A Flavonoid Mixture, Dual Inhibitor of Cyclooxygenase and 5-Lipoxygenase Enzymes, Shows Superiority to Glucosamine/ Chondroitin for Pain Management in Moderate Osteoarthritic Dogs

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ABSTRACT

Osteoarthritis (OA) is a multi-factorial disease with a large metabolic component involving the accumulation of arachidonic acid (AA) metabolites that contribute to joint deterioration. Laboratory studies have shown that specific flavonoid mixtures, composed of baicalin and catechin, act to inhibit cyclooxgenase-1 (COX-1) and COX-2 in a balanced manner with additional 5-lipoxygenase (5-LOX) inhibitory activity. The safety and efficacy of the flavonoid formulation, FlexileRx™, however, is not known in dogs. Enzyme inhibition results for COX-1, COX-2, and 5-LOX demonstrate that, compared to celecoxib, meloxicam, naproxen, ibuprofen, carprofen, and aspirin, only FlexileRx has balanced COX and additional 5-LOX enzyme inhibition activity. In a multi-site, double-blind, randomized, direct-comparator trial in dogs weighing at least 15 lbs, FlexileRx (n=33) showed statistically significant improvement in pain scores over the combination formulation of chondroitin sulfate, glucosamine hydrochloride, and manganese ascorbate (n=36) (Cosequin®DS) using veterinarian and owner visual analog scale (VAS) assessments. At both the interim (28 days) and final analysis (56 days), FlexileRx was more than twice as effective as CosequinDS at relieving pain. Adverse events were generally mild in both groups. This study demonstrates that FlexileRx is a relatively fast-acting therapy for reduction of pain scores in dogs with OA.

INTRODUCTION

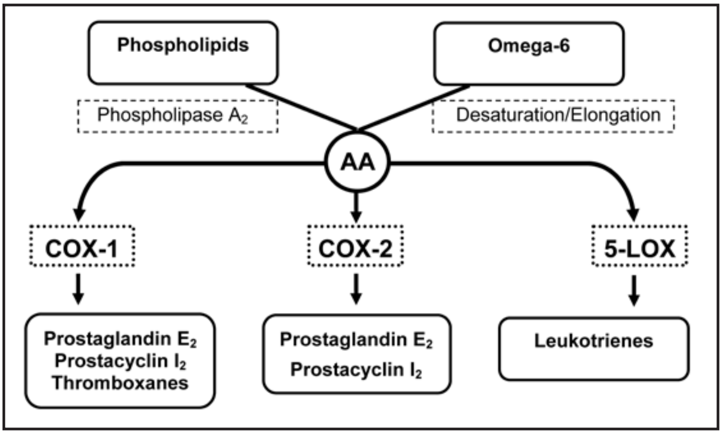
Fatty acid imbalances are commonly seen in human patients with chronic inflammatory conditions such as arthritis. In both human and canine populations, diet contributes tremendously to intake of AA in the form of omega 6 oils, including AA. Arachidonic acid is derived from the dietary essential fatty acids, linoleic acid, and α–linolenic acid by sequential desaturation and elongation, respectively.[1] This increased consumption of omega-6 fatty acids and AA in the diet has shifted the balance of fatty acid metabolism toward an increase in pro-inflammatory metabolite generation *via* the COX and 5 LOX enzymatic pathways (Figure 1).

Fatty acid levels monitored in bone have been shown to be 50-90% higher in OA patients compared to controls.[2] In addition, depending on the severity of OA, there is an associated accumulation of total and essential fatty acids in the chondrocytes of the joint in human OA patients, suggesting a strong involvement of fatty acid metabolism in the pathogenesis of the disease.[3] Clinical studies have also shown a strong linkage between metabolic defects in metabolism or an overabundance of fatty acids that lead to OA.[4] Osteoarthritis can affect up to 20% of dogs over the age of one year.[5] The diets of canines has tracked with that of humans, with mass production of pet food containing high levels of AA derived from corn-based products, which ultimately lead to increased pro-inflammatory fatty acid production.

Pro-inflammatory AA metabolites have been found to play an integral role in the pathophysiology of OA.[6] Damaged cell membranes release phospholipids, which are then converted by phospholipase A2 into AA, which then enters the COX and 5 LOX metabolic pathways[7,8] and leads, ultimately, to production of a variety of inflammatory metabolites such as prostaglandins, thromboxanes, prostacyclins, and leukotrienes. These, in turn, promote an increase in inflammation systemically, as well as locally, in and around the joints (Figure 1). Hence, metabolic processes involving the accumulation of AA metabolites are an essential component of the pathogenesis of joint deterioration in OA.[9] Controlling this process of pro-inflammatory fatty acid metabolism is essential in safely treating OA in humans and canines.

Dogs are thought to be more sensitive to the effects of nonsteroidal anti-inflammatory drugs (NSAIDs) than humans. Gastrointestinal (GI) side effects such as anorexia, vomiting, and diarrhea are the most common adverse events reported.[10,11] NSAID administration to canines, in general, results in higher levels of kidney, liver, GI, musculoskeletal dysfunction, and skin reactions compared to acetaminophen.[12] Ibuprofen has been shown to induce ulcerations more readily in canines than humans due to a substantially greater level of absorption.[13,14,15] As a result, the therapeutic window for relief of pain and inflammation in canines is quite narrow.[10] Other NSAIDs are even more toxic than ibuprofen in canines. Indomethacin, in particular, as well as naproxen, have been shown to cause severe GI side effects such as ulceration, gastritis, and duodenitis,[15,16,17] and as such, should not be used in canines.[18] Although selective COX-2 inhibitors reduce the incidence of GI side-effects in humans,[19,20,21] they have not been shown to significantly reduce overall adverse events in

Figure 1: Enzyme metabolism of membrane lipids and omega-6 fatty acids from the diet



canine populations (For comparison, see US FDA, 2007). Tepoxalin, a putative synthetic "dual inhibitor" has been shown to decrease adverse events compared to other drugs, but continues to show a rather elevated toxicity profile compared to supplements such as CosequinDS.

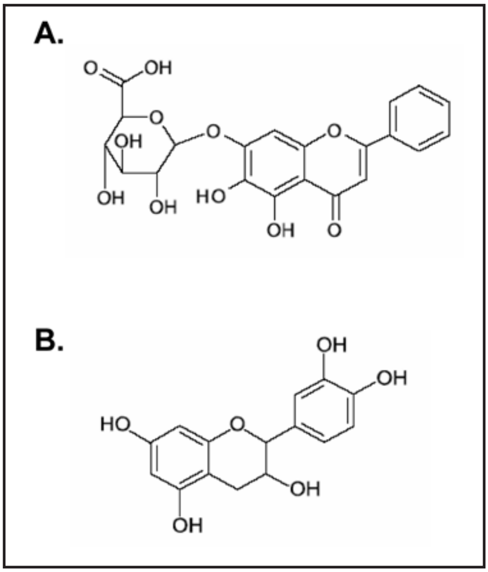
Food ingredients have been shown to impact OA in canines.[22] FlexileRx is composed of highly purified flavonoids, low molecular weight compounds, and part of the larger class of compounds known as polyphenols, which are found ubiquitously in plants, particularly fruits and vegetables.[23] Though a similar composition product exists as a prescription medical food in the human market, the safety and efficacy of FlexileRx is not known in dogs. This study measures the *in vitro* inhibition activity of FlexileRx on COX and 5-LOX enzymes and compares, *in vivo*, its clinical safety and efficacy against CosequinDS for support of joint health and measures of pain in dogs with OA.

METHODS

Enzyme inhibition studies of COX-1, COX-2 and 5-LOX were performed according to Burnett et al[24] comparing FlexileRx to celecoxib, meloxicam, naproxen, ibuprofen, carprofen, and aspirin. The base formula for FlexileRx for enzyme inhibition testing was a gift from Primus Pharmaceuticals, Inc; celecoxib was from Pfizer, Inc; and meloxicam was purchased from Boehringer Ingelheim, Inc. Naproxen, ibuprofen and aspirin were purchased from Sigma. Since glucosamine and chondroitin formulations have no known COX or 5-LOX inhibition activity, the base formula for CosequinDS was not tested in this analysis. The results of this analysis are expressed as selectively ratios based on the IC50 found in each enzyme assay for COX-1, COX-2, and 5-LOX

Treatment articles were composed of FlexileRx (250 mg per chewable tablet; Pro-Labs, Ltd.), a mixture proprietary mixture of two flavonoid molecule extracts concentrated for baicalin and catechin (Figure 2), or CosequinDS (500 mg glucosamine/400 mg sodium chondroitin sulfate/5 mg manganese/33 mg ascorbate per chewable tablet; Nutrimax Laboratories, Inc.). Baicalin and catechin, in this specific combination, have been found to have anti-inflammatory activity with very low toxicity in animals and humans.[24,25] FlexileRx and CosequinDS chewable tabs were similar in appearance, texture, and taste. Products were administered according to the dosing schedule in Table 1 as suggested by each manufacturer's recommendations.

Figure 2: Components of FlexileRx, Baicalin (A) and Catechin (B)



In order to test the safety and efficacy of this formulation, a multi-site (8), double-blind, randomized, direct-comparator trial comparing FlexileRx (n=33) to a combination chondroitin sulfate, glucosamine hydrochloride, and manganese ascorbate formulation (n=36), (CosequinDS), was performed over a two-month period (Figure 3). Animals were kept in normal domestic arrangements, and were housed either in the client's home environment or in separate animal accommodations. Dogs may have been housed with or without other animals. Food and water provisions followed normal practice for the site of housing. In two cases, due to the client's absence, client dogs were boarded for brief periods at the Study Investigator's boarding facilities, and animal care techni-

Table 1: Dosing of each treatment

A. FlexileRx Chewable Dosing			
Body Weight (lbs)	**Dosage**	**Duration of Treatment**	**Number of Tablets Dispensed**
15.0-50.0	½ tablet SID	56 days	28 tablets
50.1-100.0	1 tablet SID	56 days	56 tablets
>100.1	1½ tablet SID	56 days	84 tablets
B. CosequinDS Chewable Dosing			
Body Weight (lbs)	**Dosage**	**Duration of Treatment**	**Number of Tablets Dispensed**
15.0-24.0	½ tablet SID	56 days	28 tablets
24.1-49.0	1 tablet SID	56 days	56 tablets
49.1-100.0	2 tablet am,		
1 tablet pm	56 days	168 tablets	
>100.1	2 tablets BID	56 days	224 tablets

cians continued to follow all Study Protocol requirements such as maintaining the Owner's Daily Logs. Medical management followed normal accepted clinical practice for each study animal. All procedures complied with the standards for care and use of animal subjects as stated in the Guide for the Care and Use of Laboratory Animals (Institute of Laboratory Animal Resources, National Academy of Sciences, Bethesda, MD, USA). Further, all dogs were treated according to guidelines established and monitored by and Institutional Animal Care and Use Committee (IACUC).

Each animal included in the study had to be at least 15 lbs and have a moderate OA condition clinically manifesting as a unilateral or bilateral lameness. Diagnosis of moderate OA was based on case history and presentation of clinical signs of OA (e.g., lameness, morning stiffness, disuse atrophy, decreased range of motion in a joint, and/or joint creipitus, etc.). Each owner also signed and agreed to administer chewable tabs of FlexileRx or CosequinDS to each subject, and to keep a daily log of activity for each subject and had their canine evaluated on days 0, 28, and 56 for signs and symptoms of OA. Investigators discontinued the use of exclusionary medications according to the criteria outlined in the study protocol in order to remove any residual therapeutic effects of NSAIDS such as carprofen and disease-modifying agents such as Hills® Prescription Diet® j/d™. Subjects were excluded from the trial if they had mild (e.g., mild stiffness and lameness in affected limb with no evidence of joint crepitus, mild pain on joint palpation, and/or mild loss of range of motion) or severe OA (e.g., difficulty rising, walking and climbing, joint crepitus, pain on joint palpation, greater than 50% reduction in range of motion, and/or frequent vocalizations), or required continual, daily anti-inflammatory or analgesic medication. Subjects were excluded as well if they weighed less than 15 lbs, were pregnant or lactating, were being treated with short-term, systemic anti-inflammatory drugs (e.g., aspirin, prednisolone, dexamethasone, ketoprofen, phenylbutazone, carprofen, etodolac, or meclofenamic acid) within the 10 days prior to the study or repository anti-inflammatory drugs (e.g. methylprednisolone acetate) within the 30 days prior to the study, were treated with topical, systemic or intra-articular anti-inflammatory drugs (e.g., aspirin, corticosteroids, phenylbutazone, carprofen, ketoprofen, etodolac, or meclofenamic acid), anesthetics or analgesics (e.g. opioid narcotics) within 10 days prior to the study or chondroprotective or potentially disease modifying agents (e.g. polyglycosaminoglycans, chondroitin sulfate, sodium hyaluronate, or "nutraceuticals" including Hills® Prescription Diet® j/d™, Eukanuba Adult Plus™, and Eukanuba Senior Plus® veterinary prescription diet, or other diets that contain chondroprotective agents) within the last 21 days prior to the study. Concurrent use of these therapeutic agents was not permitted during the study. In addition, animals with lameness related to a neoplastic condition, primary neurologic disorder or immunologic disorder (e.g., lupus erythematosus, rheumatoid arthritis), infection (e.g. septic joint, abscess) or orthopedic fracture, or who had undergone surgery on the affected joint within 30 days prior to the study were also excluded. Finally, animals with disease conditions that would require surgical intervention to treat or, for which a surgical intervention was anticipated during the study, or with internal soft tissue injuries (e.g. contusions of abdominal organs) as a result of trauma, were excluded as well.

After identifying subjects and assessing the initial level of lameness, the Study Monitor obtained several sealed envelopes from the statistician that contained a set of six unique, randomized case numbers. Within each envelope, the case numbers were allocated randomly to either the FlexileRx or CosequinDS treatment groups. As needed and requested by Study Investigators, these case numbers were distributed to the Study Investigators and determined each dog's study group assignment. The body weight obtained at the pre-treatment evaluation visit was used to select the dosage for the appropriate test article (Table 1). After a two-week washout period to remove any other NSAIDs, administration of test articles on study Day 0 was done at the veterinary practice. Test articles were administered orally with or without the aid of food, and were administered daily by the client throughout the 56-day study period. The client maintained a daily log of all test article administration. An interim analysis was performed at 28 days and final analysis at 56 days using veterinarian and owner VAS assessments.

The distribution of all variables (e.g., age, sex, weight, and severity of OA for each group) was checked for approximation using the Wilk-Shapiro test. Where indicated, variance-stabilizing transformations (e.g., log transformations to reduce marked positive skew for variables such as VAS scores, or arcsine square root transformation for binomial variables) was performed on the variables, and all inferential analyses was performed on the transformed data. Alternately, nonparametric tests (i.e., rank transformation) such as Wilcoxon signed rank test (for within-group tests such as comparing pre-post values within groups) or the Kruskal-Wallis test as an omnibus test for differences among the three groups, followed by post-hoc Wilcoxon rank sum test for between-group comparisons, if indicated, may also be employed. The compatibility of the randomized treatment samples was estimated by comparing the demographic variables as well as baseline VAS measures between groups t-tests to compare differences. No adjustments were required.

Overall analyses of the outcome variables of the study (VAS as well as any created difference-score type variables) were conducted using a series of multivariate, repeated-measures, general linear model equations, predicting all post-test values from pre-test values, interim values, and group membership (e.g., FLV vs. CGA), as well as potential confounder variables such as clinic. Change was calculated for weight, veterinarian VAS rating of dog's pain (according to the stated parameters), owner VAS rating of dog's pain (according to the stated parameters), and a mean VAS rating using both veterinarian and owner values. An animal was classified as a treatment failure if it was withdrawn from the study for non-efficacy. Otherwise, it was classified as a success. Frequency distributions of treatment (success/failure) were calculated for each treatment.

The owner's and the veterinarian's VAS scores were analyzed using a general linear repeated measures mixed model analysis of variance. The model contained the fixed effects of treatment, day of study and treatment by day of study interaction, and the random effects of the clinic, clinic by treatment interaction, which was used as the error term to test the treatment effect, animal within clinic by treatment interaction, clinic by treatment by day of the study interaction, which was used to test the day of study and treatment by day of study interaction effects, and residual. The VAS score for the owner was composed of the following behaviors: displays pain, reluctance to climb or jump, slowness to rise or difficulty rising, and limping or appearing stiff.

The number of days that an owner checks "yes" for displaying pain, reluctance to climb or jump, slowness to rise or difficulty rising, crying out and limping or appearing stiff was calculated for each dog. The mean, sample size, minimum and maximum number of days for pain display, reluctant climbing, slow rising, and limping were calculated for each treatment. The percentage of days the dog displayed pain, was reluctant to climb, was slow to rise, and limped was calculated for each dog. The percentage of days was transformed using the arcsine-square root transformation prior to statistical analysis. The transformed variables were analyzed using a general linear mixed model analysis of variance. The model contained fixed effects of treatment and random effects of clinic and clinic by treatment interaction, which was used as the error term to test the treatment effect and residual. The least-squared means were back-transformed for presentation.

RESULTS

IC50 enzyme analysis showed that FlexileRx had equivalent enzymatic inhibition of COX-1 and COX-2, with three-fold less inhibition of 5-LOX enzyme (Table 2). The COX/5-LOX ratio was used because FlexileRx showed equal inhibition of COX-1 and COX-2 by IC50 measurements. No other NSAID or COX-2 inhibitor tested showed balanced inhibition of the COX enzymes, and none showed any 5-LOX inhibitory activity.

Table 2: FlexileRx enzyme inhibition of anti-inflammatory compounds

Inhibitor	COX-2/COX-1 Ratio	COX/5-LOX Ratio
Celecoxib	10	nd*
Meloxicam	2	nd
FlexileRx	1	4
Carprofen	0.5	nd
Naproxen	0.33	nd
Aspirin	0.25	nd

*No inhibition detected

Sixty-nine dogs were randomized; 33 to the FlexileRx group and 36 to the CosequinDS group (Figure 3). Adverse events were generally mild and equivalent in both groups. Two dogs were excluded from analyses as extreme outliers, one from each group (z-scores >6), and discontinued the study due to increasing pain (Table 3). No z-score in either arm exceeded 2 following removal of these two dogs. There were no significant weight changes noted in either group. One subject in the CosequinDS arm was removed due to a severe allergic reaction presumed to not be related to study drug administration. One subject in the FlexileRx arm was diagnosed with a

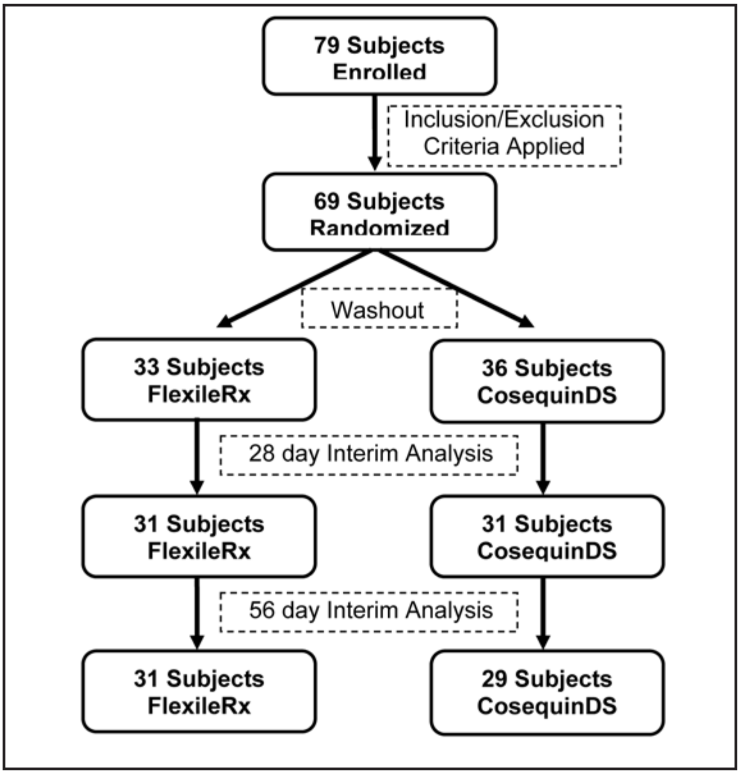
Table 3: Recorded adverse events of each treatment

AE Classification	FlexileRx (n=33)	Cosequin (n=36)	Total (n=69)
Allergy			
• Dermal Condition	0	1[a]	1[a]
GI			
• Vomiting	0	1	1
Musculoskeleta			
• Increased Pain I	1[a]	1[a]	2[a]
Tissue			
• Aural Tumor	1	0	1
• Mastocytoma		1	1[a]
• Other Tumor		1	1[a]
Other			
• Lack of energy	0	1	1
Total AEs	2 (6%)[b]	6 (17%)	8 (12%)

[a]Removed from the study, 4 others removed for non-compliance

[b]$p < .0001$

Figure 3: Study design



benign aural tumor, but completed the study. Two subjects in the CosequinDS arm were diagnosed with benign mastocytoma and “nondescript” tumors, respectively. Both were removed from the final analysis for CosequinDS. One additional dog from the FlexileRx arm was excluded from final analysis due to concurrent administration of carprofen by the owner on three separate occasions. Three dogs in the CosequinDS group were withdrawn from the study due to owner noncompliance. The interim analysis included 31 subjects in each arm, and the final analysis included 31 subjects in the FlexileRx arm and 29 in the CosequinDS arm (Figure 3).

The FlexileRx and CosequinDS groups were equivalent in demographics for weight, age, and initial pain scores. The pre-visit pain scores assessed by veterinarians were: FlexileRx 44.4 (18.8 SD) and CosequinDS 41.6 (17.5 SD). The pre-visit pain scores assessed by owners were: FlexileRx 46.4 (23.4 SD) and CosequinDS 43.5 (21.0 SD). After treatment, both groups showed statistically significant reductions in veterinarian VAS pain scores, and average ratings from baseline to interim and baseline to post-treatment intervals (Table 4). For owner ratings, the change was narrowly significant at the interim visit and narrowly non-significant at the final visit. A statistically significant difference was shown between groups via ANOVA comparison of scores, (a measure of the relative improvement of one treatment group compared to the other over time) for both the veterinarian VAS and the average (combined) VAS scores, demonstrated a statistically significant between-group difference, with the FlexileRx group showing significantly greater improvement than the CosequinDS group at the final analysis (Table 4; Figure 4). For the owner VAS scores, a similar pattern of results was observed, however, these results were statistically significant only at the final analysis.

DISCUSSION

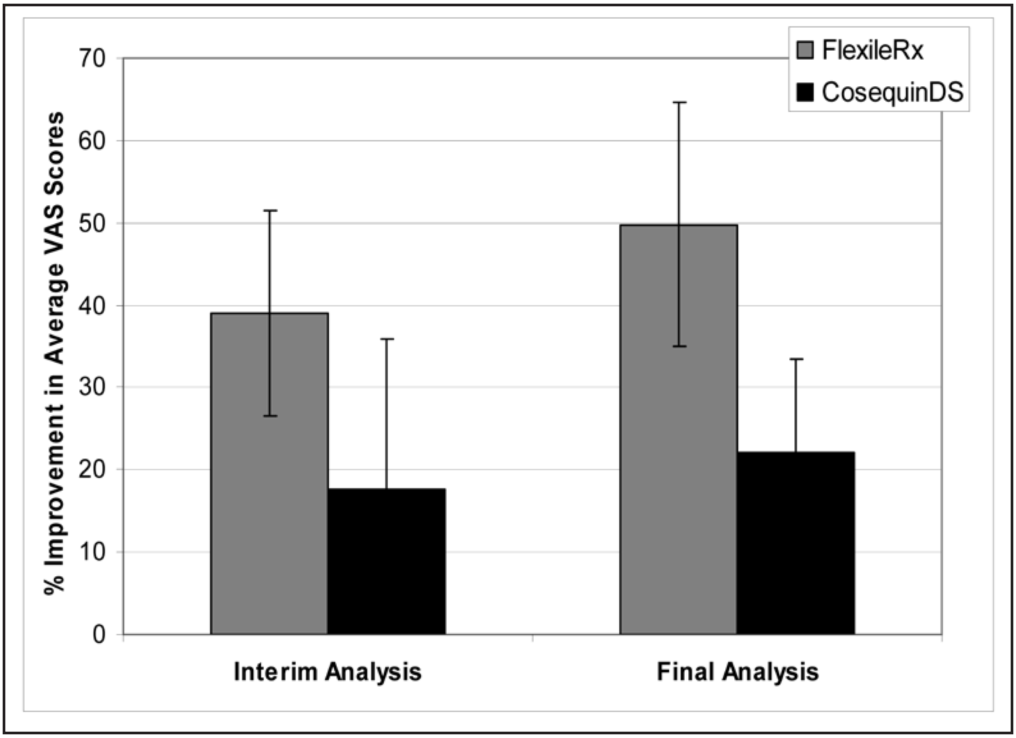
Traditional NSAIDs and COX-2 selective inhibitors are known to cause serious side effects in canines due to selective inhibition of either the COX-1 or COX-2 enzymes (US FDA, 2007). As a consequence, their utilization in dogs is limited. Veterinarians and pet owners have turned to other forms of treatment for OA, such as chondroprotective formulations containing glucosamine and chondroitin.

Balancing COX-1 and COX-2 inhibi-

Table 4

A. Interim Visit Analysis			
Variable (mean, sd)	FlexileRx (n=31)	CosequinDS (n=31)	Between group *p*-value
Weight % change	0.0% (3.3)	0.0% (3.6)	.23
Vet VAS % change	-43.7% (29.4)	-13.3% (36.3)	<.0001
Owner VAS % change	-34.3% (32.0)	-22.0% (47.3)	.24
Average VAS % change	-39.0% (25.0)	-17.7% (36.3)	.009
B. Final Visit Analysis			
Variable (mean, sd)	FlexileRx (n=31)	CosequinDS (n=29)	Between group *p*-value
Weight % change	0.0% (4.8)	-0.0% (4.6)	.51
Vet VAS % change	-53.7% (32.2)	-24.1% (50.6)	.01
Owner VAS % change	-45.9% (43.1)	-20.0% (54.2)	.04

tion activity and avoiding a 5-LOX "shunt," which occurs by blocking only the COX pathways, is important in order to avoid an imbalance of AA metabolites that can lead to gastric, renal, and skin reactions in dogs. Gastric damage is a common occurrence when NSAIDs are used to treat OA in dogs.[10,26,11] Maintenance of gastric mucosa requires the continuous generation of prostaglandins E2 (PGE2) and -I2 (PGI2) to maintain mucous production and cell membrane integrity.[27] Inhibition of COX-1 by traditional NSAIDs reduces prostaglandins required to maintain the stomach lining (or, occasionally, the mucosa of the small bowel), and may eventually lead to ulceration.[28] NSAIDs are known to shunt AA metabolism down the 5-LOX pathway, thereby increasing leukotriene B4 (LTB4) in the stomach mucosa and further exacerbating gastric ulcerations by attracting pro-inflammatory leukocytes to the site of ulceration.[29]



Tepoxalin, a “dual inhibitor” with a similar mechanism of action as FlexileRx, has been shown to reduce the production of LTB4 in gastric mucosal tissue[30] and has lower in-market GI problems (US FDA, 2007). Enzyme inhibition assays of FlexileRx suggest that it may have a similar effect in dogs by inhibiting COX-1 and COX-2 equally, and also inhibiting 5-LOX, thereby preventing the 5-LOX shunt (Table 2). Post-marketing surveillance of a human product composed of similar ingredients has shown an extremely low rate of GI adverse events. (http://www.limbrel.com/downloads/post_mkt_surv.pdf). Though there were no reported GI adverse events in this study, a much larger study or post-marketing surveillance is needed to fully judge the long-term GI safety of FlexileRx.

PGE2 and PGI2 are key regulators of salt balance in the biological system.[31] PGE2 decreases sodium re-absorption, whereas PGI2 stimulates renin production, resulting in the release of aldosterone, which in turn increases sodium re-absorption and potassium secretion.[31,32,33] Prostaglandins are also strong vasodilators that help maintain renal blood flow and urine production. In the setting of reduced circulatory volumes, the body responds by increasing blood pressure to help maintain blood flow via the production of various vasoconstrictive compounds (i.e., thromboxane, catecholomines, vasopressin).[32,33] Leukotrienes, particularly LTC4 and LTD4, are vasoconstrictive and may be important in alterations of blood pressure and renal blood flow, particularly when allowed to accumulate unopposed in patients taking COX inhibitors. Maintaining a balance between the various vasoactive end products of COX and LOX metabolism preserves the ability to respond to changing physiologic conditions. No evidence of kidney dysfunction was identified in either arm of the study, however, further clinical evidence is needed to support this assumption.

Dogs have increased sensitivity to skin reactions caused by NSAIDs. Leukotrienes are up-regulated in atopic dermatitis, which may be exacerbated by NSAIDs.[34,35] One skin reaction was reported in the CosequinDS arm, while no reactions were reported in the FlexileRx arm (Table 3). Flavonoids administered in mice prone to atopic dermatitis showed a significant decrease in the occurrence of dermatitis, suggesting that the molecules found in FlexileRx may help abate some of these skin reactions via inhibition of leukotriene production.[36]

Articular cartilage is primarily composed of type II collagen produced from pro-collagen precursors by chondrocytes,[37,38] which lends tensile strength to cartilage.[39,40] Chondrocytes also generate proteoglycans linked together with collagen forming fibrils, which make up much of the extracellular matrix of cartilage.[41] It is thought that glucosamine composed of an amino-monosaccharide precursor of a disaccharide unit of glycosaminoglycan, the building blocks of proteoglycans in cartilage,[42] and chondroitin sulfate, a polymer of galactosamine and glucoronic acid that aggregates with hyaloronic acid,[43,44] can replace the proteoglycan aggregan structure lost after damage to the joint in OA.[45,46] However, the results of prospective clinical trials have been mixed. A few trials have shown that glucosamine and chondroitin formulations can reduce the progression of natural OA or chemically induced joint damage in dogs,[47,48,49,50] while others have shown limited or no efficacy.[51,52]

There is only limited knowledge of the effect of flavonoid extracts on cartilage in animals. A tumeric extract administered to rats with a streptococcal cell wall–induced arthritic condition showed inhibition of inflammatory cell influx into the joint, reduced formation of prostaglandin, and inhibition of peri-articular osteoclast formation, which are part of the etiology involved in cartilage degradation.[53] In a double-blind, randomized study in canines, a mixture of flavonoids, superoxide dismutase, and glutathione showed improvement in hip OA.[54] A study of tumeric extracts containing curcumin and essential oils in dogs, however, showed little efficacy for OA of hip and knee in a double-blind, placebo-controlled trial.[55] The purity of the extract, as well as the poor bioavailability of curcumin, may have been the reason for the lack of observed efficacy.[56] Only one well-controlled study of OA in humans using the components of FlexileRx has been published to date.[57] Another study with a similar combined extract showed specific reduction of fatty acid inflammatory metabolites in the joint and serum of humans.[58]

The present study showed that FlexileRx (combined flavonoid extract of baicalin and catechin)[25,26] was significantly superior to CosequinDS (glucosamine, chondroitin, manganese, and ascorbate formulation) when comparing veterinarian and owner VAS assessments (Table 4; Figure 4). The length of the efficacy phase of this study may have been a limiting factor that potentially impacted the resulting efficacy of CosequinDS in this study. McCarthy et al[50] showed, for example, that the onset of action for a glucosamine and chondroitin formula took 70 days to reach statistical significance, compared to carprofen, which showed statistical significance in some measures at days 14 through 42. In at least one placebo-controlled trial, glucosamine and chondroitin in combination with manganese for OA in dogs reported no improvement.[52] FlexileRx showed statistical separation from baseline at 28 days, suggesting a much faster onset of action needed when treating OA with a statistically better adverse events profile.

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SUGGESTED READINGS

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