RUMINANT NUTRITION

Effect of anti-inflammatory compounds or antibiotic administration on receiving performance and physiological responses of transported heifers

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Abstract

The objectives of this experiment was to evaluate the effects of products with anti-inflammatory properties (yeast product [YEA; 20 g/heifer daily] or astragalus polysaccharide [APS; 20 g/heifer daily]) or an antibiotic (TUL, tulathromycin; 0.025 mL/kg body weight [BW]) on receiving performance and stress responses of transported heifers. Angus heifers ($n = 80$) were ranked by BW (315 ± 6 kg) and assigned to one of four treatments (five pens per treatment, four heifers per pen) 7 d before shipping 1,400 km (day -7): 1) fed a basal diet of ad libitum hay and concentrate supplement (CON) from day -7 to day 29; 2) YEA in supplemental concentrate from day -7 to day 7 (YEA); 3) APS in supplemental concentrate from day -7 to day 7 (APS); 4) administration of TUL at loading for shipping (day 0; TUL). Upon arrival at the receiving facility (day 1), heifers within each treatment were ranked by BW and assigned to 20 feedlot pens in the same manner as pre-transport. Daily dry matter intake (DMI) was recorded from day 1 to day 28. Full BW was recorded on days -7, -1, 0, 1, 28, and 29. Blood samples were collected on days -7, -1, 1, 4, 7, 14, and 28. Over the receiving period, average daily gain (ADG) and gain: feed did not differ ($P \geq 0.19$) for YEA, APS, and TUL, which were greater ($P \leq 0.01$) than CON. Average daily gain was also lower ($P < 0.01$) for CON vs. YEA, APS, and TUL from day -7 to day 28. During the first week of receiving, hay, concentrate, and total DMI were lower ($P < 0.01$) in CON than the YEA, APS, and TUL, but did not differ ($P \geq 0.13$) among these three groups. Hay and total DMI were still lower ($P < 0.01$) in CON vs. TUL in the second week. Total DMI was greater ($P = 0.01$) for TUL vs. YEA, and greater ($P < 0.01$) for YEA vs. CON. Serum nonesterified fatty acid concentrations were greater ($P \leq 0.05$) for CON and TUL vs. YEA and APS on day 1. Plasma cortisol concentrations were greater ($P \leq 0.05$) for YEA and CON vs. APS and TUL on day 1. Serum tumor necrosis factor- α concentrations were lower ($P \leq 0.05$) for APS vs. CON, YEA, and TUL on days 1 and 4. Plasma haptoglobin concentrations were greater ($P \leq 0.05$) for CON vs. YEA, APS, and TUL on days 1 and 4, greater ($P \leq 0.05$) for YEA, APS vs. TUL on day 1, and greater ($P = 0.03$) for YEA vs. TUL on day 4. Plasma ceruloplasmin concentrations were greater ($P \leq 0.05$) for CON vs. YEA, APS and TUL vs. APS on days 1, 4, and 7. In conclusion, YEA, APS, and TUL modulated the physiological stress responses and alleviated the performance losses caused by long-distance transportation.

Key words: acute-phase proteins, astragalus polysaccharide, receiving performance, transported heifers, tulathromycin, yeast product

Abbreviations

ADF	acid detergent fiber
ADG	average daily gain
APS	astragalus polysaccharide
BRD	bovine respiratory disease
BW	body weight
CON	control group
CP	crude protein
DM	dry matter
DMI	dry matter intake
G:F	gain:feed
IFN	interferon
IL	interleukin
LPS	lipopolysaccharide
NDF	neutral detergent fiber
NEFA	non-esterified fatty acid
NE _g	net energy for gain
NE _m	net energy for maintenance
RT	rectal temperature
TDN	total digestible nutrient
TNF- α	tumor necrosis factor- α
TUL	tulathromycin
YEA	yeast product

Introduction

Road transport is one of the most stressful events encountered by feeder cattle during their productive lives (Arthington et al., 2005). During transportation, multiple stressors that cattle experience result in an overall immunosuppression that allows the respiratory tract to be invaded by numerous opportunistic pathogens (Earley et al., 2017), which could cause morbidity and mortality from bovine respiratory disease (BRD) and losses in performance during receiving (Duff and Galyean, 2007; Cooke, 2017). Concurrently, cattle experience inflammatory and acute-phase responses (Arthington et al., 2008; Cooke et al., 2011) that impact receiving performance by increasing basal metabolism and tissue catabolism and by reducing dry matter intake (DMI) and gain:feed (G:F; Johnson, 1997). Hence, antibiotics and anti-inflammatory agents are considered as effective solutions for transport stress.

Yeast culture plus enzymatically hydrolyzed yeast could decrease uterine interleukin (IL)-6 mRNA expression in postpartum cows (Yuan et al., 2015), yeast cell wall supplementation could decrease IL-6 concentration in newly received heifers following an endotoxin challenge (Sanchez et al., 2013), and decrease acute-phase proteins in steers with ruminal acidosis caused by high concentrate (Lei et al., 2013), from which we knew yeast product (YEA) could alleviate inflammatory reactions. Similarly, astragalus polysaccharide (APS), isolated from the radix of *Astragalus membranaceus* (He et al., 2012), could inhibit lipopolysaccharide (LPS)-induced increase of pro-inflammatory cytokines mRNA expression in broilers (Liu et al., 2015) and decrease the release of IL-1 β in weaned pigs (Mao et al., 2005), which also exhibited anti-inflammatory properties. Thus, YEA and APS may alleviate inflammatory and acute-phase responses caused by long-distance transport resulting in receiving performance loss and overall health issues. Different from anti-inflammatories aforementioned, tulathromycin (TUL) was a novel macrolide antibiotic, which could be used in preventing opportunistic pathogens from invading the body resulting in the occurrence of BRD and loss of receiving performance (Rooney et al., 2005). As antibiotic resistance and residual evolved as great concerns

in the world, anti-inflammatories such as YEA and APS are attractive alternatives to antibiotics.

On the basis of this rationale, we hypothesized that YEA (Optisafyfield, Phileo, Lesaffre Animal Care, Chuzhou, China; 20 g/heifer daily), APS (Duo Tangbao, Centre, Beijing, China; 20 g/heifer daily), and TUL (tulathromycin, Draxxin, Pfizer Animal Health, Shenyang, China; 0.025 mL/kg BW) could alleviate inflammatory and acute-phase protein responses and improve receiving performance of transported heifers. Hence, the objective of this experiment was to evaluate the effects of products with anti-inflammatory properties (YEA or APS) and antibiotic (TUL) on receiving performance and physiological responses of transported heifers.

Materials and Methods

All heifers used herein were selected from 1,000 heifers shipped from Xiongte Husbandry Co., Ltd in Rizhao City, Shandong Province to Yuliang Husbandry Co., Ltd in Tongliao City, Inner Mongolia Autonomous Region. All the animals used in this study were handled in strict accordance with acceptable practices and experimental protocols reviewed and approved by the Animal Welfare Committee of China Agricultural University.

Animals and management

Eighty healthy Angus heifers, weaned 85 d before the beginning of the experiment (day -7), were selected. On day -7, heifers were ranked by initial body weight (BW; 315 ± 6 kg) and assigned to one of four treatments (five pens per treatment, four heifers per pen): 1) fed a basal diet of ad libitum hay and concentrate supplement (CON) from day -7 to day 29; 2) YEA was added into supplemental concentrate from day -7 to day 7 (YEA); 3) APS was added into supplemental concentrate from day -7 to day 7 (APS); 4) administration of TUL at loading for shipping (day 0; TUL). YEA and APS were mixed daily with concentrate from day -7 to day 7. YEA we used herein contained live yeast *Saccharomyces cerevisiae*, yeast cell wall, and selenium yeast and were added to concentrate supplement at 20 g/heifer daily. APS was added into the concentrate supplement at 20 g/heifer daily. TUL was injected subcutaneously at a rate of 0.025 mL/kg BW prior to loading on day 0. Multiplex vitamin of electrolyte product (Vitamins & Electrolytes Type I, Hebei Yuanzheng Pharmaceutical Co., Ltd, Shi Jiazhuang, China; 0.5 g/kg water) were dissolved to drinking water daily for all the heifers from day -3 to day 3, which contained no less than 11,000,000 IU/kg of vitamin A, 2,200,000 IU/kg of vitamin D₃, 2,000 mg/kg of vitamin E, 2,000 mg/kg of vitamin K₃, 500 mg/kg of vitamin B₁, 1,200 mg/kg of vitamin B₂, 200 mg/kg of folic acid, 20,000 mg/kg of vitamin C, 10,000 mg/kg of Lys, 1,000 mg/kg xylooligosaccharide, 1% potassium, 0.75% sodium, and glucose as the carrier.

From day -7 to day 0, all groups were fed Chinese wildrye hay ad libitum and 1.8 kg/heifer of a concentrate (Table 1) daily. On day 0, all the heifers in four groups were commingled and transported at the same time in three one-deck livestock trailers (Chenglong stake truck; Dongfeng Liuzhou Automobile Co., Ltd; Liuzhou, China; 9.6 by 2.55 m). The heifers were transported for 29 h from 0800 hours on June 5 to 1300 hours on June 6 from Rizhao City in Shandong Province to Tongliao City in Inner Mongolia Autonomous Region, without access to feed and water. During transportation, the driver stopped every 6 h to rest for 45 min, but cattle remained in the trailers the entire journey. Temperature ranged from 12 to 29 °C, and average was

Table 1. Ingredients of the experimental diets (% of DM) fed to heifers before and after 29-h road transport from Rizhao City in Shandong Province to Tongliao City in Inner Mongolia Autonomous Region, without access to feed and water

Ingredients	Pre-transport, day -7 to day 0	Post-transport, day 1 to day 28
	% DM basis	
Cornmeal	57.0	—
Steam-flaked corn	—	53.0
Wheat bran	11.5	—
Soybean meal	10.0	—
Cottonseed meal	—	8.0
DDGS	9.0	36.0
Palm meal	6.0	—
Wheat middling	2.0	—
Calcium	2.5	—
NaCl	1.0	—
NaHCO ₃	0.3	—
CaHPO ₄	0.3	—
MgO	0.2	—
Mineral mix ¹	0.2	3.0

¹The premix contained 200 mg/kg of Co, 2,250 mg/kg of Cu, 25,000 mg/kg of Fe, 100 mg/kg of I, 5,000 mg/kg of Mn, 50 mg/kg of Se, 3,000 mg/kg of Zn, 800,000 IU/kg vitamin A, 100,000 IU/kg of vitamin D3, and 2,600 mg/kg vitamin E.

18 °C; whereas average humidity was 35%, no precipitation was observed. Road transportation occurred mainly on public, straight, and flat tarmac highways with brief periods on rolling and about 50 km of bumpy country dirt road.

Upon arrival (d1), heifers were unloaded, weighed, blood sampled, and then assigned to 20 feedlot pens in the same manner as pre-transport for a 28-d feedlot receiving period. During the receiving period, all the heifers were fed Chinese wild rye hay *ad libitum* and 2.55 kg/heifer (dry matter [DM] basis) of a corn-based concentrate (Table 1) daily, which was offered separately from hay at 0700 hours. All the animals were allowed access to water freely all the time except during transport.

Samples of hay and concentrate ingredients were collected weekly, pooled across all weeks, and analyzed for nutrient composition (Table 2). All samples were analyzed by wet chemistry procedures for concentrations of crude protein (CP; Dumas method; Rapid N III, Elementar, Germany), acid detergent fiber (ADF), and neutral detergent fiber (NDF; Van Soest et al., 1991; modified for use in an Ankom 200i fiber analyzer, Ankom Technology Corp). Calculations of total digestible nutrient (TDN) was according to the equation proposed by Weiss et al. (1992), whereas net energy for maintenance (NE_m) and net energy for gain (NE_g) were calculated with the equations proposed by the NRC (1996).

Heifers were monitored twice daily (at approximately 0700 hours and 1500 hours) for clinical signs of BRD. Clinical signs observed included nasal and ocular discharge, labored breathing, coughing, dehydration, and lethargy. Heifers showing BRD clinical signs were removed from their pens to take rectal temperature (RT), heifers with RT of 39.5 °C or greater were treated with Enrofloxacin (12.5 mg/kg of BW, Baytril100, Bayer

Table 2. Nutrient composition of concentrate and hay (DM basis) fed to heifers before and after 29-h road transport from Rizhao City in Shandong Province to Tongliao City in Inner Mongolia Autonomous Region, without access to feed and water

Item	Pre-transport, day -7 to day 0		Post-transport, day 1 to day 28	
	Concentrate	Hay	Concentrate	Hay
CP, %	17.6	14.1	16.1	13.7
ADF, %	2.9	27	3.5	34
NDF, %	7.2	44.1	7.8	46.7
TDN ¹ , %	89.0	53.3	83.2	55.9
NE _m ² , Mcal/kg	2.20	1.32	2.34	1.29
NE _g ² , Mcal/kg	1.46	0.70	1.52	0.72

¹TDN was calculated as described by Weiss et al. (1992).

²NE_m and NE_g were calculated with the equations proposed by the NRC (1996).

Animal Health, Shawnee Mission, KS) and removed. Four heifers in CON, three heifers in APS, and two heifers in YEA were removed from the study during the first week of receiving due to BRD treatment, and no data were collected from them so our results only applied to apparently healthy cattle. No further incidences of morbidity or mortality were observed from day 1 to day 28.

Sampling

Full BW was recorded and averaged over two consecutive days before transportation (day -1 and day 0) and at the end of experiment (day 28 and day 29) to calculate average daily gain (ADG) from day 0 to day 28, also recorded on day -7 to calculate the ADG from day -7 to day 0 and day 28. Individual BW was also collected immediately on day 1 to calculate the shrink as percentage change from the BW recorded on day 1 and day 0. Concentrate, hay, and total DMI was recorded from day 1 to day 28 from each pen by collecting and weighing refusals daily. Samples of the offered and unconsumed feed were collected daily from each pen and used for DM calculation. Hay, concentrate, and total daily DMI of each pen were divided by the number of animals within each pen and expressed as kilograms per animal per day. Total BW gain and DMI of each pen from day 1 to day 28 were used for feedlot receiving G:F calculation.

Blood samples were collected before concentrate feeding on day -7, -1, 1, 4, 7, 14, and 28 via jugular venipuncture into commercial blood collection tubes (Clot Activator, 5 mL; Hebei Xinle Sci&Tech Co., Ltd, Xinle, Hebei, China) with and without sodium heparin for plasma and serum collection, respectively. Blood samples were centrifuged (3,000 × g for 30 min at 4 °C) for plasma or serum harvest, and then stored at -80 °C on the same day of collection. Plasma concentration of haptoglobin was measured by bovine-specific commercial enzyme-linked immunosorbent assay (ELISA) kit (Beijing SINO-UK Institute of Biological Technology, Beijing). Plasma concentration of ceruloplasmin was determined by a colorimetric kit (HY-M0066; Beijing SINO-UK Institute of Biological Technology); Serum concentration of cortisol was measured by a radioimmunoassay kit (HY-10062; Beijing SINO-UK Institute of Biological Technology). Serum concentration of nonesterified fatty acid (NEFA) was measured by a commercially available colorimetric kit (HY-60053; Beijing SINO-UK Institute of Biological Technology); Serum concentration of tumor necrosis

factor- α (TNF- α) was measured by commercial ELISA kit (HY-10116; Beijing SINO-UK Institute of Biological Technology, Beijing). The intra- and inter-assay CV were, respectively, 7.5% and 9.5% for cortisol, 4.5% and 6.9% for NEFA, 4.3% and 8.7% for ceruloplasmin, 7.3% and 10.0% for haptoglobin, and 6.7% and 10.5% for TNF- α .

Statistical analysis

Performance and physiological data were analyzed using PROC MIXED procedure of SAS (SAS Inst., Inc., Cary, NC) and Satterthwaite approximation to determine the denominator degrees of freedom for the tests of fixed effects. The model statement used for BW, ADG, DMI, and G:F contained the effects of treatment using pen as the experimental unit, and data were analyzed using pen within treatment as random variables. BW shrink were subjected to repeat measures over time from day 0 to day 1 using heifer as the experimental unit. Model included the fixed effects of treatment, time and their interaction, and the random effect of heifer. Blood variables were subjected to repeated measures over time using pen as the experimental unit. Models included the fixed effects of treatment, time and their interaction, and the random effect of pen. The covariance structure used was first-order autoregressive, which provided the smallest Akaike information criterion, and hence the best fit for all variables analyzed. Results were reported as least square means as well as covariate-adjusted least-square means for DMI and blood variables and separated using the predicted differences option in SAS. For all data, differences were declared at $P \leq 0.05$ and $0.05 < P \leq 0.10$ was considered a tendency. Results were reported according to main treatment effect if no interactions were significant or according to the highest-order interaction detected that contained the effect of treatment.

Results and Discussion

No treatment effect ($P = 0.60$) but time effects ($P < 0.01$) were detected for BW shrink from day 0 to day 1 (Table 3). Supporting our findings, previous researches reported equivalent BW shrink rates in feeder cattle exposed to the similar transportation schedule adopted herein (Knowles, 1999; Francisco et al., 2012; Cooke et al., 2013a, 2013b, 2013c; Filho et al., 2014; Van Engen et al., 2014). However, heifers in the current experiment had 8% weight loss whereas Arthington et al. (2003) reported a 2% to 3% loss in BW after a 3-h transportation event. This supports the hypothesis that shrink during transportation is likely associated with the duration of the transportation event as was previously suggested (Cernicchiaro et al., 2012).

Treatment effects were detected ($P < 0.01$) for ADG during day 1 to day 28 and during day -7 to day 28, but not during the initial 7 d prior to transport ($P = 0.45$) (Table 3). Heifers in CON had reduced ADG compared with YEA, APS, and TUL ($P < 0.01$), whereas ADG did not differ among YEA, APS, and TUL ($P \geq 0.49$) in both periods of time. However, treatment effects detected on ADG were not sufficient to impact ($P = 0.40$) the final BW (Table 3). Supporting our findings, yeast culture (Phillips and VonTungeln, 1985) or yeast cell wall (Young et al., 2017) could improve ADG during the receiving period. In addition, a treatment effect was also detected ($P = 0.02$) for G:F because the heifers in CON had lower G:F compared with other treatments (Table 3), whereas G:F was similar ($P \geq 0.39$) among these three groups. Hence, YEA, APS, and TUL alleviated the performance losses typically observed in cattle transported for long distances (Marques et al., 2012; Cooke et al., 2013c).

Treatment effects were detected ($P < 0.01$) on hay, concentrate, and total DMI (Table 3). Hay DMI in CON was lower than YEA, APS, and TUL ($P < 0.01$), and heifers in YEA had lower hay DMI

Table 3. Effects of supplementation with yeast product, astragalus polysaccharide, or administration with tulathromycin vs. untreated control without anti-inflammatory or antibiotic on the performance of heifers submitted to transport for 1,400 km¹

Item ²	CON	YEA	APS	TUL	SEM	P-value
BW ³ , kg						
day -7	313.5	313.2	322.7	308.9	6.1	0.67
day 0	322.8	322.9	331.8	318.3	7.0	0.59
day 1	298.2	296.3	304.4	293.1	7.9	0.43
day 28	348.7	356.3	365.8	353.3	7.2	0.40
Shrink ⁴ , %	7.69	8.08	8.27	7.70	6.72	0.26
ADG ⁵ , kg/d						
day -7 to day 0	1.33	1.38	1.30	1.35	0.06	0.45
day 0 to day 28	0.89 ^b	1.15 ^a	1.17 ^a	1.22 ^a	0.04	<0.01
day -7 - day 28	1.01 ^b	1.23 ^a	1.23 ^a	1.27 ^a	0.07	<0.01
DMI ⁶ , kg/d						
Hay	5.48 ^c	5.59 ^b	5.62 ^{ab}	5.68 ^a	0.02	<0.01
Concentrate	2.54 ^b	2.55 ^a	2.55 ^a	2.55 ^a	0.002	<0.01
Total	8.01 ^c	8.14 ^b	8.17 ^{ab}	8.22 ^a	0.02	<0.01
G:F ⁷ , g/kg	103 ^b	143 ^a	140 ^a	141 ^a	6	0.02

¹Heifers were transported at the same time in three commercial livestock trailers (Chenglong stake truck; Dongfeng Liuzhou Automobile Co., Ltd; Liuzhou, China; 9.6 by 2.55 m) and supplemented with yeast product, astragalus polysaccharide, or administrated with tulathromycin and control without anti-inflammatory or antibiotic.

²YEA = 20 g/heifer daily from day -7 to day 7; APS = 20 g/heifer daily from day -7 to day 7; TUL = 0.25 mL/kg BW at day 0.

³BW on day 0 = average BW recorded on day -1 and day 0; BW on day 28 = average BW recorded on days 28 and 29.

⁴Based on BW loss during transport from day 1 to day 0.

⁵Calculated using BW on days -7, 0, and 28.

⁶Calculated from each pen but divided by the number of heifers within each pen and expressed as kilograms per heifer per day.

⁷Calculated using total DMI and BW gain of each pen from day 0 to day 28.

^{a-c}Within rows, values with different superscripts differ ($P \leq 0.05$).

than TUL ($P < 0.01$), whereas APS was intermediate not differing ($P \geq 0.13$) from YEA or TUL. Concentrate DMI in CON was lower than YEA, APS, and TUL ($P < 0.01$), and did not differ among these three groups ($P \geq 0.54$). Similar to hay DMI, total DMI was lower in CON than YEA ($P < 0.01$), and lower in YEA than TUL ($P = 0.01$), but APS was intermediate not differing ($P \geq 0.14$) from YEA or TUL. When DMI was analyzed within each week of the receiving period, heifers in the CON group had reduced hay, concentrate, and total DMI compared with YEA, APS, and TUL for the first week ($P < 0.01$), but were similar in the latter groups ($P \geq 0.44$). During the second week, hay DMI was still lower in CON than TUL ($P < 0.01$), and no difference ($P \geq 0.18$) was found among APS, YEA, and TUL (Table 4). Total DMI followed the same trend as hay DMI, which was lower in CON than TUL ($P < 0.01$) and YEA ($P = 0.05$), and no differences were found among the other three groups ($P \geq 0.14$). No treatment effects were detected for concentrate intake during the second week ($P = 0.49$) as well as hay, concentrate, and total DMI during the third ($P \geq 0.20$) and fourth week ($P \geq 0.42$) of feedlot receiving (Table 4). Consistent with our findings, live yeast (Finck et al., 2014), yeast cell wall (Finck et al., 2014; Young et al., 2017), or yeast culture (Phillips and VonTungeln, 1985) have been reported to improve DMI of receiving cattle. Besides, β -glucan, one of the main components of APS, could also increase the feed intake of the weanling pigs (Mao et al., 2005). Hence, YEA, APS, and TUL could alleviate the feed intake loss often observed in transported cattle, especially in the first 2 wk of receiving, which directly impairs initial receiving ADG (Hutcheson and Cole, 1986; Araujo et al., 2010).

A tendency for a treatment $\times$ day interaction was detected for serum NEFA ($P = 0.08$; Figure 1), given that serum NEFA concentrations were greater ($P \leq 0.05$) in CON and TUL vs. YEA and APS on day 1 of receiving. These results corroborate that long-distance transportation stress stimulates fat tissue mobilization and increases circulating NEFA concentration in cattle (Cooke et al., 2013b; Filho et al., 2014), whereas YEA and

APS alleviated this outcome. Supporting our findings, Sanchez et al. (2014) also reported that yeast cell wall supplementation decreased NEFA concentration in receiving heifers. The authors supplemented yeast cell wall product (2.5 g/heifer/d) during the receiving period and reported that serum NEFA concentration was reduced in the yeast-treated group, indicating that yeast cell wall-supplemented heifers did not have to break down as much adipose tissue to provide energy for immune defenses. The possible reason could be glucocorticoids, such as cortisol, which have catabolic effects, resulting in the breakdown of adipose tissue and protein. In the present study, APS prevented the increase of circulating cortisol concentrations caused by long road transport, which may have influenced the release of NEFA. But this does not explain the decreased NEFA concentration in the YEA group, given that the effect of YEA on lipid metabolism in beef cattle still need further investigation. Hence, YEA and APS appear to modulate lipid mobilization and metabolism in heifers during stress and nutritional challenges.

A tendency for a treatment $\times$ day interaction was also detected for plasma cortisol concentration ($P = 0.09$; Figure 2). Plasma cortisol concentrations were greater ($P \leq 0.05$) for YEA and CON vs. APS and TUL on day 1. These results indicate that APS and TUL prevented the increase in circulating cortisol concentrations elicited by long road transport (Marques et al., 2012). Accordingly, Liu et al. (2015) also found that dietary supplementation of APS decreased the plasma cortisol concentration of broilers after challenged with LPS. Conversely, Finck et al. (2014) reported that a combination of live yeast (5 g/d per steer) and yeast cell wall (5 g/d per steer) supplementation decreased peak cortisol concentrations of receiving steers after LPS challenge. However, Finck et al. (2014) fed live yeast and yeast cell wall for 37 d before LPS challenge, whereas the heifers in the present study were only fed for 7 d before transport. Hence, the different feeding duration likely contributed to the divergences in treatment effects on circulating cortisol

Table 4. DMI parameters (kg/d) within each week of receiving (28 d) in heifers submitted to transport for 1,400 km and supplement with yeast product, astragalus polysaccharide, or administrate with tulathromycin and control without anti-inflammatory or antibiotic^{1,2}

Item ³	CON	YEA	APS	TUL	SEM	P-values
First week (day 1 to day 7)						
Hay	4.51 ^a	4.77 ^b	4.86 ^b	4.92 ^b	0.07	<0.01
Concentrate	2.50 ^a	2.54 ^b	2.55 ^b	2.55 ^b	0.01	<0.01
Total	7.01 ^a	7.31 ^b	7.40 ^b	7.47 ^b	0.09	<0.01
Second week (day 8 to day 14)						
Hay	5.35 ^a	5.48 ^{ab}	5.45 ^{ab}	5.57 ^b	0.08	0.09
Concentrate	2.55	2.55	2.54	2.55	0.003	0.49
Total	7.90 ^a	8.02 ^{ab}	7.99 ^{ab}	8.12 ^b	0.05	0.08
Third week (day 15 to day 21)						
Hay	5.95	6.02	6.11	6.07	0.07	0.21
Concentrate	2.55	2.55	2.55	2.55	0.002	0.55
Total	8.50	8.57	8.66	8.62	0.05	0.20
Fourth week (day 22 to day 28)						
Hay	6.10	6.10	6.08	6.14	0.05	0.70
Concentrate	2.55	2.55	2.55	2.55	0.001	0.42
Total	8.65	8.65	8.63	8.69	0.04	0.69

¹Heifers were transported at the same time in three commercial livestock trailers (Chenglong stake truck; Dongfeng Liuzhou Automobile Co., Ltd; Liuzhou, China; 9.6 by 2.55 m) and supplemented with yeast product, astragalus polysaccharide, or administrated with tulathromycin and control without anti-inflammatory or antibiotic.

²Calculated from each pen, but divided by the number of heifers within each pen and expressed as kilograms per heifer per day.

³YEA = 20 g/heifer daily from day -7 to day 7; APS = 20 g/heifer daily from day -7 to day 7; TUL = 0.25 mL/kg BW at day 0.

^{a,b}Within rows, values with different superscripts differ ($P \leq 0.05$).

Figure 1. Serum NEFA concentration in heifers submitted to transport for 1,400 km and supplement with yeast product, astragalus polysaccharide, or administrate with tulathromycin and control without anti-inflammatory or antibiotic. A treatment $\times$ day tendency was detected ($P = 0.08$). Within days, letters indicate the following treatment differences: a = YEA vs. CON ($P = 0.02$), b = APS vs. CON ($P = 0.04$), e = YEA vs. TUL ($P \leq 0.01$), f = APS vs. TUL ($P \leq 0.01$). Heifers were transported at the same time in three commercial livestock trailers (Chenglong stake truck; Dongfeng Liuzhou Automobile Co., Ltd; Liuzhou, China; 9.6 by 2.55 m). NEFA, non-esterified fatty acid; CON, control group (control without anti-inflammatory or antibiotic; $n = 5$); YEA, yeast product group (20 g/heifer daily from day -7 to day 7; $n = 5$); APS, astragalus polysaccharide group (20 g/heifer daily from day -7 to day 7; $n = 5$); TUL, tulathromycin group (0.025 mL/kg BW at loading on day 0, hypodermic injection; $n = 5$).

Figure 2. Plasma cortisol concentration in heifers submitted to transport for 1,400 km and supplement with yeast product, astragalus polysaccharide, or administrate with tulathromycin and control without anti-inflammatory or antibiotic. A treatment $\times$ day tendency was detected ($P = 0.09$). Within days, letters indicate the following treatment differences: b = APS vs. CON ($P = 0.01$), c = TUL vs. CON ($P = 0.03$), d = APS vs. YEA ($P \leq 0.01$), e = TUL vs. YEA ($P = 0.02$). Heifers were transported at the same time in three commercial livestock trailers (Chenglong stake truck; Dongfeng Liuzhou Automobile Co., Ltd; Liuzhou, China; 9.6 by 2.55 m). CON, control group (control without anti-inflammatory or antibiotic; $n = 5$); YEA, yeast product group (20 g/heifer daily from day -7 to day 7; $n = 5$); APS, astragalus polysaccharide group (20 g/heifer daily from day -7 to day 7; $n = 5$); TUL, tulathromycin group (0.025 mL/kg BW at loading on day 0, hypodermic injection; $n = 5$).

reported herein. Cortisol is well known for its negative role in the regulation of the immune system; however, in response to a pathogen, cortisol is necessary to prevent a hyperinflammatory state caused by increased concentrations of pro-inflammatory cytokines (Sanchez et al., 2013). Serum cortisol concentrations were lower in APS heifers than in CON and YEA heifers on day 1, which corresponds to lower concentrations of TNF- α . Therefore, a muted cortisol response may be a result of a lesser cytokine response. In the current study, there was an increase in cortisol concentration after transportation. The impact of long-distance transportation on cortisol was variable, with research studies reporting increased (Knowles, 1999; Cooke and Bohnert, 2011) or unaltered (Arthington et al., 2003) or decreased (Van Engen et al., 2014) circulating cortisol concentrations after transportation. Researches indicated that the most stressful aspects of transportation seem to be loading or unloading and the duration cattle spent in the truck; the stress response

decreases over time as livestock adjust and habituate to the transportation process in the truck on long hauls, resulting in reducing cortisol concentrations (Knowles et al., 1995).

A tendency for a treatment $\times$ day interaction was also detected for serum TNF- α ($P = 0.10$; Figure 3) because serum TNF- α concentrations were reduced ($P \leq 0.05$) for APS vs. CON, YEA, and TUL on days 1 and 4. These results indicated that APS supplementation alleviated the increase in circulating TNF- α concentrations elicited by road transport (Hulbert et al., 2011). Supporting our findings, Liu et al. (2015) reported that dietary APS could inhibit LPS-induced increase of pro-inflammatory cytokines (IL-6, IL-1 β , and TNF- α) mRNA expression in broilers. Mao et al. (2005) also demonstrated that supplementation of β -glucan obtained from APS decreased the release of IL-1 β in weanling pigs, especially at the dose of 500 mg/kg. The possible mechanism could be APS strongly suppressed nuclear factor- κ B activation and downregulated the phosphorylation

Figure 3. Serum TNF- α concentration in heifers submitted to transport for 1,400 km and supplement with yeast product, astragalus polysaccharide, or administrate with tulathromycin and control without anti-inflammatory or antibiotic. A treatment $\times$ day tendency was detected ($P = 0.10$). Within days, letters indicate the following treatment differences: b = APS vs. CON ($P \leq 0.01$), d = YEA vs. APS ($P \leq 0.05$), f = APS vs. TUL ($P \leq 0.05$). Heifers were transported at the same time in three commercial livestock trailers (Chenglong stake truck; Dongfeng Liuzhou Automobile Co., Ltd; Liuzhou, China; 9.6 by 2.55 m). TNF- α , tumor necrosis factor- α ; CON, control group (control without anti-inflammatory or antibiotic; $n = 5$); YEA, yeast product group (20 g/heifer daily from day -7 to day 7; $n = 5$); APS, astragalus polysaccharide group (20 g/heifer daily from day -7 to day 7; $n = 5$); TUL, tulathromycin group (0.025 mL/kg BW at loading on day 0, hypodermic injection; $n = 5$).

Figure 4. Plasma haptoglobin concentration in heifers submitted to transport for 1,400 km and supplement with yeast product, astragalus polysaccharide, or administrate with tulathromycin and control without anti-inflammatory or antibiotic. A treatment $\times$ day interaction was detected ($P \leq 0.01$). Within days, letters indicate the following treatment differences: a = YEA vs. CON ($P \leq 0.05$), b = APS vs. CON ($P \leq 0.05$), c = TUL vs. CON ($P \leq 0.01$), e = YEA vs. TUL ($P \leq 0.05$), f = APS vs. TUL ($P = 0.03$). Heifers were transported at the same time in three commercial livestock trailers (Chenglong stake truck; Dongfeng Liuzhou Automobile Co., Ltd; Liuzhou, China; 9.6 by 2.55 m). CON, control group (control without anti-inflammatory or antibiotic; $n = 5$); YEA, yeast product group (20 g/heifer daily from day -7 to day 7; $n = 5$); APS, astragalus polysaccharide group (20 g/heifer daily from day -7 to day 7; $n = 5$); TUL, tulathromycin group (0.025 mL/kg BW at loading on day 0, hypodermic injection; $n = 5$).

of extracellular signal-regulated kinase and c-Jun N-terminal kinase, which were important signaling pathways involved in the production of TNF- α and IL-1 β , resulting in suppressing the production of TNF- α and IL-1 β (He et al., 2012). Similar to APS, live yeast was also reported to inhibit IL-6 and IL-8 production in differentiated porcine intestinal epithelial cells in vitro (Zanello et al., 2011), and live yeast and β -glucan prepared from *Saccharomyces cerevisiae* could reduce TNF- α expression in mice with colonic inflammation (Jawhara et al., 2012). Furthermore, 30 and 60 g/d doses of YEA could decrease uterine IL-6 mRNA in postpartum cows (Yuan et al., 2015), and yeast cell wall supplementation decreased serum IL-6 concentration in receiving heifers (Sanchez et al., 2013). In vitro studies utilizing human blood observed an increase in the activity of natural killer cells toward tumor cells, decreased the production of interferon- γ , and increased antioxidant activity when blood

cell cultures were incubated with yeast and yeast extracts (Jensen et al., 2008). Therefore, it appears that components of YEA are able to modulate immunity directly through actions on immune cells and may act as an antioxidant, as well as an anti-inflammatory agent (Sanchez et al., 2013). However, no difference was observed for plasma TNF- α concentration between YEA and CON heifers in the current study, given that the effects of YEA on inflammatory cytokines in beef cattle still need further investigation.

A treatment $\times$ day interaction was detected for plasma haptoglobin ($P \leq 0.01$; Figure 4) and plasma ceruloplasmin ($P = 0.03$; Figure 5). Plasma haptoglobin concentrations were greater ($P \leq 0.05$) for CON vs. YEA, APS, and TUL on days 1 and 4, greater ($P \leq 0.05$) for YEA, APS vs. TUL on day 1, and greater ($P = 0.03$) for YEA vs. TUL on day 4. Plasma ceruloplasmin concentrations were greater ($P \leq 0.05$) for CON vs. YEA, APS,

and TUL on days 1, 4, and 7. These results indicated YEA, APS, and TUL alleviated the acute-phase protein response elicited by long-distance transport. Supporting our findings, previous researches also documented an acute-phase response in beef cattle on a similar 24-h road transport (Francisco et al., 2012; Cooke et al., 2013b; Filho et al., 2014). Accordingly, circulating concentrations of acute-phase proteins in transported cattle have been negatively associated with receiving performance (Berry et al., 2004; Qiu et al., 2007; Araujo et al., 2010), which can be attributed to altered basal metabolism, increased tissue catabolism, and reduced feed efficiency during an acute-phase response (Johnson, 1997). Marques et al. (2012) also reported that feed and water deprivation during transport elicited acute-phase reactions, likely because of the death of rumen microbes and subsequent release of endotoxins into the circulation (Chin et al., 2006; Carroll et al., 2009). Hence, the acute-phase reaction can be attributed to the increase in cortisol concentration, breakdown of body reserve, and the death of ruminal microbes due to nutrient restriction which was consistent with the results of our study.

Supporting our hypothesis, YEA, APS, and TUL alleviated acute-phase protein responses elicited by transport. This outcome can be attributed to the decreased plasma cortisol concentrations during feedlot receiving, given that cortisol stimulates the bovine acute-phase protein reaction (Cooke et al., 2011, 2012). APS also alleviated the inflammatory responses elicited by transport based on differences detected for TNF- α between APS and CON heifers. In addition to its anti-inflammatory effect, APS also exhibited antioxidant (Li et al., 2010), antiviral (Chen et al., 2014), and immune-enhancing properties (Wang et al., 2009; Yang et al., 2013) in swine and poultry. Yin et al. (2009) reported that supplementing APS to the diet for early-weaned pigs increased ileal digestibility and BW gain and feed efficiency. Yuan et al. (2006) also reported dietary supplementation of APS could improve ADG, due to increased intake and enhanced immune function of weaned pigs. To the best of our knowledge, our study is the first research to evaluate the effect of APS on the receiving performance of transported cattle. Our result showed APS effectively alleviated the performance losses caused by long-distance transport, likely by alleviating the changes in

metabolism and feed intake regulated by inflammatory cytokine during an acute-phase response (Johnson, 1997). Similar to APS, YEA also exhibited anti-inflammatory property, though a significant difference in serum TNF- α concentration between YEA and CON was not detected in our study. As mentioned earlier, YEA decreased uterine IL-6 mRNA in postpartum cows (Yuan et al., 2015) and decreased serum IL-6 concentration in receiving heifers (Sanchez et al., 2013). Except for its anti-inflammatory property, live yeast in the YEA could consume oxygen to keep rumen anaerobic, which is advantageous for beneficial anaerobic bacteria and disadvantageous for harmful aerobic bacteria resulting in improving the microbial balance of gastrointestinal tract (Chaucheyras-Durand et al., 2008). Major components of yeast cell wall, α -D-glucan, β -D-glucan, and mannan oligosaccharide (Kogan and Kocher, 2007), were reported to improve the overall health of the digestive tract by binding and eliminating pathogens from the gut, thus preventing pathogens from colonizing on the gut wall in pigs (Eicher et al., 2006; Li et al., 2006) and broilers (Spring et al., 2000), but whether the polysaccharides from yeast cell wall could avoid being degraded in the rumen still needs further research. Furthermore, selenium yeast could increase anti-oxidation ability and strengthen the immune capacity in dairy cows (Salman et al., 2009). As a novel macrolide antibiotic, TUL was widely used in preventing opportunistic pathogens from invading the body resulting in the occurrence of BRD and loss of receiving performance (Rooney et al., 2005). In our study, we also found TUL alleviated the acute-phase protein and cortisol response elicited by transport, but the reason is still unknown, given that the effects of TUL on acute-phase and stress response in beef cattle still need further investigation. As antibiotic residue accumulating in animal products, the increasing risk of antimicrobial-resistant pathogens have become great concerns around the world (World Health Organization, 2006), and hence YEA and APS could be attractive alternatives for them.

In conclusion, YEA, APS, and TUL administration modulated the physiological responses and alleviated the performance losses caused by long-distance transportation. Nevertheless, additional research is still warranted to properly determine the optimal dosage and length of YEA and APS supplementation.

Figure 5. Plasma ceruloplasmin concentration in heifers submitted to transport for 1,400 km and supplement with yeast product, astragalus polysaccharide, or administrate with tulathromycin and control without anti-inflammatory or antibiotic. A treatment $\times$ day interaction was detected ($P = 0.03$). Within days, letters indicate the following treatment differences: a = YEA vs. CON ($P \leq 0.05$), b = APS vs. CON ($P \leq 0.01$), c = TUL vs. CON ($P \leq 0.05$). Heifers were transported at the same time in three commercial livestock trailers (Chenglong stake truck; Dongfeng Liuzhou Automobile Co., Ltd; Liuzhou, China; 9.6 by 2.55 m). CON, control group (control without anti-inflammatory or antibiotic; $n = 5$); YEA, yeast product group (20 g/heifer daily from day -7 to day 7; $n = 5$); APS, astragalus polysaccharide group (20 g/heifer daily from day -7 to day 7; $n = 5$); TUL, tulathromycin group (0.025 mL/kg BW at loading on day 0, hypodermic injection; $n = 5$).

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Conflict of interest statement

Authors declare that there are no conflicts of interests. Mention of trade names or commercial products in this article is solely for the purpose of providing scientific information and does not imply recommendation or endorsement by China Agricultural University and Oklahoma State University.

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