

1 **pHyloGASTRO® IN THE TREATMENT OF EQUINE GASTRIC ULCER LESIONS**

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20 **Highlights**

21 1. Equine Gastric Ulcer Syndrome (EGUS) is the most common disease of the equine
22 stomach with a high prevalence.

23 2. Nutraceutical compounds have been shown to have a positive effect on preventing or
24 healing naturally occurring gastric ulcers.

25 3. pHyloGASTRO[®] is a herbal feed composed of medical herbs that act on restoring the
26 acid-base balance.

27 4. pHyloGASTRO[®] seems to be an effective feed additive for the improvement of gastric
28 lesions.

29 5. We believe that the 6-week treatment period, recommended by the manufacture, is too
30 short, since often gastric mucosal lesions did not completely heal in our treated group.

31

32 **Abstract**

33 Equine Gastric Ulcer Syndrome (EGUS) is the most common disease of the equine
34 stomach with high prevalence of both squamous and glandular disease reported in various
35 populations.

36 The aim of this study was to evaluate the effectiveness of a phytotherapeutic compound
37 (pHyloGASTRO®) in the therapy of EGUS.

38 **Materials and methods.** The study was performed as a randomised double-blinded single
39 centre study. The study population was composed of 19 equids which were submitted to
40 gastroscopy before and after a six-week treatment with feed additive (10/19)
41 (pHyloGASTRO®, 4Union B.I.O. srl, Italy) or a placebo (9/19). Severity grade was
42 evaluated on a scale from 0-4. The variables of interest were gastric lesion score and
43 improvement grade. Changes and comparisons of variables were performed by
44 contingency table analyses. P level of significance was set at 0.05 in all analyses.

45 **Results.** In terms of gastric lesion scores, the treated group improved significantly
46 compared to the placebo group.

47 **Discussion and conclusions.** pHyloGASTRO® seems to be effective in the treatment of
48 EGUS. Further studies are needed to verify whether prolonged administration of
49 pHyloGASTRO® could be more effective in completely healing gastric lesions.

50

51 **Key words**

52 Equids, EGUS, treatment, nutraceutical compounds, pHyloGASTRO®

53

54 1. Introduction

55 Gastric ulceration is the most common disease of the equine stomach with a high
56 prevalence of both squamous and glandular disease reported in various populations [1-3].
57 The term Equine Gastric Ulcer Syndrome (EGUS) was first adopted by the EGUS Council
58 in 1999 and includes a complex of pathological conditions characterized by the presence
59 of ulcers in the terminal portion of the oesophagus, in the proximal (squamous) and distal
60 (glandular) parts of the stomach, and in the proximal part of the duodenum of equids [4].
61 Recently various authors [5-7] and the European College of Equine Internal Medicine
62 (ECEIM) Consensus Statement [8] have provided a new nomenclature of EGUS and
63 proposed updated guidelines regarding pathophysiology, diagnosis, and treatment [5,8].
64 Many drugs have been investigated and are available for the treatment and management
65 of EGUS [8-11]. The proton pump inhibitor omeprazole has been found to be very efficient
66 in both treating and preventing gastric ulcers in horses [8]. Other drugs such as histamine₂
67 antagonists or gastric mucosal protectors have shown less efficacy than omeprazole in the
68 treatment of EGUS [8,11,12].

69 Along with pharmacological therapies, nutraceutical compounds appear to have a positive
70 effect on preventing or healing naturally occurring gastric ulcers [13-20]. Thus, interest in
71 more natural products has been growing. The purpose of this study was to evaluate the
72 effect of the feed additive pHyloGASTRO[®] (Union B.I.O. srl, Italy) on the treatment of
73 spontaneously occurring gastric ulcers of the squamous mucosa in a population of equids.
74

75 2. Methods

76 2.1 Materials

77 The study population was composed of 19 equids (ten Standardbred trotting horses and
78 nine Amiata donkeys). The equids were equal regarding distribution of gender and breed.
79 None of the animals showed clinical signs of EGUS, were athletes and were used for
80 reproduction. Inclusion criteria: 1) all the equids were affected by gastric ulcers at
81 gastroscopy; no changes in the feeding and environment during the study period were
82 made.

83 2.2 Study design

84 The study was performed as a randomised double-blinded single centre study and the
85 protocol was approved by the Ethical Committee of the University of Pisa [no. 9069/2014].
86 Group allocation and blinding: once enrolled into the study, horses were randomly
87 allocated to a dose group by pulling their names out of a hat. One investigator (F.B.) was

88 responsible for randomisation while another investigator (S.B.) remained blinded to the
89 group allocation until scoring was completed and recorded.

90 Ulcers were diagnosed by gastroscopy performed under sedation after 12 hours of fasting
91 and 4 hours of water deprivation as reported in the literature [21]. Severity grade was
92 evaluated on a scale from 0-4 as proposed by others [4]. Gastroscopy was always
93 performed by the same operator (S.B.), as indicated by others [22]. For the examination, a
94 300 cm scope (Karl Storz, Germany) and a portable processor (Gastropack, Karl Storz,
95 Germany) were used. The images were stored on a DVD recorder. The stomach was
96 insufflated with air through an air-flow system attached to the biopsy channel of the scope
97 until the internal stomach folds appeared flattened. Feed material adhering to the non-
98 glandular mucosa was flushed away with sterile water in order to visualize the entire non-
99 glandular portion of the stomach, including the greater curvature, the lesser curvature, and
100 the dorsal fundus. The number and degree of ulcers were recorded in accordance with the
101 Equine Gastric Ulcer Council (EGUC) recommendations [4].

102 Equids were divided in two groups: the “placebo group” was composed of 9/19 animals
103 (median age 10 years); the “treated group” was composed of 10/19 animals (median age 8
104 years). The two treatment groups were clinically equal regarding distribution of gender and
105 breed. The “treated group” was treated with pHyloGASTRO[®] (Union B.I.O. srl, Italy) at a
106 dose of 60 ml per equid BID PO for 6 weeks, while the “placebo group” was treated BID
107 with a similar-looking same-volume placebo for 6 weeks. Both pHyloGASTRO[®] and
108 placebo were administered using a feeding device. The administration was always
109 performed by the same operator (C.G.). pHyloGASTRO[®] is composed of medical herbs
110 (*Althaea officinalis*, *Aloe barbadensis*, *Hoedeum vulgar*, *Malva sylvestris*, *Glycyrrhiza*
111 *glabra*, *Echinacea angustifolia*, *calendula officinalis*, *Clay ventilated*) powered by *Matrix*
112 *UB*[®] (the aqueous extract of *Olea europaea*, a phyto-active enhancer). The medical herbs
113 previously reported showed antiinflammatory, cytoprotective, antioxidant, mucus healing,
114 and acid-base balance restoring activities (table 1) [23-38]. A clinical examination was
115 carried out daily for each animal to monitor gastro-intestinal side effect. All the equids were
116 submitted to a gastroscopy after the 6-week treatment.

117 2.3 Statistical analysis

118 The variables of interest were gastric lesion score and improvement grade. Changes and
119 comparisons on variables were performed by contingency table analyses. Significance
120 was set at 0.05 in all analyses. All the analyses were performed using a GraphPad Prism
121 6.0 (USA).

122

123 **3. Results**

124 All the equids in the study were affected by gastric ulcers in the non-glandular mucosa
125 (Equine Squamous Gastric Disease, ESGD) [5,8]. No health problems or side effects
126 (diarrhoea, stipsis, disorexia or anorexia, colic) related to treatment with pHyloGASTRO[®]
127 were observed during the all study period. The feed additive was readily accepted by all
128 the pHyloGASTRO[®]-treated horses in the same manner as the placebo.

129 Before treatment, the “treated group” equids showed 2/10 grade 1, 6/10 grade 2, 1/10
130 grade 3, while no equids showed grade 4; the “placebo group” equids showed 3/9 grade 1,
131 3/9 grade 2, 3/9 grade 3, while no equids showed grade 4. The pre-treatment distribution
132 of gastric lesion scores was not significantly different between the two groups.

133 After 6 weeks of treatment, the “treated group” showed 2/10 equids with grade 0, 7/10
134 with grade 1, 1/10 with grade 3, while no animals showed grades 2 and 4; the “placebo
135 group” showed 2/9 with grade 0, 2/9 with grade 1, 3/9 with grade 2, and 2/9 with grade 3,
136 while no animals showed grade 4. Outcomes for both “placebo” and “treated” groups are
137 reported in table 2.

138 The “treated group” improved significantly compared to the “placebo group” (p=0.04).
139 Concerning the improvement score of the gastric lesions, equids treated with
140 pHyloGASTRO[®] showed a significantly (p=0.0001) higher improvement than equids
141 treated with the placebo (Table 3).

142 No differences were found between the two groups considering complete healing of gastric
143 lesions vs improvement.

144

145 **4. Discussion**

146 EGUS is a complex disease, which for nearly 30 years has been recognized as a highly
147 prevalent condition both in training and at rest horses [5,8,11]. A new nomenclature of
148 EGUS along with updated guidelines regarding pathophysiology, diagnosis, and treatment
149 have recently been proposed [5-8]. In particular, the European College of Equine Internal
150 Medicine (ECEIM) committee recognizes that the terminology for EGUS needed
151 clarification and proposes the nomenclature of Equine Squamous Gastric Disease (ESGD)
152 and Equine Glandular Gastric Disease (EGGD) [15].

153 The pharmacology products most commonly used for the treatment of gastric ulcers in
154 horses focus on blocking gastric acid secretion and increasing stomach pH, which creates
155 a permissive environment for physiological ulcer healing [8,10-11]. However, the research

156 for methods to treat or prevent gastric ulcers effectively without requiring the continued
157 administration of costly pharmaceutical agents together with issues regarding withdrawal
158 times or side effects is a new trend not only in human medicine, but also in veterinary
159 medicine.

160 In order to meet this growing need for more natural products, this study aimed to evaluate
161 the effectiveness of pHyloGASTRO[®] in the treatment of EGUS in adult equids. Our results
162 showed an easy administration and ingestion of pHyloGASTRO[®] by the treated horses,
163 with no health problems or side effects related to the treatment. A total of 44.4% of the
164 “placebo” horses and 80% of the “treated” horses showed an improvement or a complete
165 healing of the ulcers.

166 The improvement in the degree of ulceration score in the “placebo” group was similar
167 compared to previous studies [17]. An improvement in placebo-treated patients has been
168 reported in humans [39-41] and some studies have been published in veterinary medicine
169 [42-43].

170 Also the improvement in the degree of ulcerations in the “treated” group is in line with a
171 previous study [17], which investigated the effect of a nutraceutical compound and found
172 an improvement of 77.8% of the horses treated.

173 Comparing the two groups, statistical calculations revealed a significant reduction in
174 gastric mucosal lesions in the “treated” horses compared to the “placebo” group after six
175 weeks of administration of the nutraceutical feed. This is in line with findings reported in
176 previous papers where different nutraceutical compounds were tested [14-15,17,19-20].

177 Concerning the gastric lesion scores, equids treated with pHyloGASTRO[®] improved more
178 significantly ($p=0.0001$) than equids treated with the placebo. Our results are in line
179 findings reported in the literature [17,19-20].

180

181 **5. Conclusions**

182 pHyloGASTRO[®] seems to be an effective feed additive for the improvement of gastric
183 lesions. However, the treatment period of six weeks, recommended by the manufacture,
184 seems too short, since the gastric mucosal lesions had often not completely healed in the
185 treated group. Thus, further studies are needed to verify whether a prolonged
186 administration of pHyloGASTRO[®] could be more effective in obtaining a complete healing
187 of gastric lesions. A limitation of the study could be the lack of a group treated only with the

188 *Matrice UB*[®] solution. The addition of this group could lead to understanding whether the
189 improvement to EGUS lesions was due to medical herbs, to *Matrice UB*[®] or both.
190

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Medical herbs	Mechanism of action	Literature
<i>Althaea officinalis</i>	Anti-inflammatory, cytoprotective	[23,24]
<i>Aloe barbadensis</i>	Anti-inflammatory, cytoprotective, mucus healing	[23]
<i>Hordeum vulgare</i>	Cytoprotective, mucus healing, acid-base restoring	[25]
<i>Malva sylvestris</i>	Anti-ulcerogenic activity	[26-28]
<i>Glycyrrhiza glabra</i>	Gastric healing	[29-31]
<i>Echinacea angustifolia</i>	Oxidant-antioxidant balance	[32]
<i>Calendula officinalis</i>	Anti-ulcer, anti-inflammatory effect	[33]
<i>Clay ventilated</i>	Ulcer healing	[34]
<i>Olea europea</i>	Gastroprotective agent, antioxidant activity	[35-38]

310 Table 1 – Mechanism of action of medical herbs that are compounds of
311 pHyloGASTRO® (Union B.I.O. srl, Italy).

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PLACEBO GROUP	
Pre-treatment lesion score	Post-treatment lesion score
3	3
1	0
2	2
3	3
1	0
1	1
2	1
3	2
2	2
TREATED GROUP	
Pre-treatment lesion score	Post-treatment lesion score
3	3
1	1
3	1
2	1
1	0
2	0
2	1
2	1
2	1
2	1

325 Table 2 – Pre and post treatment lesion score outcome in “placebo” and “treated” groups.

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327

		Improved			No change	P
		-3	-2	-1	0	
Start vs 6 weeks	Control group	0	0	4/9	5/9	0.0001
Start vs 6 weeks	Treated group	0	2/10	6/10	0/10	

328 Table 3 – Change in gastric lesion scores before and after 6-week period between
329 “control” and “treated” groups.

330