



Antinol®

THE EXECUTIVE SUMMARY 2026

www.Antinolstudies.com



Page

Table of Contents

1	What is Antinol® PCSO-524®
2	Unique features of Antinol® / Point of difference
5	Therapeutic Uses / Anti-inflammatory Activity

Antinol® clinical research – Osteoarthritis

8	1) The Preliminary study of the clinical outcome of using the PCSO-524 polyunsaturated fatty acid compound (Antinol®) in treatment of canine OA and degenerative spinal disease
9	2) PCSO-524 compared to NSAID for post-operative recovery in canines undergoing stifle surgery
10	3) Effect of PCSO-524 on OA biomarkers and weight-bearing properties in canine osteoarthritis
11	4) PCSO-524 compared to the NSAID firocoxib for recovery post-surgery in canines undergoing medial patellar luxation repair
11	5) The effectiveness of marine based fatty acid compound and NSAIDS for treatment of canine osteoarthritis: A preliminary study
12	6) The effectiveness of disease modifying osteoarthritis agents and carprofen for treatment of canine osteoarthritis:
13	7) PCSO-524 report clinical results of nineteen dogs with tracheal collapse that received PCSO-524, A lipid extract of New Zealand green lipped mussels (Perna canaliculus)
14	8) The Effectiveness of marine based fatty acid compound (PCSO-524) and firocoxib in the treatment of canine osteoarthritis
14	9) The clinical study of PCSO-524 (Antinol®) as nutraceutical in canine allergic skin disease
15	10) The effectiveness of marine based fatty acid compound (pcso-524) and firocoxib in the treatment of canine osteoarthritis
16	11) Use of PCSO-524 and cyclosporin for treatment of immune-mediated polyarthritis in dogs
16	12) PCSO-524 (Antinol®) Use in Fighting Cocks for Treatment of Chronic Pododermatitis
17	13) Clinical improvement in canine pulmonary hypertension with Perna canaliculus oil (PCSO-524) add-on therapy: Effects on exercise tolerance and cough
18	14) PCSO-524 as Adjunctive Therapy for Noninfectious Pododermatitis in Rabbits
19	Safety in Canine / Safety in Feline
21	Research In laboratory animal / In vitro research
24	Reference

What is Antinol® (PCSO-524®)?

Antinol® is a natural anti-inflammatory supplement for the veterinary market containing a patented lipid extract isolated from the New Zealand green-lipped mussel, *Perna canaliculus*, called PCSO-524®.



Antinol® contains PCSO-524® in combination with olive oil, and a small amount of vitamin E added as an antioxidant.

The patented process involves extracting the oil from green lipped mussels which are first stabilised and freeze-dried.

Early in vitro and in vivo research indicated significant anti-inflammatory properties. However, this research also revealed inconsistencies in the results due to the poor stabilisation of the lipids. Subsequent research and further development culminated in the stabilised patented lipid extract PCSO-524® found in Antinol®.

PCSO-524® contains a unique combination of free fatty acids, sterol esters, polar lipids, and carotenoids, and has been shown to be a 5-lipoxygenase (LOX)¹ and cyclooxygenase 2 (COX-2) modulator² providing a potent anti-inflammatory effect.³⁻⁶ The majority of the research using PCSO-524® has been in support of its anti-inflammatory activity, particularly in arthritis, where it has been compared to non-steroidal anti-inflammatory drugs (NSAIDs) in several animal clinical trials.

The manufacture and extraction process of PCSO-524® has been developed over many years and is covered by several international patents.

The extraction is undertaken using supercritical fluid extraction (SFE) technology which uses liquid carbon dioxide (CO₂) as a solvent. CO₂ is an ideal solvent as it becomes liquid under increased pressure and after extracting the oil the pressure is raised, and the CO₂ turns back into a gas leaving the extract intact.

PCSO-524® is produced in Nelson, New Zealand where the green-lipped mussels are farmed in pristine waters.

The stabilisation process and freeze drying of the mussels is conducted by Pharmalink International (PIL) shareholder and manufacturing partner MacLab and the extraction is completed in a state of the art facility owned by Pharmalink Extracts Limited. The patented PCSO-524® extract is sold in more than 40 countries around the world in soft-gel capsules, blister packed in aluminium foil, which are encapsulated and packaged by a number of GMP-approved facilities around the globe.

Unique features of

Antinol[®]

/ Point of difference

The unique lipid extract within Antinol[®] is different in structure compared with other marine oils (i.e. fish oils) in **the chemical bonding of the omega fatty acids and incorporates a wide diversity of lipid classes.**

91 individual fatty

There are over 91 individual fatty acids reported within the lipid extract with only 16 at concentrations greater than 1% of the total fatty acids ⁷

Anti-inflammatory compound

Specific fractionation studies have shown a range of anti-inflammatory compounds found within the PCSO-524[®] matrix ^{8,9}

The Primary Component

The primary anti-inflammatory component of the lipid mix has not been identified but has been determined to be more complex than just the DHA / EPA component

Integrity

The anti-inflammatory action of the whole extract (PCSO-524[®]) is more effective than the sum of its parts

The importance of a stabilised extract

The patented extraction process has been refined over a number of years and produces an extract with consistent anti-inflammatory results due to the stable, consistent nature of the product. The early research informed us that a non-stabilised mussel powder could not consistently produce positive results, crude extracts were vulnerable to chemical change over time providing variable or unpredictable results.



- Most green-lipped mussel (GLM) extracts on the market are not stabilised extracts and therefore may be vulnerable to change over time. No other product has the stabilisation process used by PIL to manufacture Antinol®. Comparison of different mussel extracts for their anti-inflammatory activity reveal a wide variability in effectiveness, showing the stabilised lipid extract to be far superior¹⁰

- Comparison of similar clinical trials using a non-stabilised mussel extract¹¹ to Antinol®¹² for treatment of osteoarthritis in dogs have shown stronger outcomes for Antinol®

- Comparison of PCSO-524® to other available over the counter treatments for osteoarthritis in a rat trial, place it in the top two products of a group of 27, with the other top product being the stabilised GLM powder from which Antinol® is made¹⁰

- A clinical trial comparing Antinol® to fish oil for treatment of osteoarthritis in dogs has shown considerable clinical benefit for Antinol® over fish oil. In conjunction with this, the results showed a significantly decreased biomarker of cartilage breakdown in the Antinol® group, which was increased in the fish oil group¹³

- Clinical trials have also demonstrated the superiority of Antinol® to other nutraceuticals commonly used for arthritis or joint disease in dogs. These include glucosamine, chondroitin, and avocado soy-bean unsaponifiables^{12, 14}



Analytical profile of Antinol®

- Analysis of the oil by thin layer chromatography shows several lipid classes including cholesterol esters, triglycerides, free fatty acids, diglycerides, cholesterol, phospholipids and monoglycerides ^{2,6} See Table 1

Table 1 Lipid class composition of Lyprinol²

Lyprinol lipid class	Solvent elution (% MTBE in hexane)	Total Lyprinol (%)
Sterol esters	1-5	5.8
Triglycerides	5-10	26.4
Free fatty acids	10-25	53.7
Sterols	25-20	8.0
Phospholipids (polar lipids)	50-100*	6.1

This includes the olive oil component of the capsules. MTBE = methyl-tert-butyl ether

*Includes 100% methanol fraction (to remove all remaining polar material from the column)

- The major fatty acids present in PCSO-524® are shown in Table 2.
 - Of the 91 fatty acids reported, 16 were at concentrations greater than 1% of the total fatty acids, see Table 2.

In decreasing order of abundance, these were:

20:5n-3 (EPA),
 C16:0 (Palmitic acid),
 22:6n-3 (DHA),
 C16:1n-7 (Palmitoleic acid),
 C14:0 (Myristic acid),
 C18:0 (Stearic acid),
 18:1n-5 (Octadecenoic acid),
 C18:4n-3 (Stearidonic acid),
 C20:4n-6 (Arachidonic acid),
 C18:2n-6 (Linoleic acid),
 C18:3n-3 (Alpha-linolenic acid),
 and C20:1n-9 (Gondoic acid) ⁷.

	FA	Weight %
EPA	20:5n-3	21.2 ± 0.4
Palmitic	16:00	18.4 ± 0.2
DHA	22:6n-3	13.1 ± 0.1
Palmitoleic	16:1n-9,7,5	10.3 ± 0.2
Myristic	14:00	8.42 ± 0.14
Stearic	18:00	3.34 ± 0.05
Octadecenoic	18:1n-5	3.15 ± 0.03
Stearidonic	18:4n-3	2.70 ± 0.17
Arachidonic	20:4n-6	1.73 ± 0.09
Linoleic	18:2n-6/9,1	1.74 ± 0.03
Alpha-linolenic	18:3n-3	1.61 ± 0.04
Gondoic acid	20:1n-9	1.60 ± 0.09

Table 2
 Composition of major fatty acids present in PCSO-524®⁷

Therapeutic uses

The primary recommendation for Antinol® use is for arthritis and other inflammatory conditions.

Anti-inflammatory Activity

There are two major inflammation pathways relevant to pain in osteoarthritis (OA). These are the cyclooxygenase pathways (COX-1 and COX-2) and the lipoxygenase pathway, which can be separated into 3-arms (15-LOX, 12-LOX and 5-LOX) of which the 5-LOX pathway is the best studied for OA.

COX and LOX pathways are inflammatory cascades that are initiated in ordinary cells from the lipid content that makes up the cellular membranes. Initiation and control of the inflammatory process are complex and governed by an array of biomolecular mechanisms. One important pro-inflammatory mechanism is associated closely with the cell-membrane-bound fatty acid arachidonic acid, which becomes converted into other compounds in the body that are potent pro-inflammatory substances. These pathways are shown in Figure 1.

The composition of the cellular fatty acids within cells is an area of particular interest when looking at the effects of dietary or supplemental fatty acids in the body (i.e. PCSO-524®). The composition can directly influence inflammatory processes in the body. In fact, research is now suggesting that **fatty acids within the diet can alter OA risk and severity**¹⁵.

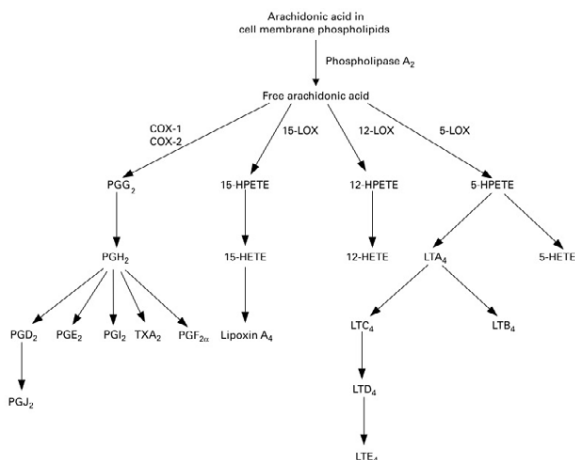


Figure 1 Pathways of eicosanoid synthesis from arachidonic acid. COX, cyclooxygenase; HETE, hydroxyeicosatetraenoic acid; HPETE, hydroxyperoxyeicosatetraenoic acid; lipoxygenase; LT, leukotriene; PG, prostaglandin; TX, thromboxane.¹⁶

Antinol®

working in conjunction with NSAIDs,
or to replace NSAID use

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most widely used drugs for arthritis conditions in humans and animals.

One of their main mechanisms of action is inhibition of the COX enzyme (shown with its link to the inflammatory mediators produced from arachidonic acid in Figure 1), which in turn, inhibits the production of prostaglandins, especially PGE₂, one of the key inflammatory mediators known to cause inflammation and therefore pain, which is strongly implicated in OA ¹⁷.

NSAIDs are also well known for their potential gastrointestinal side effects, including the development of gastric ulceration. A review of the use of NSAIDs in dogs notes that monitoring them for gastric ulceration is difficult as there are no practical screening tests to detect early signs of gastric injury, with clinicians needing to be vigilant for signs of injury ¹⁸. Ideally, treatment for OA should be as effective as NSAIDs without these debilitating side effects.

Supplementation with Antinol® has been shown in a canine study to be as effective as NSAIDs for improving the weight-bearing capacity of the affected limb, with superiority in clinical assessment seen with Antinol® only ¹². This study also saw a slightly enhanced effect when both NSAIDs and Antinol® were given together.

In one study examining the use of Antinol® post joint-surgery in canines, adverse events including vomiting and gastrointestinal irritation were seen in the NSAID group, but not the group that was prescribed Antinol® ¹⁴. The same trial also saw a reduction in time to regain use of the affected limb with Antinol® in comparison to NSAID treatment.

Studies in laboratory animals support these findings with PCSO-524® an effective treatment in rats for osteoarthritis ¹⁰. The same researchers went on to demonstrate that unlike the NSAIDs tested (that were also effective), PCSO-524® was not gastro-toxic.

In 2003, it was shown that PCSO-524® could be used alongside either NSAIDs or low-dose prednisone for increased benefit¹⁹.

The research demonstrated that the combined use of pharmaceuticals and PCSO-524® might be beneficial together to decrease the gastro-toxicity associated with the use of NSAIDs and to increase treatment effect.



Antinol® clinical research –
Osteoarthritis



Antinol® clinical research – Osteoarthritis

There have been several clinical trials looking at efficacy in **canine osteoarthritis of the hip, stifle, and shoulder joints**, as well as its effect in the **post-surgical treatment** of animals undergoing joint surgery. These trials are outlined in the following section.



1. The Preliminary study of the clinical outcome of using the PCSO-524 polyunsaturated fatty acid compound (Antinol®) in treatment of canine OA and degenerative spinal disease

Thai Journal of Veterinary Medicine. 2012. 42(3): 311-317¹⁹

This trial included 84 mixed breed dogs with **OA of the hip, shoulder or stifle (n=64)** or **neurological signs of cauda equina syndrome (n=20)**.

All dogs were given **50mg / 10kg per day of PCSO-524**, with primary outcome being improvement in clinical assessment after 4 weeks of treatment.

In both of the OA groups, between 88-90% of the dogs showed clinical improvements, see Table 3 , and in the cauda equina group, improvement of neurological signs was seen in 85% of the group.

Clinical outcomes (%(n))	Improve	Not improve	Progress (worse)
Clinical lameness	90.3% (28/31)	9.67% (3/31)	0% (0/31)
Owner preference	87.09% (27/31)	9.6% (3/31)	3.22% (1/31)
Radiographic findings	16.12% (5/31)	77.42% (24/31)	6.45% (2/31)

Table 3 Clinical outcomes of OA at hip and shoulder joints with PCSO-524 treatment after 4 weeks¹⁹

Specifically, on a 5-point lameness scale in dogs with hip and shoulder OA

35% improved by 1 point,
48% improved by 2 points, and
6% improved by 3 points,
whilst **none of the dogs scores decreased**, see Table 4.

Clinical outcomes (% (n))	Worse >1 score	No difference	Better 1 score	Better 2 score	Better 3 score
Lameness score	0% (0/31)	9.67% (3/31)	35.48% (11/31)	48.38% (15/31)	6.45% (2/31)
Radiographic score	6.45% (2/31)	77.42% (24/31)	9.6% (3/31)	6.45% (2/31)	0% (0/31)

Table 4 Lameness score of OA at hip and shoulder after four weeks of PCSO-524¹⁹

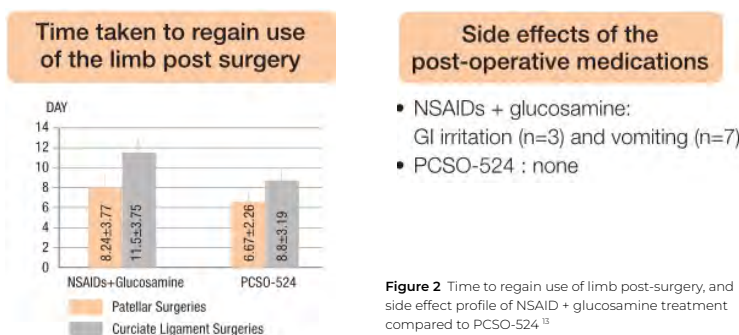
Results from this study suggest **improved clinical outcomes for the majority of dogs with PCSO-524 supplementation in OA**, slightly less of an improvement was seen in the cauda equina group. Additionally, **85% of the owners** stated that they were happy with the treatment.

2. PCSO-524 compared to NSAID for post-operative recovery in canines undergoing stifle surgery

*Poster presentation: World Small Animal Veterinary Association 38th Annual Congress. 2013*¹³

This report includes 28 dogs given PCSO-524 (16 weeks) or NSAIDs (7 days) and glucosamine sulphate (16 weeks) post joint surgery.

Results suggest a large clinical improvement in lameness and a reduced amount of time to regain use of the affected limb in the PCSO-524 group in comparison to the NSAID/glucosamine group. There was also a **considerable difference in the side-effects** found between the two treatments, see Figure 2.



This brief report suggests **clinical improvements using PCSO-524 post-surgery for 16 weeks**, superior to the use of NSAIDs for seven days and glucosamine sulphate for 16 weeks.

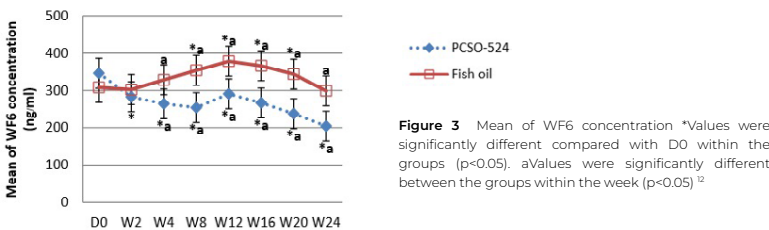


3. Effect of PCSO-524 on OA biomarkers and weight-bearing properties in canine osteoarthritis

*Thai Journal of Veterinary Medicine 2015. 45(2): 157-165*¹²

This trial included 66 mixed breed dogs with x-ray confirmed OA split into two treatment groups for 24 weeks.

These were 1) **PCSO-524** (5 mg/kg) and 2) **fish oil** (2,000 mg/d). The dogs were all placed on a standardised diet to minimise variability. The primary outcome was serum chondroitin sulphate epitope (WF6), which is an indicator of cartilage breakdown. Other measures were weight-bearing scores measured with peak vertical force gait analysis and range of motion (ROM).



The results show an increase in WF6 in the fish oil group and a decrease in the PCSO-524 group. The mean of serum WF6 of the PCSO-524 group (262.46±118.06 ng/ml) was significantly ($p<0.05$) less than that of the fish oil group (324.76±133.65 ng/ml) after 24 weeks of administration, see Figure 3.

Clinical outcomes also improved significantly for the PCSO-524 group, with weight-bearing improving above 25% and up to 88% of dogs improving their lameness scores, as opposed to 32% of dogs in the fish oil group.

See Table 5 for changes in weight-bearing properties.

Joint	Patients with OA in hip joints (percentage of mean [SD])					Patients with OA in shoulder joints (percentage of mean [SD])				
	D0	W2	W8	W16	W24	D0	W2	W8	W16	W24
PCSO-524	64.5 (6.43)	79.3 (4.32)	82.1 (8.42)	88.7 (5.11)	89.2 (5.81)	68.1 (4.18)	81.4 (7.12)	86.7 (3.84)	89.3 (6.18)	91.2 (2.12)
Fish oil	66.8 (8.41)	68.4 (5.31)	70.1 (9.21)	71.5 (8.76)	72.3 (3.14)	67.8 (9.42)	68.9 (7.63)	70.4 (8.43)	71.2 (9.44)	71.6 (4.56)

Table 5 Weight bearing properties measured by peak vertical force gait analysis. Data were analysed as percentage of expected weight bearing in each leg: 60:40, forelimbs: hind limbs¹²

This study suggests very positive clinical effect and a significant reduction in a measure of cartilage breakdown for dogs with OA treated with PCSO-524. The treatment was far superior to treatment with a standard dose of fish oil. The results suggest that PCSO-524 is protective against cartilage breakdown in dogs with osteoarthritis.

4. PCSO-524 compared to the NSAID firocoxib for recovery post-surgery in canines undergoing medial patellar luxation repair *Thai Journal of Veterinary Medicine 2015. 639-643*²⁰

This trial included 30 Pomeranian dogs undergoing surgery for medial-patellar luxation repair. The dogs were split into 3 groups post-surgery,

- 1) **firocoxib** (5 mg/kg/d);
- 2) **PCSO-524** (10 mg/kg, twice daily),
- or 3) **a combination of both firocoxib and PCSO-524.**

All treatments were given for 14 days from the day of surgery. The primary outcome measure was **interleukin 1-beta (IL-1 β)** chosen for its role as a biomarker for joint inflammation and bone loss especially in rheumatoid arthritis²².

The results show a very similar pattern of decline for IL-1 β levels in the firocoxib and the combined firocoxib/PCSO-524 group. The levels of PCSO-524 alone fell more slowly than the other groups over the 14 days recorded.

The role of IL-1 β in OA remains unclear²² and this study suggests that **effect of PCSO-524 is not mediated via this cytokine pathway.**

5. The effectiveness of marine based fatty acid compound and NSAIDs for treatment of canine osteoarthritis: A preliminary study *WSAVA Congress 2015*

A prospective block-randomized single-blinded study. **Thirty client-owned dogs** that had clinical and radiographic evidence of hip or stifle osteoarthritis. Dogs were assigned randomly into 3 treatment groups of 10 dogs each:

- 1) **PCSO-524,**
 - 2) **NSAIDs**
 - and 3) **The combination of NSAIDs and PCSO-524 (NSAIDs-PCSO).**
- Each group received the therapeutic agents orally for 4 weeks.

Peak vertical force (PVF) was measured by **force plate gait analysis**. Hematology and blood chemistry values were evaluated prior to treatment and at the 2nd and 4th week post treatment. Comparisons between groups by repeated measurement demonstrated indifferences of PVF, hematology and blood chemistry values.

Analyses within each group determined that the PVF prior to treatment and the second week of study and the end of study increased significantly in all groups ($p < 0.05$).

The mean changes of PVF at the fourth week of treatment were;
 3.88 ± 1.35 , 4.23 ± 0.74 , 5.36 ± 0.94 % BW, in PCSO-524, NSAIDs and NSAIDs-PCSO groups respectively. The BUN value in NSAIDs group tended to increase when compared to baseline values ($p < 0.05$), however all BUN values were within the normal range.

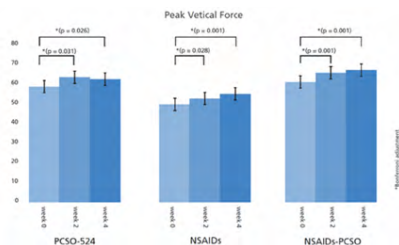


Figure 4 Multiple comparison of PVF in each group between prior to treatment, the 2nd and 4th week post treatment at p -value < 0.05

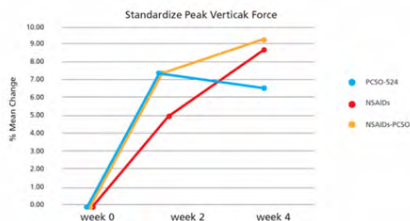


Figure 5 Percent mean change of PVF in each group between prior to treatment, the 2nd and 4th week post treatment

6. The effectiveness of disease modifying osteoarthritis agents and carprofen for treatment of canine osteoarthritis

*Thai Journal of Veterinary Medicine. 2016. 46(3): 363-371*¹¹

This trial included 40 mixed breed dogs with x-ray confirmed OA split into four different treatment groups for four weeks.

1) PCSO-524 (200 mg/d); 2) carprofen (2.2 mg/kg b.d.); 3) combination of PCSO-524 and carprofen; and 4) a nutraceutical supplement containing a combination of glucosamine HCL, chondroitin sulphate and avocado-soybean unsaponifiables (GC-ASU).

Outcome measures were changes in kinetic force plate gait analysis - peak vertical force (PVF); gait observation and complete orthopaedic examination (OAS).

Results show overall that **the combination of PCSO-524 / carprofen was superior to all of the other treatments**. The GC-ASU performed the worst of all the treatments.

The PVF within-group analysis showed a significant increase (improvement) for three of the four groups, with no significant improvement seen in the GC-ASU group. After four weeks, the adjusted PVF was increased in the PCSO-524/carprofen group up to above 9% mean change. The results were slightly lower for carprofen only, and around 6.5% change for the PCSO-524 only group, see Figure 6.

The combined measures of the OAS showed a significant decrease in symptom score across these same groups with a clinical improvement equivalent to between 7.8-9.4%.

PCSO-524 performed better in this assessment than carprofen alone, and the combination of the two was superior to either alone.

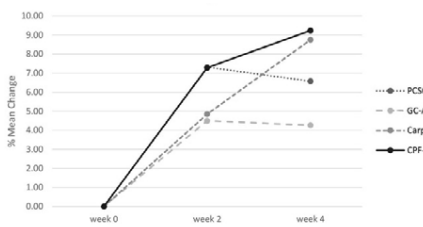


Figure 6 Adjusted PVF values across treatment groups¹¹

This study suggests that **the combination of PCSO-524 and carprofen together was superior to other treatments for management of canine OA**.

Results were seen in both objective and clinical assessment.

7. PCSO-524 report clinical results of nineteen dogs with tracheal collapse that received PCSO-524, A lipid extract of New Zealand green lipped mussels (*Perna canaliculus*)

Journal of Modern Veterinary Medicine (MVM) 2016⁴³ 25: 79-82

Nineteen dogs presented with cough and diagnosed with **tracheal collapse** based on inspiration / expiration chest radiography between December 2013 and April 2015; The recruitment was only small dogs ;7 Chihuahuas, 4 Yorkshire terriers, 4 Pomeranians, 2 Papillons, 1 Pug, and 1 Maltese respectively. The age range of these 19 dogs were from 63 months (5 years and 3 months) to 199 months (16 years and 7 months) in which considered as the senior life stage.

At baseline the body condition score of 12 dogs were scored as obese, 5 dogs were lean, and 2 dogs were at normal weight. **Weight control protocol had been instructed to each Pet Owner to follow throughout 12 months of study period.**

Antinol were applied as the conjunctive supplementation to the supportive treatment of each dog. Antinol dosage was **2 caps per day as the loading dose in first 14 days and on maintenance dose 1 cap per day starting from Day 15 onwards.** The evaluation of coughing were done at the home environment which dog were most comfort and least stress.

According to the study had been found the change of incidence rate of Cough from D0 to D360 were **improved in 16 dogs that survived for 12 months** the results as shown in Table 6.

Three dogs were excluded from the study: 1 died of pulmonary edema, 1 died of advanced valvular heart disease, and 1 discontinued PCSO-524® due to dosing difficulty by the owner.

Table 6 The results of Coughing score of each case by the time of post treatment with Antinol

	Dogs	baseline*	0.5 month	1 month	2 months	3 months	6 months	12 months
1	Chihuahua A	100	90	70	50	40	50	5
2	B	100	80	80	40	0	50	20
3	C	100	100	100	100	100	50	0
4	D	100	90	50	-	-	-	-
5	E	100	0	0	0	0	0	0
6	F	100	0	10	25	25	10	0
7	G	100	100	50	50	50	50	-
8	Yorkshire terrier A	100	0	0	0	10	0	0
9	B	100	0	10	0	10	10	0
10	C	100	95	10	10	10	10	-
11	D	100	50	60	60	100	0	50
12	Pomeranian A	100	40	80	80	80	30	50
13	B	100	15	40	30	40	40	20
14	C	100	50	10	10	20	10	0
15	D	100	0	0	0	0	0	0
16	Papillon A	100	0	0	0	0	0	0
17	B	100	50	50	40	20	10	10
18	Pug	100	70	50	40	40	50	50
19	Maltese	100	100	120	90	60	20	60

*Cough at baseline is assumed to be 100

8. The Effectiveness of marine based fatty acid compound (PCSO-524) and firocoxib in the treatment of canine osteoarthritis

Poster Presentation: Veterinary Orthopaedic Society Conference, March 2018

This randomized study involved **31 mixed breed dogs with x ray confirmed OA of stifle joint**. They were split into 2 groups for four weeks of treatment;

1) PCSO-524 200 mg (4 caps) q24hr PO and

2) Firocoxib (FCX) 5 mg/kg q24hr PO & PCSO-524 200 mg (4 caps) q24hr PO.

Outcome measures were **Computer-assisted Force Plate gait analysis** (OR6-7,AMTI, Watertown MA) and **Owner assessment Canine brief pain inventory score (CBPI)**.

The results showed **a non-significant effect of the treatment on the adjusted Peak Vertical Force (PVF) value ($p=0.447$) among the 2 treatment groups**. The comparison within group revealed significant increases in the PVF value at week 2 and week 4 in both treatment groups compared to their pretreatment values ($p<0.05$). Change in mean PVF of $7.81(\pm 1.27)$ and $6.19(\pm 1.8\%BW)$ [mean($\pm$ SE)] were detected in PCSO-524 and FCX+PCSO-524 groups respectively.

CBPI values compared between the two groups was non-significant ($p=0.4359$). CBPI comparison within both groups showed significant decreases at 2 and 4 weeks compared with their pretreatment value ($p<0.05$).

9. The clinical study of PCSO-524 (Antinol®) as nutraceutical in canine allergic skin disease

Oral Presentation: The World Veterinary Congress 2018

This study included **31 allergic dogs with chronic pruritis with other skin diseases excluded**. Dogs were split into 3 treatment groups based on degree of pruritis, distribution, extension of the lesions and skin and coat condition; Group 1: mild, Group 2: moderate, and Group 3: severe.

All dogs received **PCSO-524 loading dose 10 mg/kg q12hr PO for 2 weeks** followed by **a maintenance dose of 10 mg/kg q24hr PO**.

All dogs were evaluated at 2, 4, 8, 12 and 16 weeks for clinical response.

The assessment made by the owners (PVAS Score) and Vets (CADESI-03 score).

The results demonstrated that **PCSO-524 had beneficial effects on improvement in skin and coat condition and a reduction in PVAS score in Group 1**. Similarly, vet evaluation revealed greater reduction in pruritis score in Group 1 (50%) with less effects in Group 2 (44.44%) and Group 3 (40%) as in Table 7 below.

The results of this study suggested **PCSO-524 had beneficial effect in atopic skin allergy with a greater effect in mild cases**. The effect was less in more severely affected atopic dogs, probably due to the severity degree of inflammation they experienced. PCSO-524 may be used as treatment of canine atopic dermatitis.

	Number of dogs with improvement (%)			Time at improvement seen (weeks)		
	Group 1 PCSO-524 (n=12)	Group 2 PCSO-524 +AH (n=9)	Group 3 PCSO-524 +Pred (n=10)	Group 1 PCSO-524 (n=12)	Group 2 PCSO-524 +AH (n=9)	Group 3 PCSO-524 +Pred (n=10)
Skin & coat condition	9/12 (75%)	3/9 (33.33%)	5/10 ^{bc} (50%)	5.33 $\pm$ 1.56 ^c	7.33 $\pm$ 2.70	12 $\pm$ 2.09 ^a
Degree of pruritus (PVAS)	6/12 (50%)	4/9 (44.44%)	4/10 (40%)	4 $\pm$ 0.95	4.67 $\pm$ 1.40	5 $\pm$ 1.17
Lesion score (CADESI-03)	11/12 ^{bc} (91.67%)	3/9 ^a (33.33%)	4/10 ^a (40%)	4.55 $\pm$ 1.28 ^c	4.67 $\pm$ 2.45	10.50 $\pm$ 2.12 ^a

Table 7 The Skin&coat,PVAS and CADESI score after treatment and the time point of improvement seen by group in weekly basis.

10. The effectiveness of marine based fatty acid compound (pcso-524) and firocoxib in the treatment of canine osteoarthritis

Journal of BMC Veterinary Research 2019 15:349

This randomized double blinded study included **79 mixed breed dogs that had hip and/or stifle OA** with X-ray confirmation. The dogs were randomly split into 3 different treatment groups;

- 1) **Firocoxib 5mg/kg q24hr PO & PCSO-524 placebo (4 caps a day q24hr PO);**
- 2) **PCSO-524 4 caps a day, q24hr PO & Firocoxib Placebo;** and
- 3) **combination of Firocoxib and PCSO-524** for 28 days of treatment.

Outcome measures were changes in Kinetic force plate gait analysis-Peak Vertical Force (PVF), the Orthopedic Assessment Score (OAS), Canine Brief Pain Inventory score (CBPI), and serum prostaglandin E2 concentration (PGE2).

Results showed overall that within-group comparisons saw **a significant increase in PVF over the 4-week treatment period for all three treatments** (Firocoxib, PCSO-524 and the combination group) ($p < 0.05$).

The mean increase in PVF were 3.25 (± 4.13), 2.01 (± 3.86), and 4.11 (± 4.69)%BW [mean ($\pm$ SD)] respectively, see Table 8.

Table 8 PVF values at pre treatment (day0), day 14, day 28 for each group and the change from baseline

	Time	Firocoxib	PCSO-524	Combination	P-value*
PVF (%BW)	Day 0 (PVF)	64.79 $\pm$ 5.98 ^a	62.01 $\pm$ 6.85 ^a	59.97 $\pm$ 9.38	0.069
	Day 14 (PVF)	67.82 $\pm$ 6.70 ^b	63.82 $\pm$ 6.15 ^b	62.71 $\pm$ 9.15	
	Mean change $\pm$ SD	3.03 $\pm$ 4.67	1.82 $\pm$ 3.22	2.74 $\pm$ 4.41	
	Day 28 (PVF)	68.05 $\pm$ 6.29 ^b	64.01 $\pm$ 6.52 ^b	64.08 $\pm$ 9.99	
	Mean change $\pm$ SD	3.25 $\pm$ 4.13	2.01 $\pm$ 3.86	4.11 $\pm$ 4.69	

SD standard deviation

^a ^bp-value < 0.05 from Tukey's Studentized Range within each treatment

*p-value from repeated measurement analysis for 3 treatments

The OAS showed non-significant changes in all treatment groups.

There were **no significant decreases in CBPI Pain severity score (PSS) and CBPI interference scores (PIS) between groups**. The concentration of serum PGE2 significantly decreased ($p < 0.05$) in the combination group only, see Table 9.

The study also found **significant increases in BUN and creatinine ($p < 0.05$) compared to pre-treatment in the Firocoxib and combination groups, but not in the PCSO-524 group at day 28**, but all other values in all dogs remained within the normal range.

The results of the study suggest that within each group of a combination (PCSO-524 and Firocoxib), PCSO-524, Firocoxib showed the significant improvement of weight bearing ability but not in the comparison between.

Table 9 PGE2 level adjusted baseline (MEAN $\pm$ SE at pre treatment(day 0), day 14 and day 28

PGE2 level after adjusted baseline (Mean + SE) at pre-treatment (day0), day14 and day28					
Time		Firocoxib	PCSO-524	Combination	P-value**
Adjusted PEGE2a (pg/mL)	Day 0	1815.795 $\pm$ 0.00	1815.795 $\pm$ 0.00	1815.795 $\pm$ 0.00 ^a	0.639
	Day 14	1721.642 $\pm$ 88.889	1780.773 $\pm$ 85.645	1791.691 $\pm$ 82.430 ^a	
	Day 28	1717.807 $\pm$ 94.695	1805.974 $\pm$ 91.239	1589.641 $\pm$ 87.814 ^b	

** p-value from repeated measurement ANCOVA for 3 treatments

^a, ^b p-value < 0.05 from multiple comparison within each treatment using Bonferroni test

^c Covariates appearing in the model are evaluated at PEG2 of every group at week 0= 1815.795 pg/mL

11. Use of PCSO-524 and cyclosporin for treatment of immune-mediated polyarthritis in dogs

The Journal of Thai Veterinary Practitioners 2020 32:66-77

An 8 years old Chihuahua dog was admitted to the Small Animal Hospital at Chulalongkorn University due to signs of depression, lethargy, lameness and joint effusion. Hematological examination and test of synovial fluid indicated **Immune-Mediated Polyarthritis (IMPA)**; see Figure 7 for x-rays.

Prednisolone, Gabapentin and Amoxicillin-clavulanic acid were prescribed for the treatment.

Abnormally increase of ALT, ALK and AST enzyme was observed 1 week later, therefore, the treatment was changed to **Cyclosporin, Gabapentin, and PCSO-524®**.



Figure 7 The radiographic images of immune mediated Polyarthritis in this case

The clinical signs continued to improve after the adjustment of prescription and **Cyclosporin and Gabapentin were terminated after 3 and 4 months, respectively**. A follow-up examination at 4 months later showed no signs of lameness and joint effusion and **no adverse effects caused by the long-term use of PCSO-524®**.

The success of IMPA treatment is a result of rapid diagnosis and appropriate treatment protocol.

Follow-up for treatment evaluation is necessary during the treatment course in order to reduce the impact on health and minimize the medication dosage without risk of causing adverse effects or recurrence of the disease.

12. PCSO-524 (Antinol®) Use in Fighting Cocks for Treatment of Chronic Pododermatitis

The Journal of Thai Veterinary Practitioners 2020 32:83-93

2-year old fighting cock had been showing sign of swollen left plantar and left tarsometatarsal joint and lameness of the left leg for 2 months; see Figure 8. Radiographic examination found lysis of the left tarsometatarsal bone. Significant amount of red and white blood cells was found at the lesion and bacterial culture showed negative result.

The treatment consisted of NSAID; 0.5 mg/kg meloxicam sid for 2 weeks, antibiotic; 125 mg/kg Amoxicillin-clavulanic acid bid for 4 weeks, and 1 capsule of PCSO-524 (Antinol®) sid for 5 weeks. The kinetic gait analysis was performed weekly during the follow-up to evaluate the improvement and pressure on the foot pads was measured by determining **Peak vertical force (PVF) of each leg**.



Figure 8 The image of fighting cock with swollen left plantar and left tarsometatarsal

After 2 weeks, the animal started to show improvement of clinical signs as partial weight bearing was restored and increased by approximately 30%, but the pad swelling was still present. Increased weight bearing of the left leg was observed after 3 weeks and the animal was able to run and chase female chickens. **After 5 weeks**, walking mobility and weight bearing was increased from 30% to 45% and the swelling of the left foot was reduced.

This clinical study demonstrated efficacy of PCSO-524 (Antinol®) in treatment of foot-pad inflammation in chickens. The antibiotic was for infection control and the NSAIDs and PCSO-524 (Antinol®) were used to reduce pain and inflammation. **Long-term use of NSAIDs was limited due to adverse effects on kidney and gastrointestinal tract, therefore it was discontinued after 2 weeks of the treatment.** Only nutraceutical supplementation, PCSO-524 (Antinol®), was prescribed for 5 weeks. **Omega-3, one of the major components of PCSO-524 (Antinol®), is widely accepted for its anti-inflammatory effect**

13. Clinical improvement in canine pulmonary hypertension with Perna canaliculus oil (PCSO-524) add-on therapy: Effects on exercise tolerance and cough

PLOS One | <https://doi.org/10.1371/journal.pone.0333526>

This prospective, randomized, placebo-controlled trial tested **green-lipped mussel oil (PCSO-524) added to sildenafil-based therapy in dogs with pulmonary hypertension (PH)**, mostly secondary to myxomatous mitral valve disease. **After 70 days, owner-assessed exercise tolerance improved significantly in the PCSO-524 group** ($P = 0.009$), and the **improvement in coughing** between Day 35 and Day 70 was greater than with placebo ($P = 0.03$). The tricuspid regurgitation pressure gradient (TRPG), an echocardiographic estimate of pulmonary arterial pressure, fell in all dogs ($P = 0.001$), with no difference between groups.

Study design: Prospective, randomized (blocked by PH severity, sealed envelopes), blinded, placebo-controlled trial in client-owned dogs aged ≥ 5 years with TR velocity ≥ 3.0 m/s (classified by the authors as intermediate/high PH probability), conducted October 2018 – April 2020. 22 dogs were enrolled and 17 were analysed; most were ACVIM Stage C (B2: 3, C: 12, D: 2). Dogs with other systemic disease, heartworm, or on NSAIDs were excluded.

	PCSO-524 arm	Placebo arm
n (analysed)	8 (12 enrolled)	9 (10 enrolled)
Test product	PCSO-524 soft gel capsule: 1 capsule twice daily for 2 weeks (loading), then 1 capsule once daily	Identical-looking placebo capsule, same schedule
Standard care	Sildenafil (protocol 1 mg/kg PO q12h) plus existing conventional cardiac medications	Same
Duration	70 days (actual visits at Day 0, 35, 70)	70 days (actual visits at Day 0, 35, 70)

Outcomes (both arms):

- Clinical scores: owner questionnaire (modified Häggström/QUEST) for exercise tolerance, demeanour, appetite, respiratory effort, coughing and nocturnal dyspnoea/cough.
- Cardiac: echocardiography (incl. TRPG = $4 \times$ TR velocity²; LA/Ao, LV dimensions) and ECG.
- Bloods: CBC, serum biochemistry and NT-proBNP.

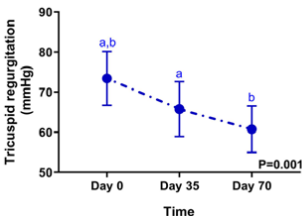


Fig 2. Tricuspid regurgitation pressure gradient of all 17 dogs. Repeated measured within subjects were analyzed for all 17 dogs ($P = 0.001$). Significant difference between day 0 and day 35 of all 17 dogs ($P = 0.03$). Significant difference between day 0 and day 70 of all 17 dogs ($P = 0.004$).

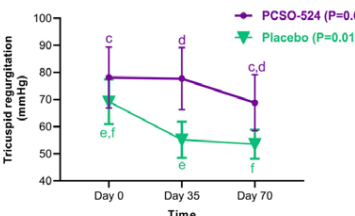


Fig 3. Tricuspid regurgitation pressure gradient in the PCSO-524 and placebo groups. Repeated measured within subjects were analyzed for each group of dogs (P model of the PCSO-524 group = 0.02, and P model of the placebo group = 0.03). Significant difference between day 0 and day 70 of the PCSO-524 group ($P = 0.03$). Significant difference between day 0 and day 35 of the placebo group ($P = 0.03$). Significant difference between day 0 and day 70 of the placebo group ($P = 0.03$).

Results

- Baseline: Groups were comparable except for higher plasma protein in the placebo group ($P = 0.02$) and more severe cough scores in the PCSO-524 group ($P = 0.03$).
- Exercise tolerance: Improved significantly within the PCSO-524 group (median score 2 $\rightarrow$ 1; $P = 0.009$; Day 70 vs Day 0 $P = 0.046$, vs Day 35 $P = 0.014$), with no change in the placebo group ($P = 0.85$). Between-group differences at each visit were not significant; the Day 35–70 change showed a trend favouring PCSO-524 ($P = 0.06$).
- Coughing: Between Day 35 and Day 70, 4 of 8 PCSO-524 dogs improved vs 0 of 9 placebo dogs ($P = 0.03$).

- TRPG: Fell in all 17 dogs ($73.4 \rightarrow 60.7$ mmHg; $P = 0.001$) and within each group (PCSO-524 $78.1 \rightarrow 68.8$ mmHg, -9.3 , $P = 0.02$; placebo $69.2 \rightarrow 53.6$ mmHg, -15.6 , $P = 0.01$), with no significant difference between groups. The authors attribute the fall to sildenafil and conclude **PCSO-524 had no additive pressure-lowering effect**.
- NT-proBNP: No significant change in either group.
- Laboratory: At Day 70 the PCSO-524 group had higher RDW ($P = 0.01$) and neutrophil-to-lymphocyte ratio ($P = 0.02$) and lower plasma protein ($P = 0.03$) than placebo; mean values stayed within reference ranges.
- Safety: The authors describe PCSO-524 as safe and well tolerated alongside sildenafil.

14. PCSO-524 as Adjunctive Therapy for Noninfectious Pododermatitis in Rabbits

Wiley Veterinary Medicine International Volume 2025,
Article ID 4177859, 9 pages <https://doi.org/10.1155/vmi/4177859>

This randomized, blinded, placebo-controlled trial tested green-lipped mussel oil (PCSO-524) added to standard care in rabbits with Grade 1–2 noninfectious pododermatitis.

After 56 days, combined hind-limb lesion size fell significantly in the PCSO-524 group (98.6 ± 53.2 mm², p = 0.002) but not in the placebo group (94.0 ± 75.6 mm², p = 0.58). No adverse events were associated with PCSO-524.

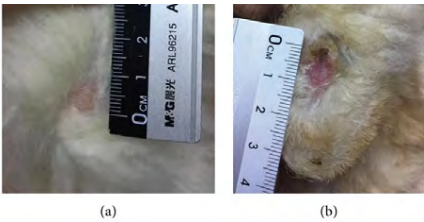


Figure 1 Visual grading of pododermatitis lesions.

(a) Grade 1 pododermatitis: a small circular area with minimal alopecia, hyperemia, and/or hyperkeratosis of the skin, but no evidence of infection or bleeding of underlying tissues. (b) Grade 2 pododermatitis: a circumscribed area with alopecia, erythema, and scaling with no signs of infection.

Study design:
Randomized (stratified by breed),
double-blind, placebo-controlled
trial in client-owned rabbits,
conducted June–December 2017.
30 rabbits were enrolled and 23
were analysed. Assessments took
place on Days 0, 28 and 56.



	PCSO-524 arm	Placebo arm
n (analysed)	13	10
Test product	PCSO-524 capsule (50 mg Perna canaliculus oil, 35 ± 5% DHA + EPA, 0.225 mg vitamin E), given daily	Visually identical capsule (50 mg sunflower oil), given daily
Standard care	Topical mupirocin, thick clean bedding, no wire-floor contact	Same
Duration	56 Days	56 Days

Outcomes (both arms):

- Lesion area: standardized hock photos, measured in ImageJ by 3 blinded assessors.
- Bloods: CBC and serum biochemistry (BUN, creatinine, total protein, albumin).
- Safety: adverse events.

Results

• **Lesion size:** The PCSO-524 group showed a significant ~46% reduction (right, left and combined hind limbs), while the placebo group did not change significantly. There was no significant difference between groups at any visit (Day 56 combined: p = 0.50).

• **Haematology:** Values stayed within normal ranges. Monocytes rose and eosinophils fell in both groups, and HLR stayed above 1:1 throughout. The only between-group difference was a higher baseline HLR in the placebo group (p = 0.03).

• **Safety:** No adverse events were associated with PCSO-524.

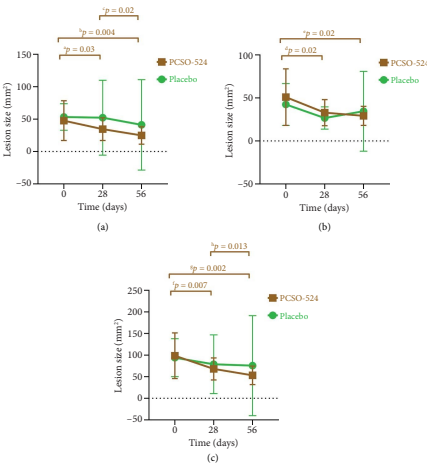


Figure 2 Changes in lesion size of hindlimbs in rabbits with pododermatitis.
(a) Right hind limb, (b) left hind limb, and (c) both hind limbs combined. Plots show the mean±SD at each visit for rabbits receiving PCSO-524 (n=13, filled squares) or placebo (n=10, filled circles). Superscripts (a–h) indicate statistically significant differences between visits within the PCSO-524 group.

Safety in canines:

Thai Journal of Veterinary Medicine 2014 44(4):505-511

A clinical trial specifically examining the safety of Antinol use in canines was conducted **using a range of doses over a period of 8 weeks** in a group of healthy Beagle dogs²³. The experiment used laboratory conditions and standardised all aspects of feeding, activity etc. of the dogs. **Antinol was given in four even groups amongst 40 dogs in doses of either 0, 100, 300, or 1000 mg/day**. The highest dose is **5X the normal recommended dose** for Antinol.

The study measured a range of biochemical tests including liver and kidney function tests, glucose, cholesterol levels, and tests of prolonged bleeding time. The dogs were also closely observed for clinical changes such as weight, feed intake, faecal excretion, physical examination and behavioural change.

Over the 8 week period there was no significant difference in any of the parameters tested in any of the groups of dogs and the authors concluded that **Antinol did not have a harmful effect**.



Safety in Felines:

Poster Presentation the 10th VPAT REGIONAL VETERINARY CONGRESS 2017

A clinical trial specifically examining the safety of Antinol use in canines was conducted **using a range of doses over a period of 28 days in 3 group of healthy Mixed breeds cats (n=7)**, aged 1 to 5 years, body weights 3 to 5 kgs.

The Antinol dosage given are as following: **1x the recommended maximum dose (2 caps daily), 2x the recommended maximum dose (4 caps daily) and 3x the recommended maximum dose (6 caps daily)**, with daily food for **28 days**.

Individual feline health and physical examinations, including vital signs, ocular, nervous, musculoskeletal, and integumentary systems, were conducted. Signs of illness and behavioural changes were recorded, as were changes in hematology and blood chemistry values. Food and water consumption, and body weight were measured every day.

The results of this study demonstrated that CBC and blood chemistry levels were within the normal reference ranges among clinically healthy normal cats administered two to four capsules of PCSO-524 per day for 28 days.

At a dose of six capsules per day, feline blood samples revealed lipemia, which may have been due to the fact of PCSO-524 comprises triglycerides (TG, 10-25%), free fatty acids (FFA, 7-12%) and sterols (ST, 12-18%) (1). **PCSO-524 supplementation at two to four capsules per day for 28 days in clinically healthy normal cats has no adverse effects**. Further study is needed to investigate the role of PCSO-524 in geriatric cats with DJD and other degenerative diseases in the future.

**Keep
happiness
in motion**





Research in laboratory animals

Testing in laboratory animals (predominantly rats) has also demonstrated either **inhibition of arthritic development** (prophylaxis) or **improvement in induced arthritic symptoms** (treatment) with PCSO-524®.

The classic test for osteoarthritis uses an arthritic adjuvant injected into the animal to produce arthritic changes in the joints. A series of Chinese studies utilising this model has shown excellent results both in the arthritic signs as well as the cytokines and inflammatory protein expression in rats ^{3, 33, 34}. These results have been supported by an Australian study showing treatment results with up to 52% greater effect than controls and an equivalence to pharmaceutical treatment ⁴.

In laboratory studies, PCSO-524® had a substantial effect on the production of cytokines known to be associated with inflammation (IL-6, IL-1 α TNF- α , IFN- α).

Feeding with PCSO-524® was associated with significantly decreased expression levels of TNF- α and IFN- α when compared to the NSAID naproxen (positive control) and, even more, when compared with extra-virgin olive oil (negative control), see Figure 11 ³.

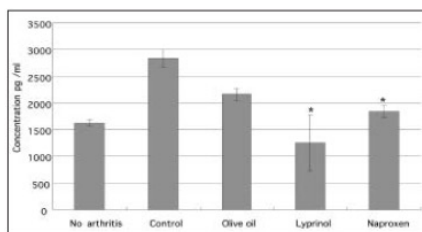


Figure 12 Amount of pro-inflammatory cytokine TNF- α – 14 days after arthritis induction in rats ³

PCSO-524® was found to be effective in both prophylactic or therapeutic treatment of induced arthritis in rats but showed **little or no activity in acute irritation assays** (carrageenan, kaolin, histamine) indicating it is not mimicking rapid-acting NSAIDs ⁵. Sub fractions of the oil also inhibited leukotriene-B4 and prostaglandin E2 (PGE2) biosynthesis in vitro. **The other significant finding across these studies was that PCSO-524® was not gastro-toxic like the drugs of the NSAID series** ⁵.

In vitro research

Anti-inflammatory effect

A significant study showing PCSO-524® to be an effective COX inhibitor was conducted in 2007². This study showed that PCSO-524® moderately inhibited ovine COX-1 and COX-2 pure enzymes in vitro. The PCSO-524® was fractionated to find the most active fraction of the oil (which was determined to be the free fatty acids) and compared with fish oil for inhibition at 1µg/ml, see Figure 13.

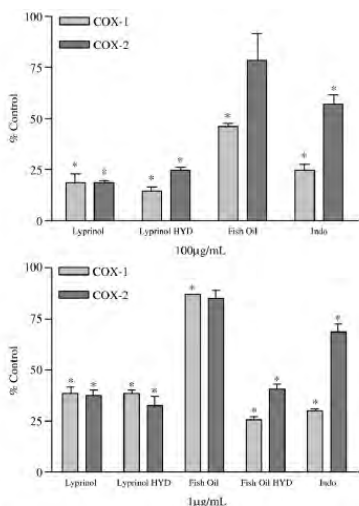


Figure 13 Inhibition of COX-1 and COX-2 by Lyprinol, fish oil and indomethacin at 100 and 1 µg/mL. Lyprinol HYD = hydrolysed Lyprinol complex and Fish oil HYD = hydrolysed fish oil complex²

The study suggests that **PCSO-524® can be used as an arachidonic acid (AA) substrate substitute in the production of prostaglandins** and that therefore it can be used as an alternative for conventional NSAIDs and fish oil treatment for the relief of the symptoms of arthritis.

Additionally, the study showed that PCSO-524® was able to selectively inhibit the different forms of COX, which highlighted the effect for longer term pain management and set it apart from the NSAIDs.

Earlier, the inhibition of the 5-LOX pathway had been demonstrated by showing the decreased activation of this pathway in monocytes incubated with PCSO-524¹. There have been several more recent studies looking into the anti-inflammatory properties and mechanisms of action.

Important new research in 2007 showed that **the isolated fatty acids of P. canaliculus have significant anti-inflammatory activity**, being effective in the LOX pathway⁶. When these free fatty acids from PCSO-524 were fractionated, a novel class of fatty acids was found called furan fatty acids³⁶. This research group then demonstrated the anti-inflammatory activity of these isolated constituents in a rat model of arthritis.

Chondroprotective effect

There is more than just an anti-inflammatory effect that has been attributed to this unique lipid extract. In vitro simulated digestion of green-lipped mussel has demonstrated not only **effective inhibition of inflammatory PGE2 production**, but also an **increased level of glycosaminoglycan (GAG) release**³⁷. These GAGs are important for the maintenance and repair of cartilage, and may be linked to the reduction in the marker of cartilage destruction - WF6, seen in animal OA research²⁰. A separate study has shown that the anti-inflammatory action of this extract in chondrocytes was similar to the pharmaceutical deracoxib when studied in vitro using canine chondrocytes³⁸.

Dosage

The recommended dosage for oral administration is based on bodyweight.

Recommended dosage for dogs & cats: 1 Antinol capsule per 20 kg. body weight

A loading dose of twice the usual dosage is recommended for **the first 14 days of treatment**.



Required caps	Dog < 10 kgs	Dog < 20 kgs	Dog > 20 kgs	Cat
First 2 weeks	2 caps daily	2 caps daily	3-4 caps daily	2 caps daily
After 2 weeks	1 cap daily	1 cap daily	2 caps daily	1 cap daily

Maintenance dose: applied after loading dose period under Vet supervision.

APPLICATION – Antinol may be fed by hand or placed on food during or before feeding. Care should be taken to ensure that the dog consumes the complete dose to maximise benefits of efficacy.

References

1. Dugas B. Lyprinol inhibits LTB4 production by human monocytes. *Allerg Immunol*, 2000. 32(7): p. 284-289.
2. McPhee S, Hodges LD, Wright PFA, Wynne PM, Kalafatis N, Harney DW, et al. Anti-cyclooxygenase effects of lipid extracts from the New Zealand green-lipped mussel, *Perna canaliculus*. *Comp Biochem Physiol B: Biochem Mol Biol*, 2007. 146(3): p. 346-356.
3. Lee CH, Butt YKC, Wong MS, Lo SCL. A lipid extract of *Perna canaliculus* affects the expression of pro-inflammatory cytokines in a rat adjuvant-induced arthritis model. *Eur Ann Allergy Clin Immunol*, 2008. 40(4): p. 148-153.
4. Singh M, Hodges LD, Wright PFA, Cheah DMY, Wynne PM, Kalafatis N, et al. The CO2-SFE crude lipid extract and the free fatty acid extract from *Perna canaliculus* have anti-inflammatory effects on adjuvant-induced arthritis in rats. *Comp Biochem Physiol B: Biochem Mol Biol*, 2008. 149(2): p. 251-258.
5. Whitehouse MW, Macrides TA, Kalafatis N, Betts WH, Haynes DR, Broadbent J. Anti-inflammatory activity of a lipid fraction (Lyprinol) from the NZ green-lipped mussel. *Inflammopharmacology*, 1997. 5(3): p. 237-246.
6. Treschow AP, Hodges LD, Wright PFA, Wynne PM, Kalafatis N, Macrides TA. Novel anti-inflammatory n-3 PUFAs from the New Zealand green-lipped mussel, *Perna canaliculus*. *Comp Biochem Physiol B: Biochem Mol Biol*, 2007. 147(4): p. 645-656.
7. Wolyniak CJ, Brenna JT, Murphy KJ, Sinclair AJ. Gas chromatography-chemical ionization-mass spectrometric fatty acid analysis of a commercial supercritical carbon dioxide lipid extract from New Zealand green-lipped mussel (*Perna canaliculus*). *Lipids*, 2005. 40(4): p. 355-360.
8. McPhee S, Kalafatis N, Wright P, Macrides T, (eds). The marine oil Lyprinol®, is a substrate for the 5-lipoxygenase enzyme in porcine neutrophils. in *Proc Aust Soc Clin Exp Pharmacol Toxicol*, 2001. 9: 95.
9. Whitehouse M, Roberts M, Brooks P. Over the counter (OTC) oral remedies for arthritis and rheumatism: How effective are they? *Inflammopharmacology*, 1999. 7(2): p. 89-105.
10. Rialland P, Bichot S, Lussier B, Moreau M, Beaudry F, del Castillo JRE, et al. Effect of a diet enriched with green-lipped mussel on pain behavior and functioning in dogs with clinical osteoarthritis. *Can J Vet Res*, 2013. 77(1): p. 66-74.
11. Kwananocha I, Vijarnsorn M, Kashemsant N, Lekcharoensuk C. Effectiveness of disease modifying osteoarthritis agents and carprofen for treatment of canine osteoarthritis. *Thai J Vet Med*, 2016. 46(3): p. 363-371.
12. Soontornvipart K, Mongkhon N, Nganvongpanit K, Kongtawelert P. Effect of PCSO-524 on OA biomarkers and weight-bearing properties in canine shoulder and coxofemoral osteoarthritis. *Thai J Vet Med*, 2015. 45(2): p. 157-165.
13. Sundaravibhata K, Mongkhon N, Meahasab P. Application of the polyunsaturated fatty acid compound PCSO-524 in the post-operative recovery of dogs that have had stifle surgery. *WSAVA 38th Ann Cong. Auckland, New Zealand* 2013.
14. Sekar S, Crawford R, Xiao Y, Prasadam I. Dietary fats and osteoarthritis: Insights, evidences, and new horizons. *J Cell Biochem*, 2017. 118(3): p. 453-463.
15. Miles EA, Calder PC. Influence of marine n-3 polyunsaturated fatty acids on immune function and a systematic review of their effects on clinical outcomes in rheumatoid arthritis. *Br J Nutr*, 2012. 107 Suppl 2: p. S171-S184.
16. Bacchi S, Palumba P, Sponta A, Coppolino MF. Clinical pharmacology of non-steroidal anti-inflammatory drugs: A review. *Antiinflamm Antiallergy Agents Med Chem*, 2012. 11(1): p. 52-64.
17. Lascelles BD, McFarland JM, Swann H. Guidelines for safe and effective use of NSAIDs in dogs. *Vet Therap*, 2005. 6(3): p. 237-51.
18. Whitehouse MW, Butters DE. Combination anti-inflammatory therapy: Synergism in rats of NSAIDs/corticosteroids with some herbal/animal products. *Inflammopharmacology*, 2003. 11(4-6): p. 453-464.
19. Mongkon N, Soontornvipart K. Preliminary study of the clinical outcome of using PCSO-524 polyunsaturated fatty acid compound in the treatment of canine osteoarthritis and degenerative spinal diseases. *Thai J Vet Med*, 2012. 42(3): p. 311-317.
20. Kongwut S, Soontornvipart K, Sarikaphuti M, Makoom P, Nganvongpanit K. Effects of serum IL-1beta of PCSO-524 and Firocoxib in dogs undergoing medial patellar luxation repair. *Thai J Vet Med*, 2015. 45(4): p. 639-643.
21. Dinarello CA. Interleukin-1 in the pathogenesis and treatment of inflammatory diseases. *Blood*, 2011. 117(14): p. 3720-3732.
22. van Dalen SC, Blom AB, Sløtjes AW, Helsen MM, Roth J, Vogl T, et al. Interleukin-1 is not involved in synovial inflammation and cartilage destruction in collagenase-induced osteoarthritis. *Osteoarthritis Cartilage*, 2017. 25(3): p. 385-396.

23. Jamikorn U, Yibchok-anun S. Effects of dietary polyunsaturated fatty acid supplement on healthy Beagle dogs. *Thai J Vet Med*, 2014. 44(4): p. 505-511.
24. Szechinski J, Zawadzki M. Measurement of pain relief resulting from the administration of Perna canaliculus lipid complex PCSO-524™ as compared to fish oil for treating patients who suffer from osteoarthritis of knee and/or hip joints. *Rheumatologia*, 2011. 49(4): p. 244-252.
25. Zawadzki M, Janosch C, Szechinski J. Perna canaliculus lipid complex PCSO-524™ demonstrated pain relief for osteoarthritis patients benchmarked against fish oil, a randomized trial, without placebo control. *Mar Drugs*, 2013. 11(6): p. 1920-1935.
26. Cho SH, Jung YB, Seong SC, Park HB, Byun KY, Lee DC, et al. Clinical efficacy and safety of Lyprinol, a patented extract from New Zealand green-lipped mussel (*Perna Canaliculus*) in patients with osteoarthritis of the hip and knee: A multicenter 2-month clinical trial. *Eur Ann Allergy Clin Immunol*, 2003. 35(6): p. 212-216.
27. Gibson SLM, Gibson RG. The treatment of arthritis with a lipid extract of Perna canaliculus: A randomized trial. *Complement Ther Med*, 1998. 6(3): p. 122-126.
28. Puente R, Illnait J, Mas R, Mendoza S, Carbajal D, Fernández J, et al. Effects of D-002, a mixture of beeswax alcohols, co-administered with green-lipped mussel extract, on osteoarthritis symptoms. *Int J Pharm Sci Rev Res*, 2014. 27(1): p. 209-216.
29. Lau CS, Chiu PKY, Chu EMY, Cheng IYW, Tang WM, Man RYK, et al. Treatment of knee osteoarthritis with Lyprinol, a lipid extract of the green-lipped mussel: A double-blind placebo-controlled study. *Prog Nutr*, 2004. 6(1): p. 17-31.
30. Audefval B, Bouchacourt P. Double-blind trial against placebo of extract of Perna canaliculus (green-lipped mussel) in osteoarthritis of the knee. *Gaz Med Fr*, 1986. 93: p. 111-116.
31. Gibson RG, Gibson SL, Conway V, Chappell D. Perna canaliculus in the treatment of arthritis. *Practitioner*, 1980. 224: p. 955-960.
32. Gandek B. Measurement properties of the Western Ontario and McMaster Universities Osteoarthritis Index: A systematic review. *Arthritis Care Res*, 2015. 67(2): p. 216-229.
33. Lau CS, Chiu PKY, Chu EMY, Cheng IYW, Tang WM, Man RYK, et al. Treatment of knee osteoarthritis with Lyprinol, a lipid extract of the green-lipped mussel: A double-blind placebo-controlled study. *Prog Nutr*, 2004. 6(1): p. 17-31.
34. Lee CH, Butt YKC, Wong MS, Lo SCL. Differential protein expression induced by a lipid extract of Perna canaliculus in splenocytes of rats with adjuvant-induced arthritis. *Inflammopharmacology*, 2008. 16(4): p. 188-194.
35. Lee C-H, Lum JH-K, Ng CK-C, McKay J, Butt YK-C, Wong M-S, et al. Pain controlling and cytokine-regulating effects of Lyprinol, a lipid extract of Perna canaliculus, in a rat adjuvant-induced arthritis model. *Evid Based Complement Alternat Med*, 2009. 6(2): p. 239-245.
36. Wakimoto T, Kondo H, Nii H, Kimura K, Egami Y, Oka Y, et al. Furan fatty acid as an anti-inflammatory component from the green-lipped mussel Perna canaliculus. *Proc Natl Acad Sci*, 2011. 108(42): p. 17533-17537.
37. Pearson W, Orth MW, Karrow NA, MacLusky NJ, Lindinger MI. Anti-inflammatory and chondroprotective effects of nutraceuticals from Sasha's Blend in a cartilage explant model of inflammation. *Mol Nutr Food Res*, 2007. 51(8): p. 1020-1030.
38. Yanez JA, Remsberg CM, Vega-Villa KR, Miranda ND, Navas J, Ohgami Y, et al. Pharmacological evaluation of Glyco-Flex® III and its constituents on canine chondrocytes. *J Med Sci*, 2008. 8: p. 98-101.
39. Beale S, Brian, Vijarnsorn Monchanok, Kawanancha Irin, Necas Alois, Lascelles X, B.Duncan. The Effectiveness of Marine Based Fatty Acid compound (PCSO-524) Alone and Combined with Firocoxib in the treatment of Canine Osteoarthritis. *Veterinary Orthopaedic Society Conference*. March 2018.
40. Vijarnsorn Monchanok, Kwanancha Irin, Kashemsant Naruedee, Jarudecha Thitichai, et al. Effectiveness of Marine Based Fatty Acid compound (PCSO-524) and Firocoxib in the treatment of Canine Osteoarthritis. *BMC Veterinary Research* 2019 OCT 17;15(1):349
41. Kwanancha Irin. *Journal of Thai Veterinary Practitioners*. 2020 (Synopsis)
42. Rungrinirundon Teerapat, Senarut Napaporn. PCSO-524 (Antinol®) Use in Fighting Cocks for Treatment of Chronic Pododermatitis. *Journal of Thai Veterinary Practitioners*. 2020 (Synopsis)
43. Nishida Koji. PCSO-524 Report Clinical Results of Nineteen Dogs with Tracheal Collapse that received PCSO-524, a Lipid Extract of New Zealand Green Lipped Mussel (Perna canaliculus). *Journal of Modern Veterinary Medicine (MVM)* Vol.24 No.163 (2016)
44. Tanrattana Chaiyot, Panitarnangit Sivavatchr, Moolasatsathorn Warawadee. Clinical Study of PCSO-524 (Antinol) as nutraceutical in Canine allergic skin disease. *World Veterinary Association Congress* 2018

PCSO-524® a unique and stabilised oil extract from Green Lipped Mussels

Mussel powder is the by product of this proprietary process. Antinol® contains no mussel powder.

Scientific Studies
and Case Reports
of PCSO-524®[Read all Publications](#)

Top Authors

-  **B. Duncan X. Lascelles, BSc, BVSc, PhD, FRCVS, CertVA, DSASIST, DECVS, DACVS, EEVSB European Specialist in Small Animal Surgery**
-  **Brian S. Beale, DVM, DACVS, West Coast Veterinarian Hospital (USA)**
-  **Monchanok Vijarnsom, DVM, PhD, Kasetsart University (TH)**
-  **Ulra Jamikorn, DVM, Ms, PhD, Chulalongkorn University (TH)**
-  **Rosama Pusoonthornthum, DVM, Ms, PhD, Chulalongkorn University (TH)**
- Total : 58 Authors in the website**

Discover Studies



Bone & Joint



Renal



Skin Disease



Cardiovascular

Smart Search

Study / Case

Published year

Filter Studies by Smart Tags

-
-
-
-
-

Antinol® Latest Studies

Sorted by recent

 **The Effectiveness of Marine Based Fatty Acid Compound (PCSO-524) and Firocoxib in the Treatment of Canine Osteoarthritis** **BMC Veterinary Research (2019) 15:349**

 **Authors:** Monchanok Vijarnsom, Irin Iwananocha, Narudee Kasemsant, Thitichai Jarudecha, Chalermpol Lekcharoensuk, Bruno Peirone, Brian S. Beale, B. Duncan X. Lascelles

This trial included 40 mixed breed dogs with x-ray confirmed Osteoarthritis split into four different treatment groups for four weeks.

This study suggests that the combination of PCSO-524 and carprofen together was superior to other treatments for management of canine Osteoarthritis. Results were seen in both objective and clinical assessment.

[VIEW](#)

Updated Study Topics

New researches and publications related to PCSO-524® and its result in clinical test submitted by veterinarians on the global conferences every year and the data keeps growing with more studies conducted

Discover More Studies

[Click to see the digital library](#)

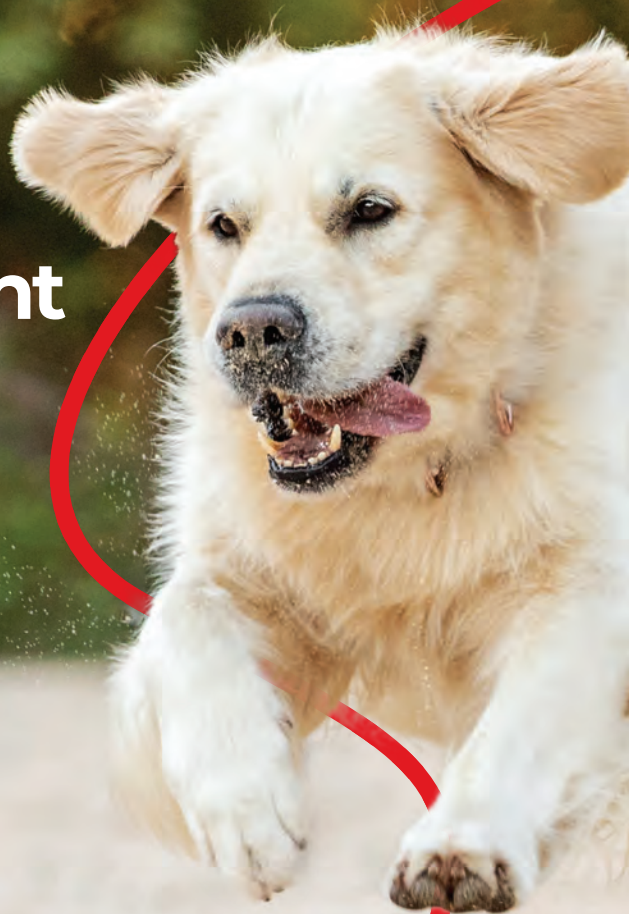
Antinol[®]

THE EXECUTIVE SUMMARY

www.Antinolstudies.com

Keep happiness in motion

A
supplement
for daily
joint care



Antinol[®]
PLUS EAB-277[®]



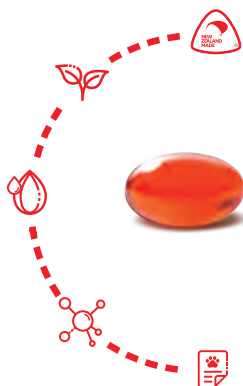
A supplement for daily joint care

Keep happiness in motion

Antinol® Rapid is a potent synergistic blend of 2 marine lipid extracts chosen for their unique enhancement formula called **EAB-277®**.

EAB-277® is the key active ingredient of this advanced formula formulated to promote optimal benefits through its synergistic efficacy contains > 90 free fatty acids full spectrum of Omega 3 including ETA, EPA, DHA as well as other key Polyunsaturated fatty acids (PUFAs) and antioxidants.

The excellency
of Antinol® Plus
EAB-277®



NATURAL

Sourcing + Farming in New Zealand

PRODUCTION PROCESS

Proprietary CO2 Supercritical
Extraction + Stabilization

ADVANCEMENT

of the Synergistic blend Potent +
Patented formula

ENHANCED BIOAVAILABILITY

and Fast Action

EFFICACY PROVEN

by Scientific Researches both
invitro and invivo

The two marine lipids used in Antinol® Plus are proprietary and exclusively produced. The exact combination of 30mg lipid fractions from **Perna canaliculus (New Zealand green lipped mussel)** and 20mg **high phospholipid krill oil** is the result of years of research combining and isolating lipid groups and essential fatty acids to find the optimal nutrient synergy.

Our proprietary high phospholipid krill oil is high in polar lipid enrichment which enhances bioactivity "Potency" of this marine oil blend formula as a result of proven efficacy.

The Antinol® Plus EAB-277® blend has been proven via laboratory tests to be **more effective than either of the individual lipids alone** in inhibiting inflammation markers such as nitric oxide, TNFα, and IL-6.

+ **Perna canaliculus**
(New Zealand)



+ **High Phospholipid Krill Oil**
(Antarctic)



**“Are my
dogs on
Antinol®?
Absolutely
+ Always!**

[Mattise + Mel, Antinol® 4 Years]

Backed by **science** and extensive research



REVIEWED
INTERNATIONALLY
BY VETERINARIANS



RECOMMENDED
BY VETERINARIANS
GLOBALLY



SAFE TO USE +
DOES NOT INTERACT WITH
OTHER MEDICATIONS



TESTED FOR
STABILITY +
PURITY



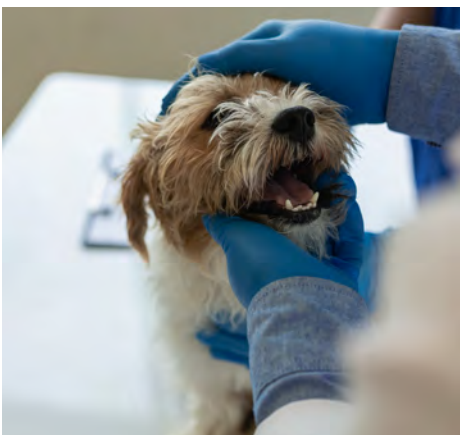
THE LEADING JOINT
AND MOBILITY SUPPORT
PRODUCT IN JAPAN

- Suitable for long-term use for disorders or as a preventative + wellness supplement
- Patented and stabilized oil extracts
- 100% natural, free from Heavy metal such as Mercury, Cadmium etc. Clear from toxins
- No synthetic preservatives or fillers
- Fully traceable and sustainable
- No report of contraindications*
- According to safety study no known adverse effects have been reported.

*The safety of this product has not been tested in pregnant or lactating animals.
May contain a minute amount of tropomyosin protein

Antinol® Plus Animal Clinical Studies:

1. Evaluation of Green Lipped Mussel/Krill Oil (EAB-277), Biotaorientalis Extract, and an NSAID for Canine Hip Osteoarthritis Pain



Study Design:

In a prospective, black-randomized, double-blinded, placebo-controlled trial, 101 client-owned dogs with hip OA (one limb more affected than the other) were assigned to one of four groups

1. EAB-277 (n=26)
2. 4CYTE (n=25)
3. meloxicam (n=24)
4. or placebo (n=26)

Osteoarthritis (OA) is a common cause of chronic pain in dogs, yet limited high-quality evidence exists to guide veterinarians on the comparative efficacy of widely marketed joint supplements.

Objective: To compare the analgesic efficacy of a green-lipped mussel plus krill oil extract (EAB-277, Antinol® Rapid), a Biota orientalis extract (4CYTE Epiitalis® Forte), the NSAID meloxicam, and a placebo in dogs with hip OA-associated pain.

Peak vertical force (PVF) via force-plate gait analysis, orthopedic assessment scores (OAS), and hematology/serum chemistry were evaluated at baseline and at 2, 4, and 6 weeks.

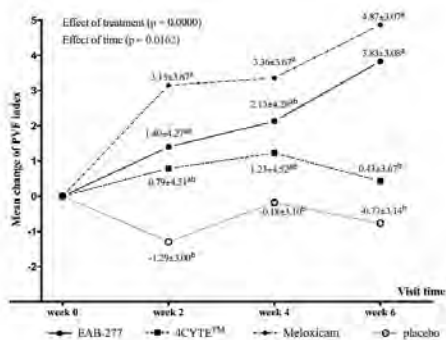


Figure 1

Figure. Mean (±SD) change from baseline in peak vertical force (PVF) of the index limb over 6 weeks. EAB-277 and meloxicam produced significantly greater improvement in limb use than 4CYTE and placebo. Differing superscript letters (a, b) indicate significant between-group differences at each time point. Reproduced from Kampa et al. (2024), Front Vet Sci, distributed under CC BY 4.0.

Results;

By week 6, both the EAB-277 and meloxicam groups showed statistically significant increases in PVF from baseline (mean change ≈3.8% and ≈4.9% of body weight, respectively), while changes in the 4CYTE and placebo groups remained non-significant and were not different from each other. Responder rates (≥2% PVF improvement) at week 6 were 69% for EAB-277, 79% for meloxicam, 40% for 4CYTE, and 8% for placebo. Overall OAS scores at week 6 were significantly lower (indicating less impairment) in the EAB-277, meloxicam, and 4CYTE groups compared with placebo. No adverse events or clinically significant hematologic/biochemical abnormalities were observed.

Conclusion: **EAB-277 produced objectively measurable improvements in limb function comparable in magnitude to the NSAID meloxicam**, while the Biota orientalis-based supplement (4CYTE) did not differ from placebo on the primary objective outcome measure, despite some benefit on subjective assessment scores.

2. Study of the effectiveness of glucosamine and chondroitin sulfate, marine based fatty acid compounds (PCSO-524® and EAB-277®), and carprofen for the treatment of dogs with hip osteoarthritis:

A prospective, block-randomized, double-blinded, placebo-controlled clinical trial



Study Design:

There were 15 dogs per group under treatment over 6 weeks.

1. Dasuquin
2. Carprofen
3. PCSO-524®
4. EAB-277®
5. Placebo

This 75 dogs' study at Khon Kaen University, Thailand was investigating the effectiveness of these compounds for the treatment of dogs with degenerative osteoarthritis and also to demonstrate the significantly superior therapeutic effect of PCSO-524® and EAB-277® compared with a placebo.

The study used **objective force plate gait analysis**, **subjective orthopedic assessment scores**, **hematology and blood chemistry profile analysis** and **subjective owner assessment scores**.

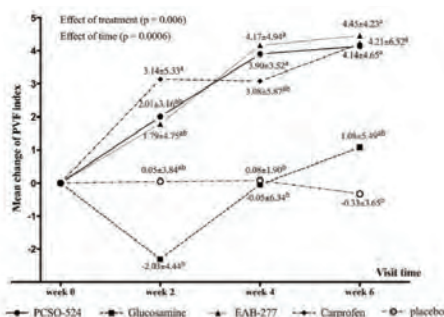


Figure 1

Graphic representation of the mean ($\pm$ standard deviation) change from baseline in PVF for each group during the study period. Different superscripts (a, b) indicate significant differences between groups for change in PVF.

Results;

Overall, the results of this study indicate that **there appear to be benefits of carprofen, PCSO-524®, and EAB-277® for the treatment of OA-pain in dogs based on the measurement of PVF.** Glucosamine/chondroitin and placebo (sunflower oil) did not appear to be associated with positive treatment effects based on the measurement of PVF.

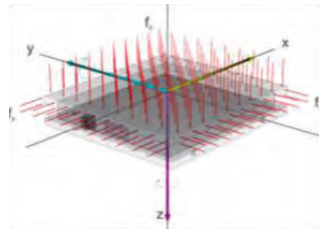
At 4 and 6 weeks after treatment, **the change in PVF of both PCSO-524® and EAB-277® were similar to that of the carprofen group.** The PVF of placebo group remained unchanged (-0.33 ± 3.65) as expected after study completed (6 weeks). The changes in PVF (significant when compared to baseline) in this study with carprofen after 2, 4, and 6 weeks were 3.14 ± 5.33 , 3.08 ± 5.87 , and 4.21 ± 6.52 , respectively.

These values are similar to those of a recent study⁽²⁸⁾ which found an increase in PVF of 3.2 ± 0.8 after 2 weeks treatment of carprofen. In that study, most enrolled dogs had hip OA, and the baseline PVF for index limb was similar in both studies (62.1 ± 13.5 and 60.7 ± 13.5).

Our result is also similar to another OA study⁽²²⁾ using the NSAID treatment firocoxib where the change in PVF of the index limb was reported to be 3.03 ± 4.67 and 3.25 ± 4.13 at 2 and 4 weeks. treatment, respectively.

Other Diagnostic Tools:

- 1) Gait analysis: Objective measurement
- 2) Provide quantitative weight bearing force
 - Force plates
 - Pressure sensitive mats



3.

A Randomized Placebo Controlled Trial - Preliminary Study of the effects of PCSO-524[®] and EAB-277[®] on Renal Protective Function in the case of long term NSAID use for osteoarthritis in dogs.

This study at Kasetsart University, Thailand is designed to **determine the potential efficacy of PCSO-524[®] on renal (kidney) protection in the long term (4 week) NSAID treatment of dogs.**

This clinical trial is being conducted on 100 owned client dogs divided into five groups: (i) NSAID: Meloxicam (Metacam, Boehringer Ingelheim Animal Health), (ii) PCSO-524[®], (iii) EAB-277[®], (iv) a combination of PCSO-524[®] with Meloxicam and (v) Placebo.

The full parameters of renal function evaluation will be conducted to monitor the renal function of the dogs in each group including the newly innovative biomarkers (SDMA test, Idexx) and the CRP inflammatory cytokine test. The study also will show the effects of EAB-277[®] on renal function.

Results;

The results showed that the combination of PCSO-524[®] with the various NSAID formulas **provided no negative effect to the dogs' kidneys** during their treatment with NSAIDs.

The results of this Renal study will include in the Meloxicam study manuscript which is under preparation process to submit Peer Review Journal.

Remarks; Unpublished data

4.

The Effect of EAB-277® on Heart Rate Variability (HRV) in Dogs with Tracheal Collapse.

This preliminary project funds veterinary students at Chiang Mai University, Thailand.

The hypothesis is **to study the effects of EAB-277® to see if it will help decrease HRV impairment due to systemic inflammatory processes** which could induce the dysfunction of the sympathetic nervous system as well as the parasympathetic nervous system.

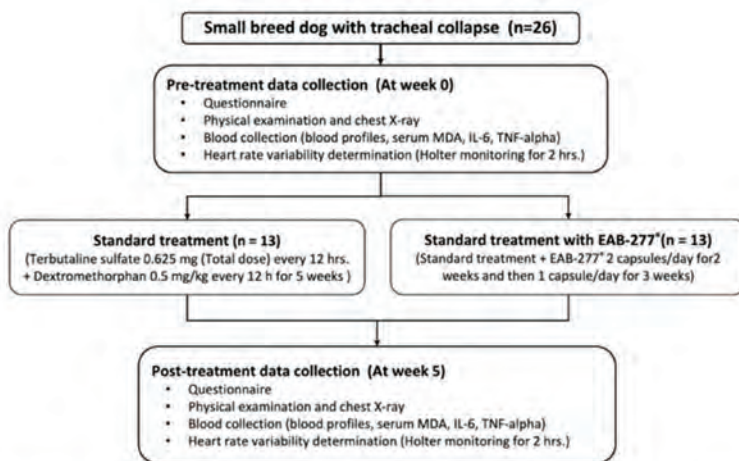


FIGURE 1 | Schematic representation of the study protocol. At pre-treatment, all dogs underwent chest X-ray, blood collection, Holter recording for 2-h. Then, dogs were divided into two groups to receive the standard treatment or standard treatment combined with polyunsaturated fatty acid EAB-277® from Green-Lipped Mussel blend for the 5 weeks. At post-treatment, all dogs underwent the re-assessment of chest X-ray, blood collection, Holter recording for 2-h to investigate cardiac sympathovagal balance, plasma oxidative stress, and inflammatory marker measurement. MDA, Malondialdehyde.

Ten small breed dogs will be used in this study and will be divided into two groups.

- The first group of five dogs comprises canine tracheal collapse patients given **standard treatment** for one month.
- The second group of five dogs comprises canine tracheal collapse patients given the **standard treatment plus EAB-277®** for one month.

Blood from all dogs will be collected for testing of morphology, blood chemistry and measurement of heart rate variability.

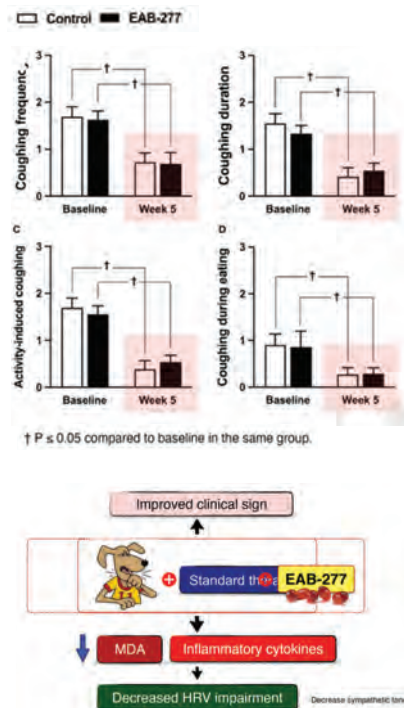


The project has been completed. However, since the results showed improvement in the EAB-277® group based on owner assessments, the study has been expanded to add objective inflammatory biomarker data which is expected to show the relation between clinical improvement and the reduction in the level of inflammation in the body based on scientific evidence developed in the study.

This expanded study was completed at the end of the third quarter of 2021 and has been published in *Frontiers in Veterinary Science*, a peer reviewed journal, in 2022.

This study demonstrated the beneficial effects of **EAB-277[®] supplementation combined with standard therapy on heart rate variability** in dogs with tracheal collapse.

Both standard treatment alone and standard treatment combined with EAB-277[®] **improved all clinical signs** as evaluated by the questionnaire.



The major findings of this study are as follows.

- First, EAB-277[®] supplementation for 5 weeks **did not affect the physical examination results, radiographic findings, or blood profile parameters** in the tracheal collapse dogs.
- Second, EAB-277[®] supplementation for 5 weeks **decreased oxidative stress and inflammatory marker compared to standard therapy** as indicated by serum MDA, canine serum IL-6 and canine TNF- α in tracheal collapse dogs.
- Third, EAB-277[®] supplementation for 5 weeks attenuated sympathovagal imbalance by **increasing parasympathetic activity** in tracheal collapse dogs.
- Fourth, using a questionnaire or evaluating TD/TI by chest X-ray was not accurate in evaluating the improvement of tracheal collapse in dogs.

Regarding clinical signs evaluated by questionnaire, **this study found improvement in clinical signs in tracheal collapse dogs after treatment compared to pre-treatment in both groups**, including a decrease in the frequency and duration of coughing, coughing induced by activities such as exercise, and eating and drinking.

A limitation of the questionnaire used in this study was the wide range of response scores and had much personal information, which could affect the reliability of the results.

This suggests that a questionnaire might not be appropriate as a prognostic tool for routine follow-up and routine examination in tracheal collapse dogs.

5.

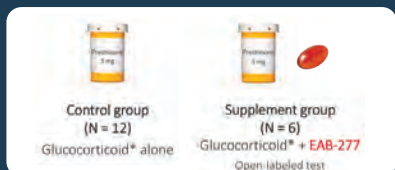
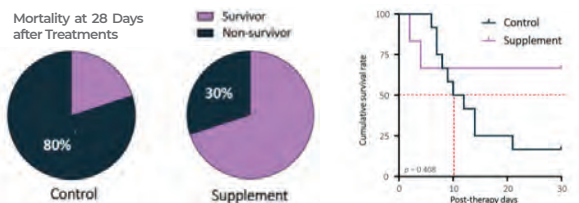
Supplementary effect of EAB-277® in Combination with Prednisolone against Immune-Mediated Hemolytic Anemia in Dogs.

This preliminary project funds veterinary students at Chiang Mai University, Thailand to determine the effects of EAB-277® in combination with Prednisolone against immune-mediated hemolytic anemia in dogs. Ten dogs will be separated into two groups (five dogs in each group).

- The first group of dogs with immune-mediated hemolytic anemia will be treated with **Prednisolone**.
- The second group of dogs with immune-mediated hemolytic anemia will be treated with **EAB-277® as the adjunctive treatment combined with the standard therapy.**

The results are expected to result in the reduction of the Prednisolone dosage in immune-mediated hemolytic anemia cases.

The results demonstrate that The mortality rate of dogs in the control group (80%) was higher than the supplement group (30%) (Figure 1a,b).



Immune-mediated hemolytic anemia (IMHA) is a common autoimmune disorder in dogs with a high fatality rate and it remains a therapeutic challenge.

The marine lipid extract, EAB-277®, is a natural anti-inflammatory nutraceutical product. However, the effects of EAB-277® in IMHA dogs has rarely been investigated.

The objective of this study is to assess the clinical effects of EAB-277® and prednisolone dose-tapering for supplemental therapy in IMHA dogs.

Prednisolone was given to 18 anemic IMHA dogs according to a standard regimen. Six dogs were supplementally treated with EAB-277® for 28 days and the remaining twelve dogs were a control group of untreated supplementations.

The Kaplan-Meier curve was used to demonstrate the survival time from a certain date to the time of IMHA dog death (Figure 1c).

The results show that the killing ability of IMHA was time-dependent.

In the control group, the survival time was 11 post-therapeutic days and the survival rate markedly declined to $16.7 \pm 10.7\%$ at 28-day post-therapeutic observation, whereas the survival rate of dogs in the supplement group was $66.7 \pm 19.2\%$ throughout the study period (log-rank test, $p = 0.408$).

When compared to pre-therapy, the supplement group's blood profiles improved ($p < 0.05$). The EAB-277® treated group showed a moderate decrease in the incidence rate (4.20 times) of prednisolone tapering compared to the control group.

The dosage reduction of prednisolone in supplement group was more than that in the control group ($p < 0.0001$).

Our results suggest that

EAB-277® supplementation may enhance clinical outcomes and lessen prednisolone dose-tapering in canine IMHA therapy.

6. Tracheal Collapse Study in Small Dogs.

These 40 small dog studies at the Mahidol Research Centre of the Mahidol Veterinary School, Thailand is designed to evaluate the efficacy of EAB-277® (Antinol® Plus) in reducing inflammation in tracheal collapse cases which is very common in small dog breeds causing the dog to have difficulty in breathing.

At present the common treatments prescribed for canine tracheal collapse are cough depressants, bronchodilators and steroids to control inflammation.

The objective of this study is to prove the anti-inflammatory efficacy of Antinol® Plus as an adjunctive supplement to the standard treatments in tracheal collapse cases to demonstrate Antinol's superior therapeutic effects, including increased exercise tolerance and less coughing.

Study Design:

There were 40 client owned dogs enrolled over 8 weeks in this study by split into 2 treatment groups as followed

- Control Group:
Standard treatment + Placebo
- Treatment group:
Standard treatment + EAB-277® supplementing

Results;

The treatment group showed improvement in respiratory effort and appetite compared to the placebo group after received the supplement on day 28 compared to day 14 ($P=0.017$ and 0.021).

Fluoroscopically, comparisons of diameter changing of tracheal height within groups showed a significant improvement in the treatment group at thoracic inlet region ($P=0.047$) when compared the changing diameter on day 14 to day 0.

Conclusion and clinical importance;

EAB-277®, the additional supplement for manage tracheal collapse in dogs can improve the quality of life and decrease percent change obtained from fluoroscopy.

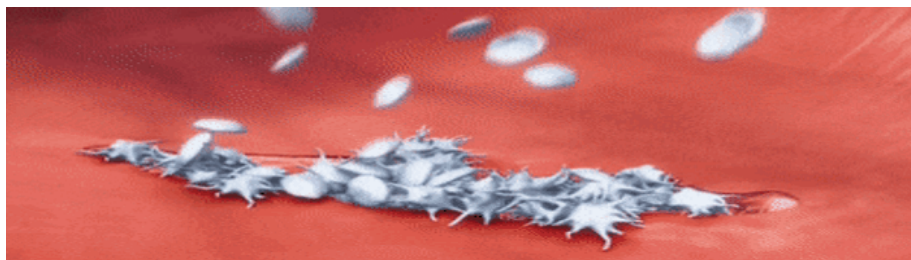
Remarks; Unpublished data



7.

Effects of marine based fatty acid compound EAB-277® on coagulopathy in dogs.

This preliminary project funds veterinary students at Kasetsart University, Thailand to investigate **whether long term supplementation of the marine based fatty acid compound EAB-277® affects blood coagulation**. If there is an effect, the study seeks to learn how long the canine patient needs to be withdrawn from the supplementation of EAB-277® prior to a surgical operation to reduce the risk of bleeding during the operation.



This preliminary study is being conducted by veterinary students on **nine dogs with a recommended dose** based on lean body weight and will **continue for three months**.

Blood samples will be collected to record

- The base line of hematology coagulation parameters
- Activated prothrombin time (apTT)
- Prothrombin time (PT)
- Thrombin time (TT)
- Collagen-epinephrine closure time (CEPI-CT)
- Collagen-ADP closure time (CADP-CT)

before prescribing EAB-277® at the outset and one, two and three months after treatment.

If there is no coagulopathy effect shown, all dogs will continue with EAB-277® and will be monitored for the above parameters on a weekly basis.

If coagulopathy is shown, then from that point EAB-277® will be withdrawn and the dogs will be followed on a weekly basis until their coagulation parameters have returned to normal.

Results;

The study demonstrated that **consumption of EAB-277® at 20 mg per kg (4 times of loading dose) continuously for 3 months did not prolong coagulation**. Although some dogs showed the higher collagen-epinephrine closure time (CEPI-CT) than Human reference range, it can not conclude that EAB-277® prolong coagulation in dogs as there is no report of Canine CEPI-CT moreover the delayed coagulation was interpreted based on > 300 sec. However the normal reference range for dogs and cats should be defined by studying in larger samples sizes.

Remarks; Unpublished data

8.

Safety Study of EAB-277® (Antinol® Plus) in Dogs.

This study at Chulalongkorn University, Thailand was proposed to evaluate the safety of EAB-277® in dogs which is required for veterinary product registration purposes. Initially a total of 40 mature beagles of 8 months in age or older were divided equally into four groups:

(i) placebo, (ii) recommended loading dose of two capsules per day, (iii) administration of six capsules once per day and (iv) administration of twenty capsules once per day



9.

Safety Study of EAB-277® (Antinol® Plus) in Cats.

This study at Chulalongkorn University, Thailand has been proposed to evaluate the safety of EAB-277® in cats which is required for veterinary product registration purposes. A total of 36 cats of 8 months in age or older were divided equally into four groups: (i) placebo, (ii) recommended dose of 1 capsule per day, (iii) administration of 3 capsules once per day and (iv) administration of 10 capsules once per day.



Results;

Animals used in the current study composed of **twenty healthy mature beagle dogs** (12 female and 8 male), body weight 9.50 ± 0.75 kg and twelve healthy mature domestic cats (8 female and 4 male), body weight 3.25 ± 0.50 kg. All animals had the body condition scores of 2 to 3 (on a 5-point scale) at the beginning of study.

Physical examination of all studied population composing of body temperature (38.4 – 38.8 °C), capillary refill time (CRT, 1 or 2 second) and fecal score (2.5 to 3.5) (on a 5-point scale) were all normal. No animals had neither constipation nor diarrhea.

Studied dogs and cats maintained their initial body condition without significant weight loss or gain. No abnormalities and illness sign of any system (ocular, nervous, musculoskeletal and integumentary systems) were observed. Blood parasite was not found for both dogs and cats.

Both dogs and cats of all four treatment groups preferred consumption of the PUFAs supplement capsules even the empty ones. No association was detected between the dose treatments and the dependent variables including blood hematology, blood chemistry, blood clotting factors, and PLI values.

Remarks; Unpublished data

References

- Franklin SP, Park RD, Egger EL. Metacarpophalangeal and metatarsophalangeal osteoarthritis in 49 dogs. *J Am Anim Hosp Assoc.* (2009) 45:112–7. doi:10.5326/0450112
- Rychel JK. Diagnosis and treatment of osteoarthritis. *Top Companion Anim Med.* (2010) 25:20–5. doi:10.1053/j.tcam.2009.10.005
- Johnston SA. Osteoarthritis. Joint anatomy, physiology, and pathobiology. *Vet Clin North Am Small Anim Pract.* (1997) 27:699–723. doi:10.1016/S0195-5616(97)50076-3
- Wright A, Anmodie DM, Cernicchiaro N, Lascelles BDX, Pavlock AM, Roberts C, et al. Identification of canine osteoarthritis using an owner-reported questionnaire and treatment monitoring using functional mobility tests. *J Small Anim Pract.* (2022) 63:609–18. doi:10.1111/jsap.13500
- Moreau M, Dupuis J, Bonneau NH, Desnoyers M. Clinical evaluation of a nutraceutical, carprofen and meloxicam for the treatment of dogs with osteoarthritis. *Vet Rec.* (2003) 152:323–9. doi:10.1136/vr.152.11.323
- Sanderson RO, Beata C, Flipo RM, Genevois JP, Macias C, Tacke S, et al. Systematic review of the management of canine osteoarthritis. *Vet Rec.* (2009) 164:418–24. doi:10.1136/vr.164.14.418
- Edamura K, King JN, Seewald W, Sakakibara N, Okumura M. Comparison of oral robenacoxib and carprofen for the treatment of osteoarthritis in dogs: a randomized clinical trial. *J Vet Med Sci.* (2012) 74:1121–31. doi:10.1292/jvms.11-0529
- Vasseur PB, Johnson AL, Budberg SC, Lincoln JD, Toombs JP, Whitehair JC, et al. Randomized, controlled trial of the efficacy of carprofen, a nonsteroidal antiinflammatory drug, in the treatment of osteoarthritis in dogs. *J Am Vet Med Assoc.* (1995) 206:807–11.
- Mansa S, Palmer E, Grondahl C, Lonaas L, Nyman G. Long-term treatment with carprofen of 805 dogs with osteoarthritis. *Vet Rec.* (2007) 160:427–30. doi:10.1136/vr.160.13.427
- Brown DC, Boston RC, Coyne JC, Farrar JT. Ability of the canine brief pain inventory to detect response to treatment in dogs with osteoarthritis. *J Am Vet Med Assoc.* (2008) 233:1278–83. doi:10.2460/javma.233.8.127
- Bhathal A, Spryszak M, Louizos C, Frankel G. Glucosamine and chondroitin use in canines for osteoarthritis: a review. *Open Vet J.* (2017) 7:36–49. doi:10.4314/ovj.v7i1.6
- Monteiro-Stegall BP, Steagall PV, Lascelles BD. Systematic review of nonsteroidal anti-inflammatory drug-induced adverse effects in dogs. *J Vet Intern Med.* (2013) 27:1011–9. doi:10.1111/jvim.12127
- Aragon CL, Hofmeister EH, Budberg SC. Systematic review of clinical trials of treatments for osteoarthritis in dogs. *J Am Vet Med Assoc.* (2007) 230:514–21. doi:10.2460/javma.230.4.514
- Beale BS. Use of nutraceuticals and chondroprotectants in osteoarthritic dogs and cats. *Vet Clin North Am Small Anim Pract.* (2004) 34:271–89, viii. doi:10.1016/j.cvsr.2003.09.008
- McCarthy G, O'Donovan J, Jones B, McAllister H, Seed M, Mooney C. Randomised double-blind, positive-controlled trial to assess the efficacy of glucosamine/chondroitin sulfate for the treatment of dogs with osteoarthritis. *Vet J.* (2007) 174:54–61. doi:10.1016/j.tvjl.2006.02.015
- Cupta RC, Canerdy TD, Lindley J, Konemann M, Minniear J, Carroll BA, et al. Comparative therapeutic efficacy and safety of type-II collagen (UC-II), glucosamine and chondroitin in arthritic dogs: pain evaluation by ground force plate. *J Anim Physiol Anim Nutr.* (2012) 96:770–7. doi:10.1111/j.1439-0396.2011.01166.x
- Scott RM, Evans R, Conzemius MG. Efficacy of an oral nutraceutical for the treatment of canine osteoarthritis. A double-blind, randomized, placebocontrolled prospective clinical trial. *Vet Comp Orthop Traumatol.* (2017) 30:318–23. doi:10.3415/VCOT-17-02-0020
- Fernandez-Martin S, Gonzalez-Cantalapiedra A, Munoz F, Garcia-Gonzalez M, Permuy M, Lopez-Pena M. Glucosamine and chondroitin sulfate: is there any scientific evidence for their effectiveness as disease-modifying drugs in knee osteoarthritis preclinical studies? A systematic review from 2000 to 2021. *Animals.* (2021) 11:1608. doi:10.3390/ani11061608
- Mongkon N, Soontornvipart K. Preliminary study of the clinical outcome of using PCSO-524 polyunsaturated fatty acid compound in the treatment of canine osteoarthritis and degenerative spinal diseases. *Thai J Vet Med.* (2012) 42:311–7.
- Soontornvipart K, Mongkhon N, Nganvongpanit K, Kongtawelert P. Effect of PCSO-524 on OA biomarkers and weight-bearing properties in canine shoulder and coxofemoral osteoarthritis. *Thai J Vet Med.* (2015) 45:157–65.
- Kwananocha I, Vijarnsorn M, Kashemsant N, Lekcharoensuk C. Effectiveness of disease modifying osteoarthritis agents and carprofen for treatment of canine osteoarthritis. *Thai J Vet Med.* (2016) 46:363–71
- Vijarnsorn M, Kwananocha I, Kashemsant N, Jarudecha T, Lekcharoensuk C, Beale B, et al. The effectiveness of marine based fatty acid compound (PCSO524) and firocoxib in the treatment of canine osteoarthritis. *BMC Vet Res.* (2019) 15:349. doi:10.1186/s12917-019-2110-7
- Suzuki Y, Fukushima M, Sakuraba K, Sawaki K, Sekigawa K. Krill oil improves mild knee joint pain: a randomized control trial. *PLoS ONE.* (2016) 11:e0162769. doi:10.1371/journal.pone.0162769
- Lafamme DP. Development and validation of a body condition score system for dogs. *Canine Pract.* (1997) 22:10–5.
- Chow SC, Shao J, Wang H. *Sample Size Calculations in Clinical Research*, 2nd ed. Boca Raton, FL: Chapman and Hall/CRC; (2003). doi:10.1201/9780203911341
- Hercoc CA, Pinchbeck G, Giejda A, Clegg PD, Innes JF. Validation of a client-based clinical metrology instrument for the evaluation of canine elbow osteoarthritis. *J Small Anim Pract.* (2009) 50:266–71. doi:10.1111/j.1748-5827.2009.00765.x
- Hielm-Bjorkman AK, Rita H, Tulamo RM. Psychometric testing of the Helsinki chronic pain index by completion of a questionnaire in Finnish by owners of dogs with chronic signs of pain caused by osteoarthritis. *Am J Vet Res.* (2009) 70:727–34. doi:10.2460/ajvr.70.6.727
- Brown DC, Boston RC, Farrar JT. Comparison of force plate gait analysis and owner assessment of pain using the Canine Brief Pain Inventory in dogs with osteoarthritis. *J Vet Intern Med.* (2013) 27:22–30. doi:10.1111/jvim.12004
- Moreau M, Lussier B, Ballaz L, Troncy E. Kinetic measurements of gait for osteoarthritis research in dogs and cats. *Can Vet J.* (2014) 55:1057–65.
- Waxman AS, Robinson DA, Evans RB, Hulse DA, Innes JF, Conzemius MG. Relationship between objective and subjective assessment of limb function in normal dogs with an experimentally induced lameness. *Vet Surg.* (2008) 37:241–6. doi:10.1111/j.1532-950X.2008.00372.x

31. McLaughlin RM. Kinetic and kinematic gait analysis in dogs. *Vet Clin North Am Small Anim Pract.* (2001) 31:193–201. doi: 10.1016/S0195-5616(01)50045-5
32. Conzemius MG, Torres BT, Muir P, Evans R, Krotscheck U, Budsberg S. Best practices for measuring and reporting ground reaction forces in dogs. *Vet Surg.* (2022) 51:385–96. doi: 10.1111/vasu.13772
33. Conzemius MG, Evans RB. Caregiver placebo effect for dogs with lameness from osteoarthritis. *J Am Vet Med Assoc.* (2012) 241:1314–9. doi: 10.2460/javma.241.10.1314
34. Venator KP, Frye CW, Gamble LJ, Waikshlag JJ. Assessment of a single intraarticular stifle injection of pure platelet rich plasma on symmetry indices in dogs with unilateral or bilateral stifle osteoarthritis from long-term medically managed cranial cruciate ligament disease. *Vet Med.* (2020) 11:31–8. doi: 10.2147/VMR.20238598
35. Chervier, C.; Cadore, J.L.; Rodriguez-Pineiro, M.I.; Deputte, B.L.; Chabanne, L. Causes of anaemia other than acute blood loss and their clinical significance in dogs. *J. Small Anim. Pract.* 2012, 53, 223–227. [Google Scholar] [CrossRef] [PubMed]
36. Borchert, C.; Herman, A.; Roth, M.; Brooks, A.C.; Friedenberg, S.G. RNA sequencing of whole blood in dogs with primary immune-mediated hemolytic anemia (IMHA) reveals novel insights into disease pathogenesis. *PLoS ONE* 2020, 15, e0240975. [Google Scholar] [CrossRef]
37. Balch, A.; Mackin, A. Canine immune-mediated hemolytic anemia: Pathophysiology, clinical signs, and diagnosis. *Compend. Contin. Educ. Vet.* 2007, 29, 217–225. [Google Scholar] [PubMed]
38. Morley, P.; Mathes, M.; Guth, A.; Dow, S. Anti-erythrocyte antibodies and disease associations in anemic and nonanemic dogs. *J. Vet. Intern. Med.* 2008, 22, 886–892. [Google Scholar] [CrossRef] [PubMed]
39. Kjølgaard-Hansen, M.; Goggs, R.; Winberg, B.; Chan, D.L. Use of serum concentrations of interleukin-18 and monocyte chemoattractant protein-1 as prognostic indicators in primary immune-mediated hemolytic anemia in dogs. *J. Vet. Intern. Med.* 2011, 25, 76–82. [Google Scholar] [CrossRef] [PubMed]
40. Cui, B.; Blois, S.L.; Bedard, C.; Wood, R.D.; Abrams-Ogg, A.C.; Beauchamp, G.; Wood, G.A. Serum interleukin 17 concentrations in dogs with immune-mediated hemolytic anemia. *J. Vet. Intern. Med.* 2021, 35, 217–225. [Google Scholar] [CrossRef]
41. Archer, T.M.; Mulligan, C.; Narayanan, L.; Riggs, C.; Fellman, C.; Thomason, J.M.; Wills, R.W.; Boothe, D.M.; Cruz-Espindola, C.; Harmon, R.; et al. Effects of oral administration of 5 immunosuppressive agents on activated T-cell cytokine expression in healthy dogs. *J. Vet. Intern. Med.* 2020, 34, 1206–1213. [Google Scholar] [CrossRef] [Green Version]
42. Swann, J.W.; Skelly, B.J. Systematic review of evidence relating to the treatment of immune-mediated hemolytic anemia in dogs. *J. Vet. Intern. Med.* 2013, 27, 1–9. [Google Scholar] [CrossRef]
43. Swann, J.W.; Skelly, B.J. Evaluation of immunosuppressive regimens for immune-mediated haemolytic anaemia: A retrospective study of 42 dogs. *J. Small Anim. Pract.* 2011, 52, 353–358. [Google Scholar] [CrossRef]
44. Swann, J.W.; Garden, O.A.; Fellman, C.L.; Glanemann, B.; Goggs, R.; LeVine, D.N.; Mackin, A.J.; Whitley, N.T. ACVIM consensus statement on the treatment of immune-mediated hemolytic anemia in dogs. *J. Vet. Intern. Med.* 2019, 33, 1141–1172. [Google Scholar] [CrossRef] [Green Version]
45. Wolyniak, C.J.; Brenna, J.T.; Murphy, K.J.; Sinclair, A.J. Gas chromatography-chemical ionization-mass spectrometric fatty acid analysis of a commercial supercritical carbon dioxide lipid extract from New Zealand green-lipped mussel (*Perna canaliculus*). *Lipids* 2005, 40, 355–360. [Google Scholar] [CrossRef]
46. Doggrell, S.A. Lyprinol-is it a useful anti-inflammatory agent? *Evid. Based Complement. Altern. Med.* 2011, 2011, 307121. [Google Scholar] [CrossRef] [Green Version]
47. Vijarnsom, M.; Kwananocha, I.; Kashemsant, N.; Jarudecha, T.; Lekcharonsuk, C.; Beale, B.; Peirone, B.; Lascelles, B.D.X. The effectiveness of marine based fatty acid compound (PCSO-524) and Firocoxib in the treatment of canine osteoarthritis. *BMC Vet. Res.* 2019, 15, 349. [Google Scholar] [CrossRef] [Green Version]
48. Mongkon, N.; Soontornvipart, K. Preliminary Study of the Clinical Outcome of Using PCSO-524 Polyunsaturated Fatty Acid Compound in the Treatment of Canine Osteoarthritis and Degenerative Spinal Diseases. *Thai J. Vet. Med.* 2013, 42, 311–317. [Google Scholar]
49. Kongwut, S.; Soontornvipart, K.; Sarikaputhi, M.; Makoom, P.; Nganvongpanit, K. Effect of Serum IL-1 β of PCSO-524 and Firocoxib in Dogs Undergoing Medial Patellar Luxation Repair. *Thai J. Vet. Med.* 2015, 45, 639–643. [Google Scholar]
50. Garden, O.A.; Kidd, L.; Mexas, A.M.; Chang, Y.M.; Jeffery, U.; Blois, S.L.; Fogle, J.E.; MacNeill, A.L.; Lubas, G.; Birkenheuer, A.; et al. ACVIM consensus statement on the diagnosis of immune-mediated hemolytic anemia in dogs and cats. *J. Vet. Intern. Med.* 2019, 33, 313–334. [Google Scholar] [Green Version]
51. Sun, P.L.; Jeffery, U. Effect of dilution of canine blood samples on the specificity of saline agglutination tests for immune-mediated hemolysis. *J. Vet. Intern. Med.* 2020, 34, 2374–2383. [Google Scholar] [CrossRef]
52. Paes, G.; Paepe, D.; Meyer, E.; Kristensen, A.T.; Duchateau, L.; Campos, M.; Daminet, S. The use of the rapid osmotic fragility test as an additional test to diagnose canine immune-mediated haemolytic anaemia. *Acta Vet. Scand.* 2013, 55, 74. [Google Scholar] [CrossRef] [Green Version]
53. Baum, K.; Telford, R.D.; Cunningham, R.B. Marine oil dietary supplementation reduces delayed onset muscle soreness after a 30 km run. *Open Access J. Sports Med.* 2013, 4, 109–115. [Google Scholar] [CrossRef] [Green Version]
54. Pampa, K.L.; Fallon, K.E.; Bensoussan, A.; Papalia, S. The effects of Lyprinol[®] on delayed onset muscle soreness and muscle damage in well trained athletes: A double-blind randomised controlled trial. *Complement. Ther. Med.* 2011, 19, 311–318. [Google Scholar] [CrossRef]
55. Liu, S.; Hu, W.; Fang, Y.; Cai, Y.; Zhang, J.; Liu, J.; Ding, Y. Extraction of oil from wet Antarctic krill (*Euphausia superba*) using a subcritical dimethyl ether method. *RSC Adv.* 2019, 9, 34274–34282. [Google Scholar] [CrossRef] [PubMed] [Green Version]
56. Yin, F.-W.; Zhou, D.-Y.; Liu, Y.-F.; Zhao, Q.; Zhou, X.; Song, L.; Qi, H.; Zhu, B.-W. The Forms of Fluoride in Antarctic Krill (*Euphausia superba*) Oil Extracted with Hexane and its Removal with Different Absorbents. *J. Aquat. Food Prod. Technol.* 2017, 26, 835–842. [Google Scholar] [CrossRef]
57. Mickleborough, T.D.; Sinex, J.A.; Platt, D.; Chapman, R.F.; Hirt, M. The effects PCSO-524(R), a patented marine oil lipid and omega-3 PUFA blend derived from the New Zealand green lipped mussel (*Perna canaliculus*), on indirect markers of muscle damage and inflammation after muscle damaging exercise in untrained men: A randomized, placebo controlled trial. *J. Int. Soc. Sports Nutr.* 2015, 12, 10. [Google Scholar] [CrossRef] [PubMed] [Green Version]
58. Piek, C.J.; Junius, G.; Dekker, A.; Schrauwen, E.; Slappendel, R.J.; Teske, E. Idiopathic immune-mediated hemolytic anemia: Treatment outcome and prognostic factors in 149 dogs. *J. Vet. Intern. Med.* 2008, 22, 366–373. [Google Scholar] [CrossRef] [PubMed]
59. Mistry, N.; Mazer, C.D.; Sled, J.G.; Lazarus, A.H.; Cahill, L.S.; Solish, M.; Zhou, Y.Q.; Romanova, N.; Hare, A.G.M.; Doctor, A.; et al. Red blood cell antibody-induced anemia causes differential degrees of tissue hypoxia in kidney and brain. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 2018, 314, R611–R622. [Google Scholar] [CrossRef] [Green Version]

60. Zoia, A.; Gerou-Ferriani, M.; Drigo, M.; Caldin, M. Case-control study of plasma mean platelet component concentration and survival analysis for dogs with immune-mediated hemolytic anemia. *J. Am. Vet. Med. Assoc.* 2018, **252**, 1384–1392. [Google Scholar] [CrossRef]
61. Lawson, C.; Smith, S.A.; O'Brien, M.; McMichael, M. Neutrophil Extracellular Traps in Plasma from Dogs with Immune-mediated Hemolytic Anemia. *J. Vet. Intern. Med.* 2018, **32**, 128–134. [Google Scholar] [CrossRef] [Green Version]
62. Mekritirat, T.; Rueangsri, T.; Keeratichandacha, W.; Soonsawat, S.; Boonyapakorn, C.; Pongkan, W. Polyunsaturated Fatty Acid EAB-277((R)) Supplementation Improved Heart Rate Variability and Clinical Signs in Tracheal Collapse Dogs. *Front. Vet. Sci.* 2022, **9**, 880952. [Google Scholar] [CrossRef]
63. Doganci, A.; Eigenbrodt, T.; Krug, N.; De Sanctis, G.T.; Hausding, M.; Erpenbeck, V.J.; Haddad, E.B.; Lehr, H.A.; Schmitt, E.; Bopp, T.; et al. The IL-6R alpha chain controls lung CD4⁺CD25⁺ Treg development and function during allergic airway inflammation in vivo. *J. Clin. Investig.* 2005, **115**, 313–325. [Google Scholar] [CrossRef] [Green Version]
64. Valencia, X.; Stephens, G.; Goldbach-Mansky, R.; Wilson, M.; Shevach, E.M.; Lipsky, P.E. TNF downmodulates the function of human CD4⁺CD25^{hi} T-regulatory cells. *Blood* 2006, **108**, 253–261. [Google Scholar] [CrossRef]
65. Swann, J.W.; Woods, K.; Wu, Y.; Glanemann, B.; Garden, O.A. Characterisation of the Immunophenotype of Dogs with Primary Immune-Mediated Haemolytic Anaemia. *PLoS ONE* 2016, **11**, e0168296. [Google Scholar] [CrossRef] [Green Version]
66. Kampa, N.; Kaenkangpoo, D.; Jitpean, S.; Srithunyarat, T.; Seesupa, S.; Hoisang, S.; Yongvanit, K.; Kamlangchai, P.; Tuchpramuk, P.; Lascelles, B.D.X. Study of the effectiveness of glucosamine and chondroitin sulfate, marine based fatty acid compounds (PCSO-524 and EAB-277), and carprofen for the treatment of dogs with hip osteoarthritis: A prospective, block-randomized, double-blinded, placebo-controlled clinical trial. *Front. Vet. Sci.* 2023, **10**, 1033188. [Google Scholar] [CrossRef]
67. Swann, J.W.; Sziadovits, B.; Threlfall, A.J.; Garden, O.A.; Chang, Y.M.; Church, D.B.; Glanemann, B. Randomised controlled trial of fractionated and unfractionated prednisolone regimens for dogs with immune-mediated haemolytic anaemia. *Vet. Rec.* 2019, **184**, 771. [Google Scholar] [CrossRef]
68. Sri-Jayantha, L.S.; Doornink, M.T.; Urie, B.K. Increased risk of select glucocorticoid adverse events in dogs of higher body weight. *Can. Vet. J.* 2022, **63**, 32–38. [Google Scholar]
69. Weingart, C.; Thielemann, D.; Kohn, B. Primary immune-mediated haemolytic anaemia: A retrospective long-term study in 61 dogs. *Aust. Vet. J.* 2019, **97**, 483–489. [Google Scholar] [CrossRef]
70. Elkholy, D.A.; Brodbelt, D.C.; Church, D.B.; Pelligand, L.; Mwacimba, K.; Wright, A.K.; O'Neill, D.G. Side Effects to Systemic Glucocorticoid Therapy in Dogs Under Primary Veterinary Care in the UK. *Front. Vet. Sci.* 2020, **7**, 515. [Google Scholar] [CrossRef]
71. Swann, J.W.; Skelly, B.J. Canine autoimmune hemolytic anemia: Management challenges. *Vet. Med.* 2016, **7**, 101–112. [Google Scholar] [CrossRef] [Green Version]
72. Alvarez, A.M.; Mukherjee, D. Liver abnormalities in cardiac diseases and heart failure. *Int. J. Angiol.* 2011, **20**, 135–142. [Google Scholar] [CrossRef] [Green Version]
73. Jamikorn, U.; Vibhok-anun, S. Effects of Dietary Polyunsaturated Fatty Acid Supplement on Healthy Beagle Dogs. *Thai J. Vet. Med.* 2014, **44**, 505–511. [Google Scholar]
74. Clarke D.L. Interventional radiology: management of tracheal and bronchial collapse. *Vet Clin North Am Small Anim Pract.* (2018) 48765–79. doi:10.1016/j.cvsm.2018.05.010
75. Hedlund C.S. Tracheal collapse. *Probl Vet Med.* (1991) 3:229–38. 3. Tappin S.W. Canine tracheal collapse. *J Small Anim Pract.* (2016) 579–17. doi:10.1111/jsap.12436
76. Tappin S.W. Canine tracheal collapse. *J Small Anim Pract.* (2016) 579–17. doi:10.1111/jsap.12436
77. Maggioro A.D. Tracheal and airway collapse in dogs. *Vet Clin North Am Small Anim Pract.* (2014) 44:117–27. doi:10.1016/j.cvsm.2013.09.004
78. Papaioannou V, Pneumatikos I, Maglaveras N. Association of heart rate variability and inflammatory response in patients with cardiovascular diseases: current strengths and limitations. *Front Physiol.* (2013) 4:174. doi:10.3389/fphys.2013.00174
79. Cooper TM, McKinley PS, Seeman TE, Choo TH, Lee S, Sloan RP. Heart rate variability predicts levels of inflammatory markers: evidence for the vagal anti-inflammatory pathway. *Brain Behav Immun.* (2015) 4994–100. doi:10.1016/j.bbi.2014.12.017
80. Yan M, Mehta JL, Zhang W, Hu C. LOX-1, oxidative stress and inflammation: a novel mechanism for diabetic cardiovascular complications. *Cardiovasc Drugs Ther.* (2011) 25:451–9. doi:10.1007/s10557-011-6342-4
81. Hussain T, Tan B, Yin Y, Blachier F, Tossou MC, Rahu N. Oxidative stress and inflammation: what polyphenols can do for us? *Oxid Med Cell Longev.* (2016) 2016:7432797. doi:10.1155/2016/7432797
82. Khoubnasabjafari M, Ansari K, Jouyban A. Reliability of malondialdehyde as a biomarker of oxidative stress in psychological disorders. *Bioimpacts.* (2015) 5:123–7. doi:10.15171/bi.2015.20
83. Cygankiewicz I, Zareba W. Heart rate variability. *Handb Clin Neurol.* (2013) 117:379–93. doi:10.1016/B978-0-444-53491-0.00031-6
84. Chueinta P, Pongkan W, Boonyapakorn C. Clinical applications of heart rate variability in dogs. *Vet Integr Sci.* (2019) 17:195–220.
85. Lahdenoja O, Hurnanen T, Kaisti M, Koskinen J, Tuominen J, Vähä-Heikkilä M, et al. Cardiac monitoring of dogs via smartphone mechanocardiography: a feasibility study. *Biomed Eng Online.* (2019) 18:47. doi:10.1186/s12938-019-0667-9
86. Thio C.H.L., van Roon A.M., Lefrandt J.D., Gansevoort RT, Snieder H. Heart rate variability and its relation to chronic kidney disease: results from the PREVEND study. *Psychosom Med.* (2018) 80:307–16. doi:10.1097/PSY.0000000000000556
87. Chou Y.H., Huang W.L., Chang C.H., Yang C.H., Kuo T.B.J., Lin S.L., et al. Heart rate variability as a predictor of rapid renal function deterioration in chronic kidney disease patients. *Nephrology.* (2019) 24:806–13. doi:10.1111/neph.13514
88. Serrao NF Jr., Porta A, Minatel V, Castro AAM, Catai AM, Sampaio LMM, et al. Complexity analysis of heart rate variability in chronic obstructive pulmonary disease: relationship with severity and symptoms. *Clin Auton Res.* (2020) 30:157–64. doi:10.1007/s10286-019-00659-z
89. Li Y, Wang J, Li X, Jing W, Omorodion I, Liu L. Association between heart rate variability and Parkinson's disease: a meta-analysis. *Curr Pharm Des.* (2021) 27:2056–67. doi:10.2174/18715273196662009051222217. Lucini D, Pagani M. Heart rate variability, autonomic regulation and myocardial ischemia. *Int J Cardiol.* (2020) 312:22–3. doi:10.1016/j.ijcard.2020.03.012
90. Tan JPH, Beilharz JE, Vollmer-Conna U, Cvejic E. Heart rate variability as a marker of healthy ageing. *Int J Cardiol.* (2019) 275:101–3. doi:10.1016/j.ijcard.2018.08.005
91. Alfonso A, Le Sueur ANV, Geraldies SS, Guimaraes-Okamoto PTC, Tsumeni MH, Santana DF, et al. Heart rate variability and electrocardiographic parameters predictive of arrhythmias in dogs with stage IV chronic kidney disease undergoing intermittent haemodialysis. *Animals.* (2020) 10:1829. doi:10.3390/ani10181829
92. Petrie JP. Practical application of holter monitoring in dogs and cats. *Clin Tech Small Anim Pract.* (2005) 20:173–81. doi:10.1053/j.ctsap.2005.05.006

93. Hsieh BM, Beets AK. Coughing in small animal patients. *Front Vet Sci.* (2020) 6:513. doi: 10.3389/fvets.2019.00513
94. Williams J, editor. Management of tracheal collapse. World Small Animal Veterinary Association World Congress Proceedings. Cape Town (2014).
95. Della Maggiore A. An update on tracheal and airway collapse in dogs. *Vet Clin North Am Small Anim Pract.* (2020) 50:419–30. doi: 10.1016/j.cvsm.2019.11.003
96. Shei RJ, Adamic EM, Chapman RF, Mickleborough TD. The effects of PCSO524(R), a patented marine oil lipid derived from the New Zealand green lipped mussel (*Perna canaliculus*), on pulmonary and respiratory muscle function in non-asthmatic elite runners. *Int J Exerc Sci.* (2018) 11:669–80.
97. Vijansorn M, Kwananocha I, Kashemsant N, Jarudecha T, Lekcharonsuk C, Beale B, et al. The effectiveness of marine based fatty acid compound (PCSO524) and firocoxib in the treatment of canine osteoarthritis. *BMC Vet Res.* (2019) 15:349. doi: 10.1186/s12917-019-2110-7
98. Zhu B, Zhang Y, Herrup K. Testing the neuroprotective properties of PCSO524((R)) using a neuronal cell cycle suppression assay. *Mar Drugs.* (2019) 17:79. doi: 10.3390/md17020079
99. Mickleborough TD, Sinex JA, Platt D, Chapman RF, Hirt M. The effects PCSO-524(R), a patented marine oil lipid and omega-3 PUFA blend derived from the New Zealand green lipped mussel (*Perna canaliculus*), on indirect markers of muscle damage and inflammation after muscle damaging exercise in untrained men: a randomized, placebo controlled trial. *J Int Soc Sports Nutr.* (2015) 12:10. doi: 10.1186/s12970-015-0073-z
100. Doggrell SA. Lyprinol-is it a useful anti-inflammatory agent? *Evid Based Complement Alternat Med.* (2011) 2011:307121. doi: 10.1093/ecam/nep030
101. Mickleborough TD, Vaughn CL, Shei RJ, Davis EM, Wilhite DP. Marine lipid fraction PCSO-524 (lyprinol/omega XL) of the New Zealand green lipped mussel attenuates hyperpnea-induced bronchoconstriction in asthma. *Respir Med.* (2013) 107:1152–63. doi: 10.1016/j.rmed.2013.04.010
102. Mongkon N, Sontornvipart K. Preliminary study of the clinical outcome of using PCSO-524 polyunsaturated fatty acid compound in the treatment of canine osteoarthritis and degenerative spinal diseases. *Thai J Vet Med.* (2012) 42:311–7. 31. Mateos R, Lecumberri E, Ramos S, Goya L, Bravo L. Determination of malondialdehyde (MDA) by high-performance liquid chromatography in serum and liver as a biomarker for oxidative stress: application to a rat model for hypercholesterolemia and evaluation of the effect of diets rich in phenolic antioxidants from fruits. *J Chromatogr B Analyt Technol Biomed Life Sci.* (2005) 827:76–82. doi: 10.1016/j.jchromb.2005.06.035
103. Pongkan W, Pintana H, Jaiwongkam T, Kredphoo S, Sivasinprasasn S, Chattipakorn SC, et al. Vildagliptin reduces cardiac ischemic-reperfusion injury in obese orchiectomized rats. *J Endocrinol.* (2016) 231:81–95. doi: 10.1530/JOE-16-0232.33. Pongkan W, Jitnapakarn W, Phetnoi V, Punyapornwithaya V, Boonyapakorn C. Obesity-induced heart rate variability impairment and decreased systolic function in obese male dogs. *Animals.* (2020) 10:1383. doi: 10.3390/ani10081383
104. Bogucki S, Noszczyk-Nowak A. Short-term heart rate variability (HRV) in healthy dogs. *Pol J Vet Sci.* (2015) 18:307–12. doi: 10.1515/pjvs-2015-0040.35. von Borell E, Langbein J, Despres G, Hansen S, Leterrier C, Marchant-Forde J, et al. Heart rate variability as a measure of autonomic regulation of cardiac activity for assessing stress and welfare in farm animals – a review. *Physiol Behav.* (2007) 92:293–316. doi: 10.1016/j.physbeh.2007.01.007
105. Lima AH, Forjaz CL, Silva GQ, Meneses AL, Silva AJ, Ritti-Dias RM. Acute effect of resistance exercise intensity in cardiac autonomic modulation after exercise. *Arq Bras Cardiol.* (2011) 96:498–503. doi: 10.1590/S0066-782X2011005000043
106. Latchman PL, Mathur M, Bartels MN, Axtell RS, De Meersman RE. Impaired autonomic function in normotensive obese children. *Clin Auton Res.* (2011) 21:319–23. doi: 10.1007/s10286-011-0116-8
107. Kenneth S, Edward A, Keith W. Duncan and Prasses's Veterinary Laboratory Medicine Clinical Pathology. 4 ed. Ames, IA: Iowa State Press. (2003).
108. Regier PJ, Grosso FV, Stone HK, van Santen E. Radiographic tracheal dimensions in brachycephalic breeds before and after surgical treatment for brachycephalic airway syndrome. *Can Vet J.* (2020) 61:971–6.
109. Jepsen-Grant K, Pollard RE, Johnson LR. Vertebral heart scores in eight dog breeds. *Vet Radiol Ultrasound.* (2013) 54:3–8. doi: 10.1111/j.1740-8261.2012.01976.x
110. Vezzosi T, Puccinelli C, Tognetti R, Pelligrà T, Citi S. Radiographic vertebral left atrial size: a reference interval study in healthy adult dogs. *Vet Radiol Ultrasound.* (2020) 61:507–11. doi: 10.1111/vru.12896
111. Zawadzki M, Janosch C, Szechinski J. Perna canaliculus lipid complex PCSO524 demonstrated pain relief for osteoarthritis patients benchmarked against fish oil, a randomized trial, without placebo control. *Mar Drugs.* (2013) 11:1920–35. doi: 10.3390/md11061920
112. Malik M. Producing consistent estimates of the power spectral density of NN sequences. *Circulation.* (1997) 96:2082–3.
113. Shukla RS, Aggarwal Y. Time-domain heart rate variability-based computer-aided prognosis of lung cancer. *Indian J Cancer.* (2018) 55:61–5. doi: 10.4103/ijc.IJC_395_17
114. Kleiger RE, Stein PK, Bigger JT Jr. Heart rate variability: measurement and clinical utility. *Ann Noninvasive Electrocardiol.* (2005) 10:88–101. doi: 10.1111/j.1542-474x.2005.10101.x
115. Pongkan W, Pintana H, Sivasinprasasn S, Jaiwongkam T, Chattipakorn SC, Chattipakorn N. Testosterone deprivation accelerates cardiac dysfunction in obese male rats. *J Endocrinol.* (2016) 229:209–20. doi: 10.1530/JOE-16-0002
116. Sivasinprasasn S, Sa-Nguanmoo P, Pongkan W, Pratchayasakul W, Chattipakorn SC, Chattipakorn N. Estrogen and DPP4 inhibitor, but not metformin, exert cardioprotection via attenuating cardiac mitochondrial dysfunction in obese insulin-resistant and estrogen-deprived female rats. *Menopause.* (2016) 23:894–902. doi: 10.1097/GME.0000000000000640
117. Pavithran P, Nandeeshha H, Shaiyapriya V, Bobby Z, Madanmohan T. Short-term heart variability and oxidative stress in newly diagnosed essential hypertension. *Clin Exp Hypertens.* (2008) 30:486–96. doi: 10.1080/10641960802251875
118. Pongkan W, Jinawong K, Pratchayasakul W, Jaiwongkam T, Kredphoo S, Tokuda M, et al. D-allulose provides cardioprotective effect by attenuating cardiac mitochondrial dysfunction in obesity-induced insulin-resistant rats. *Eur J Nutr.* (2020). doi: 10.1007/s00394-020-02394-y
119. Balasubramanian P, Asirvatham-Jeyaraj N, Monteiro R, Sivasubramanian MK, Hall D, Subramanian M. Obesity-induced sympathoexcitation is associated with Nrf2 dysfunction in the rostral ventrolateral medulla. *Am J Physiol Regul Integr Comp Physiol.* (2020) 318:R435–r44. doi: 10.1152/ajpregu.00206.2019