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Pre-Treatment with Turmeric (*C. Xanthorrhiza*) Reduces the Severity of Squamous Gastric Ulceration in Feed Restricted Horses

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Abstract

Domestic horses commonly suffer from gastric ulcers, with potential adverse health, welfare and performance effects. This study aimed to investigate the effectiveness of orally administered turmeric for prevention of gastric ulceration in horses during stable confinement and dietary manipulation. Ten horses were used in a 16-day randomized, placebo-controlled and blinded two-period cross-over study. All horses received a base diet with the treatment group also receiving 20g turmeric powder in the feed once daily. Gastric ulcer scores were determined *via* gastroscopy on Day 0, after nine days in a stable (Day 9) and after seven days of feed-fasting (Day 16). After a washout period of 10 weeks, treatment groups were reversed. Squamous ulcer scores increased during confinement and feed restriction in control horses (P<0.001), but not in turmeric treated horses (P=0.247), and squamous ulceration was more severe on Day 16 in control horses (P=0.037). Changes in glandular mucosa were less obvious in treated and control horses. These results suggest that oral supplementation of turmeric (*C. xanthorrhiza*) may be effective in reducing the severity of squamous ulceration in horses.

Keywords: Equine gastric ulcersyndrome; *Curcuma xanthorrhiza*; *C.longa*; Stomach; Supplement; Nutraceutical

Introduction

Equine gastric ulcer syndrome (EGUS) is a common disease within the domestic horse population, affecting 80-100% of Thoroughbreds in training and up to 59% of pleasure horses [1]. Colic, poor condition, poor performance and behavioural changes are considered to be major clinical signs resulting from EGUS [2,3], with adverse effects on the health and wellbeing of the horse. Risk factors include stress, high grain diets, intense exercise and the use of non-steroidal anti-inflammatory drugs (NSAIDS) [4,5]. Ulcerative and erosive conditions of the squamous and glandular mucosa, now termed equine squamous gastric disease (ESGD) and equine glandular gastric disease (EGGD), respectively [1], likely represent distinct clinical conditions of differing aetiology. Current pharmaceutical treatment options are based on suppressing the production of gastric acid and/or protecting the mucosa [1], and are often combined with nutritional and management changes to prevent reoccurrence [6]. The efficacy of gastric acid suppression for the treatment of lesions of the glandular mucosa has been questioned [7]. It can be difficult to completely eradicate risk factors for EGUS, and long term treatments are both time and financially expensive. "Nutraceuticals" and feed supplements are consequently used frequently by horse owners for treatment or prevention of gastric ulcers, with limited empirical evidence of efficacy.

Turmeric has recently become a popular supplement in horse diets for the treatment of various ailments, including gastric ulcers (authors' observation). A spice traditionally used both in food and as a medicinal treatment in southern Asia, turmeric is purported to have a large range of healing properties. *Curcuma longa* is the most commonly used and studied species; however other species such as *C. xanthorrhiza* are also used. The two species have comparable biochemical composition and biological effects [8,9]. Many of these effects have been examined in cell-, animal- and human-based studies over the last decade or so and have demonstrated that both turmeric and its major bioactive component, curcumin, have antimicrobial, antioxidant, anti-cancer, anti-inflammatory and neuroprotective effects [10,11]. Several animal model and human studies have indicated the potential for turmeric/curcumin to prevent or treat gastric ulcers, with minimal side effects [12-15].

The use of turmeric to treat or prevent gastric ulceration in horses represents a potentially simple, cost-effective and risk free treatment for a significant disease, however to date there has been no scientific investigation into this alternative. This study aims to determine if oral supplementation of turmeric will prevent the development of gastric ulcers in horses. Our research hypothesis was that daily administration of turmeric would ameliorate the development of gastric ulceration induced in horses associated with dietary modification, confinement and a previously validated feed-fasting protocol [16,17].

Materials and Methods

Horses and husbandry procedures

All horses used in this study were obtained from the Charles Sturt University teaching herd, and were of Thoroughbred or Standardbred breeding. Nine mares and one gelding (n=10) aged between 5 and 18 years old and weighing 523kg ± 51kg (mean ± sd) were used. The study was designed as a randomized, controlled, blinded, two period cross-over study. Prior to the experiment, and between periods 1 and 2, all horses were maintained on pasture with supplemental feeding of lucerne hay where necessary. Horses participated in veterinary and equine science handling and reproduction practical classes between study periods. Upon entry to the stabling complex at the commencement of each experimental period, horses were physically examined to ensure they were in good health, free from injury or illness. All procedures performed on the horses were approved by and in accordance with the Charles Sturt University Animal Care and Ethics Committee (A16027).

The horses were all housed within the same complex and randomly allocated to individual stables for each period of the study. All horses were fed 10kg ± 2kg (1.9% of their bodyweight (BW) in dry matter (DM)) oaten/clover hay (feed analysis Supplementary table 1), divided into two feeds at 8 am and 5 pm daily, except for during the final 7 day ulcer-inducing period. Immediately prior to the 5 pm meal (pre-meal feed) each horse received 100g of oaten chaff plus 50g of a powdered coconut oil (PowerStance™, Stance Equine, Mount Ommaney, Queensland, Australia) and 20mL molasses (to ensure palatability). Horses in the treatment group also received 20g of powdered turmeric daily (*Curcuma xanthorrhiza*, 2% curcumin; Stance Equine, Mount Ommaney, Queensland, Australia) in the afternoon meal. Any uneaten feed was collected, weighed and recorded to determine intake.

Table 1: Grading system for equine gastric ulcer syndrome, adapted from Andrews, et al. [2]. Summed scores were derived for the squamous mucosa based on assessment of the dorsal fundus and margoplicatus at the greater and lesser curvature. Glandular scores were determined for the ventral glandular fundus and pyloric antrum.

Grade	Squamous Mucosa	Glandular Mucosa
0	The epithelium is intact and there is no appearance of hyperkeratosis (yellowing of the mucosa)	The epithelium is intact and there is no appearance of hyperaemia
1	The mucosa is intact, but there are areas of hyperkeratosis	The mucosa is intact, but there are areas of hyperaemia
2	Small, single or multifocal (<5) lesions	Small, single or multifocal (<5) lesions
3	Large single or extensive (≥ 5) superficial lesions	Large single or extensive (≥ 5) superficial lesions
4	Extensive lesions with areas of apparent deep ulceration	Extensive lesions with areas of apparent deep ulceration

Horses were allowed free exercise for approximately one hour per day, water was available *ad libitum* and water intake was monitored. Heart rate (HR), rectal temperature (RT) and respiratory rate (RR) were monitored daily throughout, and horses were weighed weekly during the trial.

Experimental protocol

Horses were stratified on Day 0 period one according to gastric ulcer scores and randomly assigned to either treatment (n=5) or control (n=5) group for the first study period. The experimental period lasted for a total of 16 days with each animal receiving hay plus pre-meal feed daily for the first 9 days before commencing a 7 day intermittent feed deprivation protocol designed to experimentally induce ulcers [16,17]. During the ulcer induction period, all horses were deprived of the full hay ration for 24 hours every second day, resulting in a total of 96 hours cumulative feed deprivation. Once daily feeding of the small pre-meal was continued for both control and treatment groups during this period. Gastric ulcers were visualized and scored on day nine (prior to feed deprivation protocol) and again on the final day (Day 16) of the experiment, *via* gastroscopy. Upon completion of period one, horses were returned to their paddock for 10 weeks after which time the experimental protocol was repeated with treatments reversed.

All gastroscopic examinations were performed using a 3m endoscope of 9mm outer diameter (Olympus Medical Systems Corporation, Tokyo, Japan). Endoscopy was performed on horses that had been fasted overnight (16-18 hours) to ensure good visualization of gastric mucosa. Water was not withheld. Horses were sedated with xylazine (0.4mg/kg IV) and acetylpromazine (0.02mg/kg IV). Two horses required additional sedation during the procedure (butorphanol, 0.1mg/kg, IV). The stomach was insufflated with air using a manual air pump attached to the endoscopy biopsy channel until stomach folds were absent, and adherent feed was rinsed from the mucosa, to allow full observation of all regions. Lesions were scored on Day 0 (pre-treatment), Day 9 (after 8 days of stabling) and Day 16 (after 7 days of feed-fasting, as described above) based on the gastric ulcer scoring system currently recommended by the European College of Equine Internal Medicine consensus statement [1], (Table 1), and recorded as both an overall grade (0 to 4) and as the sum of scores for squamous and glandular mucosa as previously described [18]. Scores were assigned for each region: greater curvature of the margoplicatus (MPGC), lesser curvature (LC), dorsal squamous fundus (FUND), ventral glandular fundus (GLAND) and pyloric antrum (PYL), using de-identified video recordings by one researcher (SLR) who was blinded to treatment throughout the experiment.

Statistical methods

Within each treatment period, gastric ulcer severity was analyzed by separate analysis of summed ulcer scores for the squamous (MPGC, LC and FUND) and glandular (PYL and GLAND) mucosa for control and treatment groups by one-way repeated measures analysis of variance on ranks (ANOVA) using the Friedman test, with post-hoc multiple pairwise comparisons using Dunn's method. Treatment effects were evaluated at each time point (Day 0, Day 9 and Day 16) by Wilcoxon matched-pairs signed rank test. In all cases $P<0.05$ was considered significant and all analyses were performed using GraphPad Prism version 7 (GraphPad Software, San Diego, California).

Results

All horses remained well for the duration of the study, and none demonstrated clinical signs (colic, inappetance, bruxism, cribbing) suggestive of gastric ulceration. Daily health observations (HR, RT, RR)

remained stable and within normal range for all horses throughout the experimental treatment. There were no feed or water refusals. Horses maintained or increased in weight in both groups during the initial 9 day period, and body weight decreased slightly during the final 7 day intermittent feed deprivation period. There was no treatment effect on body weight. Some horses showed signs of stress (weaving, wood chewing), which increased during the feed deprivation period but could not be related to severity of gastric ulceration or to treatment. Observation of meal time aggression (teeth bared, ears laid back, lunging forward) also increased following fasted days.

Results of endoscopic grading of gastric lesions are provided in Supplementary table 2. Median (95% CI) ulcer scores on Day 1 in period 1 (0, 0-3) were significantly lower than in period 2 (2, 1-5; P=0.043); but were not different between treatment groups (placebo: 1, 0-3; treatment: 1, 0-5; P=0.530). Squamous ulcer scores increased over time (P<0.001) in the control group, but no such effect was observed in horses receiving turmeric (P=0.304, Figure 1) and median (95% CI) squamous ulcer score on Day 16 was significantly (P=0.031) lower when horses received turmeric (2, 0-6) than was observed for control animals (5, 3-6), (Figure 1). Two horses receiving turmeric evidenced summed squamous ulceration scores >6 on Days 9 and 16.

Treatment effects on glandular mucosal scores were much less marked. Glandular mucosal scores tended to increase with time (P=0.025 for horses during control treatment, and P=0.049 for horses receiving turmeric; Figure 1). Differences in glandular mucosal scores between control and treated horses were not significant on Day 0 (P=0.156) or Day 16 (P=0.242; Figure 1). At day 9, following stable confinement but prior to ulcer induction period, all horses had developed lesions in the GLAND region ranging from grade 1 to grade 3, and a significant effect (P=0.042) was observed in control horses. Glandular lesions were typically multifocal or linear areas of hyperaemia and/or superficial erosion. Lesions were more common, and tended to be more severe, in the pyloric region. One horse (H8), receiving turmeric during period two, had a grade 4 (deep and bleeding) lesions in the glandular fundus, but no pyloric lesions.

Discussion

The current study successfully induced squamous and glandular gastric ulceration in horses *via* dietary modification, box confinement and intermittent feed restriction. The severity of squamous ulceration was ameliorated in horses receiving 20g turmeric daily compared to control animals, suggesting that turmeric administration attenuated the development of gastric ulcers in horses. This finding supports results from other studies which have demonstrated similar effects in other species [12,19,20]. However, care must be exercised in extrapolating this finding from healthy, sedentary horses with induced disease, to horses with spontaneous disease, particularly as two horses developed moderate-severe squamous ulceration during turmeric administration. No treatment effect was observed on the development of glandular lesions.

Squamous ulceration is generally understood to be caused by abnormal exposure of the un-protected mucosal cells to gastric acids [21]. Dietary factors are thought to be involved in ESGD, with high grain (starch) diets known to decrease gastric pH [22]. Luthersson N, et al. [23] found that a daily starch intake exceeding 2g/kg BW could increase the risk of moderate or severe gastric ulcers. High fibre diets and/or continuous pasture grazing are thought to reduce the risk of EGUS (due to constant gut fill and pH buffering), however research on this is mixed (reviewed by Sykes, et al. [1]). Lucerne hay has been shown to be protective, resulting in a higher gastric pH [24]. Horses in this study were not fed starch concentrate, however, due to the starch content of the oaten/clover hay fed (7.9%), daily starch intake approached 2g/kg BW, potentially increasing the risk of EGUS and contributing to increased ulcer scores observed on Day 9. Lucerne hay was not fed during the study period.

Fasting has also been associated with gastric ulceration due to reduced pH of gastric fluid [17]. The intermittent fasting protocol used in this study further increased lesion scores in the squamous region in the control group, however the group treated with turmeric had

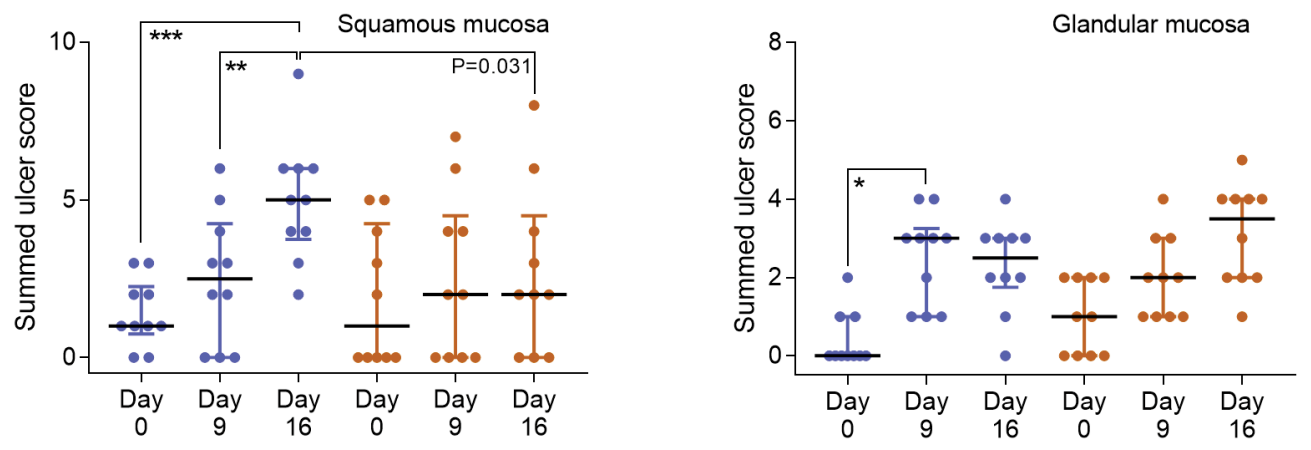

Figure 1: Gastric squamous and glandular ulcer scores following administration of turmeric (20g once daily in feed, orange) or placebo (blue). Results are presented as median (black horizontal line) and interquartile range, with all results shown. A significant (P<0.001) time effect was observed for squamous scores for horses during placebo treatment, but not when turmeric was administered (P=0.304). Significant differences at Day 9 and Day 16, relative to Day 0, are indicated for control horses (**, P=0.016; ***, P=0.001). Median squamous scores were significantly higher on Day 16 following placebo treatment than following turmeric treatment (P=0.031). Significant time effects were observed for glandular mucosal scores associated with control (P=0.025) and turmeric treatment (P=0.049); significant differences on pairwise comparison were evident only for control horses (*, P=0.042).

no such increase. All horses developed squamous lesions following the seven day induction period, even when sufficient roughage (1.9% of BW in DM) was provided daily. This observation is supported by earlier work where stall confinement (with *ad libitum* hay) induced ulceration within 7 days, compared to horses kept at pasture [17]. Mild to moderate squamous ulceration, more severe than was seen in Murray and Eichorn's study, was observed in the current study, and this may be due to the horses not having access to *ad libitum* hay to ensure optimum buffering of gastric acids, fulfillment of natural feeding behaviours or increased stress due to daily confinement. Whilst it is commonly accepted that horses require a daily dry matter intake of 2% body weight to ensure adequate gut fill and digestive functioning, this may not be sufficient to protect against gastric ulcers in conditions of stress such as confinement, particularly when fed as two meals daily. This highlights the need to ensure that good management and husbandry is in place to prevent gastric ulcers from developing and also during treatment.

One possible explanation for the apparent attenuation of gastric squamous ulceration associated with turmeric administration is reduced secretion of gastric acid, thereby reducing the extent of injury to mucosal cells in this region during fasting. This theory is supported by previous work in other species that shows turmeric has an antisecretory effect. Both a reduction in total gastric fluids and decreased acid concentration have been demonstrated following oral administration of turmeric extracts or curcumin in rat models of gastric ulcers [12,14]. It is possible that turmeric has an effect on histamine-mediated acid secretion, as *ex vivo* studies show turmeric has an inhibitory effect on H_2R and, *in vivo,* this effect is comparable to the use of the H_2R inhibitor ranitidine [12]. Further studies are required to evaluate the impact of turmeric on gastric pH in horses.

There was no effect of oral turmeric supplementation on lesions in the glandular regions of the stomach. This finding correlates with the low success rates (10-40%) of pharmaceutical treatments such as omeprazole in treating glandular ulcers in horses, compared to the effect on squamous lesions [25], and is also supported by clinical trials in humans, where treatment of duodenal ulcers (which correspond to glandular ulcers in horses) with turmeric had no effect [15]. Despite these findings, other research has demonstrated *in vivo* properties that theoretically might be protective of glandular mucosa. Turmeric, and its bioactive components such as curcumin, has potent anti-inflammatory and antioxidant effects in many laboratory and animal models [11] and increase gastric mucous production [14,20]. Specifically, it has been observed that *C. xanthorrhiza* has gastro protective effects in a rodent model [26]. In horses, it has been found that oral curcumin supplementation decrease in erythrocyte sedimentation rate, suggesting it may decrease inflammation in the body [27].

The finding that ulcer scores were greater on Day 0 in period two than in period one was unexpected, as horses had been returned to paddock accommodation with pasture grazing and supplementary lucerne hay fed daily. During this 'washout' period, horses participated in a number of student practicals, predominantly involving handling or, for the mares, reproductive examination. It is possible that yarding prior to practical classes disrupted social, dietary and water intake habits, and thereby potentiated the development of ulceration in these horses, or that ulcers that were induced during the original period had not healed during the 10 week recovery. Although pasture turnout, particularly in the company of other horses, has been associated with reduced risk for gastric ulceration [28], squamous ulceration of grade ≥ 2 has been reported in broodmares at pasture [29]. Study design accommodated for this effect, and no difference was observed between treatment and control horses on Day 0.

The endoscopic evaluation of gastric mucosal disease is challenging, and may not correspond to histological changes [30,31]. This problem is further compounded by the use of different grading systems by different authors. The gastric squamous ulceration scoring system used in the current study is that currently recommended by the European College for Equine Internal Medicine [1], modified to include summation of individual scores from different regions of the squamous mucosa, as previously described [18]. Summation of lesion scores (rather than reporting of mean score) allows discrimination of horses with more numerous or extensive lesions, as has been advocated in other scoring systems [32], although it may numerically equate horses with a single severe lesion with those with more mild but extensive changes. To date there is no clinical validation of this assumption. Indeed, the assumption that hierarchical grading systems predict more severe disease has not been proved, although intuitively the progression of lesion severity observed in the current study suggests disease progression. The adaptation and application of the squamous grading system to lesions of the glandular mucosa is not supported by the current consensus statement, and a more descriptive approach has been recommended [1]. The system used in the current study included recognition of the anatomical location of glandular lesions, as recommended, as well as descriptive results which could be assigned to numerical descriptors (grades) to permit non-parametric statistical analysis of results.

Previously reported dose rates for the use of turmeric vary widely, ranging from 80-500mg/kg BW [11]. As turmeric had not previously been experimentally studied in horses at the commencement of this study, a low dose of 20g daily (mean 37.9 ± 3.9mg/kg) was chosen as a conservative option for this initial study. Subsequent studies in horses [10] have evaluated similar doses (15, 20, 25 and 30g), while purified forms of curcumin have been trialled in horses at doses ranging from 1.06-15g [27,33]. Turmeric is considered safe with no toxic effects when administered orally in a number of species [34,35], and no negative effects were observed in this study. Future studies might consider higher and more frequent doses, or administration for a longer period prior to induction of gastric ulceration. Curcumin is widely acknowledged to be very poorly absorbed and rapidly metabolized in other species, resulting in extremely low plasma concentrations [36]. Since this study was conducted, a preliminary pharmacokinetic study in horses has shown that curcumin metabolites are found at low concentrations in equine plasma [33]. In this study, a fat source (powdered coconut oil) was included in the daily meal to assist absorption, as turmeric is lipid-soluble and absorption from the digestive tract into the portal blood is therefore improved with a lipophilic vehicle. However, as the mechanism of action has not been elucidated and topical administration of curcumin aids in the healing of oral ulcers [37], turmeric might act at a local level to similarly protect gastric mucosa.

Conclusion

This study has shown that oral supplementation of turmeric reduced the severity of squamous ulceration in horses induced by box confinement, change of diet and feed restriction. This finding supports laboratory and clinical research in other species suggesting that turmeric has antiulcer properties. As a feed supplement this may result in improved welfare, performance and financial outcomes for horses by reducing reliance on medication for prevention or treatment

of ESGD. This pilot study had a number of limitations including the limited sample size and length of trial due to ethics considerations. Additionally, as a novel study, there was no previous data on which to base dose rates, and whilst the feed-deprivation model of gastric ulcers is well documented it may not necessarily correlate with disease in the field. Further research is required to demonstrate efficacy in the prevention of spontaneous disease, to optimize dose rate and frequency, and to elucidate mechanism of action.

Appendix A: Supplementary Material

Supplementary data associated with this article can be found, in the online version

Declaration of Interest

Power Stance™ and *C. xanthorrhiza* were supplied by Stance Agriculture Pty Ltd, who also provided partial funding for the project. Other than as acknowledged below, Stance Agriculture had no role in study design, execution or interpretation of findings, nor in the decision to submit the manuscript for publication. None of the authors has any financial or personal relationships that could inappropriately influence or bias the content of the paper. Ms. Sophie Fletcher is owner of Integral Equine Nutrition (independent equine nutrition consulting), however this had no influence on the study in any way.

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