

Oral Joint Health Supplements: Chemistry, Pharmacology, and Administration Guidelines

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Abstract: Oral joint health supplements are popular in the equine industry despite, in many cases, a lack of understanding of the chemistry, pharmacology (particularly safety), and appropriate dosages of these products among owners and trainers. The most popular ingredients include glucosamine, chondroitin sulfate, and methylsulfonylmethane; however, a multitude of alternative supplements, including cetyl myristoleate, hyaluronic acid, ester-C, devil's claw, yucca, garlic, and avocado/soybean unsaponifiable extracts, are also widely available. In this article, the most up-to-date information regarding the chemistry, pharmacokinetics (primarily absorption), safety, and dosing of oral joint health supplements is relayed in a practical manner. This information can help clinicians educate clients regarding the use of supplements to ensure that horses derive as much benefit as possible.

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Complementary and alternative medical therapies, including the use of oral nutritional supplements, have become increasingly popular in the veterinary community, particularly the equine industry.¹ Among these, joint health supplements are ubiquitously employed.¹ Oral joint health supplements are popular not only because of the high incidence of osteoarthritis (OA; degenerative joint disease) in the equine population but also because of limitations of conventional medical treatment.

Despite the widespread availability and administration of oral nutritional supplements, these products are not considered to be drugs by the FDA. As a result, nutritional supplements, including equine oral joint health supplements, are poorly regulated and typically lack important pharmacologic information, such as absorption, distribution, metabolism, excretion, recommended dosages, and safety information. This dearth of basic scientific information makes it challenging for practicing veterinarians to identify quality oral joint health supplements.

Comprehensive reviews have been published regarding the medical management of equine OA² and the use of nutraceuticals in horses with OA³ (both of these reviews

include an up-to-date description of the pathophysiology of OA) as well as future OA management strategies.⁴ Together, these lay an excellent foundation for this discussion, which focuses on the rationale for the administration of various oral joint health supplements, including glucosamine, chondroitin sulfate, methylsulfonylmethane (MSM),

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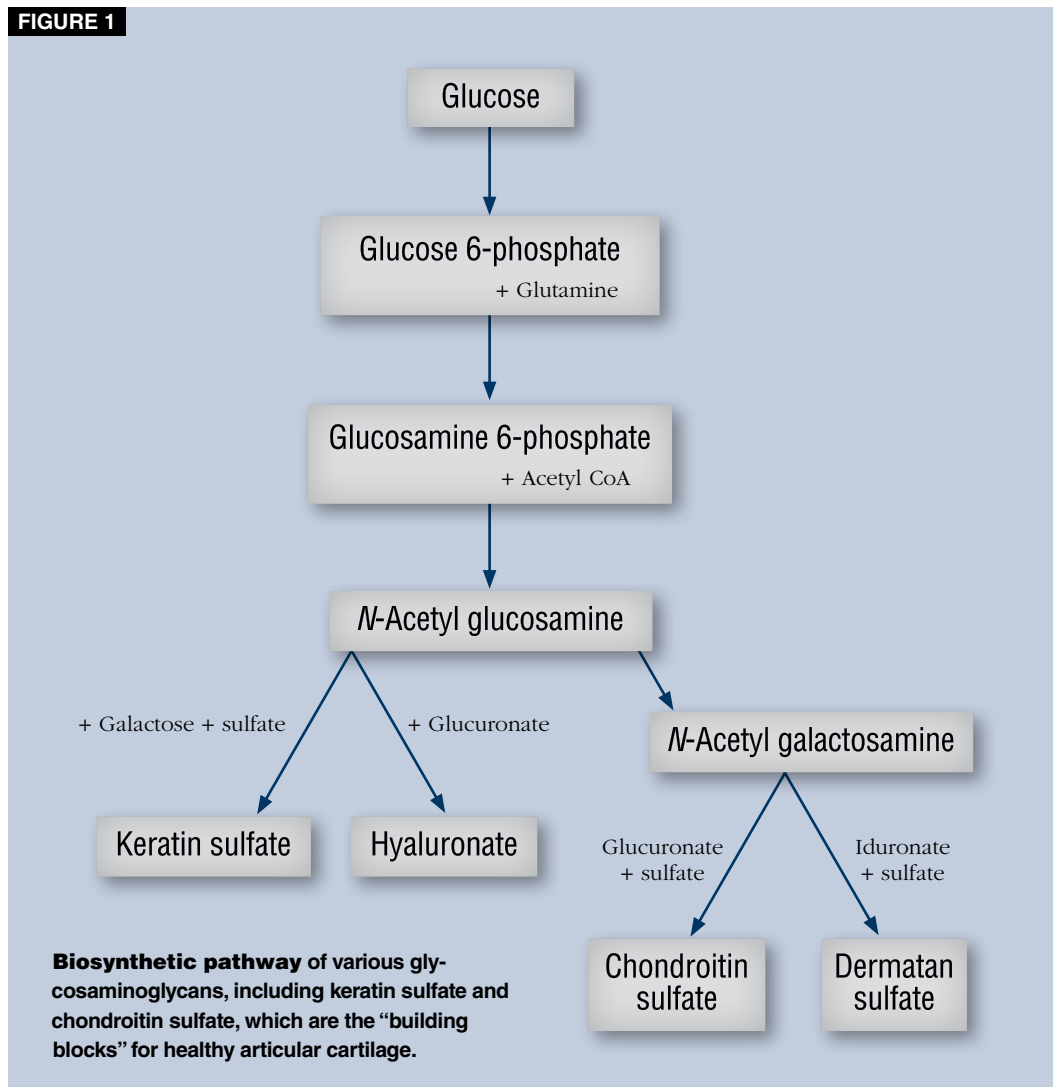


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FIGURE 1



Critical Point

Glucosamine is a water-soluble amino monosaccharide that is a fundamental building block for articular cartilage.

and avocado/soybean unsaponifiable (ASU) extracts, either alone or in combination products, to horses with OA. This article examines the chemistry of articular cartilage and some oral joint health supplement components and presents the most up-to-date and relevant pharmacologic information available. This should allow practicing equine veterinarians to remain current with the ever-increasing information regarding oral joint health supplements and to facilitate product, formulation, and dosing decisions.

Glucosamine

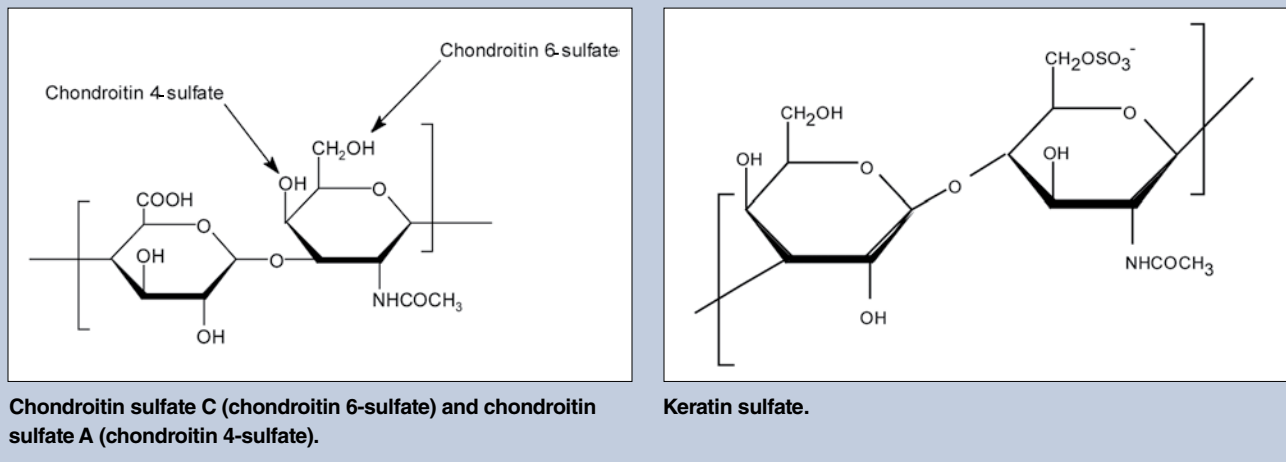
Glucosamine is a water-soluble amino monosaccharide that is a fundamental building block for articular cartilage.^{5,6} As illustrated in **FIGURE 1**, glucosamine is integral to the synthesis of various glycosaminoglycans (i.e., large molecules

comprising repeating disaccharide units), including chondroitin sulfate and keratin sulfate (**FIGURE 2**). In turn, these glycosaminoglycans are incorporated into proteoglycans, which are large molecules composed of a protein core and at least one glycosaminoglycan molecule that is covalently attached.^{7,8} Perhaps the most well-known proteoglycan is aggrecan (**FIGURE 3**), which provides compressive stiffness to articular cartilage by swelling and hydrating the framework of collagen fibrils.^{7,8}

Glucosamine is commercially available in three main forms: glucosamine hydrochloride, glucosamine sulfate, and *N*-acetyl-D-glucosamine (**FIGURE 4**). The hydrochloride and sulfate forms are both salts that stabilize glucosamine following its large-scale production.⁹ The pK_a of glucosamine is 6.91 at 98.6°F (37°C), which means that in the acidic stomach

FIGURE 2

Chemical structure of two predominant glycosaminoglycans in equine articular cartilage.



environment, dissolution of the salts generates glucosamine free base^{5,6} (FIGURE 4). The free-base form is thought to be absorbed and ultimately incorporated into various biosynthetic pathways, including the synthesis of cartilage glycosaminoglycans as described in FIGURE 1.

While all glucosamine salts are believed to generate glucosamine free base in the stomach, not all glucosamine salts deliver comparable amounts of glucosamine free base. Ninety-nine percent-pure glucosamine hydrochloride delivers approximately 80% glucosamine free base, whereas glucosamine sulfate delivers 50% to 60%.⁹⁻¹¹ Thus, if an oral joint health supplement contains 12 g of glucosamine hydrochloride, the horse is actually being fed 9.6 g of glucosamine free base. Likewise, if 12 g of glucosamine sulfate per serving is administered, the horse is receiving 6 to 7.2 g of glucosamine free base.

Glucosamine is widely regarded as safe. Even after oral administration of very high levels of glucosamine (>5000 mg/kg), no mortality was noted in mice or rats.¹² Adverse events associated with administration have not been reported in horses.^{13,14} In human trials, such as a study by Reginster et al,¹⁵ primary complaints included gastrointestinal (GI) effects (i.e., abdominal pain, diarrhea, dyspepsia), but fatigue, headache, vertigo, depressed mood, and allergic episodes were also reported; however, there were no significant differences in the reporting of adverse events between the treatment and placebo groups.

In late 2004 and early 2005, two separate

studies conducted by the research groups of Du¹³ and Laverty,¹⁴ respectively, reported that glucosamine hydrochloride was absorbed in horses following intravenous or oral administration via nasogastric intubation. Laverty et al¹⁴ reported a mean bioavailability of 5.9% following oral administration at a dose of 20 mg/kg (approximately 10 g) in eight horses, whereas Du et al¹³ identified a mean bioavailability of 2.5% after the administration of 125 mg/kg (approximately 56 g for an average horse [990 lb; 450 kg], which is fivefold to tenfold higher than typical doses) of glucosamine hydrochloride.

Chondroitin Sulfate

Chondroitin sulfate is a highly sulfated disaccharide polymer (FIGURE 2). Like glucosamine, chondroitin sulfate is a basic building block of articular cartilage and highly variable in terms of molecular weight, source, degree of sulfation, and purity.^{3,16} Chondroitin sulfate is an expensive ingredient and, therefore, is frequently criticized in terms of failing to meet label claims.¹⁷

Like glucosamine, chondroitin sulfate is generally considered safe because the LD₅₀ in mice is >10,000 mg/kg.¹⁸ Adverse events related to the administration of chondroitin sulfate alone have not been reported in horses. In the human literature, chondroitin sulfate-related adverse events are typically mild and include GI and unspecified “musculoskeletal and connective tissue” complaints, although no difference between treatment and placebo groups was noted.¹⁹

Critical Point

Perhaps the most well-known proteoglycan is aggrecan, which provides compressive stiffness to articular cartilage by swelling and hydrating the framework of collagen fibrils.

Du et al¹³ reported a bioavailability of 22% for a low-molecular-weight chondroitin sulfate product after orally administering 3 g via nasogastric intubation. This study indicates that this particular low-molecular-weight chondroitin sulfate is absorbed systemically at this dose. Most equine oral joint health supplement products recommend 0.5 to 2.4 g of various forms and purities of chondroitin sulfate, although a select few recommend up to 3.6 g; however, without further clinical trials in horses, the effective dose is still unknown.

Glucosamine/Chondroitin Sulfate Combination Products

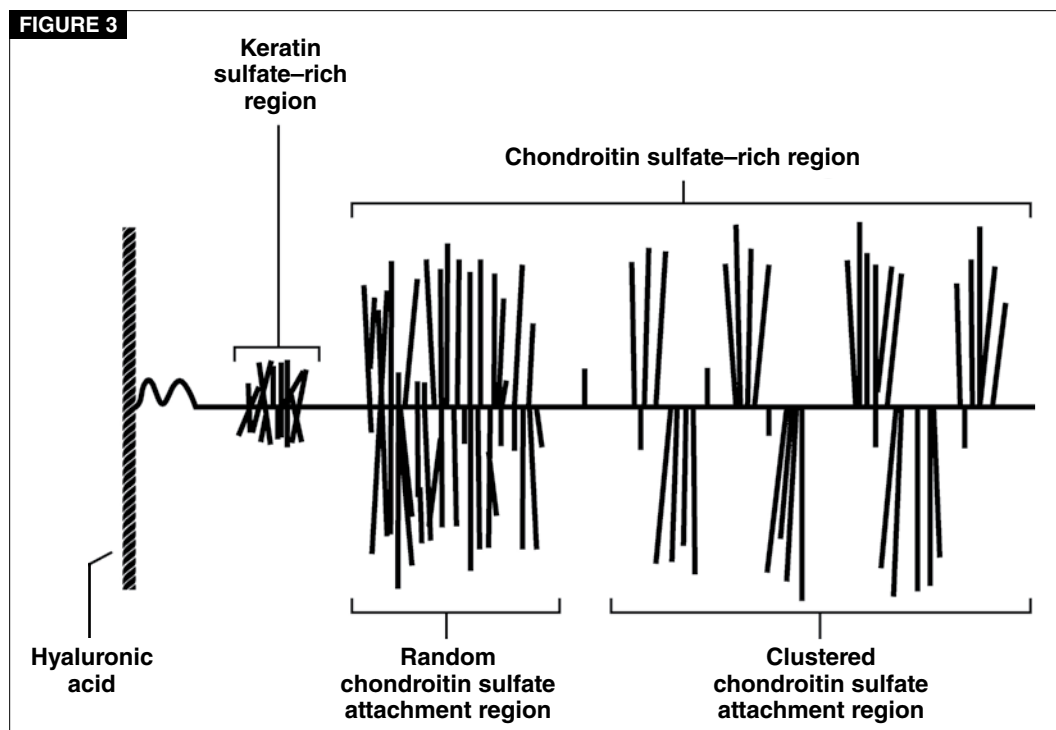
Few studies have evaluated the effect of the combination of glucosamine and chondroitin sulfate in treating equine OA. Hanson and colleagues²⁰ identified a beneficial effect in horses with navicular syndrome after the administration of 9 g of glucosamine hydrochloride and 3 g of chondroitin sulfate daily for 8 weeks. Similarly, while being treated with glucosamine/chondroitin sulfate, 25 horses with degenerative joint disease experienced significant improvement in lameness in the first 2 weeks, which remained level for the following 4 weeks.²¹ The doses used in this study

were 5.4 g of glucosamine hydrochloride and 1.8 g of chondroitin sulfate twice per day in horses weighing less than 1199 lb (545 kg) and 7.2 g of glucosamine hydrochloride and 2.4 g of chondroitin sulfate twice per day in horses heavier than 1199 lb (545 kg).²¹ Improved stride characteristics were noted in 20 veteran horses that were administered 2 to 4 g of purified chondroitin sulfate, 5 to 10 g of glucosamine hydrochloride, and 500 mg to 1 g of *N*-acetyl-D-glucosamine PO for 12 weeks.²² In terms of safety, horses administered five times the recommended maintenance dose (i.e., 18 g of glucosamine hydrochloride and 6 g of chondroitin sulfate daily for 35 days) experienced no clinically significant changes in physical, hematologic, or serum biochemical parameters.²³

In an *in vivo* study by Lippiello and colleagues,²⁴ the effect of glucosamine and chondroitin sulfate in combination was superior to that of either agent alone using a rabbit instability model of osteoarthritis. The synergistic activity of glucosamine and chondroitin sulfate was also reported by Homandberg et al²⁵ while assessing the effectiveness of this combination to protect cartilage from proteoglycan loss caused by exposure to fibronectin

CriticalPoint

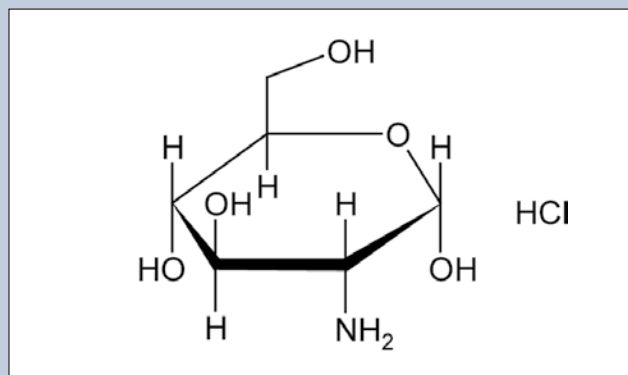
Chondroitin sulfate is a highly sulfated disaccharide polymer.



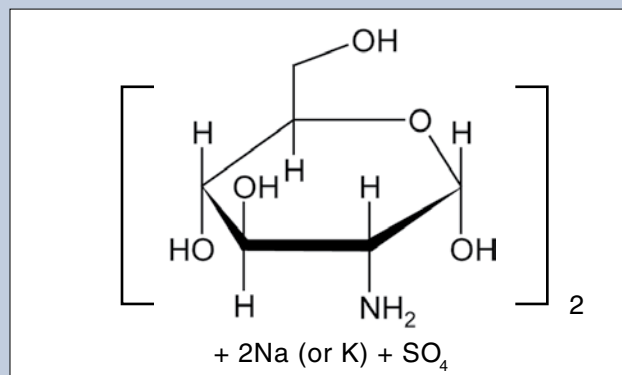
Chemical structure of aggrecan—a large proteoglycan molecule responsible for providing compressive stiffness by swelling and hydrating the framework of collagen fibrils.

FIGURE 4

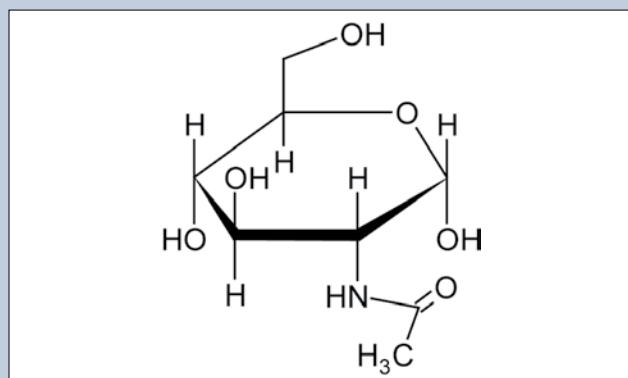
Chemical structures of the common forms of glucosamine.



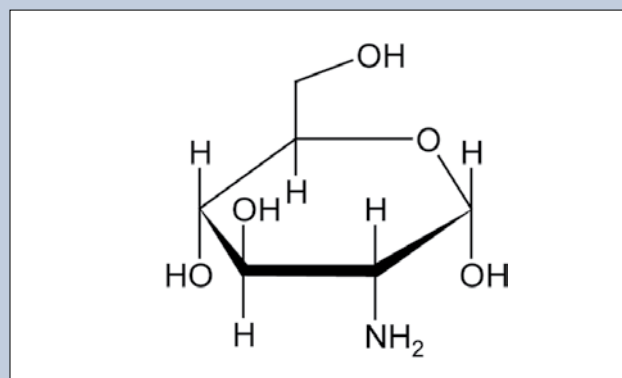
Glucosamine hydrochloride.



Glucosamine sulfate.



N-Acetyl-D-glucosamine.



Glucosamine free base.

fragments when added to bovine cartilage cultures (which are known to stimulate cytokines and matrix metalloproteinases).²⁵ This study revealed that the combination of glucosamine and chondroitin sulfate at physiologically relevant concentrations synergistically reversed fibronectin fragment-induced cartilage damage and promoted proteoglycan synthesis.²⁵

Avocado/Soybean Unsaponifiable Extracts

Unlike information regarding glucosamine and chondroitin sulfate, the history of how ASU extracts were discovered to be potential disease modifiers for OA is unclear. Nonetheless, ASU extracts have been studied in human OA for the past decade and have just recently been introduced to the North American equine industry. ASU extracts are produced by isolating the oils from avocados and soybeans, collecting the unsaponifiable fractions (i.e., the oils that remain after hydrolysis and do not

form soaps), and combining these unsaponified oils in various ratios (1:2 is typical).²⁶

In humans, 300 mg of ASU (4.6 mg/kg per 143-lb [65-kg] person) PO per day appears to be the standard recommended dose. No LD₅₀ or pharmacokinetic/pharmacodynamic information was identified while preparing this article. As summarized in a systematic review of four human clinical trials, the adverse effects associated with ASU extract administration were infrequent and mild.²⁶ The predominant complaints were related to the GI system and were reported with equal frequency in the treatment and placebo groups.²⁶ In horses, the safety of ASU (in combination with glucosamine and chondroitin sulfate) was evaluated in 20 horses during an 84-day period using a randomized, blinded, and placebo-controlled study.²⁷ No significant changes in complete blood counts, serum biochemistry parameters, body weight, or physical examination findings were noted.

CriticalPoint

ASU extracts are produced by isolating the oils from avocados and soybeans, collecting the unsaponifiable fractions (i.e., the oils that remain after hydrolysis and do not form soaps), and combining these unsaponified oils in various ratios (1:2 is typical).

Reported in vitro mechanisms of action and the beneficial effects of ASU in well-designed clinical trials conducted in humans spurred the evaluation of ASU in horses.²⁸ In a blinded and placebo-controlled clinical trial, 16 horses underwent surgical induction of an osteochondral defect in one middle carpal joint on day 0.²⁸ Horses were randomly divided into two groups: the ASU extract group was administered the supplement mixed with molasses, while the placebo group received only molasses from day 0 to 70. Beginning on day 14, all horses were exercised on a treadmill five times weekly until completion of the study. Outcome measures included clinical evaluation, radiography, serum and synovial fluid analyses, gross and histologic examination, and assessment of the articular cartilage matrix. Results indicated that induction of the osteochondral defect resulted in a significant increase in joint pain and disease. While treatment with ASU extracts did not have an effect on pain or lameness, a significant reduction in the degree of articular cartilage erosion and synovial hemorrhage was observed. In addition, there was a significant increase in glycosaminoglycan synthesis by articular cartilage compared with the placebo group. The administered dose used in this study could not be calculated based on the published information; however, the authors specifically stated that no adverse effects were noted and the product was easily administered to horses when it was mixed with a small volume of molasses. This study, which is the only in vivo veterinary trial published to date to evaluate the efficacy of ASU extracts, concluded that while this product did not ameliorate clinical signs of OA, a disease-modifying effect was noted compared with placebo-treated horses.²⁸ Therefore, the authors suggested that it may be best to combine ASU extracts with clinical sign-modifying agents in clinical practice.

Avocado/Soybean Unsaponifiable Extract/ Glucosamine/Chondroitin Sulfate Combination Products

The ASU extract product used in the equine clinical trial described above contained only ASU extracts and will not be made available in the United States.^a At present, the only ASU extract product available in North America is

sold in combination with glucosamine and chondroitin sulfate.

With the use of an in vitro equine chondrocyte and osteoblast model activated with interleukin [IL] 1 β or tumor necrosis factor- α to express the inflammatory mediators cyclooxygenase-2 (COX-2) and prostaglandin E₂ (PGE₂), a glucosamine/chondroitin sulfate/ASU extract combination product was evaluated for its anti-inflammatory properties.²⁹ This study found that the combination product down-regulated both COX-2 and PGE₂. Furthermore, pretreatment of the cultures before cytokine activation profoundly inhibited COX-2 and PGE₂ production compared with activated levels in the control cultures.²⁹ Au et al^{30,31} determined that the glucosamine/chondroitin sulfate/ASU extract combination profoundly inhibited the expression of COX-2 in equine chondrocytes and human fibroblasts, the chemokines IL-8 and monocyte chemoattractant protein 1 in human chondrocytes, some cytokines (tumor necrosis factor- α , IL-1 β), inducible nitric oxide synthase, and mitogen-activated protein kinase 14 (also known as *p38*) in monocytes or macrophages. Inhibition of expression with the use of a glucosamine/chondroitin sulfate/ASU extract combination in equine and human chondrocytes and monocytes/macrophages was better than that seen with the use of glucosamine or chondroitin sulfate alone.

The manufacturer-recommended dose of ASU extracts in the available product is 2100 mg per two level scoops (32.2 g of product), which is equivalent to approximately 5 mg/kg for a 990-lb (450-kg) horse.

Methylsulfonylmethane

Considering the popularity of methylsulfonylmethane (MSM), there is exceedingly little information regarding its chemistry, pharmacology, efficacy, and mechanism(s) of action or safety, particularly in the veterinary literature. MSM is an organosulfur molecule (CH₃SO₂CH₃) naturally found in foods such as fruit, alfalfa, corn, tea, coffee, and milk³² and is metabolized in the body from dimethyl sulfoxide (DMSO).³³

^aPersonal communication with Dr. David Frisbie, Gail Holmes Equine Orthopaedic Research Center, Department of Clinical Sciences, College of Veterinary Medicine and Biological Sciences, Colorado State University (May 2006).

The rationale for administration is twofold. First, MSM is a sulfur-containing molecule that can be used by the body to synthesize various connective tissues.³³ Second, because MSM is related to DMSO, which has been used in managing musculoskeletal disorders, many users believe that MSM is therefore also advantageous for musculoskeletal pain, including that associated with OA.

To date, only two human clinical trials involving MSM have been conducted, both of which reported improvements in pain, mobility, and swelling.^{33,34} Doses of 1.5 and 6 g/day PO of MSM were administered without major adverse events. Minor patient-reported adverse events included bloating, constipation, indigestion, fatigue, decreased concentration, insomnia, and headache, but no difference between the incidences of these signs existed between the treatment and placebo groups.³³

MSM is considered safe: the LD₅₀ is >20 mg/kg in mice.³⁵ No pharmacologic information exists in the human literature, but Horváth et al³⁶ found that no adverse events or mortality occurred in rats when 2 g/kg PO of MSM was administered once, and no postmortem gross or renal histologic changes were noted following administration of 1.5 g/kg PO for 90 days.

Typical recommended dosages of MSM in equine supplements range from 5 to 10 g/day PO. Kim et al³³ used 6 g/day (approximately 90 mg/kg; divided into 3 g q12h) in humans. Extrapolating from the human dose, it is possible that horses can be safely supplemented with higher amounts of MSM than the currently recommended 5 to 10 g/day; however,

this suggestion should be confirmed in controlled clinical trials.

Other Ingredients

In addition to the compounds discussed above, a medley of other ingredients are commonly found in equine oral joint health supplements, including ester-C, hyaluronic acid or sodium hyaluronate, cetyl myristoleate, yucca, garlic, and a variety of amino acids, vitamins, and herbs. Many of these compounds are based on structural elements of articular cartilage and therefore may predominantly serve as precursor molecules. Considering that glucosamine and chondroitin sulfate have proven to possess numerous additional mechanisms for promoting joint health, it will be interesting to observe how the use of other supplements will evolve. This is certainly an area worthy of further research.

Conclusion

The use of oral joint health supplements in the equine industry continues to increase, often without veterinary consultation. This article can help practicing equine veterinarians better convey to their clients more appropriate means of using oral joint health supplements. 🐾

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CriticalPoint
Considering the popularity of methylsulfonylmethane, there is exceedingly little information regarding its chemistry, pharmacology, efficacy, and mechanism(s) of action or safety, particularly in the veterinary literature.

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1. Aggrecan, a proteoglycan, provides

- a. a scaffolding for bony remodeling.
- b. compressive stiffness to articular cartilage.
- c. a and b
- d. none of the above

2. Glycosaminoglycans in articular cartilage

- a. serve as building blocks for proteoglycans such as aggrecan.
- b. include chondroitin sulfate.
- c. are typically sulfated.
- d. all of the above

3. Glucosamine is commercially available as

- a. a sulfate form.
- b. a hydrochloride form.
- c. N-acetyl-D-glucosamine.
- d. all of the above

4. A few research trials involving a glucosamine/chondroitin sulfate combination product have

- a. shown a beneficial effect in treating horses with degenerative joint disease.
- b. shown that these products do not have a beneficial effect.
- c. demonstrated significant changes in clinical measurement (e.g., physical,

hematologic, and serum biochemical parameters).

- d. none of the above

5. Oral joint health supplements are popular in the equine industry due to

- a. the high incidence of osteoarthritis.
- b. widespread availability of the products.
- c. interest in complementary and alternative therapies.
- d. all of the above

6. Typical adverse events associated with glucosamine administration in horses include

- a. gastrointestinal upset (vomiting and diarrhea).
- b. lameness.
- c. urticaria.
- d. none of the above (No adverse events in horses have been reported.)

7. Which statement regarding MSM is correct?

- a. It is a well-studied product, which explains why it is so widely used.
- b. It is popular but does not work.
- c. It is popular, but further research must be conducted to evaluate its efficacy.
- d. It is not used in horses; only its metabolite, DMSO, is safe.

8. Glucosamine is integral to synthesis of

- a. keratin sulfate.
- b. chondroitin sulfate.
- c. a and b
- d. none of the above

9. Which statement regarding studies of ASU extract use is correct?

- a. No studies have evaluated its use in horses.
- b. Kawcak et al²⁸ did not find any benefit to using it.
- c. It appeared to improve signs of pain and have a disease-modifying effect.
- d. While it did not improve signs of pain, it appeared to have disease-modifying properties.

10. The use of ASU extracts in horses

- a. has not been reported.
- b. is associated with serious adverse effects, according to the only clinical trial reported to date.
- c. can effectively protect articular cartilage from trauma in performance horses.
- d. may be beneficial in horses with OA, particularly if it is combined with clinical sign-modifying agents.

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