

NUTRACEUTICALS IN VETERINARY MEDICINE WITH SPECIAL EMPHASIS ON OSTEOARTHRITIS



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Nutraceuticals in Animals

According to North American Veterinary Nutraceutical Council, Inc.

A veterinary nutraceutical is defined as:

“A substance which is produced in a purified or extracted form and administered orally to patients to provide agents for normal body structure and function and administered with the intent of improving the health and well-being of animals.”

Improvement of health

Prevention and treatment of diseases

Some Facts About Nutraceuticals

- **Nutraceuticals are from Nature's Basket**
- **Nutraceuticals have been used for thousands of years. "Let Food Be Thy Medicine" (Hippocrates).**
- **Currently, nutraceutical industry is worth \$250 billion a year.**
- **About 80% of people outside the US and Europe consume one or more nutraceuticals.**



Some Facts About Nutraceuticals (Cont.)

- **Approximately 150 million Americans consume at least one dietary supplement daily.**
- **Nutraceuticals are cost effective compared to pharmaceuticals.**
- **In general, most nutraceuticals are effective and well tolerated with a wide margin of safety. Fear factor of side effects is little.**
- **Unlike foods, nutraceuticals are not generally recognized as safe, nor can one assume that they are all safe.**
- **> 50% FDA approved drugs are from plant or other biological sources.**

Common Nutraceuticals

- Curcumin/Turmeric
- Ginseng (Korean, Chinese, etc)
- Fenugreek
- Astaxanthin
- Shilajit
- Anthocyanins
- Glucosamine HCl/sulfate
- Chondroitin sulfate
- Quercetin
- Amla (*Phyllanthus emblica*)
- *Boswellia serrata*
- Type II collagen
- Methylsulfonylmethane (MSM)
- Hyaluronic acid (Hyaluronan)
- Green tea extract
- *Ashwagandha* (Indian ginseng)
- Krill oil fatty acids
- *Terminalia chebula*
- Resveratrol
- Omega-3 fatty acids
- Chromium³⁺
- St. John's wort
- *Ginkgo biloba*
- *Cannabis sativa*
- Berberine
- *Garcinia cambogia*
- Green lipped mussels
- Devil's claw

Nutraceuticals with Toxic Potential

- Goldenseal
- *Ginkgo biloba*
- Green tea extract
- Green coffee bean/caffeine
- *Garcinia cambogia*
- *Aloe vera*
- Bitter melon
- Kava kava
- St. John's wort
- Ephedrine alkaloids
- Pennyroyal oil
- Pequi almond oil
- Black Kohosh

*Gupta RC, Srivastava A, Lall R (2018)
Toxicity potential of nutraceuticals.
Chapter-18. Edited by Orazio Nicolotti.*



Nutraceuticals Used in Common Diseases

- Arthritis
- Obesity, metabolic syndrome, and diabetes
- GI, hepatic, renal, cardiovascular or respiratory dysfunction
- Neurodegenerative diseases
- Depression or anxiety
- Allergies and Dermatitis

**Most nutraceuticals exert antioxidant, anti-inflammatory, immunomodulatory and cytoprotective effects.*

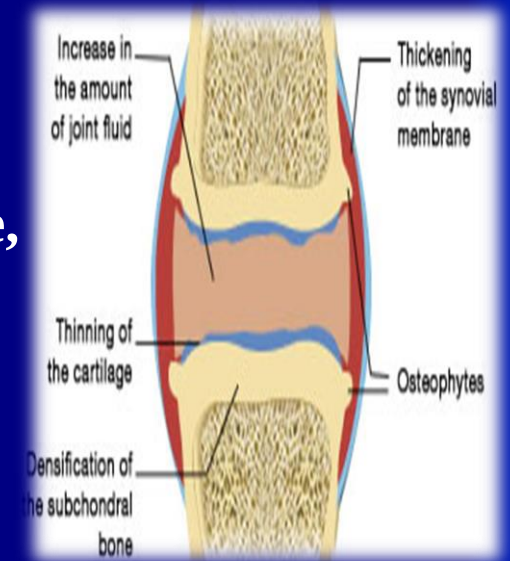
**In OA, chondroprotective effect*

Nutraceuticals Used in Joint Health

- Glucosamine HCl/sulfate
- Chondroitin sulfate
- Curcumin/Turmeric
- Shilajit (herbo-mineral)
- Amla (*Phyllanthus emblica*)
- *Boswellia serrata*
- Type II collagen
- Hyaluronan
- *Terminalia chebula*
- Eggshell membrane
- C-Phycocyanin
- Avocado/Soybean (ASU)
- Resveratrol
- Chromium³⁺
- Methylsulfonylmethane (MSM)
- Krill oil fatty acids
- Omega-3 fatty acids
- *Cannabis sativa/Hemp*
- Green lipped mussels
- Devil's claw
- Vitamin E

Osteoarthritis (OA)

- *OA is an inflammatory joint disease characterized by chronic and progressive cartilage degeneration, osteophyte formation, subchondral sclerosis, bone marrow lesions, hypertrophy of bone at the margin, and changes in the synovial membrane.*
- **Is OA one disease or combination of diseases?**
- **OA is a disease which not only affects cartilage, but the entire joint and surrounding muscles.**
- **Cartilage has no blood supply or nerve supply, and gets nutrition from the joint fluid.**



Osteoarthritis (OA)

- **OA commonly affects humans, dogs, and horses.**
- **OA affects 20% of the adult and 80% of the geriatric population in the US.**
- **Approximately 70-80% of arthritic patients are obese.**
- **Severely affected humans and animals are unable to walk and limited in their daily activities.**
- **Causes of arthritis include:**
 - **Aging, injury, excessive or lack of exercise, nutritional deficiency, obesity, genetic predisposition, infection, etc.**

The Current Canine Population

The global dog population is estimated at 900 million!

- United States: >90 million
- Russia: 15.9 million
- Germany: 8.6 million
- UK: 8.5 million
- France: 7.3 million
- Italy: 7 million
- Spain: 5.3 million
- Sweden: 5.1 million

Dog Breeds Predisposed to OA



**Large breed dogs are more prone (>45%)
to develop OA than smaller breed dogs.**

The Current Equine Population

The global horse population is estimated at 60 million!

- **North America: 19.5 million**
- **Asia: 14.3 million**
- **South America: 13.3 million**
- **Africa: 6 million**
- **Europe: 5.7 million**
- **Oceania**
(Australia, New Zealand): 400,00
- **United States: 10.26 million**
- **Mexico: 6.35 million**
- **Brazil: 5.45 million**
- **Spain: 600,000**
- **UK: 400,000**

Pathophysiology of OA

1

- Imbalance of anabolic and catabolic processes in the joint. Enzymes produced in chondrocytes digest the ECM, leading to erosion of the cartilage.
- In OA cartilage, the number of chondrocytes and their ability to regenerate the EMC are reduced.
- The nucleotide-binding and oligomerization domain-like receptor containing protein 3 (NLRP3) inflammasome.
- Chondrocytes in damaged cartilage overproduce and release cytokines (IL-1 β and IL-6) and transcription factor TNF- α .

2

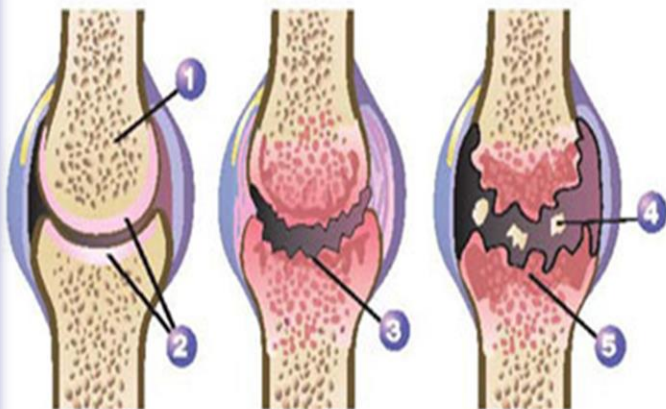
- NMDAR subunit N2B appears to regulate chondrocytes intrinsic function.
- Stimulation of MAPK and its phosphorylation, matrix metalloproteinases (MMP-1, MMP-3, MMP-10, and MMP-13), aggrecanases, iNOS, COX-2, phospholipase 2A, and platelet activating factor (PAF).
- Mitochondrial damage and dysfunction.
- Excess production of ROS, RNS, and PGE₂.

3

- Cause inflammation, subchondral bone thickening, breakdown and depletion of cartilage-specific type II collagen and proteoglycan.
- Ultimately, loss of cartilage structure and function.
- Is chondroptosis a cause or effect of cartilage destruction?

Pathophysiology of OA

Evolution of Osteoarthritis

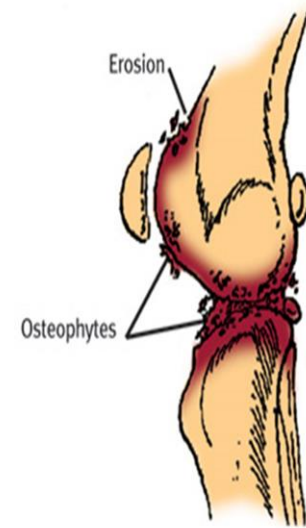


1. Bone
2. Cartilage
3. Thinning of cartilage
4. Cartilage remnants
5. Destruction of cartilage

The Canine Stifle (Knee)



NORMAL BONES



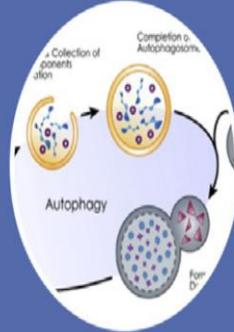
OSTEOARTHRITIS

Pathophysiology of OA



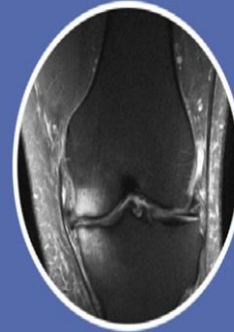
Primary causes

- Joint injury & altered biomechanics
- Ageing
- Systemic metabolic derangement



Secondary causes (mediators)

- Inflammation
- Altered cellular and organelle metabolism
- Circadian rhythm
- Calcium signaling



Outcomes

- Joint tissue damage
- Pain & pain sensitization
- Osteophytes
- Bone marrow lesions

Continuum of OA biology

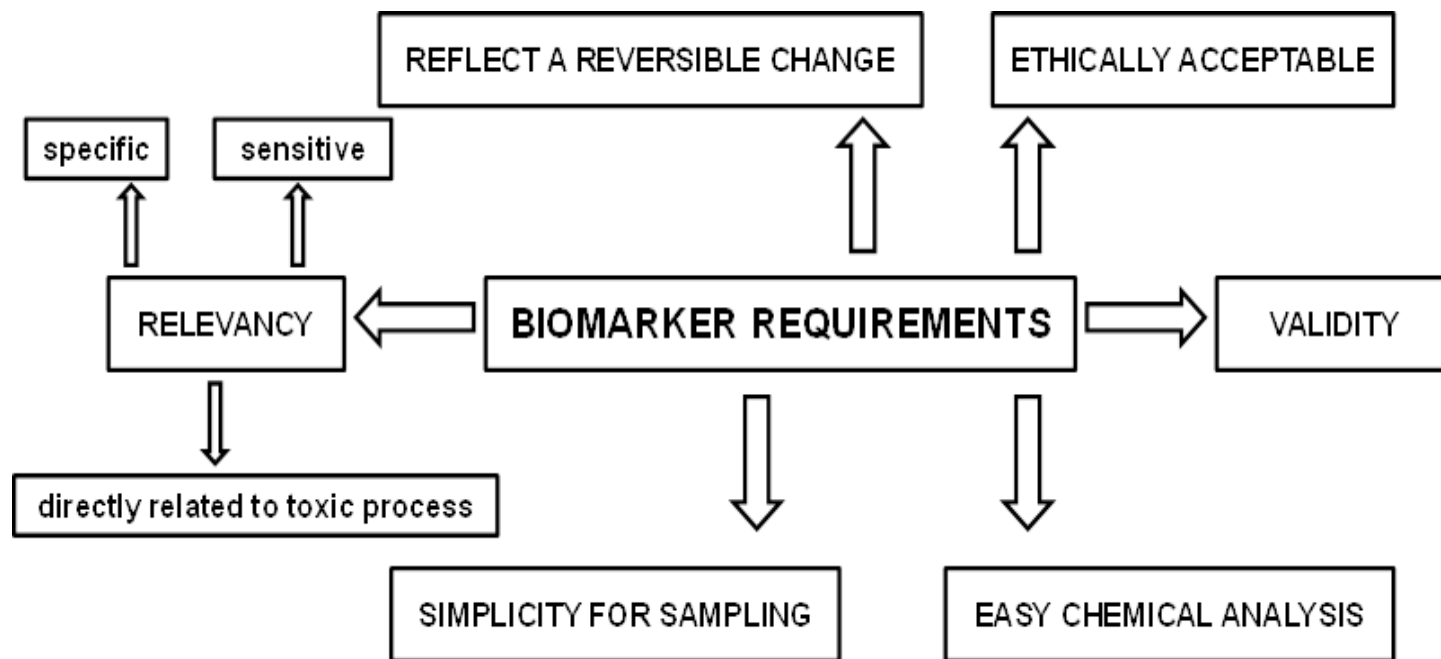
Source: Osteoarthritis and Cartilage

Symptoms of OA

- Pain upon manipulation of the joint and limb
- Decreased stability, mobility, and loading
- Stiffness of joints
- Palpable effusion
- Bone rubbing against bone
- Crepitus (popping and cracking of the joint)

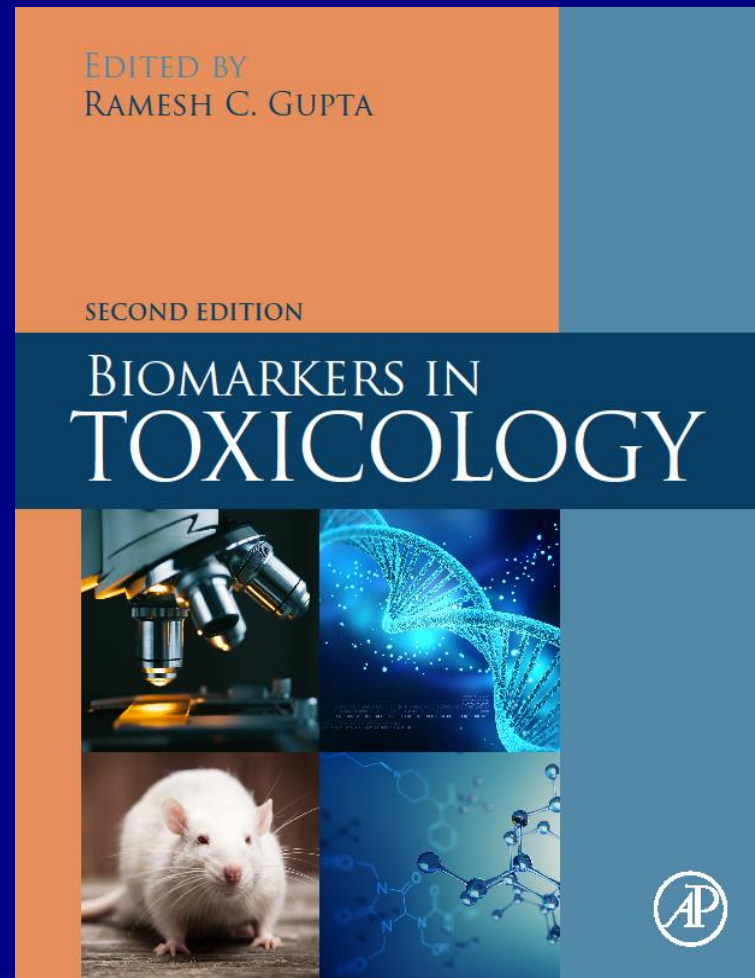
BIOMARKERS OF OA?

Biomarkers are indicators or measurable changes at the molecular, biochemical, cellular, physiological, morphological, or behavioral level in response to a disease or xenobiotic.



BIOMARKERS OF OA (Cont.)

- *Gupta, Srivastava, Lall & Sinha (2019) Osteoarthritis biomarkers. Biomarkers in Toxicology. Chapter-52.*
- Cytokines, TNF- α , TSG-6, COMP, MMPs, Type I and type II collagen, PGE2, C-RP, fractalkine, ghrelin, hyaluronan, lubricin, etc.
- Radiographic findings
- miRNAs and lincRNAs
 1. Diagnosis
 2. Prognosis
 3. Therapeutic progress



BIOMARKERS (miRNAs)

Tissue-Specific miRNA	Target Organ
miR-122	Liver
miR-192	Liver & GIT
miR-1, miR-133a, miR-133b	Muscle
miR-206	Skeletal muscle
miR-208	Heart
miR-216a, miR-216b, miR-217	Pancreas
miR-9, miR-124a, miR-323	Brain
miR-126	Vascular
miR-140	Human cartilage
miR-98	Rat cartilage
miR-9, miR-16, miR-22, miR-33a; miR-92a-3p; miR-98; miR-370; miR-140; miR146a, miR-222, miR-373; miR-16-5p; miR-26a-5p; and miR-634.	Osteoarthritis

BIOMARKERS OF OA (Cont.)

- *Gupta, Srivastava, Lall & Sinha (2019) Osteoarthritis biomarkers. Biomarkers in Toxicology. Chapter-52.*
- Classification of OA Biomarkers using **BIPED**:
 - B**urden of disease
 - I**nvestigative
 - P**rognostic
 - E**fficacy of intervention
 - D**iagnostic
- 1. Biomarkers of oxidative/nitrosative stress
- 2. Biomarkers of inflammation and pain
- 3. Biomarkers of cartilage degeneration and loss, and imaging
- 4. Circulatory, synovial fluid, and urine biomarkers

Source: *Osteoarthritis and Cartilage*

Diagnosis of OA

Signs and symptoms:

Pain associated with inflammation

- 1. Pain measurement by observation**
- 2. Pain measurement by Ground Force Plate**

Radiographic findings:

Narrowing of joint space

Destruction of cartilage

Cartilage fragments in the joint space

Osteophyte formation

Objectives in Managing & Treating OA

1

- Alleviate symptoms of OA-associated pain & immobility

2

- Slow the progression of OA

3

- Increase functionality/mobility, and thereby improve the quality of life

Managing & Treating OA (Cont)

Ideally a nutraceutical for OA should provide:

- Improvement of clinical signs
- Restoration of homeostasis in joints
- Restoration of viscoelasticity
- Restoration of lubrication
- Anti-oxidative/anti-nitrosative
- Anti-inflammatory
- Analgesic
- Chondroprotective/anti-chondroptosis
- Enhancement of anabolic processes
- Inhibition of catabolic processes
- Reversal of molecular pathogenesis as a basis of OA treatment: *Kim et al (2018) Int J Mol Sci 19: 674.*

Managing & Treating OA (Cont)

Traditional treatment involves:

- NSAIDs (COX inhibitors)
- Drugs (grapiprant, diacerein, tramadol, etc)
- Physiotherapy
- Surgery (joint replacement)
- Acupuncture
- Lifestyle changes (diet, exercise, weight loss, etc.)

NSAIDs

- **Common NSAIDs:**
 - **Carprofen (Rimadyl)**
 - **Diclofenac (Voltaren)**
 - **Meloxicam (Metacam)**
 - **Firocoxib (Previcox)**
 - **Mavacoxib (Trocoxil)**
 - **Celecoxib- Selective COX-2 inhibitor**
 - **Rofecoxib (Vioxx) = withdrawn**
 - **Side effects:**
 - **GI, cardiac, hepatic and renal dysfunction**
 - **Reduced appetite and vomiting**
 - **Inhibit bone healing**
- *NSAIDs cause >100,000 hospitalizations and 1,600 deaths among arthritis patients each year.**

Pain Assessment

- In clinical trials, on a monthly basis, each dog/horse is evaluated for OA associated pain for a period of five months, using a Glasgow scoring system.

1

- Overall Pain

2

- Pain Upon Limb Manipulation

3

- Pain After Physical Exertion

Overall Pain

Measured on a scale of 0-10 to provide a broad range of inclusion of daily activities:

No Pain = 0

Mild Pain = 2.5

Moderate Pain = 5

Severe Pain = 7.5

Severe and Constant Pain = 10

Pain Upon Limb Manipulation

- Limbs are manipulated in a forward, backward, and circular motion.
- The three joints for evaluation include shoulder joint, elbow joint, and stifle joint.
- Each dog is evaluated for crepitus (popping and cracking of the joint), as well as vocalization due to pain.
- Measured on a scale of 0-4:

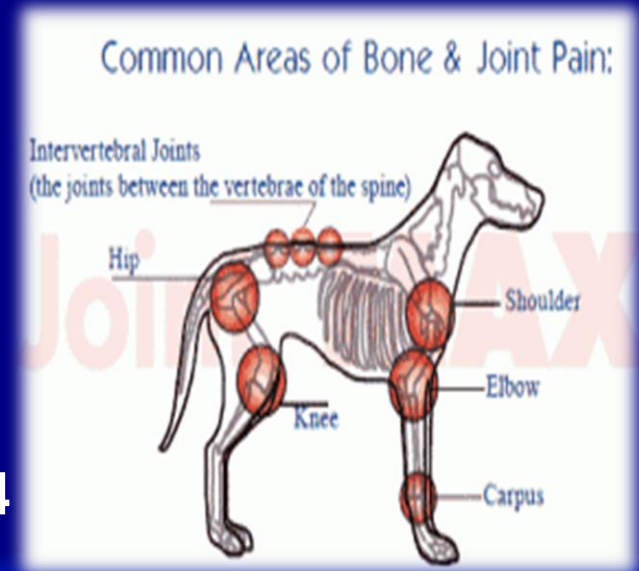
No Pain = 0

Mild Pain = 1

Moderate Pain = 2

Severe Pain = 3

Severe and Constant Pain = 4



Pain Upon Physical Exertion

- **Dog is exercised for 2-5 minutes and re-evaluated for pain.**
- **Measured on a scale of 0-4:**
 - No Pain = 0**
 - Mild Pain = 1**
 - Moderate Pain = 2**
 - Severe Pain = 3**
 - Severe and Constant Pain = 4**

Dogs/Horses are considered moderately arthritic if:

- **Overall Pain = 4-6**
- **Pain upon limb manipulation = 2-2.5**
- **Pain after physical exertion = 2-2.5**

Ground Force Plate

- Quantitatively measures lameness-associated pain in each leg.
- System consists of plates, sensors, and a computer.
- Parameters:
 - Peak vertical force (N/kg body weight)
 - Impulse area (N s/kg body weight)



Gupta RC, et al (2012) J. Anim Physiol & Anim Nutr. 96: 770-777.

Glucosamine and Chondroitin

- **Glu HCl and CS are the most commonly used supplements in OA due to their efficacy, safety, and low cost.**
Doses: Dogs: Glu HCl (2g/day) and CS (1.6g/day) for 150 days.
Horses: Glu HCl (5.4 g) and CS (1.8 g) twice daily for the 1st month, and once daily thereafter for 150 days.
- **Both are components of the extracellular matrix (ECM) of articular cartilage.**
- **Glu is considered as a building block of cartilage because it is involved in the normal growth and repair of cartilage.**
- **Glu reduces expression of MMPs (MMP-1, MMP-3, and MMP-13).**
- **CS is a sulfated GAG, and a constituent of aggrecan, the major proteoglycan of articular cartilage.**

Glucosamine and Chondroitin

In combination, these two supplements offer synergistic effects:

- Suppress the synthesis of iNOS, COX-2, PGEs, and NFκB, thereby reducing NO and PGE₂ levels, and exert antioxidative/antinitrosative and anti-inflammatory effects.
- Increase synthesis of hyaluronan/proteoglycan and collagen.
- Stimulate chondrocyte metabolism, thereby providing chondroprotective and cartilage repair effects.
- Provide hydration and cushioning effect, reducing the progression of OA and joint pain and improving joint mobility.
- Found to be safe and well tolerated in OA dogs and horses.

Type II Collagen

- **The main collagen component of hyaline cartilage.**

Dose:

Dogs: 10 mg/day for 150 days.

Horses: 120 -160 mg/day for 150 days

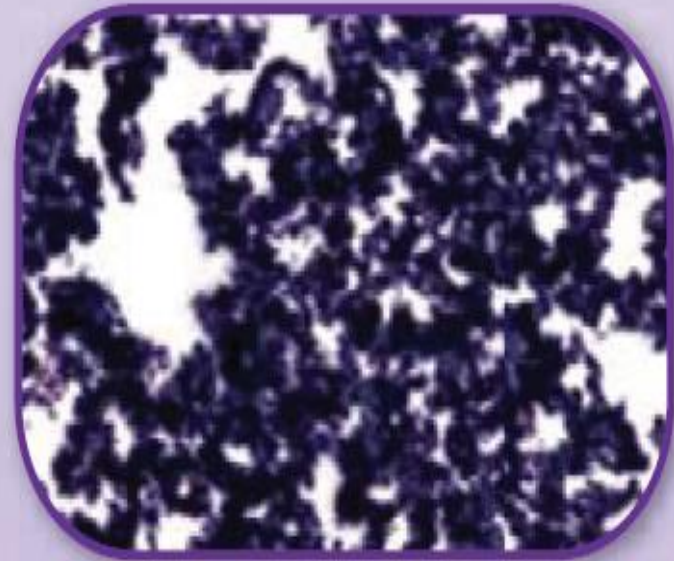
- **Functions through a process called oral tolerization, which takes place in the small intestine where food is being absorbed.**
- **It prevents the immune system from attacking and damaging its own joint cartilage.**
- **It reduces inflammation and pain associated with OA, and improves joint mobility and flexibility.**
- **Safe and well tolerated in OA dogs and horses.**

Type II Collagen

Electron microscopy photographs of *undenatured* vs. denatured type II collagen.

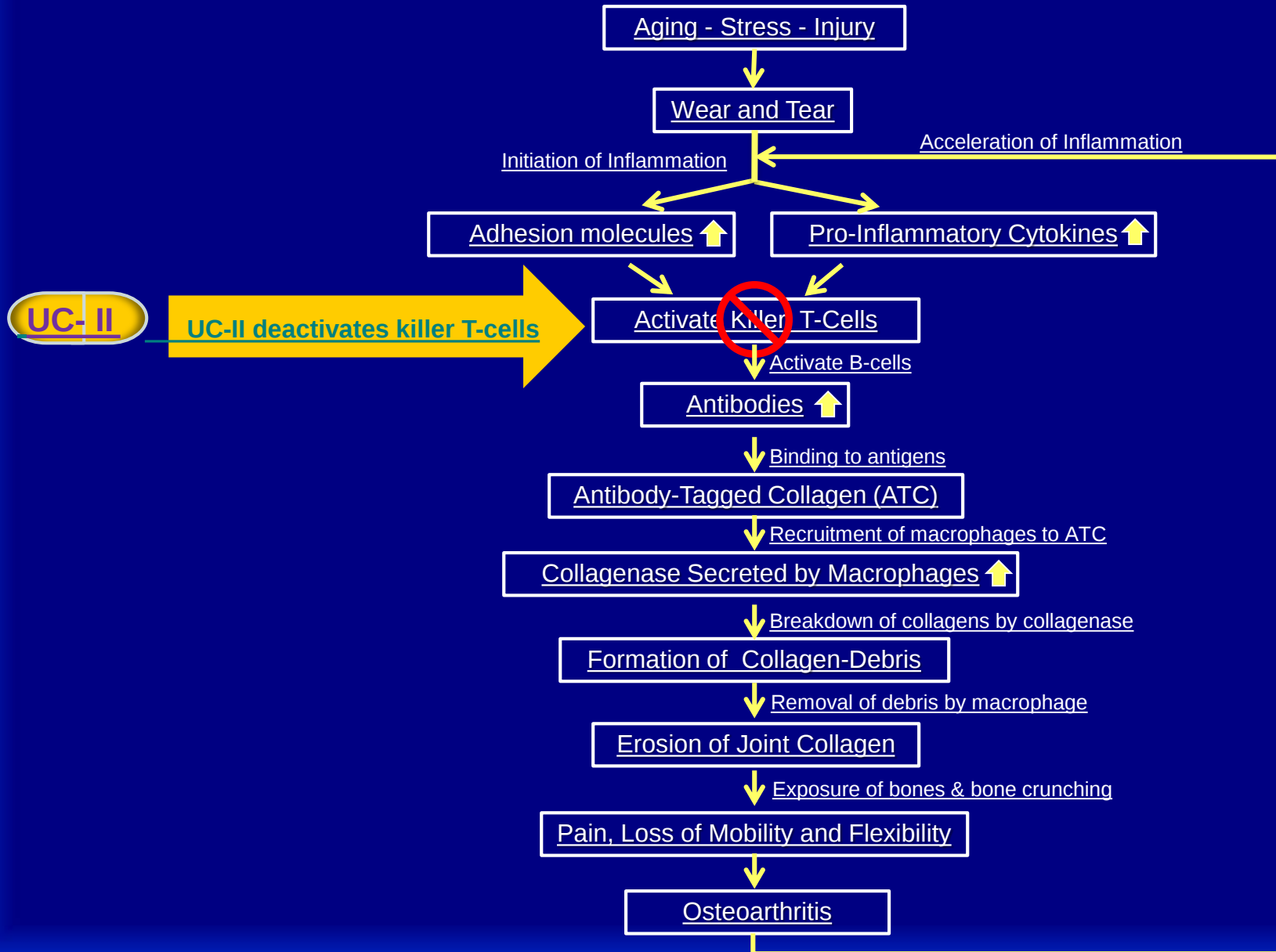


UC-II® *Undenatured*

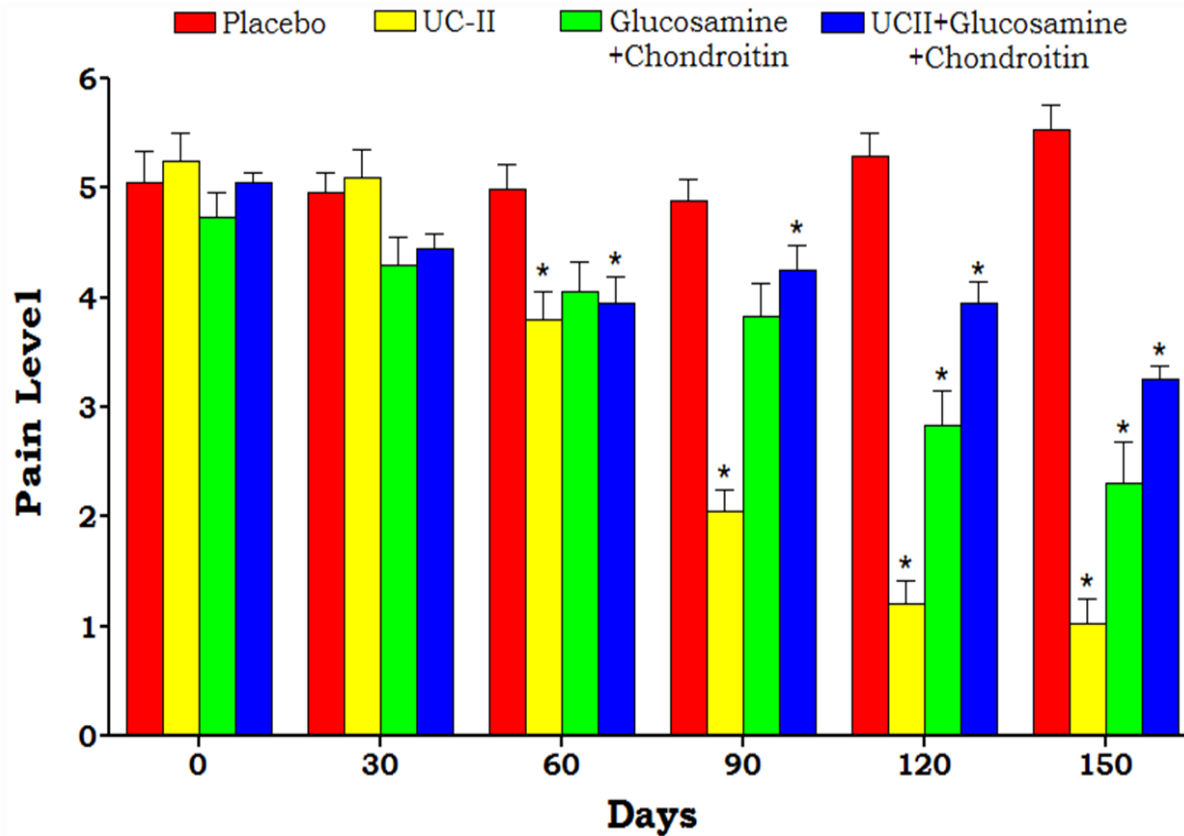


Brand X Denatured

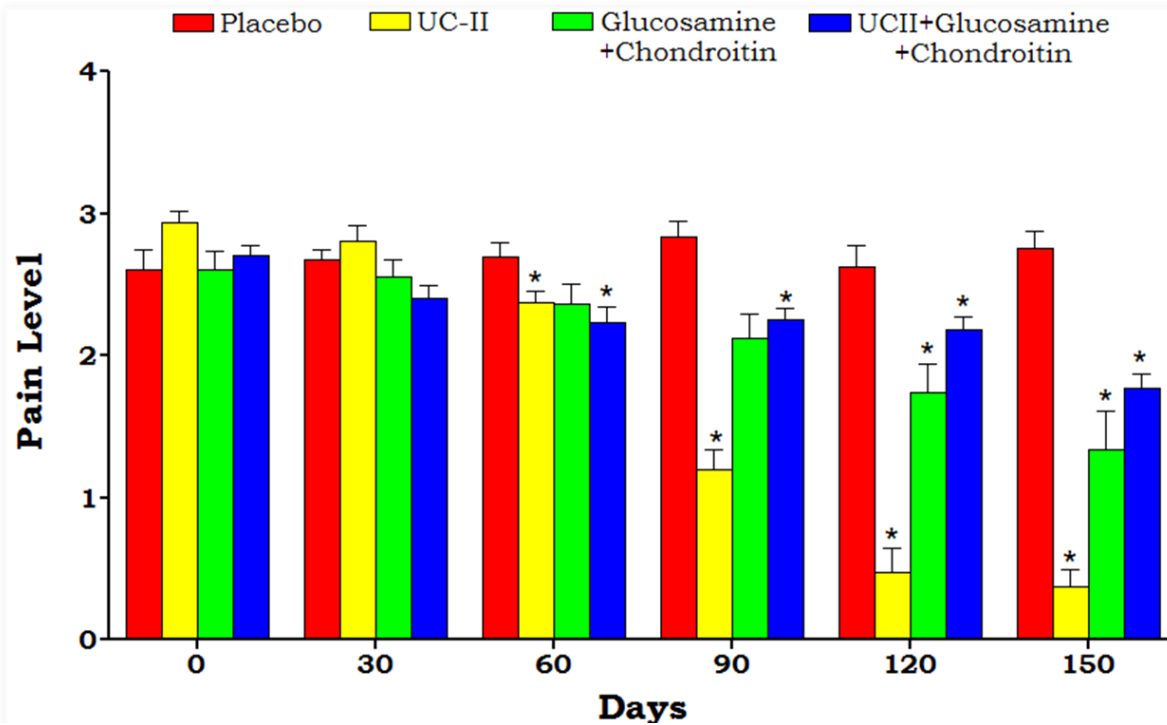
Mechanism of Action of UC-II in OA



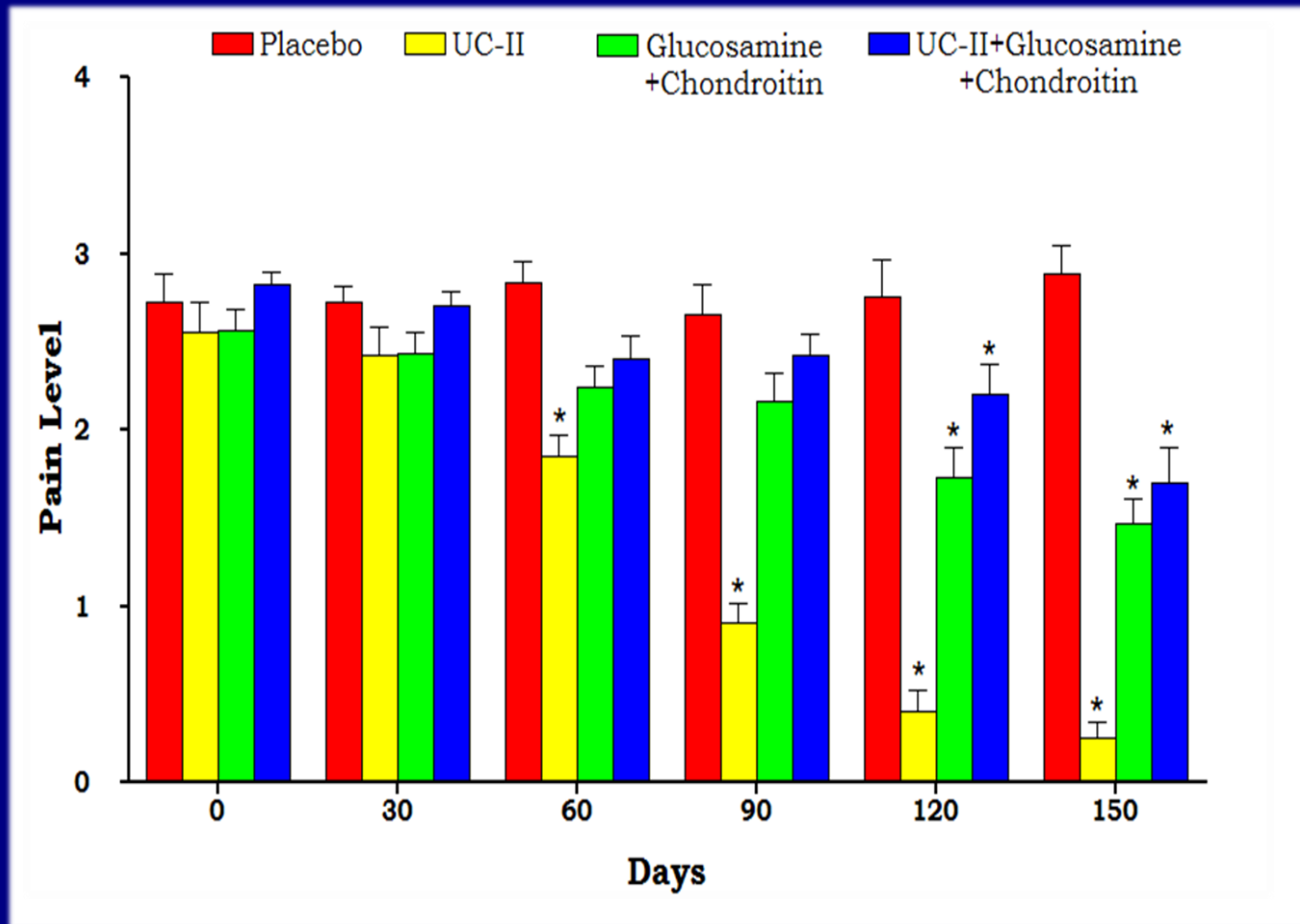
Overall Pain



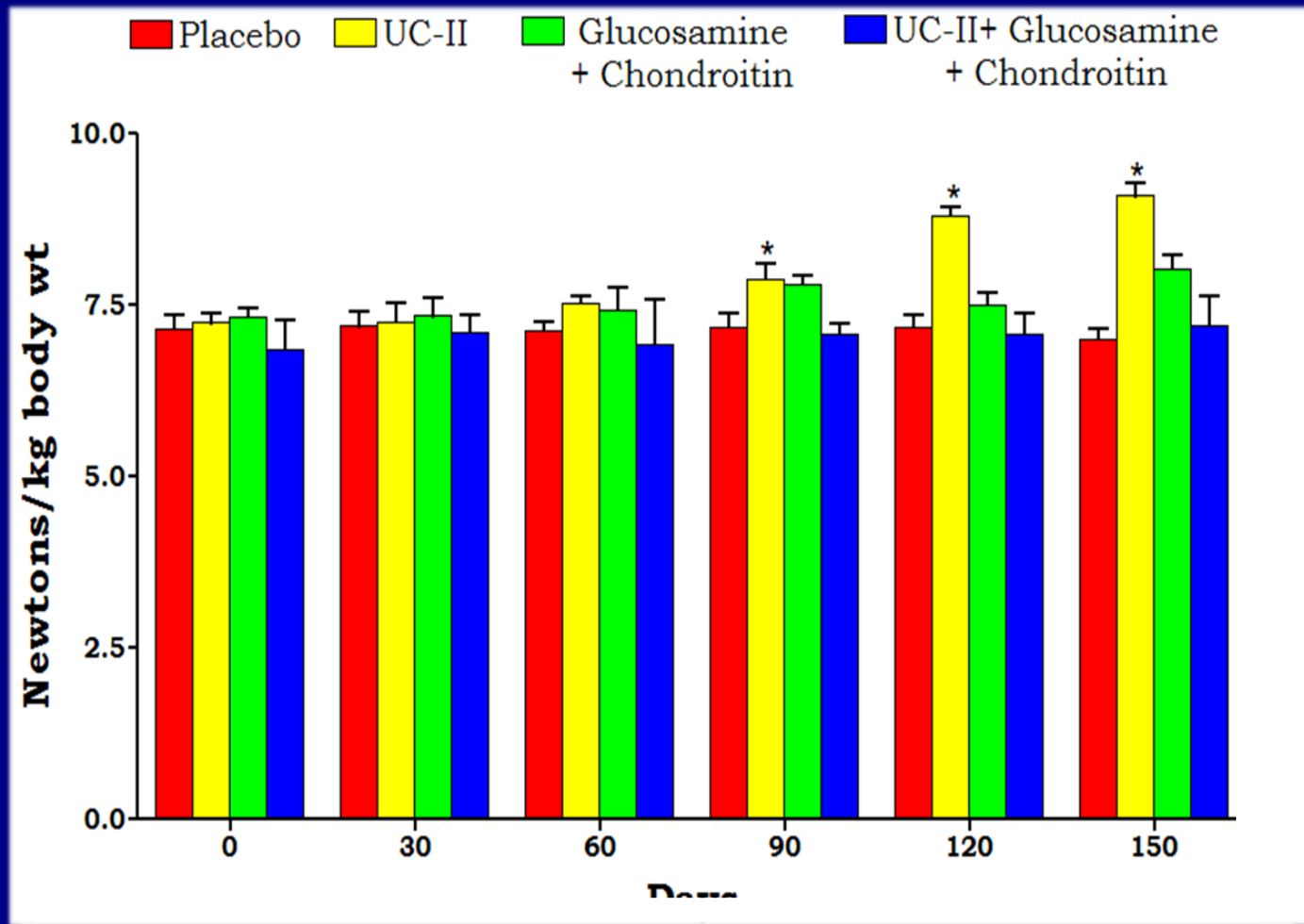
Pain Upon Limb Manipulation



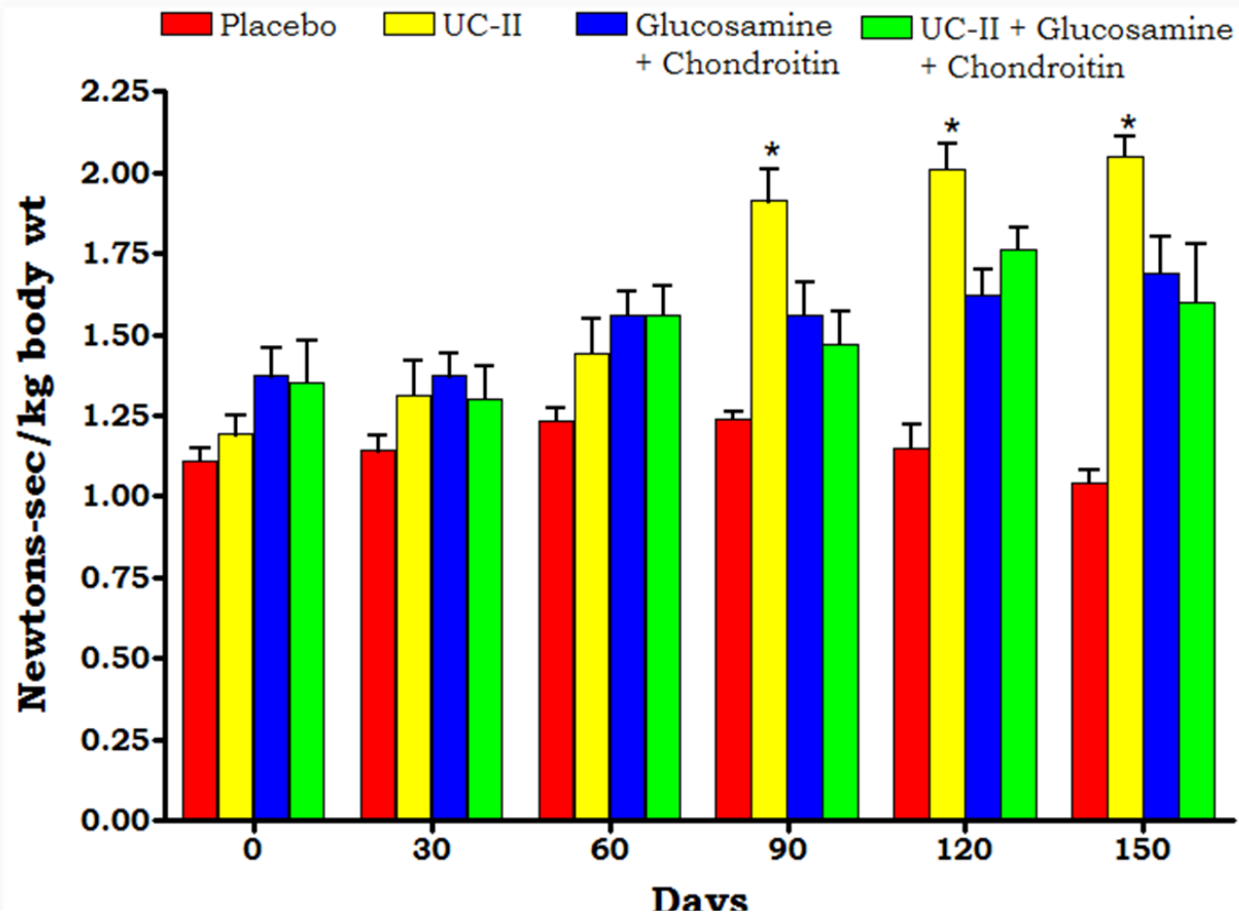
Pain After Physical Exertion



GFP: Peak Vertical Force



GFP: Impulse Area



Gupta RC, et al (2012) J Anim Physiol & Anim Nutr. 96: 770-777.

Type II Collagen Alone or in Combination with GLU & CS

DeParle LA et al (2005) J Vet Pharmacol Ther. 28: 385-390.

D'Altilio M, et al (2007) Toxicol Mech Methods. 17(4): 189-196.

Peal A, et al (2007) J Vet Pharmacol Ther. 30(3): 275-278.

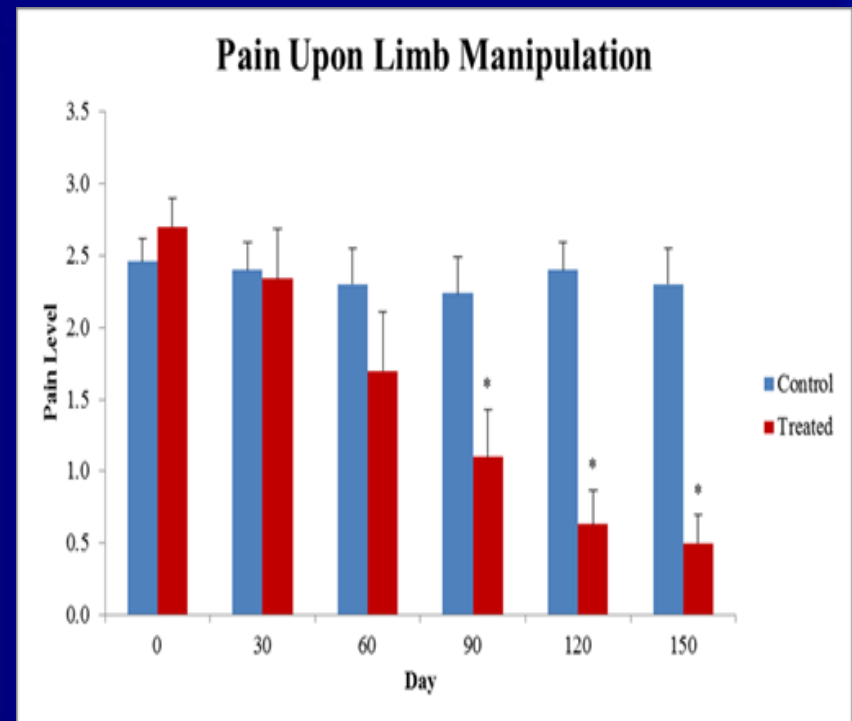
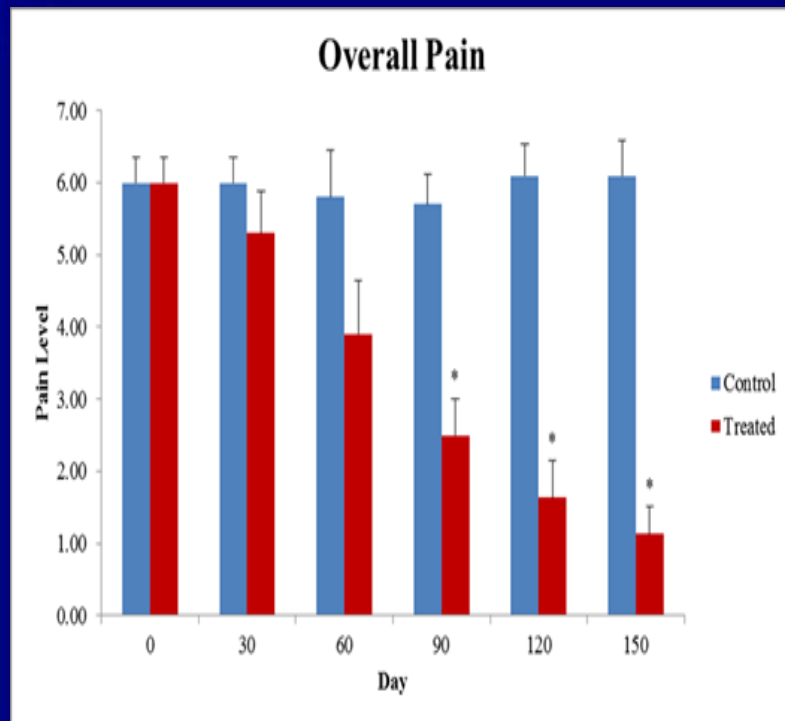
Gupta RC, et al (2009) J Vet Pharmacol Ther. 32: 577-584.

Marone PA, et al (2010) Toxicol Mech Methods. 20(4): 175-189.

Gupta RC, et al (2012) Anim Physiol Anim Nutr. 96: 770-777.

Terminalia chebula Extract (TCE) in Dogs

TCE has many active principles (chebulagic acid, chebulinic acid, corilagin, hydrolysable tannoids, etc). Dose: 500 mg bid for 150 days.



***Terminalia chebula* Extract (TCE)**

Effect of TCE on ESR

Parameter	Control/ Treated	Day 0	Day 30	Day 60	Day 90	Day 120	Day 150
ESR	Control	4.00 ± 2.01	3.80 ± 2.06	4.30 ± 2.43	4.30 ± 2.68	7.20 ± 5.70	5.20 ± 3.45
	Treated	2.40 ± 0.68	2.00 ± 0.32	1.20 ± 0.37	1.30 ± 0.77	0.63 ± 0.47 *	0.38 ± 0.38 *

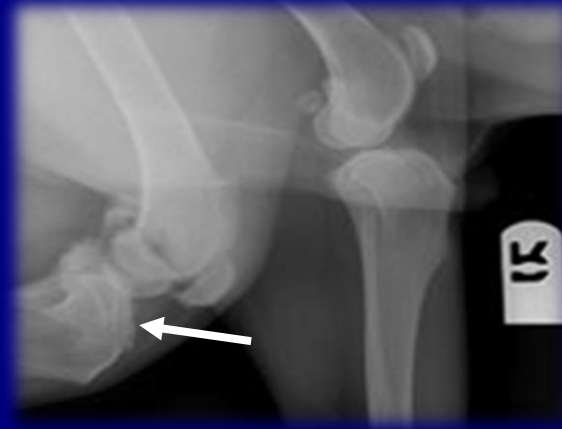
*** Values are significantly different from Day 0 (P < 0.05).**

Radiographic Evidence

Radiographs of the left stifle of a dog on placebo has exostosis involving the distal femur, proximal tibia, and patella.



Day 0



Day 150

Radiographic Evidence (cont.)

Radiographs of the right humero-radial joint (elbow) of a dog receiving *T. chebula* extract showed a slowed progression of bone formation in a typical arthritic joint.



Day 0



Day 150

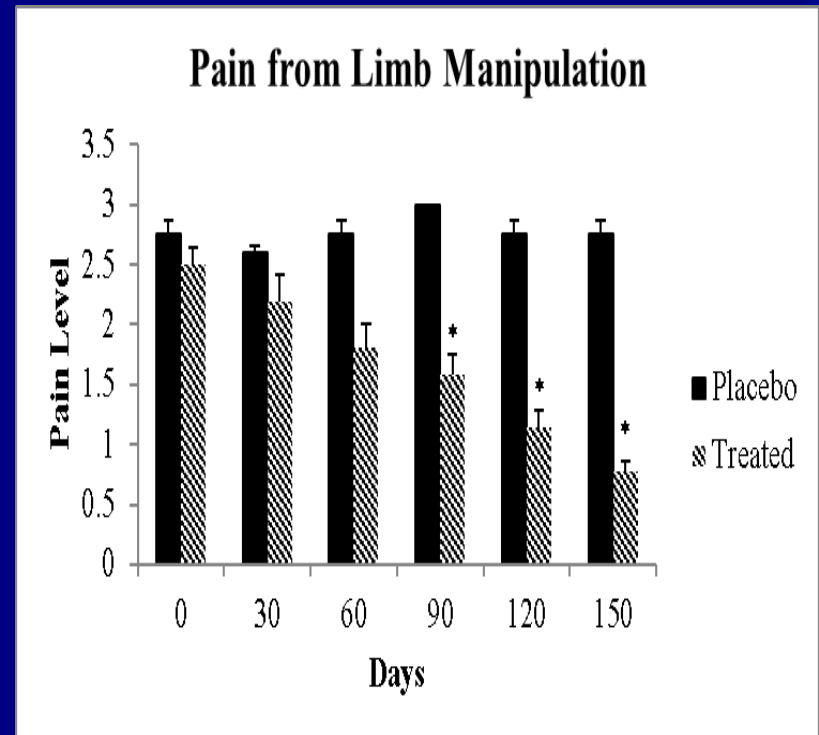
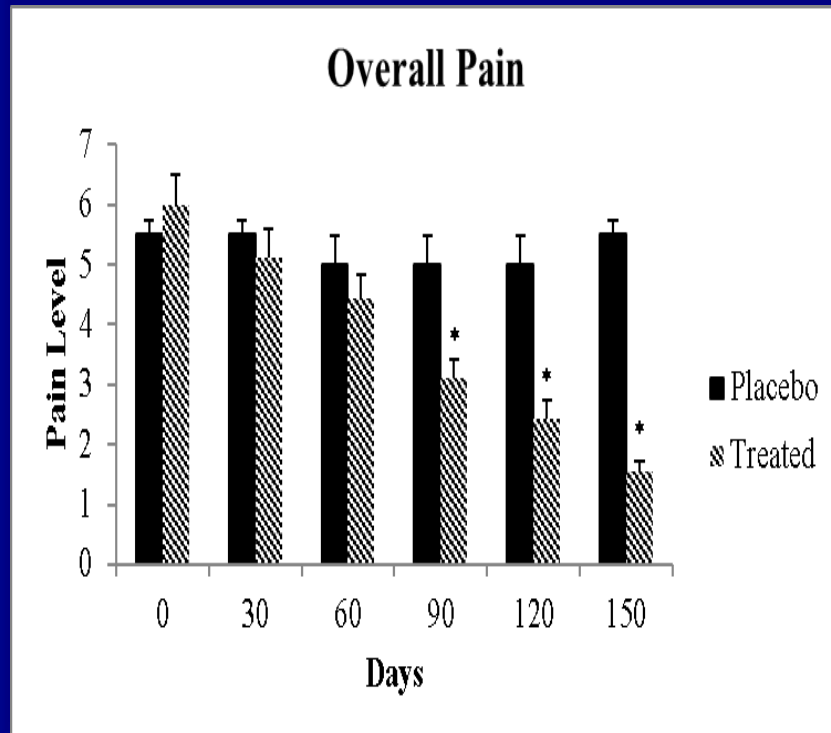
***Terminalia chebula* Extract (TCE)**

- TCE provided significant antioxidant, anti-inflammatory, and anti-arthritic effects.
- Dogs showed significant improvement as early as 90 days with maximum effects on day 150.
- TCE was found to be safe and well tolerated in moderately OA dogs.
- *Murdock N, Gupta RC, Vega N, et al. (2016) J Vet Sci Technol. 7(1): 1-8.*

Crominex[®]-3+ in Dogs

Crominex[®]-3+:

Dose: Trivalent Chromium (1 mg); *Phyllanthus emblica* (Amla) extract (15 mg), and Purified Shilajit (15 mg) in two divided doses for 150 days.



Crominex[®] -3+ in Dogs (Cont.)

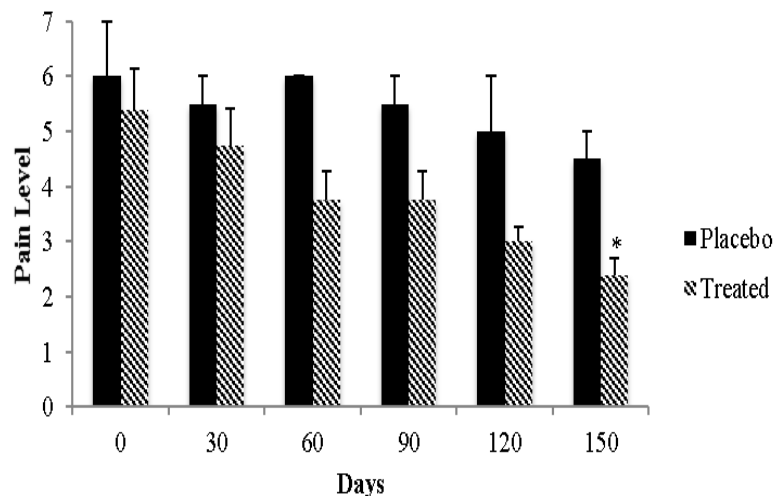
- Provides significant antioxidant, anti-inflammatory, and anti-arthritic effects.
- Dogs showed significant improvement within 90 days and horses showed improvement within 30 days.
- Crominex[®] -3+ was found to be safe and well tolerated in moderately OA dogs and horses.
- *Fleck A, Gupta RC, et al (2014) J Vet Sci Anim Husb.1:4.*
- *May K, Gupta RC, et al (2015) J Vet Sci Res. 2(1): 014.*

Shilajit

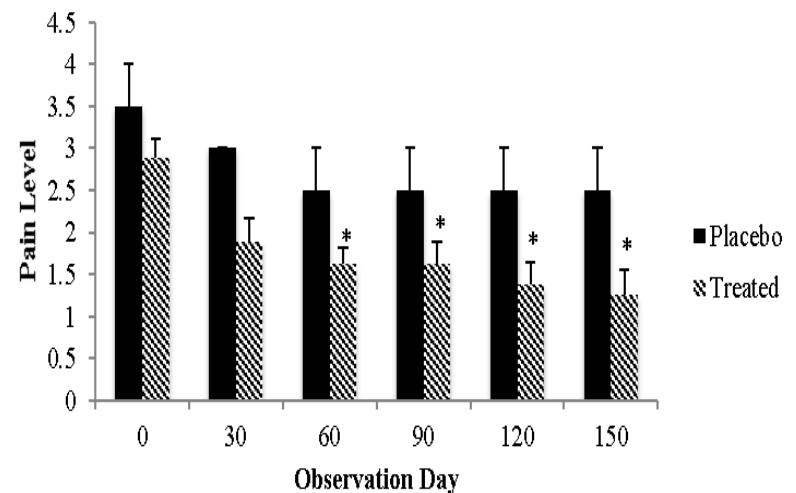
- Exudate from the sedimentary rocks of the Himalayan Mountains at an altitude of 10,000 feet.
- Active constituents: dibenzo- α -pyrones (DBPs) and fulvic acids.

Dose: 500 mg twice daily for 150 days

Overall Pain



Pain During Limb Manipulation



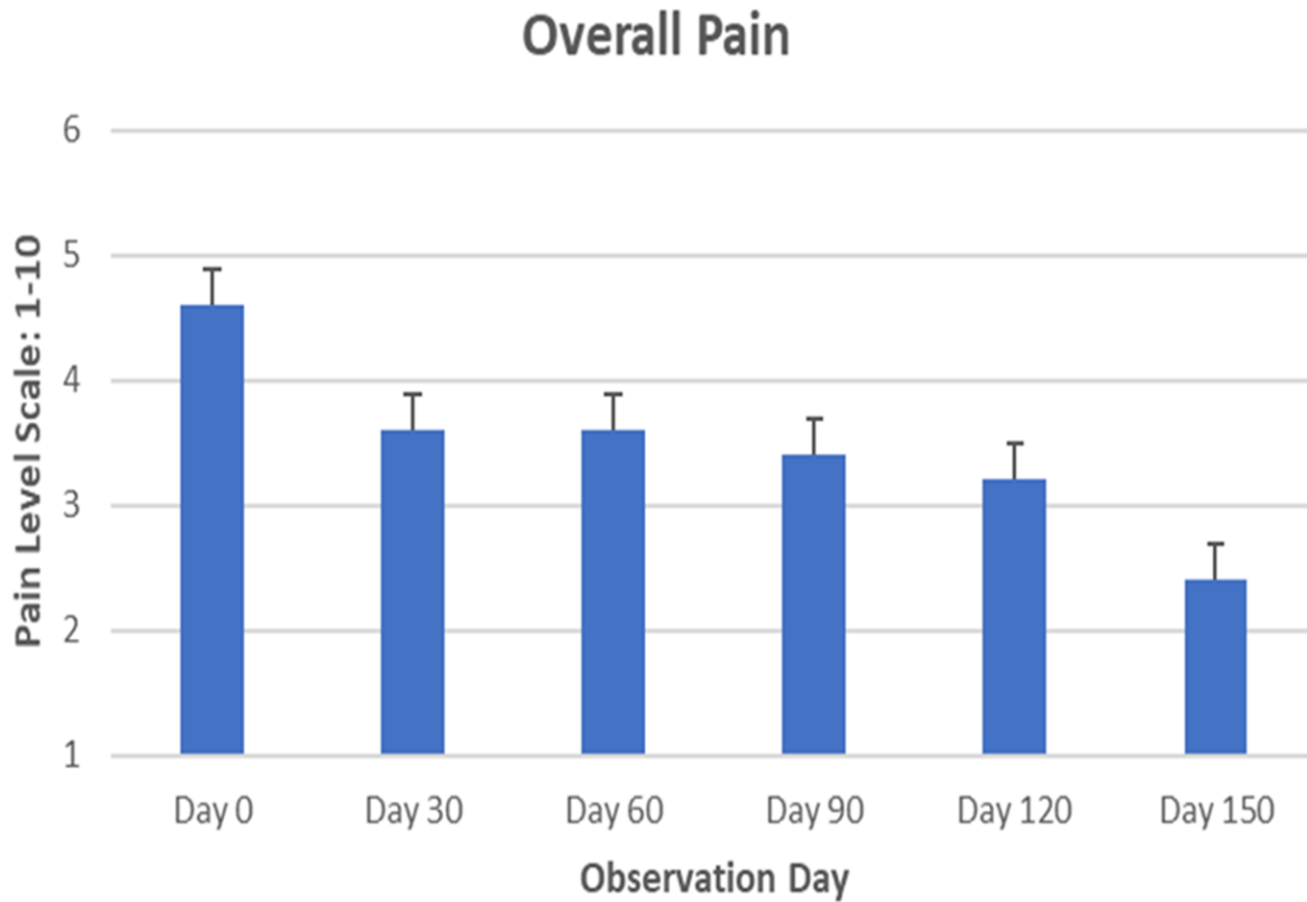
Purified Shilajit

- Shilajit exerts antioxidative, anti-inflammatory, immunomodulatory, and anti-arthritic effects.
- Shilajit also exerts anti-aging, anti-diabetic, adaptogenic, cardioprotective, and antibacterial effects.
- Shilajit provides anti-arthritic effects in moderately OA dogs without producing any side effects.
- *Lawley S, Gupta RC, et al (2013) J Vet Sci Anim Husb 1(3).*

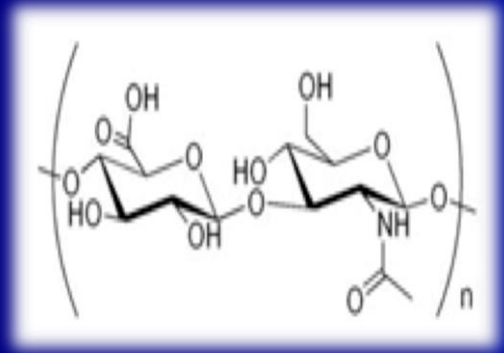
FLEXCHOICE

- FlexChoice is a product of Vets Plus Inc, and consists of krill oil, hyaluronic acid, astaxanthin, *Boswellia serrata* extract, Green lipped mussel, and ITPGS (iron transport tocopheryl polyethylene glycol succinate).
- In a clinical trial, moderately arthritic dogs received FlexChoice daily for 150 days. On a monthly basis, each dog was evaluated for full physical, pain associated with OA, and liver, kidney, and heart function biomarkers.
- FlexChoice provides significant anti-arthritic effects in OA dogs without producing any side effects.

FLEXCHOICE (Continue).



Hyaluronic Acid (Hyaluronate or hyaluronan)



- Hyaluronic acid (HA) is a non-sulfated GAG and is an important component of cartilage ECM.
- HA is injected into the joint (Dog: 4 mg; Horse: 40 mg) once, twice or thrice a week, depending on severity.
- HA prevents the degradation of cartilage and may promote its regeneration. HA also exerts anti-apoptotic, anti-inflammatory (by attenuating PGE₂), cytoprotective, and immunomodulatory effects.
- HA interacts with pain receptors and reduces pain by decreasing nerve impulses and nerve sensitivity.
- Products: Legend (Bayer) in the US, Hyonate (elsewhere).
- Adverse effects: muscle cramping and swelling in the arms/legs.

Hyaluronic Acid (Hyaluronan or Hyaluronate)

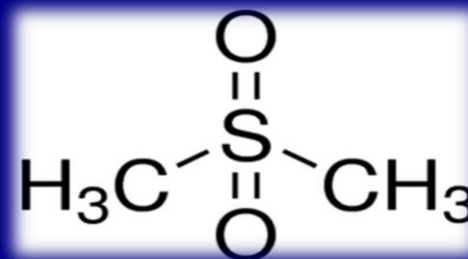
- Osteoarthritis
- Ophthalmic conditions:
dry eye disease,
glaucoma, and
cataract surgery
- Dermal conditions
- Wound healing
- Cancer
- *Gupta RC, Lall R, Srivastava A, Sinha A (2019) Hyaluronic acid: Molecular mechanisms and therapeutic trajectory. Front Vet Sci. 6: Article 192. pp. 1-24.*

Omega-3 Fatty Acids

- **Dose: 69 mg (EPA+DHA)/kg/day for 84 days.**
- **Increase in EPA (13.3-fold) and DHA (3.3-fold) in blood.**
- **Reduce the levels of IL-1 α , IL-1 β , TNF- α , COX-2, and several MMPs.**
- **Decrease inflammatory activity by reducing PGE₂, and increase collagen synthesis.**
- **Can modulate mammalian targets of rapamycin (mTOR) signaling, leading to chondroprotective activity.**
- **Decrease apoptosis and autophagy in chondrocytes, and reduce aggrecanase and collagenase activities.**
- **Proven to be effective in improving joint flexibility and mobility in dogs.**

Methylsulfonylmethane (MSM)

- MSM is a naturally occurring organosulfur compound present in some plants, and used in combination with glucosamine and/or chondroitin.

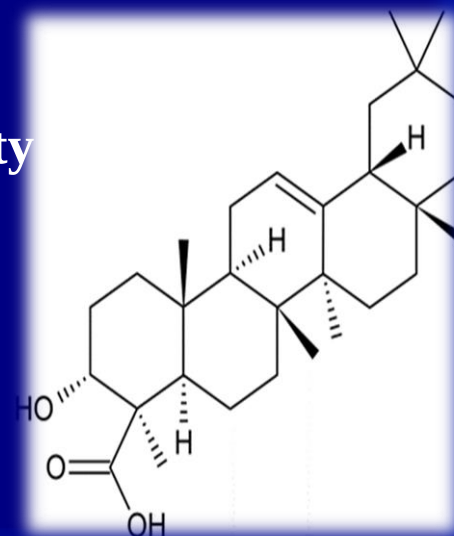


Dose: Dogs (250-500 mg/day); Horses (10-15 g/day).

- Assists in maintaining normal connective tissue.
- Exerts anti-inflammatory, antioxidant, and analgesic activities, thereby providing anti-arthritic effects.
- MSM is not a strong anti-arthritic nutraceutical.
- Dogs need to be examined regularly for adverse effects (liver and kidney functions, GI upset, and lens opacity).

Boswellia serrata Extract

- *B. serrata* (Indian Frankincense) extract has six boswellic acids.
- Out of 6 boswellic acids, Acetyl-keto-beta-boswellic acid (AKBA, 2-3% of total extract) is important for health effects.
- Boswellic acids exhibit anti-inflammatory effects by inhibiting lipoxygenase, MMP-3, and leukotriene synthesis.
- Dose: 150 mg/day in dogs
- 5-Loxin (a product of PLT Health Solutions, Inc. having 30% AKBA) provides increased joint mobility within a week.
- 5-Loxin & Nutraquin+ are safe and well tolerated.
- Huo Luo Xiang Ling Dan (HLXLD) also contain boswellic acid, and exerts anti-arthritic effect.



CURCUMIN



- Curcumin is an active ingredient of the turmeric (*Curcuma longa*) roots.
- It exerts antioxidant, anti-inflammatory, immunomodulatory, and anti-arthritic effects.
- Curcumin decreases synthesis of iNOS, NO, PGE2, IL-6, IL-9, COX-2, MMP-3, MMP-9, NF- κ B and TNF- α .
- Curcumin provides chondroprotective effect.
- It increases synthesis of Type II collagen.
- Dose: 4 mg/kg, bid.
- Curcumin can be given in combination with boswellic acid, Type II collagen, green tea extract or resveratrol.

New Zealand Green-Lipped Mussel (GLM)

- **Doses: 77 mg/kg/day in dogs; 25 mg/kg/day in horses.**
- **GLM is a rich source of GAGs, omega-3 fatty acids, and eicosatetraenoic acid (ETA).**
- **GAGs exert anti-inflammatory and joint lubricating activities, thereby producing anti-arthritic effects.**
- **ETA acts as inhibitor of COX-2 and lipoxygenase activities.**
- **GLM increased plasma levels of EPA and DHA.**
- **Reduction in lameness and pain associated with OA in dogs without improvement in joint movement.**

Avocado/Soybean Unsaponifiables (ASU)

- For optimal effects, ASU is used in the ratio of one-third avocado oil and two-third soybean oil.
- Active ingredients: Sterol-rich hydrolyzed lipid fraction
- Dose in Dogs: 300 mg every 3rd day for 15 weeks.
- ASU can inhibit the activities of iNOS, MMP-13, IL-1 β , IL-6, IL-8, and PGE2, and collagenase.
- ASU stimulates the expression of TGF- β 1 and β 2 genes in chondrocytes.
- ASU also stimulates ECM synthesis.
- Prevents/repairs erosion of the cartilage, and slows joint space narrowing.
- No dramatic effect on OA associated inflammatory pain reduction.
- Avocado green leaves: Acute heart failure, in addition to liver, lung and kidney toxicity (*Toxicon*, 2019, 164: 16-19).



Other Nutraceuticals

- Devil's claw (wood spider)



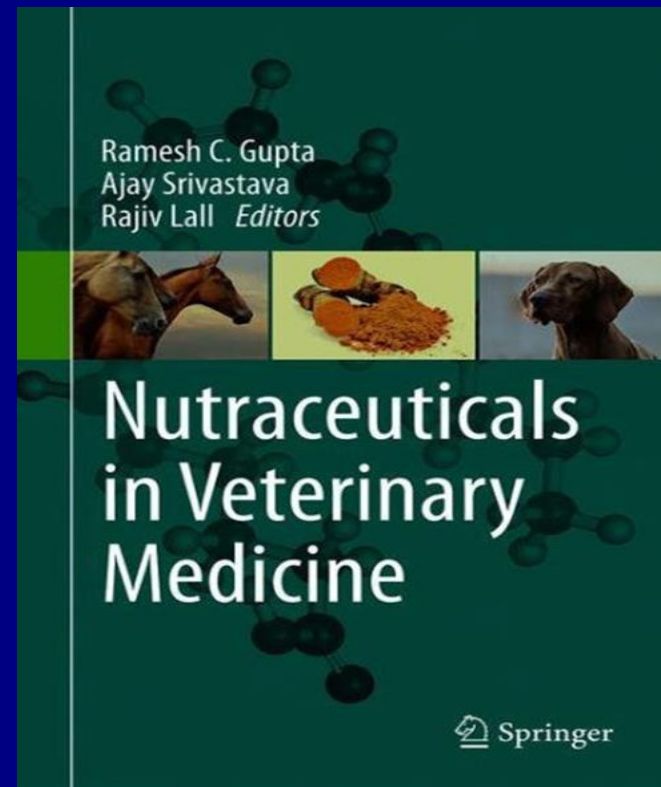
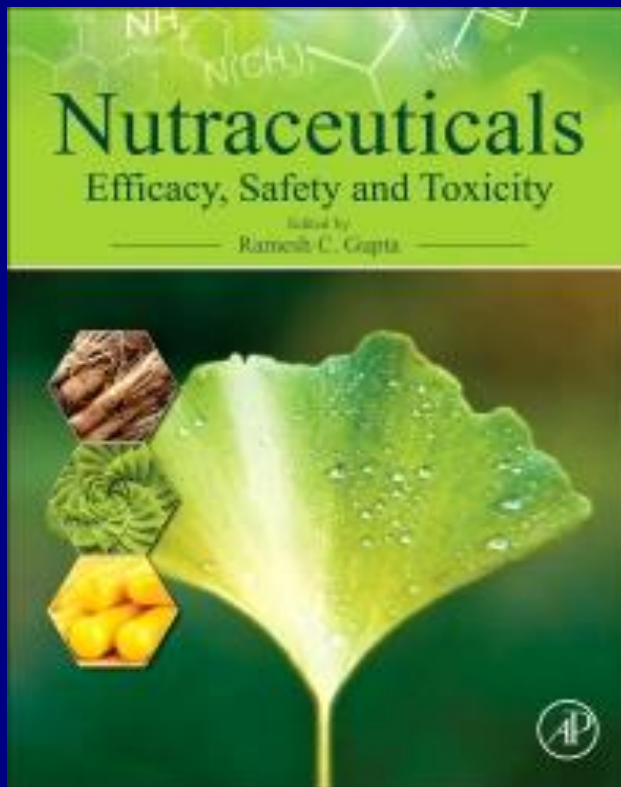
- C-Phycocyanin (PHYCOX, Dechra Pharmaceuticals, UK)
- Resveratrol
- Eggshell membrane
- Bovine lactoferricin
- Botulinum toxin A
- Sauchinone
- microRNAs: miRNA-98 in rat, and miRNA-140 in human



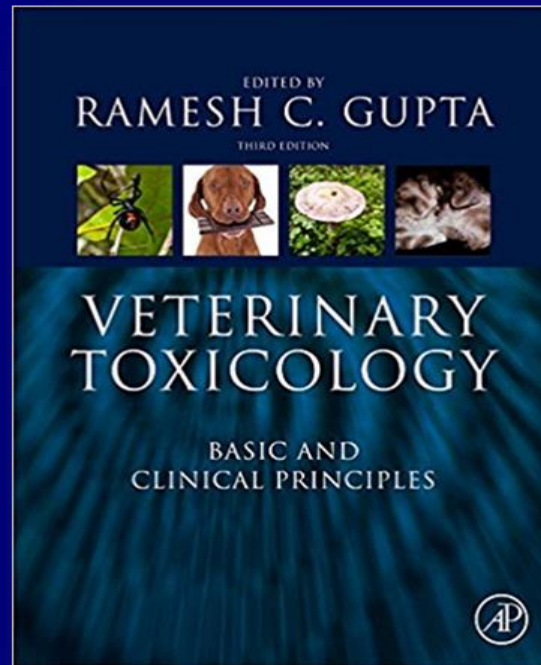
Conclusions and Future Directions

- Type II collagen, FlexChoice, Crominex 3+, *T. Chebula* extract, Glucosamine + Chondroitin sulfate, and Shilajit have shown significant anti-OA effects.
- Mechanistic rationale needs to be provided.
- Sensitive and validated biomarkers need to be discovered for diagnosis, prognosis, and therapeutic progress.
- Long-term clinical trials need to be carried out for judicious use of nutraceuticals in OA that can be acceptable nationally and internationally.

FURTHER READING



VETERINARY TOXICOLOGY



Gupta RC (2018) Veterinary Toxicology: Basic and Clinical Principles. 3rd edn. Academic Press/Elsevier, Amsterdam, 1205 p.

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