

Phytotherapy compared to omeprazol therapy in equine gastric ulcers

Margaréta Kulcsár¹, Michaela Karamanová¹, František Novotný¹, Zuzana Vilhanová¹,
Martina Pettenello¹, Csilla Tóthová²

University of Veterinary Medicine and Pharmacy, University Veterinary Hospital,
¹Equine Clinic, ²Clinic of Ruminants, Košice, Slovak Republic

Received December 14, 2021

Accepted October 10, 2022

Abstract

The aim of this study was to offer an alternative therapy for gastric ulcers in horses as the interest in natural products is growing not only among practitioners but also horse owners. We compared the treatment of equine gastric squamous mucosa ulcers by omeprazol and by nutraceutical herbal mixture PREVUL (Dzsar Ltd., FitoCavallo, Hungary). A total of 36 horses, 18 geldings, 15 non-pregnant mares and 3 stallions were diagnosed with Equine Squamous Gastric Disease (ESGD) by gastroscopy. Horses were randomly divided into three groups. The first group was treated with 4 mg/kg omeprazole paste (Peptizole, Norbrook, United Kingdom) *per os* once daily on empty stomach for 28 days. The second group received 20 g of pulverized herbal mixture PREVUL twice daily in cracked oats for 28 days. The third experimental group received 2 mg/kg omeprazole *per os* once daily on empty stomach followed by 15 g of PREVUL mixed with cracked oats twice daily for 28 days. Ten healthy horses were used as control to evaluate the palatability and voluntary intake of PREVUL. Control gastroscopy was performed after 30 days. The use of PREVUL alone $P < 0.05$ or in combination with omeprazole paste $P < 0.01$ appears to improve the healing of gastric ulcers in horses.

Alternative therapy, EGUS, herbs, H2 inhibitors, prevention

Gastric ulcers are a problem that domestication brought to the equine population. Typical clinical symptoms of gastric ulcer are anorexia, slow feed intake, nausea and sweating during and after feeding, depression, weight loss, contracted abdomen, frequent yawning and gnawing fibrous objects (Murray et al. 1989). The introduction of gastroscopy made it possible to make a final diagnosis of Equine Gastric Ulcer Syndrome (EGUS) and follow up the treatment.

The term Equine Gastric Ulcer Syndrome was first used in 1999 to describe gastric ulceration in the horse (Andrews et al. 1999). The committee recognized that the terminology for EGUS requires clarification and proposed a new nomenclature. EGUS is now used as a general all-encompassing term to describe erosive and ulcerative diseases of the stomach. The terms Equine Squamous Gastric Disease (ESGD) and Equine Glandular Gastric Disease (EGGD) address more specifically the affected region in terms of anatomy (Sykes et al. 2015a).

The first choice treatment for EGUS are H₂-blockers, such as omeprazole along with itraconazole, ranitidine, pantoprazol, etc. Omeprazole decreases gastric acid secretion by blocking hydrogen-potassium-ATPase in the secretory membrane of parietal cells. This enzyme catalyzes the exchange of hydrogen ions for potassium ions in the final step of hydrochloric acid production by parietal cells (Andrews et al. 1999).

The interest in herbal medicine is growing worldwide as a supportive or alternative therapy for EGUS. An increasing number of studies have shown the efficacy of phytotherapy and the exact mechanism of action of active herbal ingredients.

Various medicinal plants have already been tested for their efficacy in treating ulcers. Based on previous studies and decades of practical horse-phytotherapy practice in

Address for correspondence:

Margaréta Kulcsár
Equine Clinic
University of Veterinary Medicine and Pharmacy
Komenského 73, Košice, 040 81, Slovakia

Phone: +421 907 426 853
E-mail: megihorvath@gmail.com
<http://actavet.vfu.cz/>

Hungary, PREVUL herbal mixture seemed to be the most favorable for our experiment. The herbal mixture contains a large variability of effective herbs for EGUS such as *Glycyrrhiza* spp. (licorice), *Matricaria chamomilla* (chamomile), *Althaea officinalis* (marshmallow), *Trigonella foenum-graecum* (fenugreek), *Calendula officinalis* (marigold), *Linum usitatissimum* (flaxseed), *Mentha piperita* (peppermint) and *Hypericum perforatum* (St. John's wort).

The active ingredients of the herbs used in this study have several properties, such as anti-inflammatory, antioxidant, cytoprotective, and promoting exfoliation. Licorice has been shown to increase mucus production and blood supply to damaged gastric mucosa, thereby promoting its healing (Bennett et al. 1980). The use of chamomile in animals with gastric ulcers significantly reduces the size of the ulcer. Its chemical composition promotes prostaglandin synthesis, which increases mucosal protection, accelerates ulcer healing and inhibits ulcer formation. It has anti-inflammatory, sedative and antispasmodic effects (Rezq and Elmallh 2010). The antiulcer effect of marshmallow is related to the reduction of oxidative stress and histamine release. Furthermore, its mucous substances have a coating effect, which is of paramount importance in the protection of damaged mucosa (Farzaei et al. 2013). Fenugreek seed presumably reduces mucosal damage by enhancing the antioxidant potential of gastric mucosa (Sameh et al. 2015). The active ingredients of marigold have anti-inflammatory properties and play a role in the regulation of exfoliation and cell permeability. This herb is also a natural source of antioxidants (Butnariu and Coradini 2012). Flaxseed contains mucous substances with a cytoprotective effect and it is rich in omega-3 fatty acids with anti-inflammatory and surface-coating effect. The antiulcer effect of peppermint is presumably due to its antisecretory, prostaglandin-mediated antioxidant and cytoprotective effects (Ibrahim et al. 2006). St. John's wort is a proven herbal remedy for mild to moderate forms of depression, however, a study has shown that the plant extract is nearly as effective as esomeprazole in preventing ethanol-induced gastric ulcers and has a higher binding affinity for gastric proton pumps than esomeprazole (Sargul et al. 2020).

The aim of our study was to investigate the possibility of an alternative and/or complementary therapeutic solution for the treatment of gastric ulcers in horses.

Materials and Methods

The study included 46 warmblood horses, aged 4–21 years with BCS 5–8 according to the Henneke scale (Henneke et al. 1983). Thirty-six horses, 18 geldings, 15 non-pregnant mares and 3 stallions were diagnosed with ESGD by gastroscopy (300 cm scope diameter of 12 mm-Carl Storz, Germany) and 10 healthy horses with grade 0 on the scale of 0–4 (Table 1), were used only for feeding the herbal mixture to evaluate the possible differences between the voluntary intake of the product by horses affected and non-affected by ESGD.

Table 1. The scoring system for gastric ulcers in horses with Equine Gastric Ulcer Syndrome (MacAllister et al. 1997).

Lesion number score	Description
0	No lesions
1	1–2 localised lesions
2	3–5 localised lesions
3	6–10 lesions
4	> 10 lesions or diffuse (or very large) lesions
Lesion severity score	Description
0	No lesion
1	Appears superficial (only mucosa missing)
2	Deeper structures involved (greater depth than 1)
3	Multiple lesions and variable severity 1, 2, and/or 4
4	Same as 2 and has active appearance
5	Same as 4 plus active haemorrhage or adherent blood clot

Table 2. The herbal content of PREVUL.

English name	Latin name
Chamomile	<i>Matricaria chamomilla</i>
Fenugreek	<i>Trigonella foenum-graecum</i>
Liquorice	<i>Glycyrrhiza glabra</i>
Marshmallow	<i>Althaea officinalis</i>
Pot Marigold	<i>Calendula officinalis</i>
St. John's wort	<i>Hypericum perforatum</i>
Flaxseed	<i>Linum usitatissimum</i>
Peppermint	<i>Mentha piperita</i>

Horses with ESGD were randomly divided into three groups. The first group was treated with 4 mg/kg omeprazole paste (Peptizole, Norbrook, United Kingdom) *per os* once daily on empty stomach for 28 days. The second group received 20 g of pulverized herbal mixture PREVUL (Dzsar Ltd., FitoCavallo, Hungary) (Table 2), twice daily in cracked oats for 28 days. The third experimental group received 2 mg/kg omeprazole (Peptizole, Norbrook, United Kingdom) *per os* once daily on empty stomach (Sykes and Jokisalo 2014), followed by 15 g of PREVUL mixed with cracked oats twice daily for 28 days. The group of healthy horses was given 20 g PREVUL twice daily in cracked oats for 28 days. Control gastroscopy was performed after 30 days. None of the horses had a history of non-steroidal anti-inflammatory drug therapy, or shown any signs of fever or systemic disease during the previous

6 months before the experiment. Horses were vaccinated against influenza and tetanus and dewormed twice per year. Horses affected by ESGD were showing some of the common signs of low grade stomach pain, or discomfort. The owners reported "bad behavior" when tightening the girth, sometimes pawing, chewing on wood, flehmen, refusal to finish grain meal, refusal to finish their hay portion, yawning and strange postures, like "taking a bow".

All horses were stabled in individual boxes with access to paddocks and possibility to graze for a maximum of 6 h per day. Horses were given meadow hay, salt block and fresh water *ad libitum* and 1.5 kg of cracked oats twice daily. During the study, the horses were exercised three days per week for 2 h.

Gastroscopic examination of horses was part of the clinical evaluation of patients and for each horse included in our study, informed consent was obtained from the owners. Horses were fasted 14–16 h and water was withheld 4 h before the gastroscopy. Ulcers were diagnosed by gastroscopy (300 cm scope diameter of 12 mm, Carl Storz, Germany) under sedation performed by the same practitioner to ensure uniformity. After the introduction of gastroscope, the stomach was insufflated with air through an air-flow system until all internal mucosal folds appeared flattened. Feed adhering to the nonglandular mucosa was flushed away with sterile water for visualization of the greater curvature (curvatura major), the lesser curvature (curvatura minor), dorsal fundus and margo plicatus. The number and degree of ulcers were described and recorded in accordance with the Equine Gastric Ulcer Council (EGUC) recommendations and are reported in Table 1 (MacAllister et al. 1997). Horses were checked before and on day 13 after treatment.

Results were statistically analyzed using One-way ANOVA for nutrition components, followed by Wilcoxon test for disability. Values of $P < 0.01$ and $P < 0.05$ were considered to be significant. GraphPad Prism 8.0 software (GraphPad Software Inc., San Diego, USA) was used for statistical analysis.

Results

Before treatment, the PREVUL-treated group showed 5/12 grade 1, 4/12 grade 2, 3/12 grade 3, while no horse showed grade 4 (Fig. 1, Table 3). The omeprazole-treated group showed 4/12 grade 1, 5/12 grade 2, 3/12 grade 3 and 1/12 grade 4 (Fig. 2, Table 3). The third group with the combination of omeprazole and PREVUL showed 3/12 grade 1, 5/12 grade 2, 3/12 grade 3 and 1/12 grade 4 before the treatment (Fig. 3, Table 3). The pre-treatment distribution of gastric lesions scores was not significantly different between the three groups.

Table 3. Differences in the degree of disability in horses treated with omeprazole, combination of omeprazole and PREVUL, and PREVUL before (BT) and after (AT) the treatment (mean \pm SD).

Treatment	Time of investigation		P value
	BT	AT	
Omeprazole	2.08 \pm 0.95	1.17 \pm 0.94	< 0.05
Omeprazole + PREVUL	2.17 \pm 0.94	0.92 \pm 0.79	< 0.01
PREVUL	1.89 \pm 0.86	0.74 \pm 0.78	< 0.05

P value – significance of Wilcoxon test

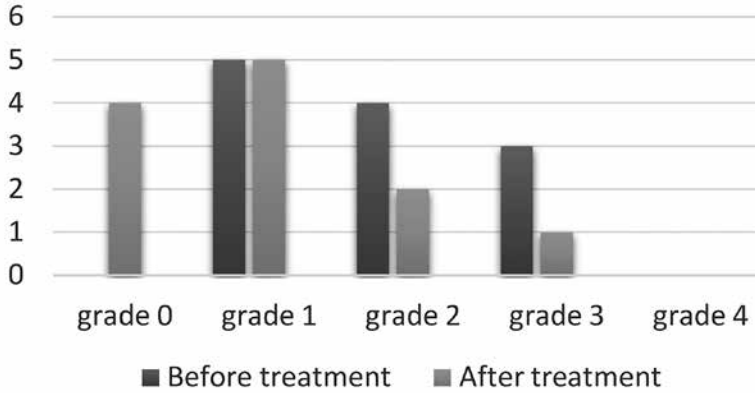


Fig. 1. Gastric lesion scores before and after treatment with PREVUL herb mixture

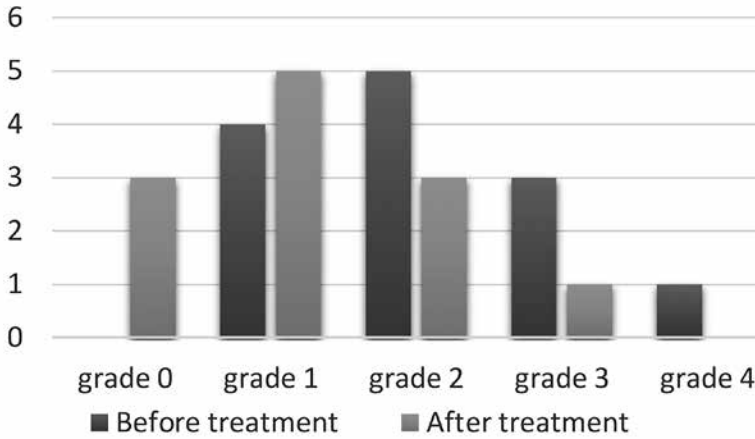


Fig. 2. Gastric lesion scores before and after treatment with omeprazole

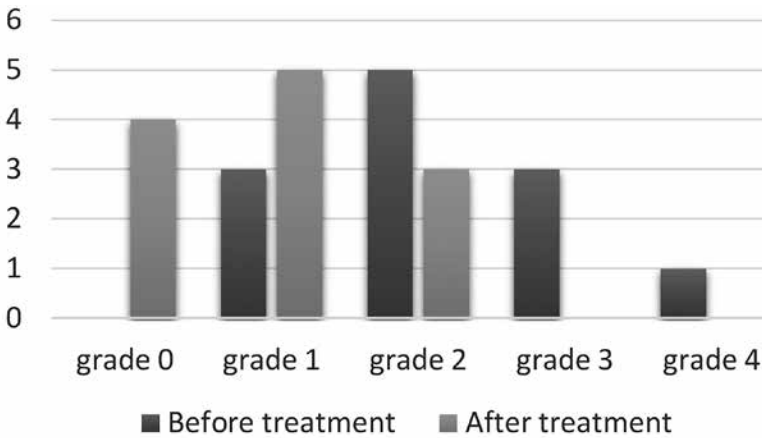


Fig. 3. Gastric lesion scores before and after treatment with omeprazole and PREVUL herb mixture

After 28 days of treatment, gastroscopic evaluation in the PREVUL group indicated 4/12 grade 0, 5/12 grade 1, 2/12 grade 2, 1/12 grade 3; $P < 0.05$ (Fig. 1, Table 3); the omeprazole group showed 3/12 grade 0, 5/12 grade 1, 3/12 grade 2, 1/12 grade 3; $P < 0.05$ (Fig. 2, Table 3) and the reduced dose of omeprazole and PREVUL group indicated 4/12 grade 0, 5/12 grade 1, 3/12 grade 2 and none of the horses showed grades 3 and 4; $P < 0.01$ (Fig. 3, Table 3). The post-treatment distribution of gastric lesions scores was not significantly different between the two groups. No side effects like diarrhoea, lack of appetite or even colic were observed in any group. The feed additive was perfectly accepted by all the PREVUL treated horses. However, the group of 10 healthy horses seemed to be more selective and 3 horses refused to eat their meal, when PREVUL was mixed with the ration. Significant reduction in grades of ulcers was observed in all three groups of horses.

Discussion

Successful therapy of ESGD is not possible without changes in the management, including dietary changes, reduction of exercise, stress levels, transportation, pain and increasing turnout. Most horses diagnosed with ESGD need pharmacologic therapy as well, especially when there is a need to remain in training, or on a high performance level (Andrews et al. 1999). Nonglandular lesions respond well to agents that increase gastric juice pH. Proton pump inhibitors and H₂-receptor antagonists are the most commonly used classes of drugs in the horse (Niedźwiedź et al. 2013).

Free access to fibrous feed or frequent forage feeding is widely considered to reduce the risk of gastric ulceration. The more the horse chews, the more saliva is produced and the better its buffering effect is on the acid environment of the stomach. A wide range of nutraceuticals and feed supplements are now available, including pectin-lecithin complexes, sometimes in combination of antacids, yeasts, hydrolyzed collagen, alfalfa chaffs and different mixture of herbs. The popularity of these products reflects the owners' urge to "go natural" but also to be effective, save money, and avoid horse hospitalization (Woodward et al. 2014).

Recent investigations showed a reduced efficacy in omeprazole-treated horses with EGGD, compared with ESGD. Only 36% of glandular ulcers healed when treated with omeprazole (4 mg/kg orally every 24 h) compared to a 78% healing rate in horses with diagnosed ESGD. The reason for this is not known, but likely it is a reflection of the different pathogenesis causing EGGD compared to ESGD. As such, glandular ulcers deserve to be considered as a related but distinct disease to the traditional ESGD ulcers (Sykes et al. 2015b).

Plant extracts and herbs are known sources of natural antioxidants that can protect against oxidative stress and thus play an important role in the chemoprevention of diseases resulting from lipid peroxidation. Many herbal extracts have already been tested for their gastroprotective effects in experimental animals. Bennett et al. (1980) demonstrated the antiulcer effect of deglycyrrhizinated licorice preparations in a rat model of aspirin-induced gastric mucosal damage. It has been found that the composition promotes healing by enhancing mucus production and blood supply to the damaged gastric mucosa, thereby enhancing its healing (Van Marle et al. 1981; Da Nagao et al. 1996). Masoomeh and Kiarash (2007) reported the antiulcer effect of carbenoxolone from licorice as it inhibits gastrin secretion. This has been explained by the fact that the licorice compound increases the concentration of prostaglandins in the digestive tract, which promotes mucus secretion from the stomach (Nazim and Difuzza 2019).

Karbalay-Doust and Noorafshan (2009) decreased the number and area of ulcers in rats with ethanol-induced gastric ulcer with oral administration of 400 mg/kg

Matricaria chamomilla extract. Morshedi et al. (2016) published the effect of oral administration of 250 and 500 mg/kg *Matricaria chamomilla* powder on ibuprofen-induced gastric ulcer in rats. The results showed that the use of *Matricaria chamomilla* at a dose of 500 mg/kg significantly reduced the size of the ulcers compared with the 250 mg/kg group. Although they cannot reduce the amount of gastric acid, apigenin and α -bisabolol were inhibitors of indomethacin, stress, alcohol-induced gastric ulcer and ulcer formation in rats. In another study, α -bisabolol has also been shown to reduce the healing time of ulcers caused by chemical stress or heat coagulation (Szelenyi et al. 1979).

In the experiment of Fazaei et al. (2013) the aqueous extract of marshmallow roots stimulated phagocytosis and the release of oxygen radicals and leukotrienes from human neutrophils *in vitro*. The aqueous extract also induced the release of cytokines, interleukin-6, and tumour necrosis factor from human monocytes *in vitro*. In addition, the marshmallow extract significantly increased superoxide dismutase enzymes (SOD) activity after indomethacin administration. The antiulcer effect of this herb is associated with a reduction in oxidative stress and histamine release. The observed gastroprotective effect is attributable to the active ingredients in the extract, such as flavonoids and mucus polysaccharides (Al-Snafi 2013).

The ulcerogenic properties of the aqueous suspension of peppermint were also evaluated in different ulcer models in rats. The suspension has a significant effect on basal gastric secretion induced by pylorus ligation, indomethacin or harmful chemicals and showed significant protection in all models used. These findings were supported by histopathological examination of gastric tissue and determination of the non-protein sulphhydryl content in the stomach. The antiulcer effect of the peppermint suspension is presumably due to its antisecretory, prostaglandin-mediated antioxidant and cytoprotective effects (Ibrahim et al. 2006).

The effect of the fenugreek seed (*Trigonella foenum graecum*) on ethanol-induced gastric ulcer was studied in comparison with omeprazole. The aqueous extract and gel fraction isolated from the seeds showed a significant ulcer protective effect. The cytoprotective effect of the seeds appeared to be not only due to the antisecretory effect but also to the effect on mucosal glycoproteins. Fenugreek seeds also prevent the increase in ethanol-induced lipid peroxidation, presumably by enhancing the antioxidant potential of the gastric mucosa, thereby reducing mucosal damage. Histological examination showed that the soluble gel fraction from the seeds was more effective in preventing the development of lesions than omeprazole. These observations show that fenugreek seeds have an antiulcer effect (Semeh et al. 2015).

Nutraceuticals, especially herbs, are very popular amongst horse owners and represent an interesting topic of research in every field of human and veterinary medicine. The results of our experiment, along with the results of the studies described above, show that phytotherapy is a successful adjunctive treatment for gastric ulcers.

The use of the herbal mixture PREVUL in our trial alone appeared to improve healing. We assume that in certain cases of ESGD, a complete or partial replacement of drug therapy by phytotherapy might be possible. This may reduce the cost of gastric ulcer therapy. Omeprazole therapy can be too expensive to be affordable by many owners, thus leaving ESGD untreated. Untreated gastric ulcers can lead to gastric rupture which is fatal for the horse.

According to our study, the PREVUL herbal mixture showed to be a good proton pump inhibitor and produced a significant decrease in the intensity and grade of ulceration for horses. Although no side effects were observed during and shortly after the research, the long-term use of the herbal mixture requires further research, as well as the use of phytotherapy as a prevention for gastric ulcers.

Acknowledgements

The authors thank the company Dzsar Kft.-FitoCavallo, Hungary, for providing us with samples of the herbal mixture administered to the horses in our study. This research was funded by Scientific Grant Agency of the Ministry of Education, Science, Research and Sport of the Slovak Republic, VEGA (1/0208/21).

References

- Al-Snafi AE 2013: The pharmaceutical importance of *Althaea officinalis* and *Althaea rosea*: A review. *Int J Pharm Technol Res* **5**: 1378-1385
- Andrews F, Bernard W, Byars D 1999: Recommendations for the diagnosis and treatment of equine gastric ulcer syndrome (EGUS). *Equine Vet Educ* **11**: 262-272
- Bennett A, Clark-Wibberley T, Stamford IF, Wright JE 1980: Aspirin-induced gastric mucosal damage in rats: cimetidine and deglycyrrhizinized liquorice together give greater protection than low doses of either drug alone. *J Pharm Pharmacol* **32**: 151
- Butnariu M, Coradini CZ 2012: Evaluation of biologically active compounds from *Calendula officinalis* flowers using spectrophotometry. *Chem Cent J* **6**: 35
- Da Nagao Y, Sata M, Suzuki H, Tanikawa K, Itoh K, Kameyama T 1996: Effectiveness of glycyrrhizin for oral lichen planus in patients with chronic HCV infection. *J Gastroenterol* **31**: 691-695
- Farzaei MH, Rahimi R, Abbasabadi Z, Abdollahi M 2013: An evidence-based review on medicinal plants used for the treatment of peptic ulcer in traditional Iranian medicine. *Int J Pharmacol* **9**: 108-124
- Henneke DR, Potter GD, Kreider JL, Yeates BF 1983: Relationship between condition score, physical measurements and body fat percentage in mares. *Equine Vet J* **15**: 371-372
- Ibrahim AM, Abdulqader A, Jaber M, Mohammed AS, Shoeb Q, Syed R 2006: Antisecretagogue, antiulcer and cytoprotective effects of 'peppermint' *Mentha piperita* L. in laboratory animals. *J Med Sci* **6**: 930-936
- Karbalay-Doust S, Noorafshan A 2009: Antiulcerogenic effects of *Matricaria chamomilla* extract in experimental gastric ulcer in mice. *Iran J Med Sci* **34**: 198-203
- MacAllister CG, Andrews FM, Deegan E, Ruoff W, Olovson SG 1997: A scoring system for gastric ulcers in the horse. *Equine Vet J* **29**: 430-433
- Masoomeh MJ, Kiarash G 2007: *In vitro* susceptibility of *Helicobacter pylori* to licorice extract. *Iran J Pharm Res* **6**: 69-72
- Morshedi M, Gol A, Mohammadzadeh A 2016: The effect of *Matricaria chamomilla* on the treatment of ibuprofen-induced gastric ulcers in male rats. *Hormozgan Med J* **20**: 270-275
- Murray MJ, Grodinsky C, Anderson CW, Radue PF, Schmidt RG 1989: Gastric ulcers in horses: a comparison of endoscopic findings in horses with and without clinical signs. *Equine Vet J Suppl* **7**: 68-72
- Nazim AM, Difuzza E 2019: Phytochemical constituents and pharmacological effects of licorice. In: Ozturk M, Hakeem KR (Eds): *Plant and Human Health*, Volume 3. Springer Cham, Switzerland, pp 1-21
- Niedzwiedz A, Kubiak K, Nicpoń J 2013: Endoscopic findings of the stomach in pleasure horses in Poland. *Acta Vet Scand* **55**: 45
- Rezq AA, Elmallh M 2010: Anti-ulcer effect of cinnamon and chamomile aqueous extracts in rat models. *J Am Sci* **6**: 209-216
- Sameh SZ, Basim AS, Ali AAS, Hekma AAEL 2015: Protective effects of ginger and marshmallow extracts on indomethacin-induced peptic ulcer in rats. *J Nat Sci Biol Med* **6**: 421-428
- Sargul HS, Sheila MN, Zahra AA, Hazem AAB, Nadir MQ 2020: Gastroprotective activity of *Hypericum perforatum* extract in ethanol-induced gastric mucosal injury in Wistar rats: A possible involvement of H⁺/K⁺-ATPase α inhibition. *Helijon* **6**: e 05249
- Sykes BW, Hewetson M, Hepburn RJ, Luthersson N, Tamzali Y 2015a: European college of equine internal medicine 309 consensus statement-equine gastric ulcer syndrome in adult horses. *J Vet Intern Med* **29**: 1288-1299
- Sykes BW, Sykes KM, Hallowell GD 2015b: A comparison of three doses of omeprazole in the treatment of equine gastric ulcer syndrome: a blinded, randomized, dose-response clinical trial. *Equine Vet J* **47**: 285-290
- Sykes BW, Jokisalo JM 2014: Rethinking equine gastric ulcer syndrome: Part 1 - terminology, clinical signs and diagnosis. *Equine Vet Educ* **26**: 543-547
- Szelenyi I, Isaac O, Thiemer K 1979: Pharmacological experiments with compounds of chamomile. III. Experimental studies of the ulcerprotective effect of chamomile. *Planta Med* **35**: 218-227
- Van Marle J, Aarsen PN, Lind A, van Weeren-Kramer J 1981: Deglycyrrhizinized liquorice (DGL) and the renewal of rat stomach epithelium. *Eur J Pharmacol* **72**: 219-225
- Woodward MC, Huff NK, Garza F, Keowen ML, Kearney MT, Andrews FM 2014: Effect of pectin, lecithin, and antacid 374 feed supplements (Egusin®) on gastric ulcer scores, gastric fluid pH and blood gas values in horses. *BMC Vet Res* **10**: S4