This document represents a compilation of clinical trials, research and studies on Glyco FLEX® 3 and the active ingredients in Glyco FLEX® products. These projects have been conducted over the last seventeen years at leading universities or by independent researchers. All of these studies have been sponsored in some way by VetriScience® Laboratories. The ingredients and products used in these studies have been supplied by VetriScience® and are the same ingredients used in Glyco FLEX® products. The GlycOmega™ (Perna canaliculus) used in these studies is exclusive to VetriScience® Laboratories.

Because Glyco FLEX® is an animal health product, we do not purport to cure, mitigate, treat, or prevent any disease. The conclusions reached in these studies are the observations of independent researchers and, as such, should not be misconstrued as a claim made by VetriScience® regarding the benefits of Glyco FLEX®. These studies were conducted to better understand scientifically how the product and ingredients work, not to support any claim.

Please contact your VetriScience® Sales Representative for questions regarding label claims or quality control procedures, to obtain information about Glyco FLEX® products or VetriScience® Laboratories, or to request additional information about these studies.

Studies featured in this publication have been assigned a reference code number. Please specify this number when requesting studies.
## Glyco FLEX® 3 Canine Clinical Trials and Studies

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## Research on Active Ingredients in Glyco FLEX® Products

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In a randomized, double-blind, crossover design dog study, a stifle osteoarthritis (OA) model was used to determine if Glyco FLEX® 3 could reduce cartilage breakdown and help normalize joint function. The dogs were randomized into two groups: the treatment dogs (Glyco FLEX® 3) and the control group. After a wash-out period, the two groups were crossed over for treatment and control. Force plate analysis was performed on each of the dogs. Then synovial fluid was collected from the stifle joint and analyzed for markers of joint inflammation and degradation. The responders had significant improvement in lameness after treatment, with a 41% increase in Peak Vertical Force (PVF) and 44% increase in Vertical Impulse (VI) over the pre-treatment value in the dogs. There was a significant decrease in mean synovial PGE2 and soluble collagen (SC) levels in the treatment group as compared to the control group. Other synovial markers in the responders had trends for lower levels, compared to the control group. The results of the study support that Glyco FLEX® 3 may reduce the severity of cartilage breakdown and synovitis, and help normalize joint function in dogs with stifle joints affected by OA.

**SUMMARY**

- Glyco FLEX® 3 may reduce the severity of cartilage breakdown and synovitis, and help normalize joint function in osteoarthritic stifle joints.

- The results of this in vivo (VSL 120) study more than correlate/parallel those from other in vitro (VSL 130 and VSL 260) studies.
VLS 110


Glyco FLEX® 3 was shown safe in dogs administered at a high dosage for 56 days. The results of the urinalysis, buccal mucosal bleeding test, blood chemistry panel, immunoglobulin levels and complete blood count were all within normal ranges. Results from this study show that Glyco FLEX® 3 had no adverse biochemical, hematologic, hemostatic, physiological, immunological, or allergenic effects.

VLS 100


100 veterinarians were surveyed by an outside marketing firm and asked to evaluate the effectiveness and their satisfaction with Glyco FLEX® products used in their practice. Glyco FLEX® was administered most frequently for joint problems associated with arthritis, hip/elbow dysplasia followed by post-surgical use, joint injury, and then general joint problems. Principal signs of improvement included reduced pain, improved range of motion, increased mobility, and improved attitude. Over 85% of veterinarians rated Glyco FLEX® products as good or excellent in reducing joint symptoms. The majority of veterinarians rated Glyco FLEX® products as good to excellent for the long-term management of degenerative joint disease.
Canine chondrocytes were used in cell culture experiments to assess the effects of the Glyco FLEX® 3 tablets on key markers of inflammation. Glyco FLEX® 3 tablets showed positive reductions in nitric oxide (NO), soluble collagen, tumor necrosis factor-alpha, IL-6, PGE2, and matrix metalloproteinase-3 (MMP-3), which are key markers of inflammation. Glyco FLEX® 3 appears to reduce cartilage breakdown, inhibit cytokine-induced NO and PGE2 production, and reduce proteolytic breakdown. These in vitro results appear to demonstrate some of the key pathways and mechanisms by which Glyco FLEX® 3 functions in the joint. This study also shows that Glyco FLEX® 3 tablets appear to have anti-inflammatory and antioxidant properties.

**SUMMARY**

» When used on a canine-specific cartilage cell line, Glyco FLEX® 3 appears to have anti-inflammatory and antioxidant properties.

» Glyco FLEX® 3 appears to reduce cartilage breakdown, inhibit cytokine-induced NO and PGE2 production, and reduce proteolytic breakdown.

» Results from this in vitro (VSL 130) study more than correlate/parallel other in vitro (VSL 260) and in vivo (VSL120) studies.
Dimethylglycine was evaluated for its effects on collagen-induced inflammation in rats. Only 22% of the rats treated with DMG showed any signs of swelling and inflammation compared to 100% of controls. This work resulted in a U.S. Patent #5,026,728 being granted in June of 1991 for the use of DMG to ameliorate inflammation associated with arthritis.

The purpose of this study was to look at the ability of *Perna canaliculus* to reverse inflammation in a collagen-induced inflammatory mouse model. At the beginning of the study all mice had the same degree of inflammation. The Perna mice showed significant reversal of inflammation and swelling at the end of the study. In this model, Perna was found to be effective in reducing inflammation.
DMG was evaluated for its ability to reduce the onset of inflammation and swelling in a collagen-induced inflammatory rat model. The control rats showed a 58.3% incidence of inflammation; the rats in the DMG group only showed a 29.6% incidence. In this model, DMG was found to be effective in reducing the occurrence of inflammation.

Perna canaliculus was evaluated for its ability to reduce the onset of inflammation and swelling in a collagen-induced inflammatory rat model. The control rats showed a 58.3% incidence of inflammation; the rats in the Perna group only showed a 16.6% incidence. Of those rats that developed inflammation in the Perna group, the degree of inflammation was 37% less based on paw size compared to the control group. In this model, Perna was found to be effective in reducing the occurrence of inflammation.
Prevention of Inflammation with Perna Canaliculus and DMG

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<th>Group</th>
<th>Incidence of Inflammation</th>
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<tr>
<td>Control</td>
<td>58.3%</td>
</tr>
<tr>
<td>Perna and DMG Combination</td>
<td>22.2%</td>
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The combination of *Perna canaliculus* and DMG was evaluated for its ability to prevent the onset of inflammation and swelling in a collagen-induced inflammatory rat model. The control rats showed a 58.3% incidence of inflammation; the rats in the DMG and Perna combination group only showed a 22.2% incidence. In this model, the DMG and Perna combination was found to be effective in reducing the incidence of inflammation.

120 patients suffering from radiographically confirmed osteoarthritis of the knee were administered whole freeze-dried *Perna canaliculus* for 12 months. 92% of the patients reported overall improvement in areas including: less pain, decreased inflammation, greater range of motion, and improved exercise tolerance. The practitioner’s assessment showed that 83% of the patients made either good or excellent progress. A significant number of patients were able to reduce pain medication and use of NSAIDs by 50% or more. Radiographic evaluation revealed that some patients had reversal of the narrowing of the joint space of the tibial femoral joint, suggesting an anabolic effect of Perna. In one patient, arthroscopic evaluation revealed the formation of new viable cartilage matrix covering a large osteochondral defect. The results of this study suggest that Perna may support articular cartilage regrowth and appears to be effective for the management of pain and inflammation in the knee joint.
Canine chondrocytes were used in cell culture experiments to assess the effects of the main active constituents in Glyco FLEX® 3 on key markers of inflammation. *Perna canaliculus*, Glucosamine, MSM, DMG, and Grape Seed Extract showed positive reductions in nitric oxide (NO), soluble collagen, tumor necrosis factor-alpha, IL-6, PGE2 and matrix metalloproteinase-3 (MMP-3), which are key markers of inflammation. The main active components of Glyco FLEX® 3 appear to reduce cartilage breakdown, inhibit cytokine-induced NO and PGE2 production, and reduce proteolytic breakdown. These in vitro results may demonstrate some of the key pathways and mechanisms by which the main components of Glyco FLEX® 3 may function in the joint. The study shows that the active components of Glyco FLEX® 3 appear to have anti-inflammatory and antioxidant properties.

When used on a canine-specific cartilage cell line, the main active ingredients in Glyco FLEX® 3 appear to have anti-inflammatory and antioxidant properties.

The main active ingredients in Glyco FLEX® 3 appear to reduce cartilage breakdown, inhibit cytokine-induced NO and PGE2 production, and reduce proteolytic breakdown.

The results from this in vitro (VSL 260) study more than correlate/parallel results from other in vitro (VSL 130) and in vivo (VSL 120) studies.

This cell culture study was designed to show the effectiveness of *Perna canaliculus* on certain inflammatory markers. Perna showed a statistically significant response in reducing pro-inflammatory cytokines (TNF-alpha and IL-12 p40). This study shows that Perna appears to reduce key markers of inflammation.
The purpose of the study was to evaluate the ability of *Perna canaliculus* to reduce superoxide (a free radical) production in cell culture using activated rat neutrophils. In this model, Perna demonstrated more than 1.2 times the activity of Aspirin in inhibiting superoxide production.

**SUMMARY**

» *Perna canaliculus* was shown to be better than aspirin in inhibiting superoxide production from activated neutrophils in a dose dependant manner.

The purpose of the study was to evaluate how *Perna canaliculus* may reduce inflammation. Perna demonstrated reduction of certain inflammatory pathways including those involving cytokines (TNF-alpha, IL-1, IL-2 and IL-6), cyclooxygenase enzyme (COX-2), and IgG (immunoglobulin G), suggesting that Perna may have a role in reducing inflammation.

**SUMMARY**

» Perna inhibited IgG production and reduced pro-inflammatory cytokines TNF-alpha, IL-1, IL-2 and IL-6 in cell culture models.

» Perna inhibits the COX-2 enzyme system.

» Results demonstrate possible mechanisms by which Perna can modulate inflammatory mediators.
An ingredient combination found in Glyco FLEX® is patented in Austria, Belgium, Switzerland/Liechtenstein, Cyprus, Germany, Denmark, Spain, Finland, France, United Kingdom, Greece, Italy, Luxembourg, Monaco, Netherlands, Portugal, Sweden, Ireland, Albania, Lithuania, Latvia, Macedonia, Romania and Slovenia. European Patent No. 1 227826.

United States Patents for DMG use include #5,026,728, 5,118,618 and 4,994,492.

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**SUPPLEMENTAL LITERATURE REFERENCES**

### Perna canaliculus


### Methylsulfonylmethane (MSM)


### Glucosamine


For a copy of an abstract from the Reference List above, please contact your VetriScience® Sales Representative.