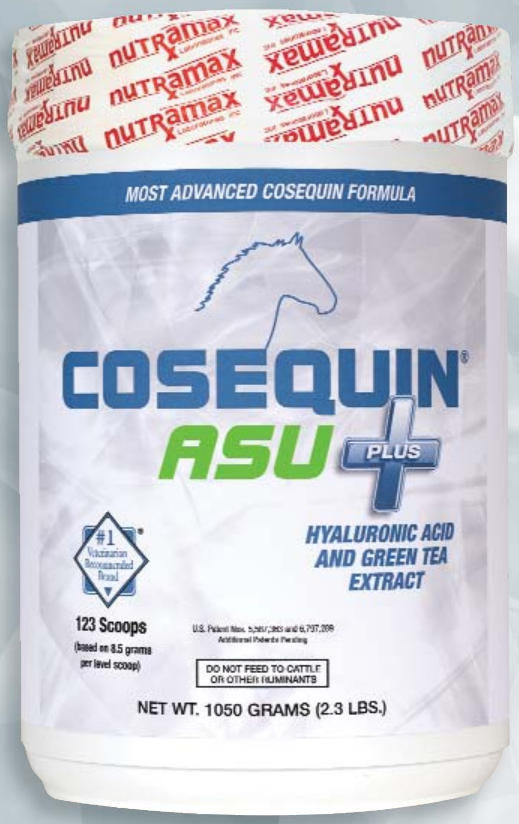
COSEQUIN® ASU PLUS

#1 Veterinarian Recommended Brand®

- The *most* advanced Cosequin joint health formula providing the next level of support
- Comprehensive, multi-faceted joint health management
- Glucosamine, chondroitin sulfate, and avocado/soybean unsaponifiables (ASU) – PLUS high quality hyaluronic acid (HA) and Green Tea Extract
- Supported by cutting edge scientific data
- All-in-one convenience



123 Scoops
(based on 8.5 grams per level scoop)

NET WT. 1050 GRAMS (2.3 LBS.)

U.S. Patent Nos. 5,587,363 and 6,797,289
Additional Patents Pending

What the Research Shows

Cosequin® ASU PLUS is the most advanced Cosequin formula

- The combination of HA and ASU, glucosamine, and chondroitin sulfate (ASU/glu/CS) significantly lowered PGE_2 production in IL-1β-stimulated equine chondrocytes (see figure 1); effects were better than HA alone or ASU/glu/CS. The decrease in PGE_2 production was associated with inhibition of activation of NF-κB, a mediator that helps "switch on" the inflammatory response.[1]

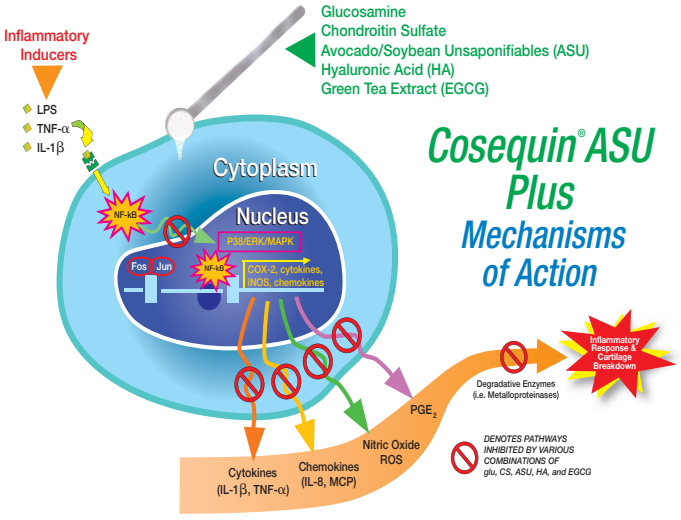
- Another study showed that ASU and EGCG (epigallocatechin gallate, an extract from green tea) significantly decreased COX-2 expression (see figure 2) and PGE_2 production in cytokine-activated equine chondrocytes. The combination was better than either agent alone. As above, effects were associated with inhibition of NF-κB activation (see figure 3).[2]

These *in vitro* studies show that the ingredients in Cosequin ASU PLUS have effects at multiple places along the inflammatory pathway.

The use of Cosequin ASU PLUS may be beneficial to provide joint health protection when other modalities are used

- Addition of enrofloxacin to equine chondrocyte cultures was shown to up-regulate PGE_2 production. This increase was inhibited by the combination of ASU/glu/CS.[3] **So while intra-articular administration of an antibiotic may be needed to control infection, ASU/glu/CS may help minimize any adverse effects on cartilage caused by the antibiotic.**

- Inflammatory mediators increased PGE_2 production and activation of matrix metalloproteinase-9 (MMP-9), an enzyme that breaks down cartilage, in equine chondrocytes. Adding the anti-inflammatory phenylbutazone to the cultures decreased PGE_2 production as expected, while phenylbutazone and ASU/glu/CS together also decreased MMP-9 activation.[4] **Based on these results, administration of ASU/glu/CS may help when using phenylbutazone to maximize attenuation of both inflammatory mediators and enzymes, which all play a role in cartilage breakdown.**



Mechanisms of action shown *in vitro* of ingredients in Cosequin ASU PLUS help attenuate expression of multiple proinflammatory mediators. This attenuation helps minimize cartilage degradation and supports joint comfort.

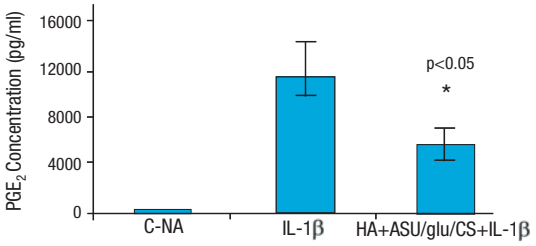


Figure 1: Combination of HA and ASU/glu/CS inhibits PGE_2 production in equine chondrocytes. (C-NA=non-activated control) (*=statistical significance relative to IL-1β)

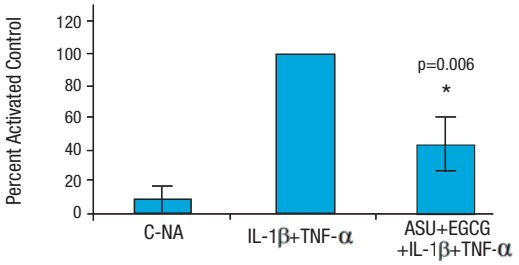


Figure 2: Combination of ASU and EGCG inhibits COX-2 expression in equine chondrocytes. (C-NA=non-activated control) (*=statistical significance relative to IL-1β+TNF-α)

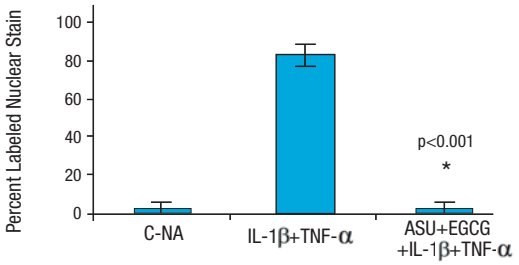


Figure 3: Combination of ASU and EGCG inhibits nuclear translocation (activation) of NF-κB. (C-NA=non-activated control) (*=statistical significance relative to IL-1β+TNF-α)

Cosequin® ASU PLUS contains FCHG49® Glucosamine, TRH122® Sodium Chondroitin Sulfate, and NMX1000® Avocado/Soybean Unsaponifiables, Nutramax Laboratories® proprietary veterinary researched specifications.

▼ Source: Surveys conducted in the Fall of 2002, March 2004, and September 2007 of equine veterinarians who recommended oral joint health supplements.

REFERENCES:

1. Heinecke LF, Grzanna MW, et al. Inhibition of prostaglandin E2 production by hyaluronan and the combination of avocado/soybean unsaponifiables, glucosamine, and chondroitin sulfate in activated equine chondrocytes, in *Proceedings.* 2010 ACVS Symposium.
2. Heinecke LF, Grzanna MW, et al. Inhibition of cyclooxygenase-2 expression and prostaglandin E2 production in chondrocytes by avocado soybean unsaponifiables and epigallocatechin gallate. *Osteoarthritis and Cartilage* 2010;18:220-227.
3. Mochal CA, Heinecke LF, et al. Antibiotics induce prostaglandin E2 production in equine chondrocytes: induction is inhibited by avocado soybean unsaponifiables, glucosamine and chondroitin sulfate, in *Proceedings.* 2009 ACVS Symposium;xii.
4. Dougherty JJ, Heinecke LF, et al. Effect of phenylbutazone and the combination of avocado soybean unsaponifiables, glucosamine and chondroitin sulfate on metalloproteinase activity in equine chondrocytes, in *Proceedings.* 2009 ACVS Symposium;xxxi-xxxii.

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