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Research Article

Efficacy and Safety of a Joint Health Nutritional Supplement for Subjects with Non-arthritic Knee Joint Pain: A Double-blind, Placebo- and Active-Controlled, Randomized Clinical Trial

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Abstract

We evaluated the efficacy and safety of FlexPro MD® (FP-MD), a combination of krill oil, astaxanthin, and hyaluronic acid, in adults with non-arthritic knee joint pain. This multicenter, double-blind, placebo- and active-controlled study randomized 140 adults 1:1:1 to oral glucosamine hydrochloride/chondroitin sulfate (GC), FP-MD, or placebo once daily for 8 weeks. Mean percentage decreases in clinician-rated WOMAC pain scores were 35% (FP-MD), 21 % (GC), and 20% (placebo) at week 2, and 55% (FP-MD), 35% (GC), and 30% (placebo) at week 8. Overall, the mean percentage decrease in pain was significantly greater ($P<0.0001$) for FP-MD than for either GC or placebo subjects. FP-MD subjects experienced significantly greater reductions in WOMAC pain scores compared with GC ($P=0.004$) and placebo ($P=0.011$) at week 8 (post-hoc pairwise comparisons). Reductions in patient-reported VAS pain scores followed a similar pattern. FP-MD was three times more effective than GC for pain reduction (63% of FP-MD vs. 16% of GC subjects pain free at week 8). Incidence of adverse events was low (7 [14.9%] GC subjects; 5 (10.2%) FP-MD subjects), with headache being most commonly reported. Once-daily FP-MD supplementation significantly reduced joint pain, measured by both clinicians and subjects, compared with both GC and placebo, and was well tolerated.

Keywords: Arthralgia; Astaxanthin; Chondroitin; Glucosamine; Hyaluronic acid; Joint pain; Krill oil; Osteoarthritis, VAS; WOMAC

Introduction

Joint pain, which is reported by a large percentage of adults in the US and Europe, is one of the most common reasons people try complementary medicine. [1] In a national health statistics report published in 2016, pain was noted to be a primary cause of disability in adults; to have an important impact on United States health care expenses; and to decrease quality of life. [2] In a survey of the incidence of joint pain,[3] knee pain was reported by 18% of respondents, followed by shoulder (9%), hip (7%), and finger (7%) pain. Globally, as of 2018, USD$2.45 billion was spent annually on bone and joint health ingredients, with a market estimated value of USD$4 billion by 2026. [4] As of 2016, nearly 30% (USD$721 million) of joint health product spending in the US was on glucosamine-chondroitin supplements.[5] Oxidative stress and inflammation are known to play major roles in the pathophysiology of both Osteoarthritis (OA) and Rheumatoid Arthritis (RA)[6] and may have a substantial impact on overall joint health in healthy individuals. Excessive inflammation can damage tissues and interfere with the balance of biochemical pathways.[7] Unfortunately, the average Western diet results in an unbalanced Polyunsaturated Fatty Acid (PUFA) intake, with intake of omega-6 PUFAs outweighing that of omega-3 PUFAs [8] The resulting imbalance in omega-6:omega-3 ratio may shift

the body toward an inflammatory state [7].

Key proinflammatory compounds are derived from omega-6 PUFAs (arachidonic acid), including 2-series prostanoids and 4-series leukotrienes, whereas important anti-inflammatory compounds derived from omega-3 PUFAs include 3-series prostanoids and 5-series leukotrienes as well as resolvins and protectins.[7] Fish and fish-oil supplements are the primary dietary sources of the two biologically important omega-3 fatty acids, Docosahexaenoic Acid (DHA) and Eicosapentaenoic Acid (EPA),[7] but the intake of these important fatty acids from Western diets is low. This low intake of omega-3 PUFAs may be associated with increased inflammatory processes in the body.[7] Specifically, eicosanoid metabolites of omega-3 PUFAs down-regulate expression of multiple compounds associated with a proinflammatory state, including Tumor Necrosis Factor (TNF), inducible Nitric Oxide Synthase (inducible NOS, iNOS), C-Reactive Protein (CRP), Cyclooxygenase-2 (COX-2), interleukin (IL)-1β, IL-2, IL-6, and Matrix Metalloproteinases (MMPs). [9] Numerous studies have investigated the immunomodulatory effects of omega-3 PUFAs on joint health. In vitro studies indicate that incorporation of omega-3 PUFAs into articular cartilage chondrocyte membranes results in a dose-dependent reduction in proteoglycan-degrading enzymes and proinflammatory compounds (e.g, IL-1α, TNF, and COX-2).[10] A meta-analysis of 17 randomized, controlled trials that assessed the analgesic effects of omega-3 PUFA supplementation for inflammatory joint pain found statistically significant improvements in patient-reported pain, minutes of morning stiffness, number of painful and/or tender joints, and Nonsteroidal Anti-Inflammatory Drug (NSAID) consumption.[11] In addition, supplementation with a combination of lemon verbena and omega-3 PUFAs significantly reduced symptoms of pain and stiffness compared with placebo in a randomized controlled trial of adults with joint discomfort [12].

A powerful antioxidant that can play a key role in reducing inflammation, astaxanthin is a naturally occurring xanthophyll carotenoid with a strong capacity to quench Reactive Oxygen Species (ROS).[13] The molecular structure of astaxanthin allows it to span the plasma membrane, including the synovial membrane.[14] Astaxanthin suppresses inflammatory mediators, including NO, COX-2, and nuclear factor-κB (NF-κB) both in vitro and in animal models.[15] Astaxanthin also has inhibitory effects on macrophage activation, which play an important role in inflammation. Matrix metalloproteinases are responsible for the degradation of most extracellular matrix proteins and also mediate tissue remodeling. Importantly, astaxanthin has been shown to reduce the expression and activity of macrophage MMPs and the expression of proinflammatory mediators, including TNF, IL-1β, IL-6, iNOS, and COX-2.[16] In human studies, astaxanthin (12 mg/day) reduced pain in pilot studies of patients with RA[17] and carpal tunnel syndrome,[18] and demonstrated a dose-dependent anti-inflammatory effect on uveitis.[19] Synovial joints are complex structures containing articular cartilage, the synovial joint cavity, and a fibrous capsule lined by a synovial membrane that secretes synovial fluid.[20] A key component of synovial fluid is Hyaluronic Acid (HA), a glycosaminoglycan with unique rheologic properties that allow it to function as a lubricant and shock absorber.[21] Hyaluronic acid is also present in joint cartilage and connective tissue, as well as other tissues, and may play a role in bone remodeling [21].

Hyaluronic acid is characterized by a high rate of turnover; approximately one-third of the 15 g of HA found in a 70-kg person turns over daily. Reactive oxygen species are thought to catabolize HA within the joint, and this process appears to account for the approximate 12-hour half-life of native HA molecules within the synovial fluid. [22,23] If the activity of ROS in synovial fluid is excessive, then HA may be cleared faster than it can be replaced. As noted previously, HA may be important in bone remodeling, and intra-articular injection of HA has been shown to reduce pain in inflamed joints and promote wound healing.[21] Balazs and Denlinger [1993] were the first to propose the concept of viscosupplementation (intra-articular injections of HA into osteoarthritic joints) to improve mobility and articular function and decrease pain.[24] Subsequently, the clinical efficacy of various formulations of both high and low molecular weight HA has been evaluated.[25] Studies in large animal joint pain models indicate that intra-articular administration of HA with molecular weights within the range of 0.5 to $1.0x10^6$ Da is generally more effective in reducing indices of synovial inflammation and restoring the rheologic properties of synovial fluid than HA with molecular weight $>2.3x10^6$ Da.[25,26] Low molecular weight HA formulations may penetrate the extracellular matrix of the synovium better than high molecular weight formulations [25].

Clinically, oral administration of HA was responsible for improving clinical symptoms, including pain reduction, in pilot studies of patients with knee OA.[27,28] Krill oil has acceptance as a dietary supplement that can help provide a source of DHA and EPA, as well as astaxanthin. Krill oil is distinct from other marine oils by providing the omega-3 fatty acids in the phospholipid form, thereby acting as a superior delivery system for the fatty acids and astaxanthin to the body.[29] The phospholipid form of astaxanthin confers stability and enhances antioxidant potency. [29] Astaxanthin delivered with an emulsifier, or in the form to emulsify the compound, like a phospholipid, results in physiologic concentrations that are three times higher than levels delivered without an emulsifier and results in detectable blood levels for up to 100 hours after oral administration.[30] In a randomized, double-blind, placebo-controlled study of patients with OA or RA, 300 mg krill oil once daily was associated with a significant reduction of CRP levels, pain, stiffness, and functional impairments [31].

FlexPro MD® (FP-MD) is a unique joint health formulation, combining the powerful antioxidant astaxanthin with key omega-6 and omega-3 fatty acids as phospholipids from krill oil and a lower molecular weight HA for improving joint lubrication. The FP-MD formulation was designed to address the root cause of joint degradation and the pain caused by oxidative stress, with the phospholipid-bound omega-3 PUFAs in krill oil providing greater absorption of astaxanthin, DHA and EPA, and HA [32] compared to unbound formulations. As described above, there was sufficient evidence at the time our study was designed that astaxanthin, krill oil, and HA, as sole agents, may positively influence joint health The primary objective of our study was to evaluate the efficacy of this unique formulation of bioactive agents, FP-MD, compared with placebo in adults with non-arthritic knee joint or soft tissue pain. Secondary objectives were to compare the efficacy of FP-MD with a commercially available active control, glucosamine hydrochloride and chondroitin sulfate (GC), and to evaluate the safety and tolerability of FP-MD as a joint health formulation solution.

Materials and Methods

Subjects

Adults (men and women) 18 to 80 years of age who had confirmed to the best of their knowledge that their knee joint pain was due to idiopathic inflammation of the joints or soft tissue caused by a sports, work-related, or other injury and was not due to OA or RA were included in the study. Subjects had not taken any anti-inflammatory medications or supplements for at least 5 days and had not taken fish oils for at least 10 days before the baseline visit. Subjects who had been told by a Health Care Professional (HCP) that their pain was "probably" or "definitely" due to OA or RA were excluded from study participation, as were subjects who: had a history of allergies to aspirin or other NSAIDs; had undergone total knee replacement in the contra-lateral knee during the 6 months before the screening visit; had received an intra-articular glucocorticoid injection in a lower joint during the 3 months before the baseline visit; had an isolated lateral compartment disease defined by joint space loss in the lateral compartment only; had received chondrocyte transplants in any lower extremity joint; had comorbid conditions that restricted knee function; or had received glucocorticoid treatment before the washout period. Pregnant or nursing women were also excluded from participation.

Study Design

This was a multicenter, randomized, double-blind, placebo- and active-controlled study in which subjects were randomized 1:1:1 to receive oral GC, FP-MD, or placebo once daily for 56 days (8 weeks). ST&T Research International, the clinical research organization managing the study, assigned each subject a code number and generated the random allocation sequence. Study visits occurred at baseline and weeks 2, 4, and 8.

Study Products

FP-MD is a commercially available dietary supplement containing a proprietary combination of 321 mg Superba® Antarctic krill (Euphausia superba) oil (Aker BioMarine Antarctic US LLC; Metuchen, NJ, USA), 2 mg Zanthin® Natural Astaxanthin derived from Haematococcus pluvialis, and 30 mg Flexonic® sodium hyaluronate (the sodium salt of HA) produced from fermentation by Streptococcus zooepidemicus (Valensa International; Eustis, FL, USA). All subjects received 2 opaque gelatin-based capsules for once-daily administration to maintain blinding of subjects and study personnel. Subjects randomized to GC received a commercial GC combination (2 tablets daily) for a total daily dose of 1500 mg glucosamine hydrochloride and 1200 mg chondroitin sulfate. Subjects randomized to FP-MD received 1 FP-MD capsule and 1 placebo capsule containing palm oil. Subjects randomized to placebo received 2 palm oil capsules daily. At each study visit, an adequate supply of the assigned study product was dispensed to each subject to last until the next visit. Subjects were instructed to take both capsules once daily each morning with breakfast and to record the time of day that capsules were actually taken using a daily diary (electronic or paper).

Rescue Medication

Rescue pain medication was allowed throughout the study for the following two reasons. First, if, after 3 weeks of therapy, the subject's pain level had increased from baseline and/or the knee joint flexibility was less than at baseline, and the subject requested it, then rescue medication in the form of the subject's usual pre-study pain medication was administered and the subject was terminated from the study. Second, if a subject wanted to discontinue from the study because of pain or discomfort, then the subject was offered a pain reliever of his or her choice to take for 48 hours, after which the subject could choose to continue on the originally randomized study product or discontinue from the study.

Ethics

The study was conducted according to the guidelines of the Declaration of Helsinki, regulations stated in the Federal Code of Regulations for Good Clinical Practices, and all local and national regulations. The ACERIS Institutional Review Board reviewed and approved all study materials, and subjects provided informed consent before screening procedures were initiated. The study was retrospectively registered on ClinicalTrials.gov on July 6, 2017 (NCT03209895).

Assessments

Efficacy: Efficacy assessments included investigator and subject

evaluations of pain assessment and pain intensity, Range of Motion (ROM) of subjects' knees, and a 6-minute walk test. Subject evaluations of pain were completed daily, and all other assessments were measured during study visits at baseline (day 0) and after 2, 4, and 8 weeks of supplementation. The investigator evaluation of pain assessment and pain intensity was based on a modified Western Ontario and McMaster Universities Osteoarthritis Index™ (WOMAC) [33] numerical rating scale (NRS) scoring of 1 to 10 [34] for the five standardized questions on pain. Specifically, the five WOMAC pain questions were: "How would you rate your pain on a scale of 1 to 10, with 1 being "no pain whatsoever," and 10 being "severe pain requiring intervention with pain-relieving agents," with regard to (a) walking on a flat surface; (b) going up and down stairs; (c) at night while in bed (does the pain disturb your sleep?); (d) sitting or lying down; and (e) standing? Total possible WOMAC pain scores ranged from 5 to 50, and the first assessment during a study visit was recorded as WOMAC 1. At the end of each study visit, a second WOMAC assessment (WOMAC 2) was also completed by the investigator for test-retest reliability. WOMAC 1 and WOMAC 2 values were recorded and analyzed. A self-administered visual analog pain assessment and pain intensity rating scale (VAS) was completed daily by subjects using an online portal (subjects without internet access used a daily diary). [35] The five VAS questions were also scored on a scale of 1 to 10. VAS questions were as follows: "How would you rate your pain on a scale of 1 to 10, with 1 being "no pain whatsoever," and 10 being "severe pain requiring intervention with pain-relieving agents," with regard to (a) walking on a flat surface; (b) going up and down stairs; (c) bending; (d) sitting or lying down; and (e) standing? Total possible VAS scores ranged from 5 to 50. Of note, the investigator-administered WOMAC and self-administered VAS were similar, except item (c), bending. Range of motion of subjects' knees was measured using a QualCraft goniometer (AliMed, Dedham, MA). Initial extension or flexion ROM (angles where pain was first perceived) was measured by having a subject extend each knee until the subject first felt pain. Pain was quantified on a scale of 1 to 10 (10 being extreme pain), and the angle of extension and pain level were both recorded. This process was repeated for knee flexion. Maximum extension or flexion ROM was also measured. Knee extension and flexion were increased until the knee could not be flexed or extended any further, and angles and pain levels were recorded (pain was recorded as 0 if a subject had no pain associated with maximum extension or flexion). Subjects also completed a 6-minute walk test, which indirectly measured joint mobility by comparing the change in a distance that a subject could walk at a rapid pace [36]. A subject with a pain score of ≤9 out of 50 possible points on the WOMAC or VAS was considered 'pain-free' for interpretation of treatment effect.

Pharmacodynamic: For subjects receiving FP-MD, blood was drawn at baseline and weeks 4 and 8, and was analyzed for gene expression markers. Total RNA was purified from whole blood samples preserved in PAXgene® tubes, converted to cDNA following random and oligo[dT] priming, and analyzed by real-time quantitative PCR using custom plates containing fluorescent TaqMan® primer/probe assays (Applied Biosystems, Foster City, CA). Changes in mRNA expression of 7 genes related to the inflammatory response were identified and quantified: IL-1β, IL-6, NF-κB, NO synthase 2A (NOS2A), prostaglandin synthase 2 (PTGS2, the gene for the COX-2 enzyme), transforming growth factor β3 (TGFβ3), and TNF. TATA-binding protein (TBP) mRNA served as the endogenous control for sample-to-sample normalization of the indicator gene assay.

Safety: At each study visit, adverse events (AEs) were reported by subjects, and vital signs were measured. Laboratory values (e.g, complete blood count, blood chemistries, liver function tests) were assessed at baseline and week 8.

Statistical Analysis

Analysis Groups: The efficacy analysis group included all subjects who completed the 8-week study and had a pain level ≥10 for the five questions assessed by either the WOMAC or VAS at least one time during the study. Subjects with a pain level of <9 were defined as "pain free". The safety analysis group included all randomized subjects.

Sample Size: No formal statistical power analysis was completed to determine the study sample size. The enrollment goal was 45 subjects per group to account for a higher than expected potential dropout rate during an 8-week study, a lower than expected inter-subject correlation coefficient, or a lower than expected effect size.

Efficacy Analyses: A primary efficacy endpoint was not prespecified in the statistical analysis plan. A 1-way Analysis of Variance (ANOVA) was used to determine treatment differences between the three product groups for the mean WOMAC and VAS pain scores at week 8. Linear regression analyses of WOMAC scores were used to predict pain response over time for each group. Post hoc analyses were completed to confirm the results of the primary analyses. An analysis of covariance (ANCOVA) model with treatment group as a factor and baseline WOMAC score as the covariate was used for pairwise comparisons of the mean percent change from baseline between the 3 treatment groups at each time point (2, 4, and 8 weeks). A similar ANCOVA model was used for pairwise comparisons of VAS scores at each time point. For the ROM assessments by goniometer, a pain-related functionality formula was used to determine the total increase in ROM of the knee for a given pain level (because the degree of flexibility and

a subject's pain level at specific measurement within ROM are nested variables); the result is the corrected ratio of ROM added to the inverse of the pain level. Paired t-tests were used to analyze changes in initial and maximum ROM flexion and extension for each knee from baseline to week 8.

Pharmacodynamic Analyses: For the gene expression analyses, fold change values were derived by the ΔΔCt method to generate log2 fold change values for groups or individual samples for each indicator gene, and log2 fold change values were then transformed to true scale for display and reporting purposes. A fold change <1 indicates decreased expression and a fold change >1 indicates increased expression. Independent and paired t-tests were used to compare changes in gene expression levels between baseline and weeks 4 and 8. For efficacy and pharmacodynamic analyses, the method of mean imputation was used for missing data and $\alpha = 0.05$. Safety data were summarized descriptively.

Results

Baseline Demographics and Clinical Characteristics

Between October 8, 2010 and June 13, 2011, 140 subjects with a mean age of 47.1 years (range, 18-80) were enrolled at four US study sites. Baseline demographic characteristics, WOMAC pain scores, and VAS pain scores were similar for the three product groups (Table 1).

Characteristic	GC n=47	FP-MD n=49	Placebo n=44
Subjects with demographic data, n	38	42	43
Age, mean (range), years	45.2 (20, 64)	49.1 (25, 72)	47.0 (18, 80)
Sex, n (%)			
Women	21 (55)	23 (55)	22 (51)
Men	17 (45)	19 (45)	21 (49)
Race/ethnicity, n (%)			
White	26 (68)	32 (76)	29 (67)
Black	6 (16)	4 (10)	5 (12)
Asian	6 (16)	3 (7)	2 (5)
Hispanic	0 (0)	3 (7)	4 (9)
Other	0 (0)	0 (0)	3 (7)
BMI, mean (range), kg/m^2	26.6 (18.4, 37.3)	27.2 (18.9, 43.6)	26.4 (16.0, 40.8)
Subjects included in efficacy analyses, n	32	40	35 [1]
Average WOMAC 1 score, mean ± SD	22.4 ± 8.3	22.4 ± 7.6	20.8 ± 7.7
Average WOMAC 2 score, mean ± SD	19.4 ± 8.7	21.8 ± 9.3	20.0 ± 8.2
Average VAS score, mean ± SD	19.3 ± 7.9	21.2 ± 7.9	18.6 ± 7.1

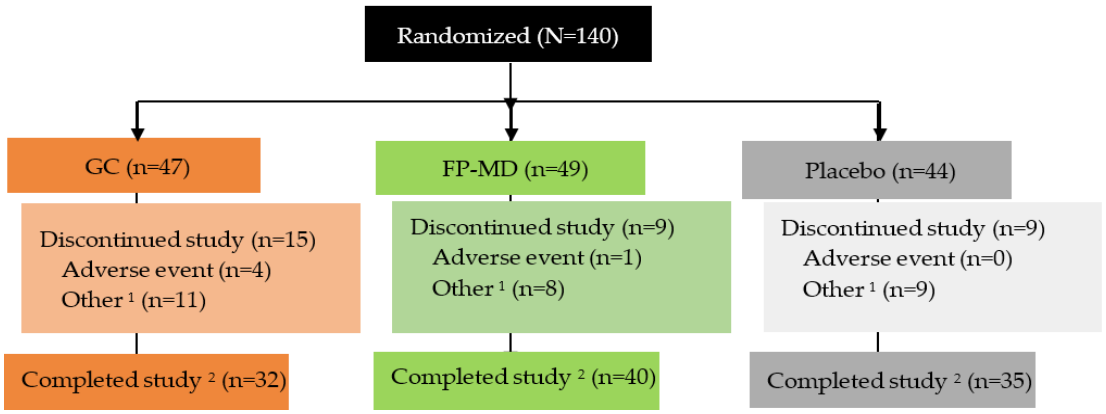
[1] n=34 for baseline WOMAC scores; FP-MD, FlexPro MD; GC, glucosamine hydrochloride and chondroitin sulfate; SD, standard deviation; VAS, visual analog scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

Table 1: Baseline Demographic and Clinical Characteristics by Treatment Group.

Disposition

The 140 enrolled subjects were randomized to GC (n=47), FP-MD (n=49), and placebo (n=44), and 107 subjects completed the study (Figure 1). Fifteen subjects discontinued from the GC group and 9 each from the FP-MD and placebo groups. Four subjects completed the 8-week study but never reached a pain level ≥10 on either the WOMAC or VAS pain scores and were excluded from

efficacy analyses. The efficacy analysis population included 103 subjects (i.e, all subjects who completed the study and had either a WOMAC or VAS score ≥10 at some point during the study).



[1]Personal reasons, primarily due to length of study; [2]Included in efficacy analyses, except 4 subjects who completed the 8-week study but never reached a pain level ≥10 for the 5 questions assessed by either the WOMAC or VAS pain scales.

Figure 1: Subject randomization and disposition. FP-MD, FlexPro MD; GC, glucosamine hydrochloride and chondroitin sulfate.

WOMAC Pain Scores

As detailed in the methods, the investigator evaluation of pain assessment and pain intensity was based on a modified WOMAC [33] NRS scoring of 1 to 10 [34] for the five standardized questions on pain, with total possible WOMAC pain scores ranging from 5 to 50. A 1-way ANOVA indicated a statistically significant difference among the three study product groups for both WOMAC 1 (F=4.04, P=0.021) and WOMAC 2 (F=5.16, P=0.0073) scores. Regression analyses for the ANOVA indicated that all three product groups had a statistically significant decrease in pain during the course of the study compared with baseline; however, the greatest reduction in pain score was seen for the FP-MD group for both the WOMAC 1 (regression coefficient for FP-MD, -3.93, P<0.001; GC, -2.66, P<0.001; placebo, -1.97, P<0.001) and WOMAC 2 assessments (regression coefficient for FP-MD, -3.93, P=0.05; GC, -1.81, P=0.006; placebo, -1.92, P=0.07). Subjects receiving FP-MD also had the greatest mean percentage decreases in pain over the course of the study based on average WOMAC pain scores. The mean percentage decrease in pain was 35% after 2 weeks of FP-MD supplementation, 44% after 4 weeks, and 55% after 8 weeks. Over the course of the study, the mean percentage decrease in pain for subjects receiving FP-MD was statistically significantly greater (P<0.0001) than either active control (GC) or placebo control (palm oil) groups. Post hoc pairwise comparisons using ANCOVA confirmed a statistically greater mean percentage decrease in pain for the FP-MD group, with P=0.004 for FP-MD vs GC and P=0.011 for FP-MD vs placebo at week 8. The mean percentage decreases in WOMAC pain scores for subjects receiving GC and placebo were equivalent by week 2 (21% for GC and 20% for placebo), with further decreases in pain scores for the GC group to 35% and for the placebo group to 30% by week 8, indicating comparable and statistically similar outcomes for the GC and placebo groups. Post hoc pairwise comparisons revealed no statistically significant differences between GC and placebo at any timepoint (P=0.562 at week 2; P=0.951 at week 4; and P=0.711 at week 8).

The placebo-adjusted values for the mean percentage decrease in pain as measured by WOMAC scores are shown in Figure 2. After 8 weeks of supplementation, the GC group had a 5% mean placebo-adjusted reduction in the WOMAC pain scores compared with a 25% mean placebo-adjusted reduction for the FP-MD group.

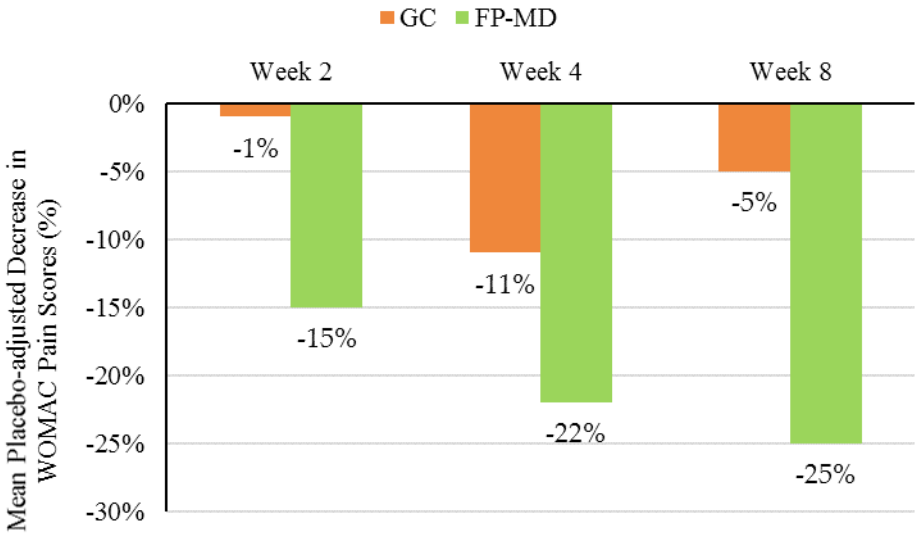
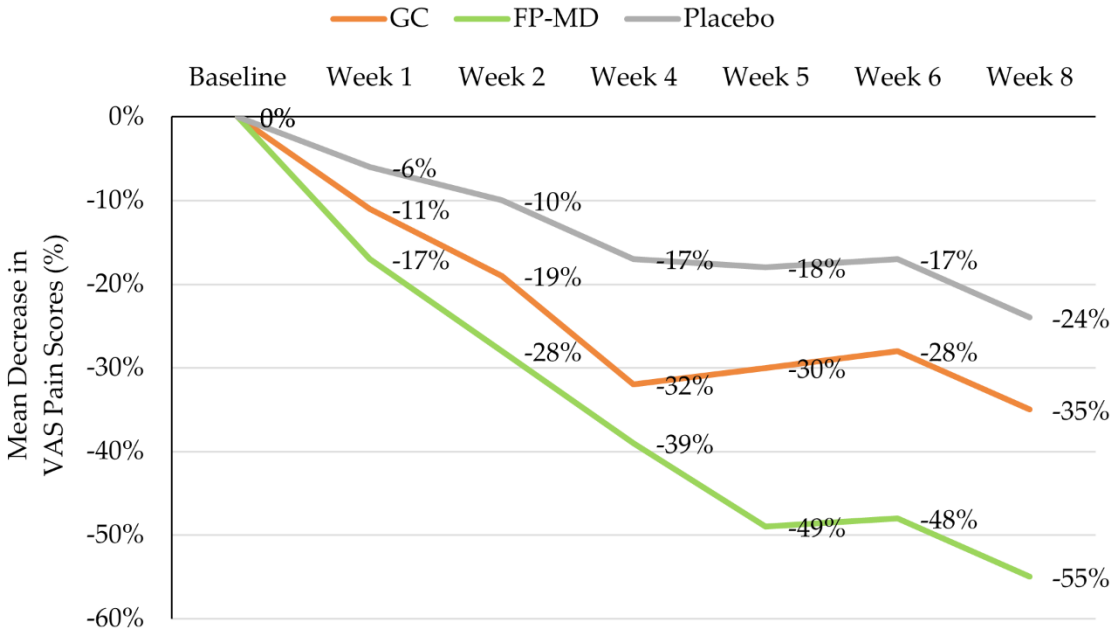


Figure 2: Percentage decrease in average WOMAC pain scores over time. Placebo-adjusted mean percentage decreases in WOMAC pain scores for GC and FP-MD groups. FP-MD, FlexPro MD; GC, glucosamine hydrochloride and chondroitin sulfate; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

VAS Pain Scores

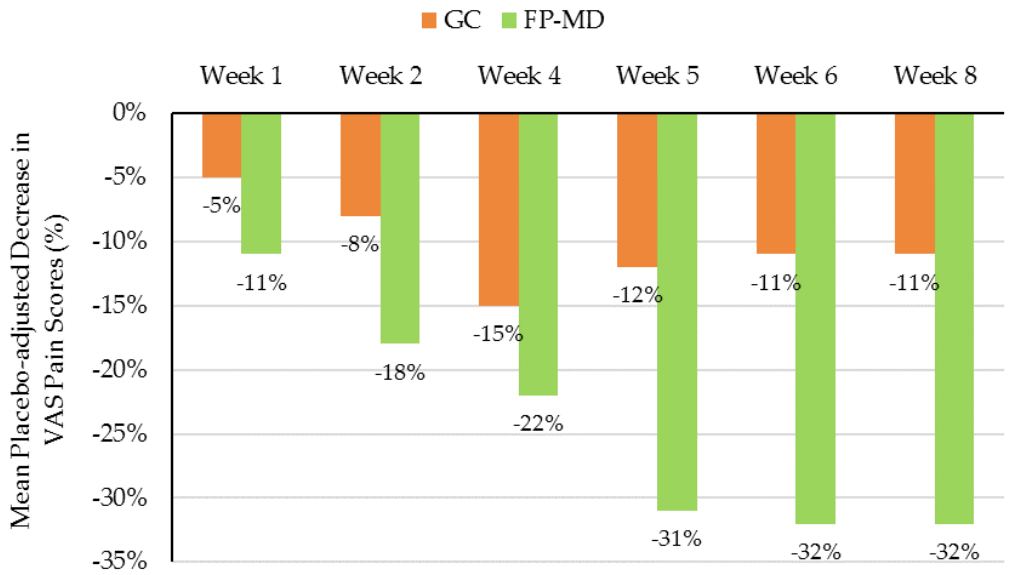
A 1-way ANOVA indicated a statistically significant difference among the three groups for mean VAS pain scores (F=7.24, P=0.0012). Regression analysis indicated that all three study groups had a statistically significant decrease in pain during the course of the study compared with baseline; however, the reduction was greatest for the FP-MD group (regression coefficient for FP-MD, -2.37, P<0.001; GC, -1.42, P<0.001; placebo, -0.90, P<0.001). Subjects receiving FP-MD also had the greatest mean percentage decrease in pain over the course of the study as measured by self-reported VAS scores (Figure 3a). Differences in VAS pain scores between study product groups were evident after only 1 week of supplementation (17% reduction for FP-MD group vs 11% for GC and 6% for placebo). By week 5, subjects receiving FP-MD had a mean percentage decrease in VAS pain scores of 49% versus 30% for GC and 18% for placebo. Post hoc pairwise comparisons revealed the treatment difference between FP-MD and placebo was statistically significant at week 5 (P=0.031). The reduction in pain scores leveled off between weeks 4 and 6 for the GC and placebo groups, and between weeks 6 and 7 for the FP-MD group. At week 6, there was a statistically significantly greater mean percentage decrease in VAS pain score for the FP-MD group compared with the GC group (P=0.030) and with the placebo group (P=0.035). By week 8, all groups had a further reduction in pain scores, with a mean percentage decrease of 55% for FP-MD, 35% for GC, and 24% for placebo. At week 8, the mean percentage decrease in VAS pain score remained statistically significantly greater for the FP-MD group compared with the GC group (P=0.039) and with the placebo group (P=0.017). Post hoc pairwise comparisons revealed no statistically significant differences for VAS pain scores between GC and placebo at any time point (all P values >0.05). Placebo-adjusted values for the mean percentage decrease in VAS pain scores are shown in Figure 3b. By week 1, the FP-MD group had a placebo-adjusted reduction in VAS pain score of 11% versus only 5% for the GC group. The magnitude of placebo-adjusted VAS pain score reductions increased through week 5 for both FP-MD and GC groups (31% for FP-MD vs 12% for GC) and then leveled off through week 8.



Group	Timepoint						
VAS Pain Scores	**Baseline**	**Week 1**	**Week 2**	**Week 4**	**Week 5**	**Week 6**	**Week 8**
GC							
Mean ± SD	19.3 ± 7.9	17.2 ± 8.0	15.7 ± 6.4	13.1 ± 5.7	13.6 ± 6.0	13.9 ± 7.4	12.6 ± 4.9
LS mean	-	-2.3	-3.8	-6.4	-6.0	-5.7	-7.1
FP-MD							
Mean ± SD	21.2 ± 7.9	17.6 ± 8.4	15.2 ± 8.8	12.9 ± 8.3	10.7 ± 5.9	10.9 ± 7.4	9.5 ± 7.2
LS mean	-	-3.0	-5.4*	-7.6†	-8.4‡	-9.3§,‖	-10.4¶,#
Placebo							
Mean ± SD	18.6 ± 7.1	17.5 ± 6.6	16.5 ± 6.8	15.1 ± 7.1	15.1 ± 6.9	15.2 ± 7.0	13.9 ± 6.7
LS mean	-	-1.6	-2.4	-3.8	-4.2	-4.0	-5.4

*P=0.028 for FP-MD vs placebo; †P=0.009 for FP-MD vs placebo; ‡P=0.006 for FP-MD vs placebo; §P=0.030 for FP-MD vs GC; ‖P=0.001 for FP-MD vs placebo; ¶P=0.028 for FP-MD vs GC; #P<0.001 for FP-MD vs placebo.

(a)



(b)

Figure 3: Percentage decrease in VAS pain scores over time. **(a)** Mean percentage decreases in VAS pain scores. *P=0.0012 for FlexPro MD (FP-MD) versus glucosamine hydrochloride and chondroitin sulfate (GC) and placebo over the course of the study based on analysis of variance for overall treatment effect. †P=0.031 for FP-MD vs placebo; ‡P=0.030 for FP-MD vs GC; §P=0.035 for FP-MD vs placebo; ‖P=0.039 for FP-MD vs GC; and ¶P=0.017 for FP-MD vs placebo based on post hoc analysis of covariance pairwise comparisons at each timepoint with treatment group as a factor and pain score as a covariate**. (b)** Placebo-adjusted mean percentage decreases in VAS pain scores for GC and FP-MD groups. VAS, visual analog scale. FP-MD, FlexPro MD; GC, glucosamine hydrochloride and chondroitin sulfate; VAS, visual analog scale.

Comparison of WOMAC and VAS Scores

The average WOMAC scores assessed at weeks 2, 4, and 8 were compared with self-administered VAS scores reported at weeks 2, 4, and 8 to determine if the investigator influenced the WOMAC results. With the exception of the week 2 WOMAC scores for the FP-MD group, the mean WOMAC and VAS pain scores were essentially equivalent in each active treatment group at each time point (Table 2), indicating no apparent investigator-testing influence. The difference in the wording of item c on the WOMAC and VAS questionnaires did not appear to affect the data. Placebo-adjusted WOMAC and VAS results were also similar (Table 2).

Product group	Week 2		Week 4		Week 8	
	WOMAC	VAS	WOMAC	VAS	WOMAC	VAS
	Mean % reduction [mean placebo-adjusted % reduction]					
GC	-21 [-1]	-19 [-8]	-32 [-10]	-32 [-15]	-35 [-5]	-35 [-11]
FP-MD	-35 [-15]	-28 [-18]	-44 [-22]	-49 [-22]	-55 [-25]	-55 [-32]
Placebo	-20	-10	-22	-18	-30	-24

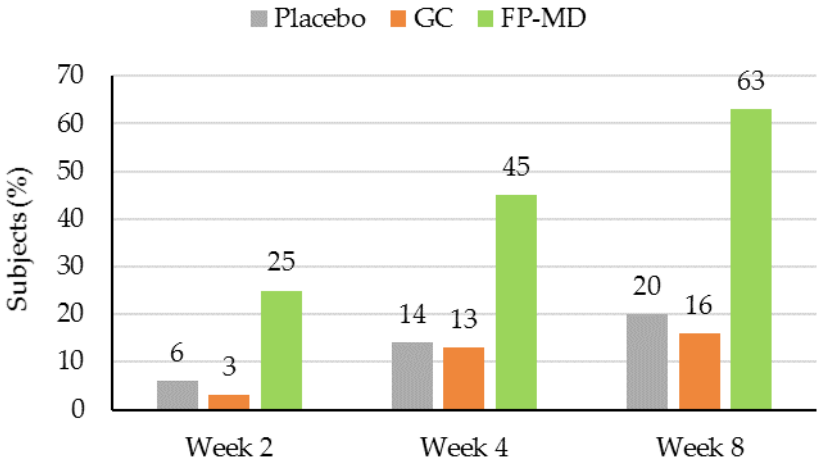
FP-MD, FlexPro MD; GC, glucosamine hydrochloride and chondroitin sulfate; VAS, visual analog scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

Table 2: Comparison of WOMAC and VAS pain scores over time.

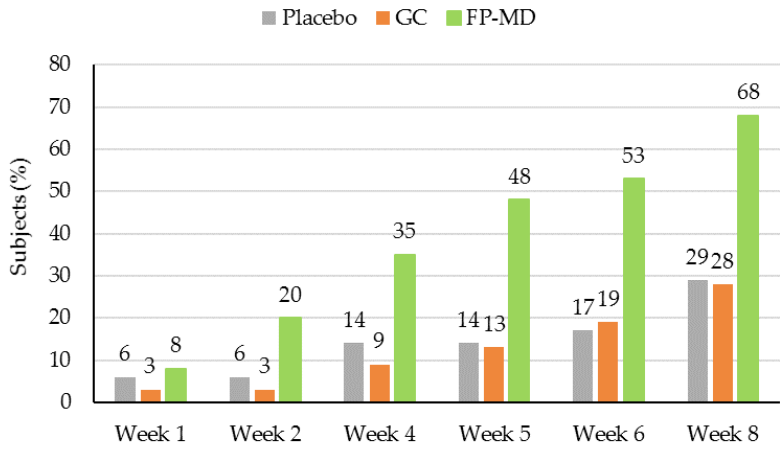
Total Pain Relief

The number of subjects who were pain free, defined as having either a WOMAC or VAS score ≤9 on the day assessed and on all subsequent assessment days, was also analyzed. After 2 weeks of supplementation, 25% of subjects receiving FP-MD were pain free as assessed by WOMAC scores and remained pain free for the duration of the study, versus 3% of GC and 6% of placebo subjects (Figure 4a). After 8 weeks of supplementation, the percentage of pain-free subjects increased in all groups, with the greatest percentage (63%) reported in the FP-MD group. Over the 8-week trial, the percentage of FP-MD subjects who were reported to be pain free increased, and those subjects who found sustained relief from pain also continued to increase with FP-MD supplementation.

The percentage of subjects who were pain free, with a score of ≤9, as assessed by VAS scores followed a similar pattern. After 2 weeks of supplementation, 20% of subjects receiving FP-MD were pain free and remained pain free for the duration of the study versus 3% of GC and 6% of placebo subjects (Figure 4b). After 8 weeks of supplementation, the percentage of pain-free subjects increased in all groups, with the greatest percentage (68%) reported in the FP-MD group.



(a)



(b)

Figure 4: Percentage of subjects in each study product group who were pain free over time. **(a)** Percentage of subjects who were pain free at timepoint shown and remained pain free for duration of study as assessed by the investigator-rated WOMAC. **(b)** Percentage of subjects who were pain free at time point shown and remained pain free for duration of study as assessed by self-reported VAS. FP-MD, FlexPro MD; GC, glucosamine hydrochloride and chondroitin sulfate (GC); VAS, visual analog scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

Goniometer Range-Of-Motion

Mean initial and maximum ROM pain-related functionality values at baseline and week 8 are shown in Table 3. All three study groups experienced improvements in both initial and maximum ROM pain-related functionality (P<0.05). The greatest amount of change from initial ROM pain-related functionality was 20.3% for the FP-MD group, and the greatest amount of change in maximum ROM functionality was 21.3%, noted for the GC group (Table 3).

Product group	**Initial ROM Pain-related Functionality**		**Maximum ROM Pain-related functionality**		**Change in pain-related functionality from baseline to week 8 (%)**	
	Baseline	Week 8	Baseline	Week 8	Initial ROM	Maximum ROM
GC	1.21	**1.35**	1.03	**1.24**	13.9	21.3
FP-MD	1.23	**1.44**	1.17	**1.27**	20.3	9.9
Placebo	1.30	**1.43**	1.10	**1.21**	12.6	11.2

FP-MD, FlexPro MD; GC, glucosamine hydrochloride and chondroitin sulfate; ROM, range of motion.

Bond font indicates a statistically significant difference compared with baseline based on paired t-tests (P<0.05).

Table 3: Change from baseline to week 8 in initial and maximum goniometer-based range-of-motion pain-related functionality.

Mean ROM-associated pain values at baseline were low for each of the three study product groups (<3 on a 10-point scale), indicating that knee extensions and flexions were not causing significant pain. Subjects receiving FP-MD or placebo did not experience statistically significant improvements in maximum extension or flexion ROM for either knee.

Six-Minute Walk Test

There were no measurable differences in the distance subjects in each group were able to walk at any time point measured (weeks 2, 4, and 8) compared with baseline (data not shown).

Pharmacodynamic Results

Gene Expression: For subjects in the FP-MD group, the mean fold change (1 fold = 10□ change) for mRNA expression of the 7 proinflammatory genes analyzed ranged from 0.73 to 1.13 at week 4 and 0.96 to 1.15 at week 8 (Table 4). The Coefficient of Variance (CV) for qPCR-generated fold change ranged from 0.8% to 1.3%, with maximal CV values ranging from 1.6% to 5.3% (within acceptable norms). Compared with baseline levels, mean fold changes in mRNA expression at weeks 4 or 8 were not statistically significantly different. Compared with baseline levels, 82% (31/38) of subjects at week 4 and 79% (31/39) at week 8 had >25% decrease in mRNA expression of at least 1 gene (Table 4).

Timepoint **Proinflammatory Gene**	**Mean Fold Change (SD)**	**Independent** **t-test** **P value**	**Paired t-test** **P value**	**Expression Decreased by >25%** **N (%)**
Week 4				n=38
IL-1β	1.13 (0.73)	0.40	0.25	10 (26.3)
IL-6	1.13 (0.59)	0.54	0.16	13 (34.2)
NF-kB1	0.73 (1.22)	0.29	0.25	7 (18.4)
NOS2A	0.84 (0.69)	0.32	0.19	12 (31.6)
PTGS2	0.90 (0.52)	0.53	0.28	9 (23.7)
TGFβ3	0.88 (0.68)	0.35	0.32	10 (26.3)

TNF	1.10 (0.60)	0.46	0.30	9 (23.7)
Week 8				n=39
IL-1β	1.12 (0.53)	0.70	0.15	6 (15.4)
IL-6	1.15 (0.58)	0.70	0.09	9 (23.1)
NF-kB1	0.96 (0.59)	0.55	0.68	6 (15.4)
NOS2A	1.05 (0.68)	0.97	0.63	13 (33.3)
PTGS2	0.98 (0.46)	0.59	0.77	10 (25.6)
TGFβ3	0.99 (0.68)	0.62	0.96	8 (20.5)
TNF	1.08 (0.57)	0.97	0.39	5 (12.8)

IL, interleukin; NF, nuclear factor; NOS2A, nitric oxide synthase 2A; PTGS2, prostaglandin-endoperoxide synthase 2; SD, standard deviation; TGF, transforming growth factor; TNF, tumor necrosis factor.

Table 4: Changes in mRNA expression of 7 proinflammatory genes between baseline and weeks 4 and 8 for the FlexPro MD group.

Safety

There were no clinically meaningful changes in vital signs or laboratory measures (e.g, complete blood count, blood chemistries, liver function tests) between baseline and week 8. Adverse events reported by any subject in any study product group are summarized in Table 5. A total of 12 subjects reported AEs, 7 (14.9%) in the GC group and 5 (10.2%) in the FP-MD group; no subjects in the placebo group reported any AEs. The most common AE was headache, reported by 2 (4.3%) subjects in the GC group and 5 (4.1%) in the FP-MD group. One subject in the GC group required hospitalization due to a serious AE (severe vertigo). Five subjects discontinued the study due to AEs; 4 subjects (8.5%) in the GC group and 1 (2.0%) in the FP-MD group. There were no clinically meaningful changes in total cholesterol, VLDL, LDL, HDL, or triglyceride levels between baseline and week 8 in the FP-MD group.

Adverse event (AE)	**GC** **n=47**	**FP-MD** **n=49**	**Placebo** **n=44**
Any AE, n (%)	7 [1] (14.9)	5 [2] (10.2)	0
Backache	3 (6.4)	0	0
Headache	2 (4.3)	5 (10.2)	0
Severe vertigo [3]	1 (2.1)	0	0
Knee injury	1 (2.1)	0	0
Discontinuation due to AE, n (%)	4 (8.5)	1 (2.0)	0

FP-MD, FlexPro MD; GC, glucosamine hydrochloride and chondroitin sulfate.

[1] Six subjects required rescue pain medication; 4 discontinued from the study.

[2] One subject required rescue pain medication but completed the study.

[3] Serious AE (required hospitalization).

Table 5: Adverse events reported by any subject in any study product group

Discussion

This double-blind, randomized, placebo- and active-controlled trial of 140 adults with knee joint and connective tissue pain demonstrated that once-daily FP-MD supplementation was associated with a significantly greater reduction in pain, as measured by both clinicians and subjects, compared with both GC and placebo. Participants experienced a rapid onset of pain reduction, as early as 1 to 2 weeks after starting supplementation, as demonstrated by a placebo-adjusted decrease in WOMAC and in VAS pain scores. Placebo-adjusted pain reduction in WOMAC scoring at week 2 of -35% for FP-MD vs -21% for GC, and a placebo-adjusted decrease in VAS pain scores at week 1 of -11% for FP-MD vs -5% for GC. The pain reduction was sustained through 2 months of supplementation, with a placebo-adjusted decrease in WOMAC pain scores at week 8 of -25% for FP-MD vs -5% for GC, and a placebo-adjusted decrease in VAS pain scores at week 8 of -32% for FP-MD vs -11% for GC. At week 8, 63% of FP-MD subjects vs 20% of GC subjects were characterized as pain free, indicating that FP-MD was three times more effective than GC in helping subjects achieve and maintain pain relief. Subjects who received FP-MD also had decreases in mRNA expression of proinflammatory cytokines compared to baseline, indicating a possible mechanism of action in pain management.

FP-MD was well tolerated by the subjects receiving this supplementation. There were few AEs in the FP-MD group, and only 1 FP-MD subject discontinued from the study due to an AE compared with 4 GC subjects. No clinically important changes in laboratory values or vital signs were identified in clinical measurements in the FP-MD, GC, or placebo groups. Downregulation of pain sensitization and inflammatory responses are important for joint health. Proinflammatory cytokines, such as TNF, are known to increase nociceptor sensitization.[37] Initiation of the NF-κB signaling pathway functions as a master switch that promotes inflammation by triggering expression of proinflammatory cytokines (e.g, TNF, IL-6, IL-1β) and COX-2.[38] Both in vitro and in vivo data indicate that FP-MD is a highly effective, tissue-specific anti-inflammatory product with the same mechanism of action as indomethacin, [39] an NSAID used to treat moderate-to-severe OA and RA. In RAW264.7 murine macrophages exposed to Lipopolysaccharide (LPS), a potent endotoxin that causes a sudden and acute inflammatory response by triggering NF-κB release, FP-MD significantly downregulated mRNA expression of proinflammatory cytokines TNF, IL-6, and IL-1β in a dose-dependent manner by interfering with the ability of LPS to trigger NF-κB release, thus inhibiting the upregulation of proinflammatory cytokines. FP-MD also increased mRNA levels of the anti-inflammatory cytokine IL-10 in LPS-stimulated macrophages. In a murine arthritis model, 30 days of oral administration of 50% or 100% of the equivalent human FP-MD dose resulted in a statistically significant decrease in mRNA expression of proinflammatory cytokines (TNF, IL-6, and IL-1β), NF-κB-dependent inflammatory markers (iNOS, COX-2), MMP1, MMP2, and CRP, and a statistically significant increase in IL-10 expression in mouse joint tissues. In this animal model, FP-MD was as effective as indomethacin in reducing expression levels of proinflammatory cytokines and inflammatory markers. In a rat model of OA induced by Monosodium Iodoacetate (MIA), oral administration of FP-MD once daily for 7 days before and 21 days after MIA injection significantly ameliorated joint pain and decreased the severity of articular cartilage destruction. In addition, FP-MD significantly reduced levels of articular cartilage degradation biomarkers, proinflammatory cytokines (TNF, IL-6, and IL-1β), and mRNA expression levels of NF-κB-dependent inflammatory markers (iNOS, COX-2) and matrix-degrading enzymes MMP1 and MMP2 in knee joint tissue. In this well-accepted model of OA, FP-MD reduced joint pain severity to a level similar to that of celecoxib-treated rats [40].

In addition to the in vitro and in vivo data just described, results of other studies support the therapeutic efficacy of the individual components of FP-MD. Astaxanthin may directly benefit joint and bone health in addition to protecting HA from degradation by ROS. Managing the activity of ROS in the synovium could address joint pain and function. [41] In a comprehensive mechanistic review of the biologic activities and health benefits of astaxanthin, Fakhri and colleagues summarized the activity of astaxanthin on cartilage and bone.[42] The expression of multiple MMPs, which play a significant role in the pathogenesis of OA, was reduced in human chondrocytes pretreated with astaxanthin and then stimulated by the proinflammatory cytokine IL-1β.[43-45] Astaxanthin also inhibits key signaling pathways involved in cartilage degradation, including mitogen-activated protein kinases (MAPK), NF-κB, and NF-E2-related nuclear factor 2 (Nrf2) signaling, which is the master sensor of oxidative stress.[43,45] These in vitro findings were corroborated using in vivo studies of rabbit and mouse models of OA in which astaxanthin reduced cartilage damage. [44,45] Similarly, in human chondrosarcoma cells pretreated with astaxanthin, glutathione peroxidase activity was significantly increased and generation of ROS, MMP-13, IL-6, TNF, and other inflammatory mediators was significantly decreased. Astaxanthin also downregulated transcriptional activation of NF-κB and activator protein 1 (AP-1) in chondrosarcoma cells.[46] Other bone- and cartilage-related effects of astaxanthin include a reduction of alveolar bone loss in an experimental model of periodontitis;[47] suppression of osteoclast formation in vitro;[48] amelioration of bone loss in animal models of osteoporosis;[48-50] and attenuation of inflammation in a rat model of gouty arthritis.[51]

Astaxanthin may have other beneficial effects within the musculoskeletal system. For example, there is evidence that the antioxidant and anti-inflammatory activity of astaxanthin may contribute to analgesic effects in animal models of chronic pain.

[52] The effects of astaxanthin on muscle function have also been investigated. In an evaluation of heat-induced oxidative damage in skeletal muscle, which leads to mitochondrial dysfunction and increased generation of ROS, astaxanthin, but not quercetin (another dietary antioxidant), preserved mitochondrial integrity and function, ameliorated oxidative stress, and reduced heat induced skeletal muscle injury.[53] In addition, a randomized, double-blind, placebo-controlled study demonstrated significantly improved walking endurance and duration as well as improved muscle strength in older adults (65-82 years) taking an orally administered astaxanthin-containing supplement compared with placebo [54].

Because of the known antioxidant, anti-inflammatory, and anti-apoptotic activities of astaxanthin, there has been extensive research into its other biologic activities beyond the joint-related immunomodulatory effects. The anti-cancer, anti-diabetic, cardioprotective, hepatoprotective, and neuroprotective effects of astaxanthin, among others,[42] have led to the proposal that astaxanthin be considered a 'longevity vitamin.'[55] Although astaxanthin is not a vitamin in the traditional sense that a severe deficiency leads to detrimental health effects, astaxanthin may play a role in chronic inflammation, the concept of inflammageing,[56] and may be important to promote healthy aging.[55] Astaxanthin delivered with an emulsifier yields physiologic concentrations that are three times higher than levels delivered without an emulsifier and results in detectable blood levels for up to 100 hours after oral administration.[30] Astaxanthin is readily absorbed in a dose-response manner from the Zanthin formulation used in FP-MD[13] because the phospholipids from krill oil act as an emulsifier to improve the absorption of Zanthin. An 8-week evaluation of a similar algal-derived astaxanthin in healthy adults who took 6 mg/day revealed no clinically important changes in laboratory measures or blood pressure values[57] but did not note the absorption of astaxanthin by the body.

In 2019, Gupta and colleagues published an extensive review of the molecular mechanisms of HA and its therapeutic effects in health and disease.[58] The authors concluded that HA has multiple functions that support its use as a joint health supplement, including articular cartilage lubrication, prevention of extracellular matrix degradation, and antioxidative/antinitrosative, analgesic, anti-inflammatory, chondroprotective, and cartilage-repair effects.[58] A systematic review found that most studies of oral HA formulations in patients with moderate knee OA treated for 1 to 4 months reported significant improvements of clinical scores, including WOMAC and VAS scores, compared with placebo-treated controls. The authors noted that the clinical evidence for oral HA products is positive and aligned with The European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) recommendations to use Symptomatic Slow-Acting Drugs for OA (SYSDOA).[58] Another review that included 6 studies of patients with knee pain/joint discomfort (but not OA) reported significant improvements in a range of outcomes, including knee pain, discomfort, stiffness, joint mechanics, and knee muscular strength in patients who received oral HA [59].

Omega-3 PUFAs have long been known to possess anti-inflammatory properties, and numerous studies have demonstrated a beneficial effect of supplementation in patients with chronic inflammatory diseases. Recent research suggests that bioactive lipid mediators, termed resolvins, that are generated in vivo from EPA and DHA may stimulate the resolution of inflammation and represent a mechanism by which omega-3 PUFAs contribute to joint health. [60] Resolvins appear to suppress immune cell activation, counteract inflammatory mediators, and have analgesic actions. [60] Also, reduced levels of proinflammatory cytokines IL-6, IL-17, and IL-23 in joints and increased levels of T regulatory cells in the spleen have been measured in mice that were genetically modified to produce high levels of omega-3 PUFAs.[61] Various formulations of glucosamine, chondroitin, or the combination have been widely used in Europe and the US as dietary supplements to support joint health and treat OA.[4,5] Although some individual studies have demonstrated the effectiveness of glucosamine and chondroitin compared with placebo in patients with knee OA, a meta-analysis published in 2018 revealed that compared with placebo, chondroitin could alleviate pain symptoms and improve function, and glucosamine could reduce stiffness, but there was insufficient evidence (only three studies) to support the superiority of the combination over placebo.[62] One of the three studies was a large, 6-month, randomized, double-blind, placebo-controlled trial of glucosamine and chondroitin in 168 adults. In a subgroup of patients with moderate to severe knee pain, glucosamine and chondroitin was superior to placebo for relief of joint pain.[63] The meta-analysis indicated no significant difference in the incidence of and discontinuations due to AEs for either component or the combination when compared with placebo [62].

In 2019, adverse reactions potentially associated with glucosamine and chondroitin sulfate were identified by the French Agency for Food, Environmental and Occupational Health & Safety (ANSES) nutrivigilance scheme.[64] Adverse reactions identified in the vigilance surveillance included digestive disorders, abdominal pain, skin rashes, itching, hepatitis, and purpura. The statement issued by ANSES noted that consumption of glucosamine and chondroitin sulfate may pose a risk for specific populations: people with diabetes, prediabetes, asthma, or receiving treatment with a vitamin K antagonist; people with a food allergy to crustaceans or insects (glucosamine-based supplements only); people on sodium, potassium, or calcium-restricted diets; pregnant or breastfeeding women, and children (due to lack of data). In addition, ANSES proposed that a maximum daily dose of glucosamine and chondroitin sulfate be determined and standardized across Europe based on safety data from robust

safety studies.[64] Glucosamine has also been reported to increase ocular pressure in people with open-angle glaucoma or ocular hypertension.[65,66] Of note, individuals on sodium-restricted diets may need to use glucosamine and chondroitin formulations containing potassium or calcium chloride instead of sodium chloride.[67] In addition, some glucosamine and chondroitin products contain manganese levels that exceed the recommended daily intake of this mineral; these products should not be used for long-term supplementation.[67]

As of July 2019, a decline in prescription opioid-related deaths was reported for the first time in the US since the 1990s. [68,69] However, opioid overuse and misuse continue to be a major public health concern.[70] FP-MD supplementation may offer an alternative to opioid analgesics that HCPs can recommend for appropriate patients. In a randomized clinical trial of 240 patients with chronic back or knee OA pain, opioids vs nonopioid medications did not result in significantly better pain-related function over 12 months.[71] Of note, people receiving opioid prescriptions for management of chronic pain tend to be older (72% ≥45 years and 29% ≥65 years).[72] The elimination of opioids from the body involves renal excretion of active metabolites, which may accumulate and lead to toxicity in older adults who have age-related declines in renal function. In addition, older adults may experience more pronounced effects of opioids at equivalent doses used in younger adults, which may explain some of the risks associated with opioid use in older patients. In addition, a meta-analysis of observational studies showed that older adults exposed to opioids had a 38% increased likelihood of fractures [73].

In a 2019 review,[74] Copsey et al. analyzed 62 clinical studies using WOMAC as the primary outcome measure, and noted the median sample size across the studies was 75 randomized subjects (interquartile range [IQR], 50-148). The smallest study randomized 20 subjects, and the largest randomized 606 subjects. Median study duration was 4.5 months (IQR 1.5-6). The review noted that assessment of WOMAC at a single time-point following intervention was the largest limitation across the 62 studies reviewed. Longer-term studies of individuals with chronic joint discomfort who may require sustained therapy are needed to evaluate the effectiveness and safety of chronic supplementation with astaxanthin, omega-3 PUFAs, and H.

Conclusions

The joint health formulation FP-MD contains active ingredients that can be effective for joint pain and discomfort and provide sustained benefit with continued use. This multicenter, randomized, double-blind, placebo- and active-controlled clinical trial demonstrated that FP-MD supplementation can rapidly reduce or eliminate joint pain and improve joint comfort in adults living with knee joint pain, with clear statistical significance compared to both placebo and GC. At week 8, the mean percentage reduction in WOMAC pain scores was similar for GC and placebo subjects, and the percentage of subjects who were pain free was actually lower in the GC group than in the placebo group. The active ingredients in FP-MD, Zanthin natural astaxanthin, proprietary hyaluronic acid, and krill oil as a source of fatty acids and phospholipids, have established an important role in joint health for individuals seeking a natural alternative to traditional therapy, and as an alternative to GC supplements that may be associated with adverse effects.

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