

We are looking for relevant scientific studies, clinical trials, and systematic reviews on the following topics: 1. Joint and cartilage support in dogs o Glucosamine and chondroitin supplementation: effects on cartilage regeneration, joint mobility, and pain reduction o Comparative studies of glucosamine/chondroitin versus NSAIDs or placebo in canine osteoarthritis 2. Anti-inflammatory and analgesic effects o Willow bark (*Salix* spp.) as a natural source of salicin: efficacy and safety in pain management for dogs o MSM (Methylsulfonylmethane): role in reducing inflammation, oxidative stress, and improving joint comfort 3. Marine-based joint support o Green-lipped mussel (*Perna canaliculus*): evidence for omega-3 fatty acids, glycosaminoglycans, and anti-inflammatory compounds in canine joint health o Clinical outcomes in dogs with osteoarthritis or mobility issues 4. Herbal support for musculoskeletal health o Devil's claw (*Harpagophytum procumbens*): analgesic and anti-inflammatory properties in veterinary applications o Safety considerations, dosage, and comparison with conventional treatments 5. Synergistic effects of multi-ingredient formulations o Combination of glucosamine, chondroitin, MSM, green-lipped mussel, willow bark, and devil's claw o Evidence for improved joint mobility, reduced stiffness, enhanced quality of life, and long-term cartilage protection Please include evidence from peer-reviewed journals, veterinary clinical trials, case studies, and systematic reviews, with references provided (including DOI or PMID).

Current evidence supports NSAIDs and green-lipped mussel for canine joint health, reveals mixed outcomes for glucosamine/chondroitin supplementation, shows promise for multi-ingredient formulations, but identifies research gaps for several herbal compounds including willow bark, devil's claw, and MSM.

Abstract

Non-steroidal anti-inflammatory drugs (NSAIDs) consistently reduced osteoarthritis signs in dogs, with studies of carprofen, meloxicam, firocoxib, and etodolac reporting strong improvements in clinical symptoms. Glucosamine/chondroitin interventions yielded mixed results. For example, one trial noted significant improvements in pain, weight-bearing, and lameness, while a meta-analysis reported a negative effect (Cohen's $d = -1.39$). Marine-based support using green-lipped mussel achieved statistically significant benefits: one study found improved clinical signs by Day 56 ($p = 0.018$) and another recorded enhanced mobility (odds ratio = 8.0, $p = 0.011$), with meta-analytic effect sizes ranging from 0.58 to 1.19. In addition, a multi-ingredient formulation combining glucosamine, chondroitin, collagen, Boswellia, green tea, and hyaluronic acid resulted in marked pain reduction (p

< 0.001). No studies addressed the effects of willow bark, devil's claw, or methylsulfonylmethane.

Key findings:

1. NSAIDs show robust efficacy in reducing clinical signs of canine osteoarthritis.
2. Glucosamine/chondroitin results are inconclusive, with outcomes ranging from significant improvement to no effect.
3. Green-lipped mussel supplements enhance joint mobility and reduce pain.
4. Multi-ingredient nutraceuticals appear beneficial in selected trials.
5. Evidence on herbal agents (willow bark, devil's claw, MSM) is lacking.

Paper search

Using your research question "We are looking for relevant scientific studies, clinical trials, and systematic reviews on the following topics:

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2. Anti-inflammatory and analgesic effects o Willow bark (*Salix* spp.) as a natural source of salicin: efficacy and safety in pain management for dogs o MSM (Methylsulfonylmethane): role in reducing inflammation, oxidative stress, and improving joint comfort
3. Marine-based joint support o Green-lipped mussel (*Perna canaliculus*): evidence for omega-3 fatty acids, glycosaminoglycans, and anti-inflammatory compounds in canine joint health o Clinical outcomes in dogs with osteoarthritis or mobility issues
4. Herbal support for musculoskeletal health o Devil's claw (*Harpagophytum procumbens*): analgesic and anti-inflammatory properties in veterinary applications o Safety considerations, dosage, and comparison with conventional treatments
5. Synergistic effects of multi-ingredient formulations o Combination of glucosamine, chondroitin, MSM, green-lipped mussel, willow bark, and devil's claw o Evidence for improved joint mobility, reduced stiffness, enhanced quality of life, and long-term cartilage protection Please include evidence from peer-reviewed journals, veterinary clinical trials, case studies, and systematic reviews, with references provided (including DOI or PMID).", we searched across over 126 million academic papers from the Semantic Scholar corpus. We retrieved the 50 papers most relevant to the query.

Screening

We screened in sources that met these criteria:

- **Population:** Does this study include domestic dogs (*Canis familiaris*) as study subjects?
- **Intervention:** Does this study investigate one or more of the following compounds: glucosamine, chondroitin, willow bark/salicin, MSM, green-lipped mussel, or devil's claw (either individually or in combinations)?
- **Condition Focus:** Does this study address joint health, osteoarthritis, mobility issues, or musculoskeletal pain in dogs?
- **Outcome Measures:** Does this study report on at least one of the following outcomes: joint mobility, pain assessment, cartilage health, inflammation markers, quality of life measures, safety parameters, or clinical signs of musculoskeletal conditions?

- **Study Design:** Is this study one of the following types: randomized controlled trial, controlled clinical trial, cohort study, case-control study, case series, case study, systematic review, or meta-analysis?
- **Publication Type:** Is this a peer-reviewed journal article, veterinary clinical trial report, or systematic review (not a conference abstract, editorial, letter, or unpublished study)?
- **Duplicate Status:** Is this study reporting unique data (i.e., not a duplicate publication of the same study data already identified)?

We considered all screening questions together and made a holistic judgement about whether to screen in each paper.

Data extraction

We asked a large language model to extract each data column below from each paper. We gave the model the extraction instructions shown below for each column.

- **Study Design Type:**

Identify the specific type of study design from the full text. Look in the methods section for precise classification. Options include:

- Randomized controlled trial (RCT)
- Double-blind controlled trial
- Prospective cohort study
- Crossover study
- Case-control study

If multiple design elements are present, list all. If unclear, note "design not clearly specified". Prioritize the most specific design description available.

- **Participant Characteristics:**

Extract detailed information about study participants, focusing on:

- Species (confirm canine)
- Total number of dogs
- Age range
- Mean/median age
- Sex distribution
- Breed characteristics
- Specific health condition (e.g., osteoarthritis stage)
- Inclusion/exclusion criteria

Record numerical values with units. If ranges are provided, list both minimum and maximum. If percentages are used for sex or breed, include those as well.

- **Intervention Specifics:**

Precisely document the intervention, including:

- Specific supplement/treatment name
- Dosage (mg/kg or total daily amount)
- Frequency of administration
- Duration of intervention

- Source/manufacturer of supplement
- Preparation method (if relevant)

If multiple intervention groups exist, extract details for each group separately. Use exact wording from the text and include any standardization or extraction methods mentioned.

- **Outcome Measures:**

List all primary and secondary outcome measures, specifically focusing on:

- Mobility assessments
- Pain reduction metrics
- Joint function evaluations
- Specific measurement tools used (e.g., visual analog scales, force plate analysis)
- Statistical methods for measuring outcomes

Include units of measurement and specific scoring systems. Prioritize clinically relevant outcomes related to joint health and pain management.

- **Key Findings and Statistical Significance:**

Extract:

- Primary statistical results
- P-values for key comparisons
- Effect sizes
- Confidence intervals (if provided)
- Clinically meaningful changes in outcome measures

Prioritize results directly addressing joint health, pain reduction, and mobility. If multiple statistical tests were used, note the primary analysis method and most significant findings.

- **Safety and Side Effects:**

Document:

- Any reported adverse events
- Frequency of side effects
- Severity of side effects
- Comparative safety between intervention and control groups

If no side effects are reported, explicitly note "No adverse events reported". Be precise about the source and context of safety information.

Results

Characteristics of Included Studies

Study	Study Design	Intervention	Duration	Primary Outcomes	Full text retrieved
Aragon et al., 2007	Systematic review of clinical trials	Meloxicam, carprofen, etodolac, P54FP, polysulfated glycosaminoglycan, chondroitin/glucosamine/manganese ascorbate, pentosan polysulphate, green-lipped mussel, hyaluronan	No mention found	Quality of evidence for efficacy in canine osteoarthritis	No (abstract only)
Sandersoln et al., 2009	Systematic review	Carprofen, firocoxib, meloxicam, etodolac, glycosaminoglycan polysulphate, licofelone, elk velvet antler, green-lipped mussel, others	No mention found	Efficacy in modifying osteoarthritis signs and structure	Yes
Barbeau-Grégoire et al., 2022	Systematic review and meta-analysis	Omega-3-enriched diets, omega-3 supplements, cannabidiol, collagen, chondroitin-glucosamine	28–180 days	Analgesic efficacy, effect size, trial quality	Yes
Pollard et al., 2006	Double-blind, placebo-controlled trial with open-label extension	Green-lipped mussel extract (SF4 Dog)	56 days (plus 56-day open-label)	Clinical signs, musculoskeletal scores, owner/veterinarian assessments	Yes
Hjelm-Björkman et al., 2007	Randomized, double-blind, controlled trial	Green-lipped mussel (Lyproflex) vs. carprofen vs. placebo	8 weeks	Mobility index, pain visual analog scale, force plate, owner/veterinarian assessments	Yes

Study	Study Design	Intervention	Duration	Primary Outcomes	Full text retrieved
Mata and Dormer, 2023	Meta-analysis of case-control trials	Green-lipped mussel, chondroitin sulphate, P54FP, Zeel, omega-3s, fish oil, glucosamine/chondroitin/hyaluronic acid, cannabidiol	21–157 days	Pain, locomotion, ground reaction force, risk ratio	Yes
Martello et al., 2022	Randomized, double-blind, placebo-controlled trial	Multi-ingredient supplement (glucosamine, chondroitin, collagen, Boswellia, green tea, hyaluronic acid)	60 days	Clinical signs, Helsinki Chronic Pain Index	Yes
Rialland et al., 2013	Crossover study	Green-lipped mussel-enriched diet	60 days (after 30-day control diet)	Peak vertical force, client-specific outcome measure, motor activity	No (abstract only)
Mccarthy et al., 2007	Randomized, double-blind, positive-controlled trial	Glucosamine/chondroitin vs. carprofen	70 days (plus 28-day withdrawal)	Pain, weight-bearing, severity (veterinarian assessment)	No (abstract only)
Canapp et al., 1999	Double-blind controlled trial	Glucosamine/chondroitin (with/without S-adenosylmethionine)	20 days (pre-synovitis induction)	Nuclear scintigraphy, lameness scores	Yes

Study design:

- Systematic reviews or meta-analyses:4 studies
- Randomized or controlled trials:5 studies
- Crossover study:1 study

Interventions:

- Nutraceuticals or supplements:10 studies (including green-lipped mussel, glucosamine, chondroitin, omega-3, collagen, cannabidiol, etc.)
- Non-steroidal anti-inflammatory drugs (NSAIDs):5 studies (carprofen, meloxicam, firocoxib, etodolac, licofelone)

- Multi-ingredient supplement:1 study
- Other interventions:5 studies (Zeel, P54FP, pentosan polysulphate, S-adenosylmethionine, etc.)

Duration:

- Duration reported:7 studies (21 to 180 days)
- No mention of duration:3 studies

Primary outcomes:

- Pain or analgesic efficacy:6 studies
- Mobility, locomotion, weight-bearing, or force plate outcomes:6 studies
- Owner or veterinarian assessments:3 studies
- Quality of evidence or trial quality:3 studies
- Osteoarthritis structure modification:1 study
- Other outcomes (nuclear scintigraphy, client-specific outcome measure, Helsinki Chronic Pain Index):3 studies

Additional notes:

- Most studies evaluated more than one intervention and more than one outcome.
- We didn't find studies that only assessed NSAIDs without also including nutraceuticals or other interventions.

Effects

Joint and Cartilage Support Agents

Glucosamine and Chondroitin:

- Mixed findings across studies:
 - McCarthy et al. (2007) reported statistically significant improvements in pain, weight-bearing, and severity compared to baseline, with a slower onset of effect than carprofen (based on abstract only).
 - Canapp et al. (1999) found that pre-treatment with glucosamine/chondroitin reduced lameness and scintigraphic activity in induced synovitis.
 - Barbeau-Grégoire et al. (2022) found a marked non-effect for chondroitin-glucosamine nutraceuticals in meta-analysis (Cohen's $d = -1.39$), recommending against their use for pain management.
 - Mata and Dormer (2023) included glucosamine/chondroitin in their meta-analysis, finding an overall risk ratio of 0.62 (95% confidence interval [0.47; 0.81], $p < 0.001$) favoring nutraceuticals, but did not isolate the effect of glucosamine/chondroitin alone.

Anti-inflammatory and Analgesic Compounds

Non-steroidal Anti-inflammatory Drugs (NSAIDs):

- Consistent evidence for efficacy:
 - Systematic reviews (Aragon et al., 2007; Sandersoln et al., 2009) reported strong evidence for NSAIDs (carprofen, meloxicam, firocoxib) in reducing clinical signs of osteoarthritis.
- Willow bark and methylsulfonylmethane (MSM):
 - We didn't find studies evaluating willow bark, devil's claw, or methylsulfonylmethane (MSM) in the included literature.

Marine-based Joint Support

Green-lipped Mussel (*Perna canaliculus*):

- Multiple studies support efficacy:
 - Pollard et al. (2006) found significant improvement in clinical signs by Day 56 ($p=0.018$), with sustained benefit on long-term administration.
 - Hielm-Björkman et al. (2007) reported significant improvements in mobility and pain (odds ratio for pain visual analog scale = 8.0, 95% confidence interval 1.52–42.04, $p=0.011$), with green-lipped mussel more effective than placebo but less than carprofen.
 - Rialland et al. (2013) observed significant improvements in peak vertical force ($p=0.003$), client-specific outcome measure ($p=0.006$), and motor activity ($p=0.02$) (abstract only).
 - Barbeau-Grégoire et al. (2022) and Mata and Dormer (2023) both found moderate to large effect sizes for omega-3-enriched diets and green-lipped mussel-based nutraceuticals (Cohen's $d = 0.58$ – 1.19).

Herbal Musculoskeletal Support

- No studies found: We didn't find studies evaluating willow bark, devil's claw, or methylsulfonylmethane (MSM) in the included literature.

Multi-ingredient Formulations

- Some evidence for benefit:
 - Martello et al. (2022) tested a supplement containing glucosamine, chondroitin, collagen, Boswellia, green tea, and hyaluronic acid, finding significant improvements in clinical signs and pain (Wilcoxon signed-rank test, $p<0.001$).
 - Mata and Dormer (2023) included multi-ingredient formulations in their meta-analysis, contributing to the overall positive risk ratio for nutraceuticals.

Adverse Effects and Safety Considerations

Study	Intervention	Effect Size	Statistical Significance	Clinical Relevance
Aragon et al., 2007	Multiple (NSAIDs, nutraceuticals)	No mention found	No mention found	High comfort for meloxicam; moderate for carprofen, green-lipped mussel, chondroitin/glucosamine
Sandersoln et al., 2009	Multiple	No mention found	No mention found	Strong evidence for NSAIDs; moderate for green-lipped mussel, glycosaminoglycan polysulphate

Study	Intervention	Effect Size	Statistical Significance	Clinical Relevance
Barbeau-Grégoire et al., 2022	Omega-3, green-lipped mussel, chondroitin/glucosamine	Cohen's d = 0.58–1.19 (omega-3/green-lipped mussel); d = -1.39 (chondroitin/glucosamine)	p=0.013, p=0.003 (green-lipped mussel)	Omega-3/green-lipped mussel effective; chondroitin/glucosamine not effective
Pollard et al., 2006	Green-lipped mussel extract	No mention found	p=0.018 (Day 56)	Significant improvement in clinical signs
Hjelm-Björkman et al., 2007	Green-lipped mussel	Odds ratio = 8.0 (pain visual analog scale)	p=0.011 (pain visual analog scale)	Green-lipped mussel more effective than placebo, less than carprofen
Mata and Dormer, 2023	Multiple nutraceuticals	Risk ratio = 0.62 (95% confidence interval [0.47; 0.81])	p<0.001	Nutraceuticals effective overall
Martello et al., 2022	Multi-ingredient supplement	No mention found	p<0.001	Significant reduction in pain and clinical signs
Rialland et al., 2013	Green-lipped mussel diet	No mention found	p=0.003 (peak vertical force), p=0.006 (client-specific outcome measure)	Improved mobility and pain
Mccarthy et al., 2007	Glucosamine/chondroitin	No mention found	p<0.001	Significant improvement in pain, weight-bearing
Canapp et al., 1999	Glucosamine/chondroitin	No mention found	p=0.01–0.04	Reduced lameness and inflammation

Effect size reporting:

- Quantitative effect size found:3 of 10 studies (1 reported Cohen's d, 1 reported odds ratio, 1 reported risk ratio)
- No quantitative effect size found:7 of 10 studies

Statistical significance:

- Statistical significance reported:8 of 10 studies
 - 3 reported p<0.001
 - 1 reported p=0.003
 - 1 reported p=0.006
 - 1 reported p=0.011
 - 1 reported p=0.013

- 1 reported $p=0.018$
- 1 reported $p=0.01-0.04$
- No statistical significance statement found: 2 of 10 studies

Clinical relevance:

- Statement of clinical effectiveness: 7 of 10 studies (described as "effective," "significant improvement," or similar)
- Statement of "not effective": 1 of 10 studies
- Statement of moderate or partial effect: 3 of 10 studies
- No clinical relevance statement found: 0 studies

Summary:

- Most studies reported statistically significant and clinically relevant effects for at least some interventions, but only 3 of 10 studies reported a quantitative effect size.

Discussion

- Strongest evidence: The included studies report the most consistent evidence for non-steroidal anti-inflammatory drugs (NSAIDs) and marine-based supplements (green-lipped mussel, omega-3 fatty acids) in managing canine osteoarthritis, with multiple systematic reviews and randomized controlled trials supporting efficacy.
- Glucosamine/chondroitin: Findings are mixed. Some randomized controlled trials reported significant improvements, but recent meta-analyses found no effect or recommended against their use for pain management.
- Multi-ingredient formulations: The studies that evaluated these reported some benefit, but the number of studies is limited.
- Herbal agents: We didn't find studies evaluating willow bark, devil's claw, or methylsulfonylmethane (MSM) in the included literature, despite their frequent inclusion in commercial joint supplements.
- Safety: Across the included studies, we didn't find mention of significant adverse events for nutraceuticals or marine-based agents in the available full texts or abstracts.
- Limitations:
 - Heterogeneity: There was substantial variation in study designs, interventions, and outcome measures.
 - Evidence gaps: No studies were found on several herbal agents of interest (willow bark, devil's claw, methylsulfonylmethane).
 - Generalizability: Findings are most applicable to osteoarthritis in client-owned dogs; less is known about other joint conditions or unstudied herbal agents.

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