving (within 8 h) and analyzed via radial immunodiffusion assay for total IgA, IgG, and IgM at TripleJ Farms in Washington. Briefly, samples were added to an agar plate containing IgG, IgA, or IgM antigens. Upon addition of a sample of precipitate ring forms on the plate, the diameter of which was compared with the supplied standards, the amount of immunoglobulin in the sample was determined.

Blood was drawn from the coccygeal vein into Vacutainer tubes (Greiner Bio-One) containing sodium heparin. Blood was centrifuged at 3,000 × g at 4°C for 20 min to separate plasma and was stored at −20°C until analysis. Samples were analyzed for glucose and β-hydroxybutyric acid (BHBA) using in-house enzymatic assays (Laarman et al., 2012) and for nonesterified fatty acids (NEFA) using a commercially available enzymatic and colorimetric assay (Fujifilm, Wako Diagnostics USA). Blood was also analyzed for the acute phase proteins and cytokines using commercially

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### Table 2. Nutritional analysis of close-up and lactation diet; weekly samples were composited by month

| Analyte (% of DM) | Close-up, MP,2 and PP3 | Lactation |
|-------------------|------------------------|-----------|
| DM (% as fed)     | 51.3 ± 4.2             | 50.3 ± 2.5 |
| CP                | 15.9 ± 1.9             | 18.2 ± 0.4 |
| Soluble protein (% of CP) | 41.3 ± 3.8         | 39.2 ± 1.2 |
| aNDF              | 49.6 ± 1.8             | 41.2 ± 0.8 |
| ADF               | 33.9 ± 1.7             | 25.6 ± 0.6 |
| Lignin            | 5.4 ± 0.3              | 4.7 ± 0.4  |
| NFC               | 21.4 ± 2.6             | 26.4 ± 0.8 |
| Starch            | 3.5 ± 1.2              | 13.0 ± 0.3 |
| Crude fat         | 2.5 ± 0.1              | 5.0 ± 0.3  |
| Ash               | 10.7 ± 0.6             | 9.3 ± 0.2  |
| TDN (%)           | 58.8 ± 0.8             | 66.7 ± 0.7 |

1Unit is % of DM unless otherwise indicated.  
2MP = multiparous.  
3PP = primiparous.

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### Table 3. P-values for all variables by main effects and interactions1

| Item                          | Trt | Wk | Parity | Trt × Wk | Trt × Parity | Wk × Parity | Trt × Wk × Parity |
|-------------------------------|-----|----|--------|----------|-------------|-------------|-------------------|
| Animal productivity          |     |    |        |          |             |             |                   |
| DMI (kg)                      | 0.47| <0.01| <0.01| 0.20      | 0.81        | 0.08        | 0.01              |
| BW (kg)                       | 0.05| <0.01| <0.01| 0.56      | 0.89        | <0.01       | 0.21              |
| Daily milk yield (kg)         | 0.02| <0.01| <0.01| 0.49      | 0.99        | 0.96        | 0.32              |
| ECM (kg/d)                    | 0.08| <0.01| <0.01| 0.30      | 0.95        | 0.92        | 0.14              |
| Feed efficiency (kg of milk/kg of DMI) | 0.08| <0.01| <0.01| 0.13      | 0.92        | 0.18        | 0.17              |
| Peak milk yield (kg/d)        | 0.28| <0.01|        |           |             |             |                   |
| Colostrum                     |     |    |        |          |             |             |                   |
| IgG (mg/dL)                   | 0.93| 0.76|        | 0.44      |             |             |                   |
| IgA (mg/dL)                   | 0.50| <0.01|        | 0.46      |             |             |                   |
| IgM (mg/dL)                   | 0.66| 0.98|        | 0.50      |             |             |                   |
| Milk composition              |     |    |        |          |             |             |                   |
| Fat (%)                       | 0.44| <0.01| 0.45   | 0.90      | 0.79        | 0.64        | 0.18              |
| Protein (%)                   | 0.50| <0.01| 0.56   | 0.94      | 0.34        | 0.04        | <0.01             |
| Lactose (%)                   | 0.75| <0.01| 0.07   | 0.96      | 0.33        | 0.85        | 0.23              |
| MUN (mg/dL)                   | 0.28| <0.01| <0.01 | 0.65      | 0.88        | 0.34        | 0.21              |
| SCS                           | 0.10| 0.03|        | 0.77      | 0.93        | 0.66        | 0.90              |
| Energy metabolite             |     |    |        |          |             |             |                   |
| Glucose (mg/dL)               | 0.63| <0.01| <0.01 | 0.62      | 0.38        | 0.14        | 0.14              |
| NEFA (mEq/L)                  | 0.87| <0.01| <0.01 | 0.05      | 0.95        | 0.22        | <0.01             |
| BHB (mg/dL)                   | 0.68| <0.01| 0.02   | 0.59      | 0.47        | 0.06        | 0.61              |
| Cytokine                      |     |    |        |          |             |             |                   |
| IL-6 (pg/mL)                  | 0.43| 0.35|        | 0.62      | 0.78        | 0.09        | 0.95              |
| IL-18 (pg/mL)                 | 0.57| 0.50|        | 0.42      | 0.72        | 0.11        | 0.28              |
| TNF-α (ng/mL)                 | <0.01| 0.93| 0.97   | 0.87      | 0.33        | 0.21        | 0.59              |
| Acute phase protein           |     |    |        |          |             |             |                   |
| Haptoglobin (mg/mL)           | 0.56| 0.24|        | 0.48      | 0.74        | 0.50        | 0.41              |
| Serum amyloid A (ng/mL)       | 0.06| <0.01| <0.01 | 0.41      | 0.71        | 0.37        | 0.57              |

1Trt = treatment; NEFA = nonesterified fatty acids; TNF-α = tumor necrosis factor-α.
available bovine-serum-reactive kits (MyBiosource); specifically, for serum amyloid A (MBS2024318; limit of detection: 6.25 ng/mL), haptoglobin (MBS1603719; limit of detection: 3 µg/mL), tumor necrosis factor-α (TNF-α; MBS2609886; limit of detection: 15.6 pg/mL), IL-6 (MBS2882335; limit of detection: 78 pg/mL), and IL-18 (MBS2022718; limit of detection: 15.6 pg/mL). Samples below limit of detection were denoted as 0.5 × limit of detection to minimize skew; no samples were above maximum range of standard curve. Interassay coefficients of variation were 15% or less and intraassay coefficients of variation were 10% or less for all samples.

**Statistics**

Normality of data was analyzed using a Shapiro-Wilks test in PROC UNIVARIATE of SAS (v. 9.4, SAS Institute Inc.). Not all variable residuals were normally distributed, and as such, all data were analyzed using PROC GLIMMIX with a lognormal distribution with identity link. Least squares means and standard error of the mean (SEM) were then back-transformed for manuscript readability. Week was used as the repeated measure with 5 variance/covariance structures [unstructured, variance components, compound symmetry, autoregressive (1), and heterogeneous autoregressive (1)] to determine Akaike information criterion values, the lowest of which was used. Interaction of treatment × week × parity was sliced post hoc by parity × week to focus on biologically relevant comparisons: comparison of ADY vs. control with each parity × week grouping. Wherever a treatment × week × parity interaction was significant, only post hoc slices that were significantly different were discussed.

Repeated and nonrepeated measures data were analyzed according to the respective predictors:

\[ Y = \mu + P_i + T_j + W_k + P \times W_{ik} + P \times T_{ij} + T \times W_{jk} + P \times T \times W_{ijk} + \varepsilon_{ijkl} \]

and

\[ Y = \mu + P_i + T_j + P \times T_{ij} + \varepsilon_{ijk}, \]

where \( \mu \) = overall mean, \( P \) = effect of parity (i = primiparous or multiparous), \( T \) = effect of treatment (j = CTRL or ADY), \( W \) = effect of week (k = −3 to 9 for nonlactation parameters or 0 to 9 for lactation), and \( \varepsilon_{ijkl} \) and \( \varepsilon_{ijk} \) = residual error. Random effects of cow and block were included.

Significance was declared at \( P < 0.05 \) and tendencies were declared at \( 0.05 \leq P < 0.10 \). Data reported throughout are back-transformed means ± SEM. The main effects and their interactions are denoted in \( P \)-values only to improve readability of the manuscript.

**Figure 2.** Dry matter intake (A) and BW (B) of primiparous and multiparous cows with or without diet supplementation with top-dressed Saccharomyces cerevisiae boulardii. CTRL-P: control diet, primiparous cows; active dry yeast (ADY)-P: ADY-supplemented diet, primiparous cows; CTRL-M: control diet, multiparous cows (lactation 2 or 3); ADY-M: ADY-supplemented diet, multiparous cows. Error bars are ±SEM.
RESULTS

Animal Productivity

Dry matter intake was affected by treatment × week × parity ($P = 0.01$; Figure 2); in wk -1, 1, and 7, ADY-P had greater DMI than CTRL-P ($P = 0.02, 0.05, 0.03$). The DMI was unaffected by main effect of treatment ($P = 0.47$). For parity, multiparous cows had greater DMI than primiparous cows ($P < 0.01$), and week intake increased as lactation progressed ($P < 0.01$). Body weight was affected by a week × parity interaction ($P < 0.01$) with ADY-P tending to have greater BW at wk 1 and 8 ($P = 0.08, 0.09$). Body weight was positively affected by treatment ($P = 0.05$) with ADY-supplemented cows having higher BW after calving (563.7 ± 12.2 vs. 588.3 ± 13.5 kg, CTRL vs. ADY).

Daily milk yield increased with ADY supplementation (36.7 ± 2.3 vs. 38.9 ± 2.4 kg/d, $P = 0.02$ Figure 3) and was also affected by week ($P < 0.01$) and parity ($P < 0.01$). Energy-corrected milk tended to increase with treatment ($P = 0.08$) and it was affected by week ($P < 0.01$) and parity ($P < 0.01$). Feed efficiency also
tended to be positively affected by treatment (1.84 ± 0.09 vs. 1.93 ± 0.1 kg milk/kg DMI; \(P = 0.08\), CTRL vs. ADY) and was affected by week (\(P < 0.01\)) and parity (\(P < 0.01\)). Peak milk yield was higher for multiparous cows than primiparous cows (\(P < 0.01\)) but was unaffected by ADY treatment (\(P = 0.28\); Figure 3). Other than the interactions noted above, no other interactions were significant.

**Colostrum and Milk Composition**

Colostrum IgG, IgA, and IgM concentrations were unaffected by treatment × parity interactions or by treatment (Figure 4). The only exception to this trend was IgA, which was greater in multiparous cows than primiparous cows (1,011 ± 37 vs. 749 ± 38 mg/dL, \(P < 0.01\)). The most abundant immunoglobulin was IgG.
Milk protein % was affected by treatment × week × parity interaction ($P<0.01$), but no post hoc slice was significant. Milk protein % was also affected by week × parity ($P=0.04$). No other interactions were significant for any milk component. Milk components were unaffected by main effect of ADY supplementation (fat %, $P=0.44$; protein %, $P=0.50$; lactose %, $P=0.75$; MUN, $P=0.28$; Figure 5). Week of lactation affected all components ($P<0.001$). Lactose tended to be affected by parity ($P=0.07$), and MUN ($P<0.01$) was affected by parity with lactose and MUN being greater in primiparous cows. Milk SCS was unaffected by ADY supplementation ($P=0.10$) but was affected by week ($P=0.03$; Figure 6).

**Blood Metabolites**

Serum NEFA was affected by treatment × week ($P=0.05$) and treatment × week × parity interaction ($P<0.01$) with ADY-P tending to have lower NEFA than CTRL-P at wk −2 ($P=0.06$) and wk 9 (0.03) and ADY-M tending to have lower NEFA than CTRL-M.
at wk 8 ($P = 0.07$). Blood glucose, BHBA, and NEFA were unaffected by main effects of treatment (Glucose: $P = 0.63$, NEFA: $P = 0.87$, BHBA: $P = 0.68$; Figure 7) but were affected by week ($P < 0.01$) and parity ($P = 0.02$). Acute phase protein serum amyloid A tended to increase in ADY-supplemented animals ($P = 0.06$), but haptoglobin was not affected by ADY treatment ($P = 0.56$; Figure 8). As for cytokines, IL-6 tended to be affected by the interaction of treatment × parity ($P = 0.09$). The TNF-α was significantly increased by ADY supplementation (1.17 ± 0.69 vs. 4.96 ± 7.7 ng/mL, $P < 0.01$; Figure 9). Proinflammatory IL-18 (IFN-γ inducing factor) was unchanged by ADY supplementation, week, or parity (IL-18; $trt P = 0.57$, week $P = 0.50$, parity $P = 0.42$). Other than the interactions mentioned above, no interactions were significant.

**DISCUSSION**

Broadly speaking, ADY are understood to improve competitive exclusion of pathogenic bacteria (McAlister et al., 2011; Hill et al., 2014), improve immunomodulation through TLR-4 signaling (Nasiri et al., 2019; Lopreiato et al., 2020), and improve total-tract digestibility (Desnoyers et al., 2009). Some studies suggest that ADY products compete with opportunistic bacteria in the intestine and keep them from overgrowing (Krehbiel et al., 2003; Seo et al., 2010; Ullah Khan et al., 2016). Among the diversity of direct-fed microbials and active dry yeasts, metabolic, productive, and immunological responses to dietary ADY products differ depending on the diet, formulation, and feeding schedule (Elghandour et al., 2015), and thus results have been inconsistent across studies (Ullah Khan et al., 2016). A recent meta-analysis (Lopreiato et al., 2020) of yeasts and yeast products highlighted mixed results, likely missing strain-specific effects on animal response. To tease apart strain-specific modes of action and animal responses, we opted, in this discussion, to focus primarily on comparing the same strain of ADY among multiple species and physiological states. While commonalities exist among various ADY species and strains in terms of productive responses, immunological responses are considered to be strain-specific (Hill et al., 2014), hence the primary focus on other research using the same strain.

**Saccharomyces cerevisiae boulardii and Productivity**

The current study investigated SCB supplementation. The ADY supplementation improved milk yield and also decreased BW loss in the first 7 wk of lactation without changes to DMI; this explains the tendency for feed efficiency to increase with SCB supplementation. In addition, energy status metabolites were unaffected by ADY supplementation. Other types of yeast products have also shown increased feed efficiency in lactating dairy cows (Casper, 2008; Moallem et al., 2009; Dias et al., 2018). During postpartum, when high producing cows are in negative energy balance, an increase in feed efficiency would be beneficial. Cows with higher BW loss during the transition period are more likely to have reproductive challenges (Poncheki et al., 2015), so the higher BW in the ADY groups suggest SCB is beneficial for dairy cows during the lactation transition.

Several possible modes of action for SCB supplementation exist, all of which center around protection of the postruminal, lower gastrointestinal tract. Low abomasal pH is not a barrier for SCB (CNCM I-1079), which survives low pH of 2.5 for several hours (Czerucka et al., 2007; Edwards-Ingram et al., 2007; Ma et al., 2018), allowing it to also impact the lower gut. In the lower gut of Holstein calves, SCB supplementation in milk replacer increases crypt depth (Fomenky et al., 2017), tight junction structure (Mumy et al., 2008), and mucin production (Fomenky et al., 2017). Further, SCB supplementation decreases pathogen load (Ma et al., 2018; Lee et al., 2019) as well as days and severity of diarrhea (Villot et al., 2019). The changes in lower gut morphology, namely crypt depth and tight junction improvements, in turn affect pathogen load, secretory
IgA secretion (Buts et al., 1990), and can increase the innate immune response (Kayser et al., 2019). It is possible that supplementation with SCB improved overall nutrient digestibility in the dairy cow. Increases in nutrient digestibility, as determined by the indigestible marker chromium oxide, were seen in both piglets fed probiotics including SCB (Giang et al., 2010) and in grower pigs fed grape pomace fermented with SCB (Yan and Kim, 2011). Total-tract digestibility has been measured for dairy cattle supplemented with other yeast products (Bitencourt et al., 2011; Ferrareto et al., 2012; Ferreira et al., 2019) but not for the specific strain used in the current study.

**Saccharomyces cerevisiae boulardii and Immunological Impacts**

Feeding ADY products can stimulate intestinal epithelial innate immunity, leading to reduced inflammation in the intestine through increases in secretory IgA

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Figure 7. Blood glucose (A), nonesterified fatty acids (NEFA; B), and β-hydroxybutyric acid (BHBA; C) concentrations in primiparous and multiparous cows with or without dietary supplementation with top-dressed *Saccharomyces cerevisiae boulardii*. CTRL-P: control diet, primiparous cows; active dry yeast (ADY)-P: ADY-supplemented diet, primiparous cows; CTRL-M: control diet, multiparous cows (lactation 2 or 3); ADY-M: ADY-supplemented diet, multiparous cows. Error bars are ±SEM.
production (Buts et al., 1990), leading to an immune-protective effect. In calves, SCB supplementation improved innate immune response by increasing oxidative bursts and phagocytosis (Fomenky et al., 2017). SCB has been shown to decrease levels of circulating cytokines such as IL-6 and TNF-α, though these studies have been performed in pigs (Collier et al., 2011), cell lines (Dahan et al., 2003), or mice (Martins et al., 2010) and have not been repeated in adult ruminants. In the current study, SCB supplementation increased TNF-α and tended to increase serum amyloid A, with only a tendency for changes in inflammatory cytokine IL-6 and no changes seen in IL-18 or haptoglobin. Taken together, these results suggest SCB may cause an acute immune response, but this response is inconsistent and does not affect all proinflammatory pathways. In canonical inflammatory pathways, TNF-α will stimulate the production of IL-6, which in turn stimulates the release of haptoglobin. Interleukin-6 increases acute phase proteins in several inflammatory diseases but has shown lower circulating levels postpartum in dairy cattle (Ishikawa et al., 2004). In this study, TNF-α spiked at wk 1 postpartum in primiparous cows, likely because damaged cells in the uterus caused a chain reaction for the release of haptoglobin and the recruitment of neutrophils. An increase in circulating TNF-α levels has been previously reported in dairy cattle supplemented with yeast products (Spaniol et al., 2015). It is not clear if an increase in circulating cytokines constitutes an improvement in the functioning of the immune system. Previous work saw a 16% increase in neutrophils with SCB supplementation in beef heifers (Kayser et al., 2019). In this study, we did not observe any effect of treatment or time on IL-18 and only saw a tendency for the interaction of treatment × parity to affect IL-6, contrary to a study in feedlot steers where ADY supplementation decreased cytokine production following an LPS challenge (Buntyn et al., 2015). The TNF-α stimulation of acute phase proteins appears to be species-specific (Nakagawa-Tosa et al., 1995), and thus, it is unclear if the tendency for serum amyloid A increase was due to TNF-α stimulation or some other mechanism. Interleukin-18 has also been cited for its immune-enhancing effects (Shi et al., 2007) and tends to increase around parturition (Muneta et al., 2005); however, there was no effect of parturition or treatment on IL-18 concentrations. Further research is required to better understand how inflammatory pathways are affected by SCB supplementation.

While the proinflammatory response was somewhat inconsistent, the acute phase response was consistent with previous studies (Alsemgeest et al., 1993; Humblet et al., 2006). Both serum amyloid A (SAA) and haptoglobin are markers of acute inflammation (Humblet et al., 2006).
et al., 2006), but interpreting results in the week after calving can be difficult due to the natural rise in SAA and Hp concentrations that occur with parturition (Alsemgeest et al., 1993; Humblet et al., 2006). From our results, it is difficult to tell if the tendency for increased SAA is due to the calving event itself or recruitment due to injury and infection postcalving, as they often occur together. Previously, it was demonstrated that SAA responds to infection (Heegaard et al., 2000) and also increases with physical stress (Alsemgeest et al., 1995) that occurs with parturition. Since SAA responds to both infection and physical stress, determining if 1 or both are the cause is difficult. In this study, SAA levels were low on the day of parturition but steadily increased through wk 4 after parturition. This is consistent with the inflammatory pathway and healing of the uterus postcalving. There was also a tendency for SAA to increase due to ADY treatment; it is unclear

Figure 9. Serum concentrations of cytokines tumor necrosis factor-α (TNF-α; A), IL-6 (B), and IL-18 (C) in primiparous and multiparous cows with or without dietary supplementation with top-dressed *Saccharomyces cerevisiae boulardii*. CTRL-P: control diet, primiparous cows; active dry yeast (ADY)-P: ADY-supplemented diet, primiparous cows; CTRL-M: control diet, multiparous cows (lactation 2 or 3); ADY-M: ADY-supplemented diet, multiparous cows. Error bars are ±SEM.
if this is due to an enhanced immune response to the stressors of parturition, or increased inflammation due to supplementation.

Altered immunological activity may contribute to energetic savings resulting in improved milk production seen in this study. An immune response increases energy demand up to 55% (Sanchez et al., 2021), or the equivalent of 1 kg of glucose utilized in a 12 h period (Kvidera et al., 2017), so alterations in immune response may conserve energy without affecting DMI. In this study, the altered immune response may have resulted in energetic savings that improved milk production without affecting DMI, though this was not directly measured. Further research could lead to better quantification of the benefits of immunomodulation of dairy cattle during the calving transition period. Future research should also focus on measuring and quantifying the energetic use of transition dairy cows fed SCB.

CONCLUSIONS

During the parturition transition, SCB supplementation increased milk production without an increase in DMI. Also, SCB appears to improve feed efficiency while maintaining body fat mobilization. This increase in efficiency suggests energetic savings in metabolic processes in the body. More research is needed to fully understand the mechanisms of energy metabolism with SCB supplementation.

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