Pferdeheilkunde – Equine Medicine 40 (2024) 5 (September/October) 473–481 DOI 10.21836/PEM20240506

Comparison of vital mushrooms and omeprazole in the treatment of equine gastric ulcer syndrome in Thoroughbred racehorses in training – a pilot study

Nina Dietzmeyer[1], Ingrid Vervuert[2] and Monica Venner[1]

[1] Equine Clinic Destedt GmbH, Destedt, Germany
[2] Institute of Animal Nutrition, Nutrition Diseases and Dietetics, Faculty of Veterinary Medicine, Leipzig University, Germany

Summary: Equine squamous gastric disease (ESGD) most notably affects Thoroughbred racehorses, with a prevalence of 80–100%. Omeprazole, the treatment of choice, has been extensively investigated in the past. However, the drug's withdrawal time is 9 days for racehorses in Germany, prohibiting its use before racing. Despite an emerging interest in vital mushrooms to treat gastric ulcers in humans, no studies have yet been published in horses. The aim of the current study was to compare an orally administered vital mushroom formulation with an orally administered buffered omeprazole powder paste formulation with regard to their impact on equine squamous gastric disease (ESGD) and equine glandular gastric disease (EGGD). After clinical and gastroscopic examination, 22 Thoroughbred young racehorses (mean ± SD age 25.7 ± 1.46 months) with lesions of the squamous and/or glandular mucosa were assigned to one of two groups. Horses received either vital mushrooms orally (CME Gastric Control Gold, CME Horses GmbH, Münster, Germany; n = 10 horses) at a dosage of 30 grams/horse for 28 days or buffered paste omeprazole orally (GastroGard®, Boehringer Ingelheim, Ingelheim am Rhein, Germany; n = 12 horses) at an initial dosage of 4 mg/kg bwt for 7 days and a cost limiting prophylactic dose of 1 mg/kg bwt for the subsequent 21 days per os once daily. After completion of the 28-day treatment duration, gastric examinations were repeated to determine lesion status. While ESGD was detected in 21 out of 22 horses, EGGD was less commonly diagnosed in a total of 16 out of 22 horses. Median squamous lesion scores (plus 25th–75th percentiles) significantly improved in horses receiving omeprazole. At the beginning of the study the squamous greater curvature revealed a median score of 2 (1–3) and a median score of 1 (0–3) after treatment on day 28 ($p = 0.016$). The squamous lesser curvature revealed a median score of 3 (2–3) at the beginning of the study and a median score of 2 (1–3) after treatment on day 28 ($p = 0.011$). No statistical significance was detected in the vital mushrooms group with a squamous greater curvature median score of 1 (0–1) at the beginning of the study and a median score of 1 (0–1) after 28 days. The squamous lesser curvature in this group revealed a median lesion score of 1 (1–2) at the beginning of the study and a median lesion score of 1 (0–2) after 28 days of treatment. No statistically significant effects of either of the two treatments were observed in the fundus, antrum, and pylorus. This pilot study shows that the treatment of ESGD with vital mushrooms was inferior to treatment with omeprazole. However, gastroscopic findings did not deteriorate under treatment with vital mushrooms, which might propose their use as supplement before racing. However, due to the missing implementation of a negative control group, we cannot draw a conclusion about whether vital mushrooms supplementation reveals a difference when compared to no treatment. The small number of animals per group constitutes the main limitation of this study. For future trials, the severity of lesions should be balanced between both treatment groups as part of a randomized controlled study.

Keywords: nutraceuticals, ß-glucans, gastric lesions, gastroscopy, EGUS, ESGD

Citation: Dietzmeyer N, Vervuert I, Venner M (2024) Comparison of vital mushrooms and omeprazole in the treatment of equine gastric ulcer syndrome in Thoroughbred racehorses in training – a pilot study. Pferdehlk Equinbe Med 40, 473–481; DOI 10.21836/PEM20240506

Correspondence: PD Dr. Monica Venner PhD, Pferdeklinik Destedt GmbH, Tift 4, 38162 Destedt; mvenner@gmx.de

Submitted: April 29, 2024 | **Accepted:** June 21, 2024

Introduction

Equine Gastric Ulcer Syndrome (EGUS) is a common disease in horses. Worldwide, not only high-performing athletes but also leisure horses and broodmares are affected[1–3]. It is essential to distinguish disease of the Pars nonglandularis (ESGD) and the Pars glandularis (EGGD) as the two anatomical regions are associated with different risk factors and treatment. A variety of management factors have been identified to favor the development of gastric ulcers at the different anatomical sites[4–6].

Racehorses are high-performing athletes, and the relationship between training and the exposure of the Pars nonglandularis to acid is well described. During gaits faster than walking, intra-abdominal pressure increases, thereby the acidic gastric content is pushed dorsally and this causes increased exposure of the squamous mucosa[7]. Additionally, racehorses are fed a high amount of starch daily in order to cover their energy requirements. However, several studies have shown that an increased starch intake is associated with an increased risk of ESGD. If the amount of starch exceeds 2 g/kg bwt an approximately 2-fold increase in the probability of ESGD grade ≥ 2/5 has been described[8]. In accordance with that, the presence of ESGD in actively trained Thoroughbred racehorses shows a prevalence of 80–100%[9–12].

The proton pump inhibitor omeprazole has established itself in numerous studies as the gold standard therapy for lesions of the squamous gastric mucosa. Omeprazole acts by binding

the H^+/K^+ ATPase proton pump on the parietal cells, thereby preventing the secretion of H^+ ions into the gastric lumen and consequently elevating the gastric pH[13,14]. Despite the proven high efficacy of this drug, the outcome of treatment is still influenced by a variety of factors, such as formulation, route of administration, gastric filling prior to oral administration, dosage and duration of treatment, and redevelopment of lesions is common[1,15,16]. In order to treat ESGD, omeprazole has to be administered daily at a dose of 4 mg/kg bwt for a minimum of 14 days, displaying a financial burden for horse owners[17,18]. In addition to that, the use of omeprazole in racehorses is limited in Germany due to doping regulations in gallop racing. A withdrawal period of 9 days was recommended by the EHSLC in 2021. This is based on a multiple administration study with GastroGard® paste (37 % w/w) at a daily dosage of 4 mg/kg bwt omeprazole for 28 days[19]. Consequently, the use of omeprazole during the 9 days prior to racing is not legal in Germany, generating great interest in providing alternative therapies.

In human medicine, there is an emerging interest and ongoing research, dealing with vital mushrooms. Due to their immunogenic, anti-inflammatory and anti-carcinogenic effects[20,21], they represent a potential alternative for the treatment of gastric ulcers. Experimental studies on their gastroprotective properties have already been carried out in rats and mice with promising results. In these studies, artificial gastric lesions were induced using acetic acid or ethanol[22,23]. Numerous supplementary feeds containing various combinations of vital mushrooms are already available for the enhancement of gastric mucosa protection and therefore prophylaxis against EGUS in horses. Although these are freely available on the market, there are currently no clinical studies proving their efficacy in horses.

The aim of the current study was to compare the efficacy of an orally administered vital mushroom formulation with an orally administered buffered omeprazole powder paste formulation in actively trained young Thoroughbred racehorses. We hypothesized that the impact of oral vital mushrooms is not significantly inferior to the impact of orally administered buffered omeprazole powder paste formulation on ESGD and EGGD in Thoroughbred racehorses in training.

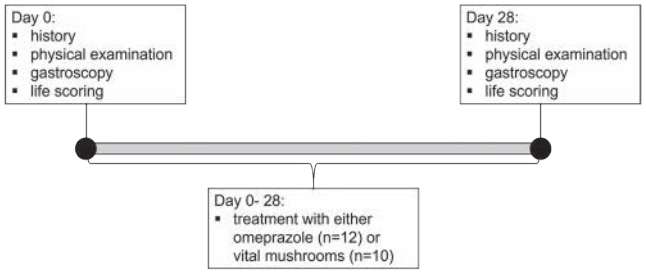

Fig. 1 Study design. At the beginning of the study (day 0), gastric lesions were scored during gastroscopy by *M. Venner* (ECEIM Diplomate). Horses were treated for a total of 28 days and received either omeprazole (n=12) or vital mushrooms (n=10). On day 28, the same procedure as described for day 0 was repeated for all horses. | *Studien Design. Zu Beginn der Studie (Tag 0) wurden die Pferde klinisch und gastroskopisch untersucht. Die Magenbefunde wurden von M. Venner (Dipl. ECEIM) bewertet. An Tag 28 wurde bei allen Pferden dieselben Untersuchungen wie an Tag 0 wiederholt.*

Materials and methods

Animals

Twenty-two actively trained young Thoroughbred racehorses, with a mean age (± SD) of 25.7 ± 1.46 months and a mean BW (± SD) of 447.3 ± 40.0 kg, and with no clinical signs of gastric disorder but with EGUS lesions detected at gastroscopy were recruited from four different racing stables and included in the current study. The study population did not receive any medication in the 4 weeks prior to the start of the study. At the beginning of the study, detailed background information was collected, including signalment, training intensity, management, and clinical history. Horses were included if their clinical examination was within normal limits, and the trainer considered them to be suitable for their ongoing routine exercise program during a four weeks period. Throughout the study, horses were kept in their usual stable environment and were fed their usual diet. The training intensity was similar for all horses in the same stable under the same trainer before the diagnosis of EGUS and throughout the study period.

Treatment

All horses were randomly assigned to one of two treatment groups. Twelve horses were allocated to the omeprazole group, and ten horses were allocated to the vital mushrooms group. Trainers and stall employees were not blinded to the treatment groups. The entire treatment period lasted for 28 days (Figure 1). The first group received a commercially available omeprazole formulation (GastroGard®, Boehringer Ingelheim, Germany) at a dosage of 4 mg/kg bwt once daily orally for 7 days. The following 21 days of treatment were continued with a prophylactic dose of 1 mg/kg bwt once daily orally. The second group received a commercially available dietary supplement containing a mixture of vital mushrooms (CME Gastric Control Gold, CME Horses GmbH, Münster, Germany) at a dosage of 30 grams/horse orally once daily for the entire treatment period of 28 days. All treatments were administered in the morning, e.g., 30 minutes prior to feeding. Trainers were asked to report possible abnormalities of the study horses throughout the entire treatment period (changing management conditions, behavioral problems, willingness to perform, injury, illness, other medications).

Gastroscopy

Each horse underwent a general clinical examination and a subsequent gastroscopy. Examinations were performed on day 0 before the onset of medication and on day 28 after completing the treatment period. Before endoscopy, the horses were fasted for 12 hours. After clinical examination, the horses were intravenously sedated with 0.01 mg per kg BW detomidinhydrochloride (Cepesedan®; CP Pharma, Burgdorf, Germany). A three-meter flexible video endoscope (Karl Storz, Tuttlingen, Germany) was inserted into the stomach through an 80 cm nasogastric tube placed via the ventral nasal passage into the esophagus. The stomach was insufflated with air, and the mucosa was rinsed with water to free it from adherent lining material to ensure an unhindered inspection

of the entire stomach. In individual cases where there was a persistent gastric filling, which would have prevented an adequate evaluation of all regions, the horses were fasted for another 4 hours, and the gastroscopy was repeated. Each region of the stomach was evaluated individually by a boarded ECEIM specialist (MV), who was blinded to the group allocation. These regions included the dorsal squamous fundus, lesser curvature of the squamous mucosa, greater curvature of the squamous mucosa, greater curvature of the glandular region, antrum, and pylorus. Each region was scored using a 0 to 4/4 scale. Squamous mucosa was evaluated as proposed by the European College of Equine Internal Medicine[1] (Table 1). Glandular mucosa was evaluated according to a previous publication by *Vondran* et al[24] (Table 2). Videos and images of the stomach were recorded for each examination.

Statistical analyses

Statistical analyses were conducted using statistical software (SPSS®, IBM®, Armonk, NY, USA). Stomach scores were calculated using the medians and the 25th and 75th percentiles. The Wilcoxon signed-rank test was performed to compare the gastric lesion scores between the different time points (day 0 vs. day 28) within one treatment group. The Kruskal-Wallis test was used to compare gastric lesion scores between the two treatment groups (omeprazole vs. vital mushrooms) at the same time point. Significance was defined as $p \leq 0.05$.

Table 1 Scoring system for the squamous regions of the equine stomach, adapted from the proposal of the European College of Equine Internal Medicine[1]. | *Bewertungssystem der nonglandulären Regionen des Pferdemagens, angepasst nach dem Vorschlag des European College of Equine Internal Medicine*[1].

Grade	Characteristics
0	Epithelium intact and no appearance of hyperkeratosis
1	Mucosa intact, but areas of hyperkeratosis
2	Small, single or multifocal lesions
3	Large single or extensive superficial lesions
4	Extensive lesions with areas of apparent deep ulceration

Table 2 Scoring system for the glandular regions of the equine stomach, as published by *Vondran* et al.[21]. | *Bewertungssystem der Drüsenregionen des Pferdemagens, veröffentlicht von Vondran et al.*[21]).

Grade	Characteristics
0	Epithelium intact and no appearance of hyperemia (reddening) or fibrinosupperative areas
1	Intact flat mucosa, but with small single or multifocal areas of reddening
2	Raised mucosa with large single or multifocal areas of reddening or fibrinosupperative areas, no signs of bleeding
3	Raised mucosa with hemorrhagic and fibrinosupperative areas
4	Ridged or depressed mucosa with severe signs of bleeding or with large and distinct fibrinosupperative areas

Results

During the course of the study none of the horses showed clinical signs typically associated with the presence of gastric ulcers (colic, inappetence, reduced general well-being). All horses in the omeprazole group (n = 12) as well as all horses in the vital mushrooms group (n = 10) completed the 28-day study period. According to the inclusion criteria, in all horses of this study EGUS lesions were diagnosed at initial gastroscopy. At the initiation of the study on day 0, squamous gastric lesions (score ≥ 1) were apparent in 21 of 22 horses. Glandular gastric lesions (score ≥ 1) were diagnosed in 16 out of 22 horses.

After completion of the treatment period, squamous gastric lesions (score ≥ 1) were still present in 20 out of 22 horses, revealing a prevalence of 91% for ESGD after treatment. Glandular gastric lesions (score ≥ 1) were still present in 17 out of 22 horses, revealing a prevalence of 77% for EGGD after treatment.

At the initial examination on day 0, in the dorsal squamous fundus the median lesion score (25th–75th percentiles) was 0 (0–1) in the omeprazole group and 0 (0–0) in the vital mushrooms group. After the treatment period on day 28, the median lesion score of that region was 0 (0–0) in both treatment groups and did not differ significantly from day 0 in either of the treatment groups (Table 3).

In the squamous greater curvature, the median lesion score was significantly higher at day 0 in the omeprazole group (score: 2; 1–3) compared to the vital mushrooms group (score:1; 0–1) ($p = 0.008$). The score decreased significantly by one degree in the omeprazole group from day 0 to day 28 (score day 0: 2; 1–3 - score day 28: 1; 0–3) ($p = 0.016$). The two time points in the vital mushrooms group revealed no significant difference (score day 0: 1; 0–1 - score day 28: 1; 0–1) (Table 3, Figure 2).

Table 3 Gastric lesion scores (Median and 25th/75th percentiles) before (Day 0) and after (Day 28) treatment with either omeprazole or vital mushrooms. Unlike letters indicate a significant difference with $p < 0.05$ between Day 0 and Day 28 within the same treatment group. Unlike symbols indicate a significant difference with $p < 0.05$ between the different treatment groups at the same timepoint. | *Magen Scores (Median und 25./75. Perzentile) vor (Tag 0) und nach (Tag 28) Behandlung mit entweder Omeprazol oder medizinischen Heilpilzen. Verschiedene Buchstaben weisen auf einen signifikanten Unterschied bei $p < 0,05$ zwischen Tag 0 und Tag 28 innerhalb derselben Behandlungsgruppe hin. Verschiedene Symbole weisen auf einen signifikanten Unterschied bei $p < 0,05$ zwischen den verschiedenen Behandlungsgruppen zum gleichen Zeitpunkt hin.*

	Omeprazole		Vital mushrooms	
	Day 0	Day 28	Day 0	Day 28
Squamous fundus	0 (0–1)	0 (0–0)	0 (0–0)	0 (0–0)
Squamous greater curvature	2 (1–3)*a	1 (0–3)b	1 (0–1)#	1 (0–1)
Squamous lesser curvature	3 (2–3)*a	2 (1–3)b	1 (1–2)#	1 (0–2)
Glandular greater curvature	0 (0–1)	0 (0–0)	0 (0–1)	0 (0–0)
Antrum	1 (0–2)	1 (0–1)	2 (0–2)	1 (1–2)
Pylorus	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–1)

Most severe lesions were found in the squamous lesser curvature (Figure 3). In the squamous lesser curvature, the median lesion score was significantly higher at day 0 in the omeprazole group (score: 3; 2–3) compared to the vital mushrooms group (score: 1; 1–2) ($p = 0.013$). The score decreased significantly by one degree in the omeprazole group from day 0 to day 28 (score day 0: 3; 2–3 - score day 28: 2; 1–3) ($p = 0.011$). The two time points in the vital mushrooms group revealed no significant difference (score day 0: 1; 1–2 - score day 28: 1; 0–2) (Table 3, Figure 4).

In the glandular greater curvature, the median lesion score at day 0 was 0 (0–1) in both treatment groups. After the treatment period on day 28, the median lesion score was 0 (0–0) in both treatment groups and did not differ significantly from day 0 (Table 3). In the antrum, the median lesion score at day 0 was 0 (0–2) in the omeprazole group. After the treatment period on day 28, this median lesion score increased by one degree to 1 (0–1), but did not differ significantly from day 0. In the vital mushrooms group, the median lesion score on day 0 was 2 (0–2) and could be reduced by one degree up to day 28 (1; 1–2). However, this tendency towards glandular healing did not reveal statistical significance (Table 3).

In the pyloric region, the median lesion score at day 0 was 0 (0–0) in both treatment groups. After the treatment period on day 28, the median lesion score was 0 (0–0) in the omeprazole group and 0 (0–1) in the vital mushrooms group and did not differ significantly from day 0 in either of the treatment groups (Table 3).

Discussion

With regard to equine squamous gastric ulceration, omeprazole still represents the gold standard treatment. In Germany, its use in actively gallop racing horses is limited, as doping regulations have defined a withdrawal period of nine days[16].

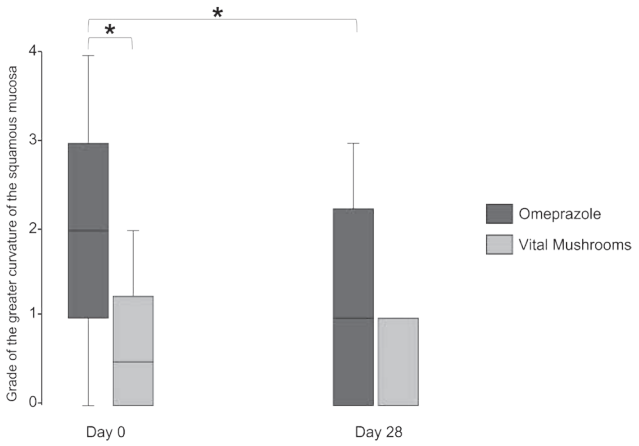

Fig. 2 Score for the squamous greater curvature before (Day 0) and after (Day 28) treatment with either omeprazole or vital mushrooms (dark grey plots for the omeprazole group; light grey plots for the vital mushrooms group). Asterisks indicate a significant difference with $p < 0.05$. | *Score der Schleimhautläsionen der squamösen großen Kurvatur vor (Tag 0) und nach (Tag 28) der Behandlung mit entweder Omeprazol oder medizinischen Heilpilzen (dunkelgraue Plots: Omeprazol-Gruppe; hellgraue Plots: medizinische Heilpilze-Gruppe). Sternchen zeigen einen signifikanten Unterschied mit $p < 0,05$ an.*

In addition to that, various other downsides must be considered in connection with omeprazole. Especially the long-term use of omeprazole, commonly applied in racing horse populations, raises concerns, as in humans after long-term omeprazole the risk of interstitial nephritis is high, although this phenomenon has not been described in equine internal medicine yet[25,26]. Another side effect with limited but strong evidence in human literature is the occurrence of rebound gas-

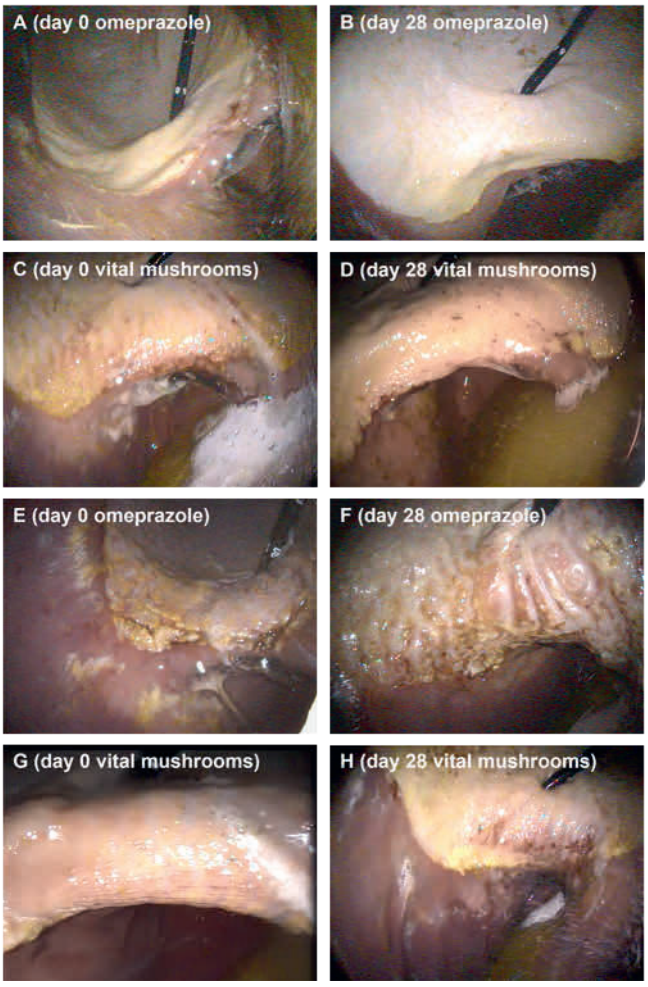

Fig. 3 Representative pictures of the gastroscopic appearance of the lesser curvature before treatment on day 0 (**A, C, E, G**) and after treatment on day 28 (**B, D, F, H**). For treatment of ESGD, horses underwent treatment with either omeprazole (**A, B, E, F**) or vital mushrooms (**C, D, G, H**). Treatment with omeprazole significantly improved the lesion scores of the squamous lesser curvature between day 0 (**A**) and day 28 (**B**), while no significant change was detected between day 0 (**C**) and day 28 (**D**) in this region of the vital mushrooms treated horses. Both treatment groups revealed horses that even deteriorated under treatment (omeprazole: **E** vs. **F** and vital mushrooms (**G** vs. **H**). | *Repräsentative Bilder der gastrokopischen Befunde der kleinen Kurvatur vor der Behandlung am Tag 0 (**A, C, E, G**) und nach der Behandlung am Tag 28 (**B, D, F, H**). Für die Behandlung von ESGD, wurden die Pferden entweder mit Omeprazol (**A, B, E, F**) oder medizinischen Heilpilzen (**C, D, G, H**) behandelt. Die Behandlung mit Omeprazol verbesserte signifikant die Läsionen der squamösen kleinen Kurvatur zwischen Tag 0 (**A**) und Tag 28 (**B**), während keine signifikante Veränderung zwischen Tag 0 (**C**) und Tag 28 (**D**) in diesem Bereich bei den mit medizinischen Heilpilzen behandelten Pferden festgestellt wurde. Beide Behandlungsgruppen zeigten Pferde, bei denen sich die Befunde der kleinen Kurvatur verschlechterte (Omeprazol: **E** vs. **F** und Heilpilze: **G** vs. **H**).*

tric hyperacidity (RGH) following cessation of proton-pump inhibitors used for periods longer than 8 weeks. RGH results from the development of hypergastrinemia and elevated levels of serum chromogranin A due to hypo/anacidity[27,28]. This phenomenon has also been proposed to contribute to the fast recurrence of ESGD in horses after the cessation of omeprazole. Recently, *Clark* et al. studied the effects of medium-term omeprazole administration and cessation on equine serum gastrin and serum chromogranin A concentrations. Interestingly, this study did not reveal an effect of treatment or discontinuation in equine serum chromogranin A concentrations. Serum gastrin levels increased in response to omeprazole treatment but returned to baseline values already within two to four days after the last administration of omeprazole, thereby not supporting the hypothesis of RGH in horses after medium-term use of omeprazole[29].

Although the gold standard omeprazole has been shown to be effective and safe in multiple studies, it is important to recognize that only approximately 77% of ESGD lesions of Thoroughbred racehorses in active training will resolve within 28 days at full dosage of orally administered omeprazole paste[15,30,31]. With regard to the long treatment duration, omeprazole also displays a cost-intensive approach. Taking account of the drawbacks, researchers are strongly interested in studying and providing alternative treatment options.

Besides of the widely accepted culinary and nutritional value of mushrooms, they are increasingly appreciated for their positive vital properties, particularly in human medicine. They possess numerous pharmacological properties, including, among others, antimicrobial, anti-inflammatory, immunomodulatory, antioxidant, antiallergic, and prebiotic activities[32–36]. The best-known and most abundant bioactive compounds in vital mushrooms are β-glucans[32]. In human research there is an emerging interest in the effects of these β-glucans on gut microbiota and intestinal health. These polysaccharides constitute a source of nutrition and energy for intestinal microbes. In human medicine, an intact gastroenteric microbiome is known to be critical for fitness[37]. It has been repeatedly described that EGUS affects fitness parameters in poorly performing racehorses[38]. It has also been suggested that a lower gastric pH in EGUS-affected horses may lead to a different microbiome[39]. Therefore, supporting the horse's gut microbiome could play an important role in the treatment of EGUS.

In the current study, a vital mushroom combination was used consisting of Agaricus blazei, Cordyceps militaris, Lentinula edodes-Shiitake, Hericium erinaceus, and Ganoderma lucidum-Reishi. The intestinal activity of their polysaccharides has mainly been investigated in mice and rats, showing that they not only exhibit gastroprotective effects but also accelerate healing of induced ulcers[22,23]. Nevertheless, one has to keep in mind that gastric ulceration in rats and mice can be induced experimentally by various methods. Usually, lesions are induced via the administration of chemical agents or direct application of necrotizing agents. In rodents lesion location is restricted to the glandular portion of the stomach, mimicking peptic ulceration in humans[40]. To evaluate the effect of vital mushroom in horses, the authors did not perform a standardized ulcer induction, as stated elsewhere[41], but investigated cases diagnosed in a screening study on clinically healthy race horses.

The idea that the utilization of polysaccharides in equine medicine might be beneficial is not new. In 2017, *Slovis* et al. showed that a polysaccharide blend of hyaluronan and schizophyllan achieved a complete resolution and/or improvement in ulcerative areas in 90% of the horses[42]. To the best of our knowledge, no studies about the efficacy of vital mushrooms to treat EGUS in actively trained Thoroughbred racing horses have been carried out so far.

The aim of this study was to compare the efficacy of a supplementary feed containing a specific vital mushroom formulation with the effect of omeprazole in young Thoroughbred racehorses in training. We hypothesized that the vital mushroom formulation is not significantly inferior to omeprazole in the treatment of ESGD.

The equine squamous gastric mucosa is commonly affected by lesions in actively racing horses[9]. The locations of gastric lesions in the horses of the current study were mainly the squamous greater ($n = 16$ from 22 total study horses) and lesser curvature ($n = 19$ from 22 total study horses). This finding is supported by other literature, which also document that the mucosa adjacent to the margo plicatus is the most affected site[43–45]. Adding both squamous regions, a total of $n = 21$ from 22 total study horses had lesions in the squamous mucosa. EGGD was diagnosed in fewer horses ($n = 16$ from 22 total study horses). This result is supported by another study by *Begg* and *O'Sullivan,* reporting that the prevalence of gastric ulcers in the squamous and pyloric region is significantly different ($p < 0.05$). They also state that the grade of the pyloric ulceration seems to be remarkably lower than that of squamous mucosa ulceration[11]. However, in another study on Korean Thoroughbred racehorses[12], no correlation between

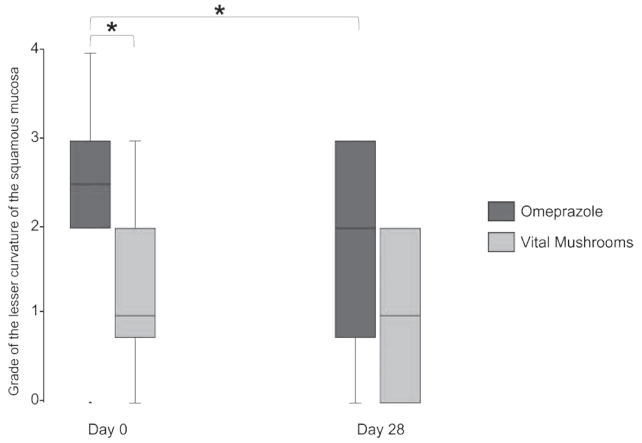

Fig. 4 Score of gastric lesions of the squamous lesser curvature before (Day 0) and after (Day 28) treatment with either omeprazole or vital mushrooms (dark grey plots for the omeprazole group; light grey plots for the vital mushrooms group). Asterisks indicate a significant difference with $p < 0.05$. | *Score der Schleimhautläsionen der squamösen kleinen Kurvatur vor (Tag 0) und nach (Tag 28) der Behandlung mit entweder Omeprazol oder medizinischen Heilpilzen (dunkelgraue Plots: Omeprazol-Gruppe; hellgraue Plots: medizinische Heilpilze-Gruppe). Sternchen zeigen einen signifikanten Unterschied mit $p < 0,05$ an.*

the severity of lesions in the squamous and pyloric region was found, suggesting that the relationship between the presence of ESGD and that of EGGD is inconsistent and that they are induced by different mechanisms.

A tendency in the vital mushrooms group towards improvement of antrum lesions after the treatment period of 28 days was observed. This observation was absent in the omeprazole group. This finding might be related to the fact that the glandular antrum of horses is more similar to the complete glandular stomach of humans, for which vital mushrooms were shown to be protective. In our study, the median lesion score of the squamous greater curvature was remarkably high in the omeprazole group (Score:3; 25%-75%: 2–3) at the beginning of the study. Surprisingly, no clinical signs were reported by the trainers, emphasizing again, that it is very often not possible to have a suspicion of gastric lesions in horses in training.

Our study shows again that the gold standard treatment, omeprazole, is able to significantly reduce lesion scores with regard to the squamous mucosa within 28 days. However, despite treatment, lesions in both the greater and lesser curvature of the squamous mucosa did neither resolve completely nor deteriorate after the prophylactic low dosage of omeprazole treatment 1 mg/kg bwt chosen in the current study. This finding is supported by several other studies, reporting squamous healing rates of up to 77% after 28 days at different dosages, ranging from 4 to 1 mg/kg bwt[46–48]. The reference dosage of 4 mg/kg bwt was chosen for 7 days and thereafter 1 mg/kg bwt was administered in the following 21 days. However, this dosage has already been proven to be effective in a previous study by *Sykes* et al[48].

In contrast to omeprazole, the vital mushrooms did not achieve the desired therapeutic effect with regard to the squamous mucosa. However, horses receiving vital mushrooms did not deteriorate in the course of the study while training continued. Hence, the application of vital mushrooms might serve as a supportive supplement for application directly prior to racing, when the application of omeprazole is prohibited.

The authors are well aware of the main limitations of this first pilot study. Besides the small sample size, the blind allocation of horses to treatment groups led to the fact that squamous lesion scores of the greater and lesser curvatures were significantly higher in the omeprazole group right from the beginning. It remains questionable if the vital mushroom formulation would have performed better or worse in horses with more severe findings. The Thoroughbreds in this study were recruited from four different trainers and stables. The fact that this study was not conducted in experimental animals housed in standardized stable conditions results in the inability to influence other factors that could induce gastric ulcers, such as diet and feeding management, stress of training, stress of the social environment, and mechanics of training. In the four weeks of treatment no changes in housing, feeding or training intensity were made. This guaranties bias by potentially influencing gastric findings. It has been well-studied that there is a correlation between the occurrence of gastric ulcers and the intensity of training among racehorses[12,45]. Given the fact that the horses in this study are at the same stage of training and have a mean age of 25.7 months with only small standard deviation of ± 1.5 months, the weight difference between the horses is, in the authors opinion, negligible. For this reason, every horse was administered the same dosage of 30 grams once daily of the vital mushroom formulation. This dosage is recommended by the supplier. With this dosage, no adverse effects were observed in the current study. It would be interesting to see, whether a doubling of the dose could further improve the performance of vital mushrooms. Although the mushrooms were inferior to omeprazole with regard to the treatment of established ESGD, it would be worth investigating if their supplementation could possibly prevent the development of ESGD.

Conclusion

With this first pilot study, we intended to examine the treatment efficacy of a vital mushroom formulation in comparison to the gold standard treatment, omeprazole, in Thoroughbred racehorses suffering from ESGD. Neither of the treatments revealed any adverse effects. The results show that the treatment of ESGD with vital mushrooms was inferior to treatment with omeprazole. The administration of omeprazole significantly reduced lesion scores in the squamous mucosa. No lesion reduction was observed in the vital mushrooms treated group. But despite ongoing race training, gastroscopic findings of all regions did not deteriorate under treatment with vital mushrooms. However, it needs to be remarked that no negative control group has been included in the current study. Moreover, lesion severity at the initial examination was significantly higher in the omeprazole group in the squamous greater and lesser curvature at baseline examination when compared to the vital mushrooms group, limiting the validity of the outcomes. Considering the facts that vital mushrooms are not prohibited prior to racing and less cost-intensive when compared to omeprazole, they might display a supportive supplement in the weeks before racing.

Conflict of interest statement

The authors exclude any conflict of interest regarding technical devices of drugs used in this study.

Acknowledgement

The authors would like to thank the manufacturers Boehringer Ingelheim and CME for providing their product for the treatment of the study horses.

References

1 Sykes BW, Hewetson M, Hepburn RJ, Luthersson N, Tamzali Y (2015) European college of equine internal medicine consensus statement – equine gastric ulcer syndrome in adult horses. J Vet Intern Med 29, 1288–1299, DOI 10.1111/jvim.13578

2 Banse HE, Andrews FM (2019) Equine glandular gastric disease: prevalence, impact and management strategies. Vet Med (Auckl) 10, 69–76, DOI 10.2147/VMRR.S174427

3 le Jeune SS, Nieto JE, Dechant JE, Snyder JR (2009) Prevalence of gastric ulcers in Thoroughbred broodmares in pasture: a preliminary report. Vet J 181, 251–255, DOI 10.1016/j.tvjl.2008.03

4 Lamglait B, Vandenbunder-Beltrame M, Trunet E, Lemberger K (2017) Description of gastric ulcers and of their suspected, associated risk factors in deceased wild equids at the réserve africaine DE sigean, France (2010–2016). J Zoo Wildl Med 48, 668–674, DOI 10.1638/2016–0249.1

5 Sykes BW, Bowen M, Habershon-Butcher JL, Green M, Hallowell GD (2019) Management factors and clinical implications of glandular and squamous gastric disease in horses. J Vet Intern Med 33, 233–240, DOI 10.1111/jvim.15350

6 Busechian S, Sgorbini M, Orvieto S, Pisello L, Zappulla F, Briganti A, Nocera I, Conte G, Rueca F (2021) Evaluation of a questionnaire to detect the risk of developing ESGD or EGGD in horses. Prev Vet Med 188, 105285, DOI 10.1016/j.prevetmed.2021.105285

7 Lorenzo-Figueras M, Merritt AM (2002) Effects of exercise on gastric volume and pH in the proximal portion of the stomach of horses. Am J Vet Res 63, 1481–1487, DOI 10.2460/ajvr.2002.63.1481

8 Luthersson N, Nielsen KH, Harris P, Parkin TDH (2009) Risk factors associated with equine gastric ulceration syndrome (EGUS) in 201 horses in Denmark. Equine Vet J 41, 625–630, DOI 10.2746/042516409 × 441929

9 Murray MJ, Schusser GR, Pipers FS, Gross SJ (1996) Factors associated with gastric lesions in Thoroughbred racehorses. Equine Vet J 28, 368–374, DOI 10.1111/j.2042–3306.1996.tb03107.x

10 Vatistas NJ, Snyder JR, Carlson G, Johnson BFG, Arthu RM, Thurmond M, Zhou h, Lloyd K (1999) Cross-sectional study of gastric ulcers of the squamous mucosa in Thoroughbred racehorses. Equine Vet, 31, 34–39, DOI 10.1111/j.2042–3306.1999.tb05166.x

11 Begg LM, O'sullivan CB (2003) The prevalence and distribution of gastric ulceration in 345 racehorses. Aust Vet J 81, 199–201, DOI 10.1111/j.1751–0813.2003.tb11469.x

12 Hwang H, Dong H-J, Han J, Cho S, Kim Y, Lee I (2022) Prevalence and treatment of gastric ulcers in Thoroughbred racehorses of Korea. J Vet Sci 23, e19, DOI 10.4142/jvs.21247

13 Videla R, Andrews FM (2009) New perspectives in equine gastric ulcer syndrome. Vet Clin North Am Equine Pract 25, 283–301, DOI 10.1016/j.cveq.2009.04.013

14 Birkmann K, Junge HK, Maischberger E, Wehrli Eser M, Schwarzwald CC (2014) Efficacy of omeprazole powder paste or Enteric-coated formulation in healing of gastric ulcers in horses. J Vet Intern Med 28, 925–933, DOI 10.1111/jvim.12341

15 Gough S, Hallowell G, Rendle D (2022) Evaluation of the treatment of equine glandular gastric disease with either long-acting-injectable or oral omeprazole. Vet Med Sci 8, 561–567, DOI 10.1002/vms3.728

16 Vokes J, Lovett A, Sykes B (2023) Equine Gastric Ulcer Syndrome: An update on current knowledge. Animals (Basel) 13, 1261, DOI 10.3390/ani13071261

17 Daurio CP, Holste JE, Andrews FM, Merritt AM, Blackford JT, Dolz F, Thompson DR (1999) Effect of omeprazole paste on gastric acid secretion in horses. Equine Vet J 31, 59–62, DOI 10.1111/j.2042–3306.1999.tb05176.x

18 Andrews FM, Frank N, Sommardahl CS, Buchanan BR, Elliott SB, Allen VA (2006) Effects of intravenously administrated omeprazole on gastric juice pH and gastric ulcer scores in adult horses. J Vet Intern Med 20, 1202–1206, DOI 10.2460/ajvr.67.11.1873

19 Viljanto M, Hillyer L, Hincks P, Pearce C, Paine SW (2018) Re-evaluation of the regulation of omeprazole in racehorses: An evidence-based approach. J Vet Pharmacol Ther 41, 469–475, DOI 10.1111/jvp.12491

20 Rop O, Mlcek J, Jurikova T (2009) Beta-glucans in higher fungi and their health effects. Nutr Rev 67, 624–631, DOI 10.1111/j.1753–4887.2009.00230.x

21 Hetland G, Tangen J-M, Mahmood F, Mirlashari MR, Nissen-Meyer LSH, Nentwich I, Therkelsen SP, Tjønnfjord GE, Johnson E (2020) Antitumor, anti-inflammatory and antiallergic effects of Agaricus blazei mushroom extract and the related medicinal basidiomycetes mushrooms, Hericium erinaceus and Grifola frondosa: A review of preclinical and clinical studies. Nutrients 12, 1339, DOI 10.3390/nu12051339

22 Gao Y, Tang W, Gao H, Chan E, Lan J, Zhou S (2004) Ganoderma lucidumpolysaccharide fractions accelerate healing of acetic acid-induced ulcers in rats. J Med Food 7, 417–421, DOI 10.1089/jmf.2004.7.417

23 Câmara Neto JF, Campelo MDS, Cerqueira GS, de Miranda JAL, Guedes JAC, de Almeida RR, Soares SA, Gramosa NV, Zocolo GJ, Vieira ÍGP, Ricardo NMPS, Ribeiro MENP (2022) Gastroprotective effect of hydroalcoholic extract from Agaricus blazei Murill against ethanol-induced gastric ulcer in mice. J Ethnopharmacol 292, 115191, DOI 10.1016/j.jep.2022.115191

24 Vondran S, Venner M, Coenen M, Vervuert I (2017) Effects of alfalfa chaff on the gastric mucosa in adult horses. Pferdehlk Equine Med 33, 66–71, DOI 10.1186/s12917–016-0733–5

25 Myers RP, McLaughlin K, Hollomby DJ (2001) Acute interstitial nephritis due to omeprazole. Am J Gastroenterol 96, 3428–3431, DOI 10.1111/j.1572–0241.2001.05345.x

26 Torpey N, Barker T, Ross C (2004) Drug-induced tubulo-interstitial nephritis secondary to proton pump inhibitors: experience from a single UK renal unit. Nephrol Dial Transplant 19, 1441–1446, DOI 10.1093/ndt/gfh137

27 Freedberg DE, Haynes K, Denburg MR, Zemel BS, Leonard MB, Abrams JA, Yang Y-X (2015) Use of proton pump inhibitors is associated with fractures in young adults: a population-based study. Osteoporos Int 26, 2501–2507, DOI 10.1007/s00198–015-3168–0

28 Helgadottir H, Bjornsson ES (2019) Problems associated with deprescribing of proton pump inhibitors. Int J Mol Sci 20, 5469, DOI 10.3390/ijms20215469

29 Clark B, Steel C, Vokes J, Shan JR, Gedye K, Lovett A, Sykes BW (2023) Evaluation of the effects of medium-term (57-day) omeprazole administration and of omeprazole discontinuation on serum gastrin and serum chromogranin A concentrations in the horse. J Vet Intern Med 37, 1537–1543, DOI 10.1111/jvim.16795

30 Doucet MY, Vrins AA, Dionne R, Alva R, Ericsson G (2003) Efficacy of a paste formulation of omeprazole for the treatment of naturally occurring gastric ulcers in training standardbred racehorses in Canada. Can. Vet. J 44, 581–5, PMID 12892289

31 Lester GD, Smith RL, Robertson ID (2005) Effects of treatment with omeprazole or ranitidine on gastric squamous ulceration in racing Thoroughbreds. J Am Vet Med Assoc 227, 1636–1639, DOI 10.2460/javma.2005.227.1636

32 Venturella G, Ferraro V, Cirlincione F, Gargano ML (2021) Medicinal mushrooms: Bioactive compounds, use, and clinical trials. Int J Mol Sci 22, 634, DOI 10.3390/ijms22020634

33 Elkhateeb WA (2020) What medicinal mushroom can do? Chem. Res. J 5, 106–118

34 Guggenheim AG, Wright KM, Zwickey HL (2014) Immune modulation from five major mushrooms: application to integrative oncology. Integr Med (ECINITAS) 13, 32–44, PMID: 26770080; PMCID: PMC4684115

35 Spelman K, Sutherland E, Bagade A (2017) Neurological activity of Lion's mane (Hericium erinaceus) J. Restor. Med 6, 16–26, DOI 10.14200/jrm.2017.6.0108

36 Jeitler M, Michalsen A, Frings D, Hübner M, Fischer M, Koppold-Liebscher DA, Murthy V, Kessler CS (2020) Significance of Medicinal Mushrooms in Integrative Oncology: A Narrative Review. Front Pharmacol. 11; 11:580656. DOI 10.3389/fphar.2020.580656.

37 Clauss M, Gérard P, Mosca A, Leclerc M (2021) Interplay between exercise and gut microbiome in the context of human health and performance. Front Nutr 8, 637010, DOI 10.3389/fnut.2021.637010
38 Lo Feudo CM, Stucchi L, Conturba B, Stancari G, Zucca E, Ferrucci F (2022) Equine Gastric Ulcer Syndrome affects fitness parameters in poorly performing Standardbred racehorses. Front Vet Sci 9, 1014619, DOI 10.3389/fvets.2022.1014619
39 Paul LJ, Ericsson AC, Andrews FM, Keowen ML, Morales Yniguez F, Garza F Jr, Banse HE (2021) Gastric microbiome in horses with and without equine glandular gastric disease. J Vet Intern Med 35, 2458–2464, DOI 10.1111/jvim.16241
40 Okabe S, Roth JLA, Pfeiffer CJ (1971) A method for experimental, penetrating gastric and duodenal ulcers in rats: Observations on normal healing. Digest Dis Sci 16, 277–284, DOI 10.1007/BF02235252
41 Svagerko P, Bridges W, Jesch E, Phillips SP, Vernon K (2021) 55 Equine gastric ulcers; a pilot study: associated biomarkers and polysaccharide supplementation as a solution. J Equine Vet Sci 100, 103518, DOI 10.1016/j.jevs.2021.103518
42 Slovis N (2017) Polysaccharide treatment reduces gastric ulceration in active horses. J Equine Vet Sci 50, 116–120, DOI 10.1016/j.jevs.2016.11.011
43 Bell RJW, Mogg TD, Kingston JK (2007) Equine gastric ulcer syndrome in adult horses: A review. N Z Vet J 55, 1–12, DOI 10.1080/00480169.2007.36728
44 Roy M-A, Vrins A, Beauchamp G, Doucet MY (2005) Prevalence of ulcers of the squamous gastric mucosa in standardbred horses. J Vet Intern Med 19, 744–750, DOI 10.1892/0891–6640(2005)19[744:pouots]2.0.co;2
45 Dionne RM, Vrins A, Doucet MY, Pare J (2003) Gastric ulcers in Standardbred racehorses: Prevalence, lesion description, and risk factors. J Vet Intern Med 17, 218–222, DOI 10.1111/j.1939–1676.2003.tb02437.x
46 Andrews FM, Sifferman RL, Bernard W, Hughes FE, Holste JE, Daurio CP, Alva R, Cox JL (1999) Efficacy of omeprazole paste in the treatment and prevention of gastric ulcers in horses. Equine Vet J 31, 81–86, DOI 10.1111/j.2042–3306.1999.tb05176.x
47 Sykes BW, Sykes KM, Hallowell GD (2014) A comparison of two doses of omeprazole in the treatment of equine gastric ulcer syndrome: A blinded, randomised, clinical trial. Equine Vet J 46, 416–421, DOI 10.1111/evj.12191
48 Sykes BW, Sykes KM, Hallowell GD (2015) A comparison of three doses of omeprazole in the treatment of equine gastric ulcer syndrome: A blinded, randomised, dose–response clinical trial. Equine Vet J 47, 285–290, DOI 10.1111/evj.12287