The Safety and Efficacy in Horses of Certain Nutraceuticals that Claim to Have Health Benefits

Ingrid Vervuert, DVM[a,*], Meri Stratton-Phelps, DVM[b]

KEYWORDS

• Supplements • Research • Evidence • Health • Horse

KEY POINTS

- Before a supplement is selected for use, it is important to first ensure that the horse is being fed a balanced ration appropriate to its individual needs.
- Different models (in vitro and in vivo) have been used to test the efficacy of dietary supplements.
- In vivo models that demonstrate how the ingredients are absorbed and metabolized to achieve a particular health benefit in the horse are preferred versus results obtained in a laboratory setting.
- Only a few nutraceuticals have shown potential to improve health above and beyond the provision of a well-balanced diet.

INTRODUCTION

The term nutraceutical was developed from the words "nutrition" and "pharmaceutical" in the early 1990s and although it is often used in the marketing of equine complementary feeds or supplements, it has no regulatory definition (see Ruth Bishop and David A. Dzanis' article, "Staying on the Right Side of the Regulatory Authorities," in this issue). Nutraceuticals are commonly described as feed ingredients that may have a beneficial effect on the health of horses. Dietary supplements discussed in this article follow the definition provided by the US National Research Council (NRC) as:

[a] Institute of Animal Nutrition, Nutrition Diseases and Dietetics, Faculty of Veterinary Medicine, Leipzig University, An den Tierkliniken 9, Leipzig 04103, Germany; [b] All Creatures Veterinary Nutrition Consulting, 3407 Millbrook Court, Fairfield, CA 94534, USA
* Corresponding author.
E-mail address: ingrid.vervuert@vetmed.uni-leipzig.de

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a substance for oral consumption by horses whether in/on feed or offered separately, intended for the specific benefit to the animal by means other than provision of nutrients recognized as essential or for provision of essential nutrients for intended effect on the animal beyond normal nutritional needs, but not including legally defined drugs.[1]

The use of equine dietary supplements has undergone a rapid expansion in the past 10 to 15 years. Owners can easily purchase a variety of different products for their horses, designed to support the health of all possible body systems. Any determination of safety and/or efficacy is difficult owing to the limited peer-reviewed studies on individual supplement ingredients or on multi-ingredient products.

The primary challenge of the equine veterinarian is to be able to critically evaluate a product to determine that it is not only safe to use, but also potentially effective and likely to result in a desired health response.

Before a supplement is selected for use in a horse at any age or life stage, it is important to first ensure that a well-balanced diet is being fed. The ration should be based on forages ($\geq$1.5 – % of body weight, as dry matter) and then may also include manufactured equine feeds and/or single ration ingredients such as oil, rice bran, or beet pulp to help meet individual nutrient requirements. Rations that only include forage, with or without such single ration ingredients, often require a vitamin and mineral supplement or a ration balancer as discussed elsewhere in this issue. In some cases, extra protein is required as forages may be low in protein and essential amino acids.

It can be confusing to determine if a dietary supplement is necessary or when a particular product may be helpful in maintaining, supporting or improving health. When dietary supplements are used concurrently with any pharmacotherapy; assessment should be made regarding potential nutrient–drug interactions that may alter the bioavailability and metabolism of either the drug or the supplement ingredients. This point is especially important with botanic ingredients. Some equine supplements contain potentially toxic ingredients (garlic, pyrrolizidine alkaloids) and use should be approached with caution or avoided completely.[2,3] Many common ingredients in equine supplements may result in a positive drug test in an equine athlete (see Ruth Bishop and David A. Dzanis' article, "Staying on the Right Side of the Regulatory Authorities," in this issue).

SUPPLEMENT EVALUATION

Before a supplement is selected for use, the following product related points should be evaluated:

1. Is species-specific research available to support marketing claims, either on the product formulation, or on well-defined active ingredients? Or is research available in other species to support the supplement claim or function and can this be reasonably extrapolated to horses?
2. Can the source of the active ingredient and the delivery per dose be justified by quoted supportive research?
3. Are active ingredients quantified by analysis, for example, 20 mg biotin per provided scoop?
4. Is there scientific evidence that the feeding of the active ingredients, is safe?
5. Is there the potential for any cross-reactivity, for example, herbs with other supplements or medicines?
6. Are the active ingredients considered allowable by any relevant regulations (eg, the Fédération Équestaire Internationale and the United States Equestrian Federation)?
7. What are the contamination risks for prohibited substances?

Nutraceutical Supplements to Support Metabolic Health

In recent years, the equine metabolic syndrome has become a widely recognized clinical condition.[4] A primary strategy to manage the equine metabolic syndrome is to ensure any required weight loss by calorie restriction (see Megan Shepherd and colleagues' article, "Nutritional Considerations When Dealing with an Obese Adult Equine," in this issue). Furthermore, the intake of hydrolysable carbohydrates (also known as nonstructural carbohydrates) should be limited to prevent high postprandial insulin responses. In an attempt to improve systemic insulin regulation, many commercial products have been developed with the aim of improving glucose regulation at the cellular level. The most popular ingredients being used are magnesium (typically either as an organic or an inorganic chelate) and chromium (as chromium yeast or chromium propionate). Evidence to support their use has largely been extrapolated from studies in humans with type 2 diabetes.[5] Dietary chromium showed minimal benefit on glucose regulation[6–8] in earlier work, but a recent study showed that oral chromium propionate (2 or 4 mg chromium/d) could potentially increase insulin sensitivity in healthy horses.[9] Data in horses with insulin dysregulation are, however, lacking. Additionally, in Europe, chromium is not approved as a feed additive; therefore, chromium-containing supplements for equines are prohibited. In horses, magnesium as a single nutrient has only limited evidence of improving insulin regulation.[10]

In humans with metabolic disorders, especially type 2 diabetes, L-carnitine supplementation can improve glucose tolerance and insulin sensitivity.[11] In obese ponies, on an energy restriction diet, L-carnitine did not improve insulin sensitivity.[12] The authors suggested that endogenous L-carnitine synthesis was sufficient to facilitate lipid and glucose metabolism in adult ponies. A variety of other ingredients have been suggested to provide metabolic support including vitamin E, selenium, iodine, biotin, grape seed extract, cinnamon, chasteberry (*Vitex agnus-castus*), and fish oil. However, robust published research to support the use of these ingredients to manage insulin dysregulation in horses is currently lacking.

Ingredients with some limited support for a beneficial effect on either insulin sensitivity or circulating glucose and insulin concentrations include short-chain fructo-oligosaccharides, psyllium, and resveratrol (a natural polyphenol with antioxidant properties), in combination with leucine.[13] However, more work is needed to confirm these findings and the doses required.

Key points

- Limited evidence available currently to support the potential to improve insulin regulation through dietary supplementation and further work is needed to confirm the potential of ingredients such as resveratrol.
- It is unlikely that any dietary supplement can replace dietary restriction, and increased exercise where possible, in managing obesity in horses, especially in so-called easy keepers.

Nutraceutical Supplements to Improve Gastric Health

Erosive and ulcerative diseases of the stomach are described by the term equine gastric ulcer syndrome.[14] However, it is recommended to specify between the squamous and glandular region as equine squamous gastric disease (ESGD) and equine glandular gastric disease as terms that more specifically describe the affected region anatomically.[14]

Several studies have confirmed an improvement of gastric ulcers by administering the drugs, cimetidine, ranitidine,[15] and particularly omeprazole.[16] In addition, to

medical treatment, optimizing feeding and housing management are highly recommended. For example, forage should be provided ad libitum or at least to a daily minimum of 1.5% of body weight as dry matter[17] (see Myriam Hesta and Marcio Costa's article, "How Can Nutrition Help with Gastrointestinal Tract-Based Issues," in this issue). In exercising horses, grain intake should be limited to a maximum of 1 g starch/kg body weight per meal.[18] Several dietary supplements claiming to support gastric mucosa health are commercially available.

Antacid-buffering supplements

It is postulated that gastric mucosal injury will be less likely in a more alkaline environment. The oral application of 30 g of aluminum hydroxide combined with 15 g of magnesium hydroxide resulted in a significantly higher gastric pH (>4) for at least 2 hours in healthy horses.[19] However, a single administration of an antacid drug combination containing 5.4 g or 8.1 g of aluminum hydroxide and 4.8 g or 7.2 g of magnesium hydroxide only very transiently increased gastric pH to 6 in just 2 of 6 horses.[20] In both studies, horses were not evaluated for gastric ulcers. Furthermore, in foals, 16-day supplementation with magnesium oxide, fortified with herbs of unknown origin, did not improve gastric mucosa health, using the weaning process as a model to induce gastric mucosal lesions[20].

Pectin–lecithin complex

Pectin is a soluble complex polysaccharide derived from the cell wall of fruits or the sugar beet. Lecithin is a phospholipid derived from soybeans. It has been postulated that lecithin is an emulsifying, lubricating agent with surfactant properties.[21] It is speculated that pectin acts with lecithin as a hydrophobic barrier on the gastric mucosal membranes, thereby having some protective function against gastric acids.

Supplementing a commercial pectin–lecithin supplement to horses fed hay (1.5% of body weight) and a starch-containing complementary feed (1% of body weight) did not affect stomach pH[22] in 1 study. However, supplementation for 10 days apparently resulted in improved healing of gastric mucosal lesions under field conditions, with uncontrolled feeding and management conditions.[23] Ferrucci and colleagues[24] also found significant improvements in gastric mucosa lesions after feeding the same pectin–lecithin supplement for 30 days (horses fed daily 5 kg hay and 5–7 kg concentrate), although there was no control group. In contrast, Murray and Grady[25] and Sanz and colleagues[26] could not find any protective effect of feeding the same commercial pectin–lecithin supplement in a gastric ulceration model using an intermittent fasting protocol.

From the published studies, beneficial effects of supplementing a pectin–lecithin containing supplement are unlikely.

Dietary oils

In humans and rats, the supplementation of arachidonic acid precursors such as linoleic acid increase endogenous prostaglandin production and decrease gastric acid output.[27] Ponies on a forage-based diet supplemented with corn oil (rich in linoleic acid; 0.3–0.4 mL/kg body weight) showed a significant decrease in maximal gastric acid output induced by a pentagastrin challenge.[28] However, gastroscopic examinations were not performed. Furthermore, supplementation of corn oil, refined rice bran oil, or crude rice bran oil (0.5–0.6 mL/kg of body weight) did not have any beneficial effects on the development of nonglandular gastric ulcers using an intermittent fasting protocol.[28]

Currently, the potential of adding dietary oils to improve gastric mucosa health needs more evidence.

Sea buckthorn berries

Sea buckthorn berries are rich in phenols, vitamins, flavonoids, fatty acids, plant sterols, lignans, and minerals.[29] These compounds have antioxidant and immunoactive properties, which might be beneficial in mucosal healing. Sea buckthorn berries do not seem to be effective in the treatment or prevention of ESGD.[30,31] Furthermore, Sea buckthorn berries–treated horses were approximately 5 times more likely to develop hyperkeratosis in the squamous mucosa than control horses, although the significance of hyperkeratosis to stomach health is not fully understood.[30,31] However, horses with equine glandular gastric disease were improved, when compared with untreated controls in stall-confined horses fed a different extract of sea buckthorn berries and pulp.[30,31] Sea buckthorn berries may have some potential to promote healing, but further work is needed especially in spontaneously occurring clinical cases.

Herbs

Herbs may also have beneficial effects owing to their anti-inflammatory properties. Six weeks of supplementation with an herbal blend in adult horses or donkeys with spontaneously occurring gastric mucosal lesions resulted in complete ESGD healing or significant improvement compared with the blinded placebo group.[32] However, information about the feeding and management was not provided.

Supplementing a Chinese herbal formulation (2 traditional herbal formulas: Xiao Yao San and Er Chen Tang) did not decrease the severity, compared with a placebo of experimentally induced ESGD, undergoing intermittent feeding.[33] The data about herb supplementation to improve gastric mucosa health is limited; thus, more equine studies are needed for further elucidation.

Mixed supplements

A blend of sea buckthorn, pectin, lecithin, L-glutamine and other ingredients,[34] when mixed with grain, decreased the number of ESGD present 14 days after omeprazole treatment was discontinued and during a week of intermittent feed-deprivation compared with unsupplemented control horses.

A 90-day blinded randomized clinical trial compared the efficacy of oral omeprazole with a dietary supplement containing oat oil rich in polar lipids, oat flour rich in β-glucan, L-glutamine, and L-threonine and extracts of the cell wall of *Saccharomyces cerevisiae* for the management of ESGD in racehorses.[35] In the first 30 days, omeprazole treatment was more effective at decreasing the squamous ulcer score by 2 or more grades than the dietary supplement. However, at day 90 both treatments were similar with respect to the changes in the squamous ulcer score. However, complete resolution of the squamous ulcers was less than 20% at day 60 and 90 of the study in both treatment groups.

Hellings and Larsen[36] fed either a placebo or a supplement consisting of organic acid-salts and B-vitamins in trotting racehorses with endoscopically verified ESGD (severity grade 2 out of 4 or higher). No significant differences were detected between supplement or placebo on ulcer score within 3 weeks of treatment. Interestingly, there was a significant improvement in ulcer severity in the placebo group (58.1%) from 3 weeks to the end of additionally 2 to 4 weeks of treatment. These findings support the requirement for a placebo group in studies evaluating dietary supplement efficacy. Sykes and colleagues[37] reported in a placebo-controlled study that a combination of pectin-lecithin complex, *S cerevisiae* and magnesium hydroxide, when supplemented 1 to 4 hours before exercise was prophylactic in preventing the development or exacerbation of existing squamous and glandular gastric ulcers in Thoroughbred horses in race training.

Woodward and colleagues[38] found that the supplementation of antacids did not prevent gastric ulceration of the squamous mucosa. However, such supplementation may have some beneficial effects on the healing process in Thoroughbred horses using the feed deprivation model to induce gastric ulcers.

Feeding a mineral or vitamin supplement containing a zine–methionine complex resulted in lower gastric ulcer scores in horses after omeprazole treatment had been finished than feeding zinc sulfate.[39]

Key points

- Different models have been used to test efficacy of dietary supplements, which makes it difficult to compare studies.
- Supplements that work under experimental conditions may not work under field conditions where multifactorial risk factors may be present with nonstandardized feeding and housing conditions.
- A few products may have some potential to support mucosal healing processes. However, no current supplements have achieved complete mucosal damage resolution nor have been consistently able to prevent ulcer formation.

Hoof Supplements

In a recent UK study on hoof management, 89% of horse owners (n = 345) reported hoof problems in the past 5 years, such as abscesses, cracks, and bruising.[40] Thirty-five percent used nutritional products targeted at the hoof and the majority were willing to try new hoof products and treatments.

Horn quality, hoof growth, and strength are influenced by several factors such as age, breed, genetics, metabolic rate, exercise, external temperature, environmental moisture, illness, trimming, shoeing, and nutrition.[41–45] Hoof horn is produced by a complex process of differentiation (keratinization) of epidermal cells that depends on the appropriate provision of nutrients such as amino acids, minerals, and vitamins.[41]

Protein and amino acids

Hoof contains high levels of amino acids, especially cystine, arginine, leucine, lysine, proline, serine, glycine, and valine, and lower levels of methionine, phenylalanine, and histidine.[42,43] The sulfur-containing amino acids cystine and methionine are crucial for the structural integrity of the keratinocyte.[44] Cystine is the oxidized dimer form of the amino acid cysteine. During keratinization and cornification, the formation of disulfide bonds between cystine units are essential in the final stages, providing cell wall rigidity and high resistance against a variety of proteolytic enzymes.[45]

Most commercially available hoof supplements add methionine as the sole sulfur-containing amino acid (personal communication Vervuert, 2020). However, it is unclear whether the synthesis of cysteine in the liver from its precursor methionine is a rate-limiting step in the keratinization process or not. The provision of cysteine might be beneficial, because this amino acid is preferentially incorporated into the epidermal lamina.[46] Surprisingly, poor hoof horn quality was related to higher methionine levels in the sole horn, compared with good horn quality.[43] From this study, the role of methionine as a sulfur source in keratinization process remains open. Hoof horn contains other amino acids, but the value of other amino acids on hoof health have not been investigated.

Calcium

Despite the relative low calcium content in hooves, calcium plays an essential role in the keratinization and cornification processes through the activation of enzymes that

initiate and regulate the terminal differentiation of the epidermal cells. Kempson[47] found improvements in hoof horn defects after the addition of calcium in combination with protein by feeding alfalfa or by adding 7.5 g limestone in 2 horses that failed to respond to a biotin supplementation. From this case report, it remains unclear whether it was the calcium and/or the provision of essential amino acids via the alfalfa that improved hoof health. Most equine diets provide sufficient calcium to cover or to exceed calcium requirements. However, the concentration and bioavailability across feeds varies.

Trace elements

Interactions and synergistic effects exist between several trace minerals; therefore, supplying a combination of trace minerals would seem potentially to be more beneficial. However, little work has been undertaken to date and many of the studies have significant limitations.

Zinc has been identified as a key mineral in the keratinization process via (i) the activation of catalytic zinc metalloenzymes, (ii) the formation of zinc finger structural proteins and, (iii) the regulation of proteins that are involved in the differentiation processes of keratinocytes.[41] Coenen and Spitzlei[43] reported lower hoof horn zinc levels in hooves of poorer quality.

No relationship between hoof horn zinc levels and biomechanical variables, such as strength or elasticity, were found in ponies fed 2 different diets.[48] However, even the restricted diet met zinc requirements. No beneficial effects on hoof horn quality were found in a field study where horses were fed 1 mg zinc/kg body weight as zinc sulfate for 12 months, although basal zinc intake was not reported.[49]

Copper activates the enzyme responsible for the formation of the disulfide bonds between the cystine links of the keratin filaments, which contribute to the structural strength by giving rigidity to the keratinized cell matrix.[41] Higami[50] found a higher incidence of white line disease in horses fed long-term diets low in zinc and copper. Over a 9-month period, the hoof wall growth rate was lower in the horses fed the zinc- and copper-deficient basal diet, compared with those where additional amino acid chelated (ie, organic) zinc and copper was added to meet requirements.[50] Copper and zinc absorption may have been enhanced by intestinal amino acid transporters. However, Siciliano and colleagues[51] compared the supplementation of inorganic and organic sources (50% intake supplied by amino acid complexes) of zinc, copper, and manganese in horses. Both diets met the respective requirements; however, hoof horn quality and growth rates were not influenced by mineral source.

Manganese is needed for the activation of enzymes involved in the synthesis of chondroitin-sulfate side chains of proteoglycans, which are essential for the formation of normal cartilage and bone. Manganese also has several indirect functions in the keratinization process.[52] Manganese also activates several enzymes that play a role in the provision of cellular energy, which is important for horn metabolism. Furthermore, manganese-containing superoxide dismutase provides a crucial defense mechanism against free radicals. However, equine diets, especially when forage-based rations are provided, are rarely deficient in manganese. There is little scientific evidence to support the provision of additional manganese.

Selenium is an essential cofactor in several enzymes including glutathione peroxidase and thioredoxin reductase.[52] The importance of selenium for membrane integrity, growth, reproduction, and immune response is well-established in horses.[52] Excessive intake of selenium results in high selenium hoof horn

levels, coronary band disease, and substantial horn cracks in horses.[53] High selenium levels disrupt the disulfide bonds between cystine units, the key step for cell wall rigidity and resistance. Selenium intake therefore should be strictly controlled according to requirements and caution is needed with respect to selenium addition through hoof products. Regional differences in soil selenium influence risk.

Role of vitamins

Biotin. During keratin formation, biotin is essential for the formation of complex lipid molecules in the intercellular cementing substance.[54] Furthermore, biotin directly stimulates the differentiation of epidermal cells.[55] Most research, therefore, has focused on biotin supplementation to improve hoof growth and hoof horn quality in several species, and is often associated with a positive effect.[56–60] However, the effects on poor hoof horn quality strongly depend on sufficient duration (>9 months) and dosage (3–4 mg/100 kg body weight/d) of biotin supplementation. Healthy horses fed forage-based diets may meet biotin requirements by hindgut microbial production. Therefore, factors that negatively impact on the intestinal microbiota, such as starch overload, may reduce microbial biotin synthesis. Beneficial effects of biotin on poor hoof horn quality have been found only when high dosages were provided, versus relying on microbial production alone. It is important to note that not all hoof problems are biotin responsive.

Other vitamins such as vitamin A, vitamin D, and vitamin E are essential in developing the integrity, structure, and quality of keratinized horn tissue. However, scientific data about the effects of supplementation on hoof growth and hoof quality are lacking in the horse.

Key points

- Research suggests that horn strength and quality are mostly improved by balancing energy and nutrient intake according to requirements rather than focusing on one single nutrient such as biotin, calcium, or zinc.
- Because copper and zinc intake can be quite variable in equine diets, the provision of these trace elements may have some beneficial potential in a hoof supplement if the current diet is deficient.
- Except for biotin, scientific data regarding the role of vitamins in hoof health are lacking.

Joint Supplements

Oral joint supplements are one of the most popular category of equine supplements in the United States[61] and Europe.[62]

Currently available equine oral joint supplements commonly use a blend of different ‘active’ components, often referred to as chondroprotective agents.[63] The main desired potential of chondroprotective substances can be summarized as:

- Increase collagen and proteoglycan synthesis of chondrocytes
- Increase hyaluronic acid synthesis in synovial cells
- Inhibit enzymes that destroy cartilage
- Inhibit fibrin synthesis in synovial and subchondral vessels

The main ingredients provided in supplements and their role in cartilage metabolism are summarized in **Table 1**.

Table 1
Ingredients which are frequently used in oral joint supplements

Ingredients	Rational Role
Chondroitin sulfate	Component of glycosaminoglycan chains
Hyaluronate	Cartilage component
Glucosamine	Precursor of glycosaminoglycan chains
Methylsulphonylmethane	Source of sulfur, a component of cartilage
Unsaponified avocado soy	Inflammation modulation
Omega 3 fatty acids	Inflammation modulation
Cetyl myristoleate	Inflammation modulation
Selenium, vitamin E	Antioxidants
Manganese, vitamin A	Co-factors in glycosaminoglycan synthesis
Copper, vitamin C, gelatin	Collagen synthesis
Herbs such as devil's claw or Indian celery	Inflammation modulation

Glucosamine and chondroitin sulfate

Glucosamine and chondroitin sulfate are probably the most commonly used chondroprotective ingredients. Pearson and Lindinger[64] conducted an extensive review of published in vivo research on glucosamine and/or chondroitin sulfate based nutraceuticals for horses. They concluded that many supplement studies were confounded by several major limitations related to the study design (eg, missing control or placebo groups, low horse numbers, undiagnosed lameness, suboptimal diagnostic parameters, or statistical interpretation), which did not allow a clear conclusion to be made about the efficacy of glucosamine and/or chondroitin sulfate–based nutraceuticals for joint health. A similar conclusion was reached in 2013, by McIlwraith[65] owing to a lack of well-designed studies.

Another major limitation of such supplements relates to their very low oral bioavailability (0%–5.9%, and 0%–32%, for glucosamine and chondroitin sulfate, respectively[66–68]). Welch and colleagues[68] did not find any blood response despite frequent blood collection after the oral intake of glucosamine (5.5–8.5 g/horse) or chondroitin sulfate (2–3.5 g/horse) in adult horses. They suggested that orally fed glucosamine and chondroitin sulfate were not absorbed owing to rapid fermentation or degradation by mucosa-associated enzymes. There is also limited published clinical evidence of efficacy; for example, in a study by Higler and colleagues,[69] supplementation for 3 months with glucosamine, chondroitin sulfate, and methylsulphonylmethane in aged horses did not improve gait kinematic data assessed on a treadmill.

In addition, it should be emphasized that high dosages of glucosamine and chondroitin sulfate were used in vitro to investigate potential mechanism and pathways on cartilage metabolism. Those high levels of glucosamine and/or chondroitin sulfate achieved with in vitro studies are not found in vivo.[70]

Perhaps owing to the lack of conclusive data on the effective dosage of oral glucosamine and/or chondroitin sulfate supplementation, there is a considerable variation in the concentration of glucosamine and/or chondroitin sulfate in commercial products. For example, Oke and colleagues[71] reported a range of glucosamine concentrations from 1.7 to 29.6 mg/50 mg product. According to information provided on the product labels, the average recommended daily dose ranged from 1800 to 12,000 mg glucosamine for an average sized mature horse.[71]

Dietary oils

Omega 3 fatty acids such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) have gained interest as potential modifiers of inflammation.[72] The supplementation

of either a marine derived omega 3 fatty acid source (alpha linolenic acids 2 g, EPA 7.6 g, docosapentaenoic acid 1.7 g, and DHA 26.6 g) or a vegetable source (flaxseed with 38 g alpha linolenic acids) did not impact synovial prostaglandin E2 levels in healthy horses.[73] However, there is some evidence that the metabolism of the flaxseed alpha linolenic acids to EPA and DHA might be restricted, suggesting a possible advantage of direct EPA and DHA supplementation, for example, by feeding a marine-derived omega 3 fatty acid source. However, in an experimentally induced synovitis model in horses, the supplementation of a marine-derived omega 3 fatty acids source (per 100 kilograms of body weight: alpha linolenic acids 0.36 g, docosapentaenoic acid 0.36 g, EPA 1.93 g, and DHA 5.43 g) did not modify synovial inflammation processes, despite higher synovial levels of EPA and DHA acid compared with the control group.[73]

Conjugated linoleic acid has been shown to have anti-inflammatory effects in several animal species.[74] Plasma and synovial omega-6 arachidonic levels were decreased in horses after feeding 1% of a conjugated linoleic acid–containing supplement. However, the degree of inflammation after an intraarticular lipopolysaccharide challenge, as indicated by joint temperature and synovial prostaglandin E2, remained unchanged.[75]

Cetyl myristoleate is another fatty acid that may have beneficial effects on the modification of inflammatory responses by cytokines and the arachidonic acid cascade.[76] Cetyl myristoleate is included in several commercial joint supplements; however, well-designed studies are lacking to be able to give recommendations according to the efficacy.

Vegetable extracts

Resveratrol. Resveratrol (3,4,5-trihydroxystilbene) is a natural polyphenolic compound found in many plants such as red grapes, peanuts, blueberries, some pines, and the roots and stalks of Japanese knotweed. Resveratrol has been proposed to have antioxidative properties owing to its free radical scavenging.[77] In a placebo-controlled study, feeding 3 weeks of a commercially available oral resveratrol (450 mg twice per day for 3 weeks, per the manufacturer's recommendation) did not affect phagocytic activity, oxidative burst function, or cytokine production in horses.[78]

Ememe and colleagues[79] reported some beneficial effects of the supplementation of a product (30 g) containing resveratrol, hyaluronic acid and *S cerevisiae* (2000 mg of resveratrol, 200 mg of sodium hyaluronic acid, and the carrier *S cerevisiae*) on blood antioxidative capacity in lame horses; lameness was not evaluated.

A combined therapy with resveratrol supplementation (containing 1000 mg of resveratrol and the carrier *S cerevisiae*) for 4 months after intra-articular injection of triamcinolone in the centrodistal and tarsometatarsal joints improved lameness assessed by an objective sensory system and subjective rider's assessment.[80] However, only 8 of 21 supplemented horses and 7 or 20 placebo horses had returned to full work at the end of the 4-month observation period. In addition, the lameness examination by an experienced veterinarian still identified 15 of 21 and 15 of 20 horses in the supplementation or placebo groups, respectively, with a lameness grade of 3 out of 3 at the end of the study.

From the present data, beneficial effects of resveratrol on equine osteoarthritis are questionable.

Avocado and soybean unsaponifiables

Vegetable extracts from avocado and soybean oils have been considered for the treatment of OA. Avocado and soybean unsaponifiables are complex mixture of compounds, such as fat-soluble vitamins, sterols, and triterpene alcohols.[81] An extensive meta-analysis suggested some beneficial effects of avocado and soybean unsaponifiables treatment in humans, but not in horses.[82]

Other substances

A blend of lipids from the New Zealand green lipped mussel (*Perna canaliculus*), shark cartilage (*Galorhinus galeus*), abalone (*Haliotis sp*), and *Biota orientalis* lipid extract have been shown to decreased inflammation in a cartilage explant model in vitro.[83] A supplement containing glucosamine sulfate, shark chondroitin sulfate, methylsulphonylmethane, boswellic acid dry extract 65%, *Ananasus comosus* extract, L-glutamine, feverfew dry extract, and hyaluronic acid fed to horses before induced joint inflammation (intra-articular lipopolysaccharide) resulted in lower synovial prostaglandin E2 levels and total nucleated cell counts compared with the placebo group.[84] However, it remains still unclear whether such results obtained in a joint inflammation–induced model are comparable with naturally occurring joint inflammation in horses.

Feeding a commercial product containing chondroitin sulfate 162 g/kg, glucosamine 190 g/kg, vitamin C 80 g/kg, methylsulphonylmethane 256 g/kg, DHA 66 g/kg, and EPA 34 g/kg improved lameness grade, ridden and groundwork scores, and "ease of movement," when compared with feeding a placebo.[85] However, a main limitation of this study was that 30% of the horses were not lame and the rest of the horses had a low lameness score with an unknown lameness diagnosis. Furthermore, dosage of the product was not mentioned in the study.

Herbs

As an alternative to drug treatments, popular herbs include devil's claw (*Harpagophytum procumbens*), Indian celery (*Apium graveolens*),[86] and blue green algae.[87]

Devil's claw (*H procumbens*) for example, is widely used owing to its potential anti-inflammatory properties.[88] Devil's claw is an extract obtained from the root of the *H procumbens*. A clear mechanism for any anti-inflammatory action still needs to be established, although it is purported to inhibit the arachidonic, and subsequently the inflammatory cyclo-oxygenase, and the lipo-oxygenase pathways.[89] Despite the high number of supplements containing devil's claw, other than the pharmacokinetics of its active chemical constituent harpagoside,[90] the results of clinical studies have not been published in horses. Furthermore, devil's claw is a banned substance in competing horses. Currently, the results are very inconclusive, and more research is necessary to give recommendations about their efficacy.

Key points

- Despite the global use of joints supplements, scientific evidence is limited regarding their efficacy on naturally occurring osteoarthritis in horses.
- Currently, it is not possible to come to a conclusion regarding the efficacy of oral joint supplements in horse.

DISCLOSURE

The authors declare that they have no financial conflicts of interest.

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