Osteoarthritis of the Knee with a Polyherbal Supplement and MSM with Vitamin C: A Randomized, Double-Blind, Placebo-Controlled Study

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Introduction

Of all the arthritides, osteoarthritis (OA) is the most common, affecting nearly 23 million Americans.[1] Symptomatic OA of the knee occurs in 6% of the population greater than 30 years, and results of community-based surveys have shown that the incidence increases with age.[2]

Interest in the medicinal use of nonpharmaceutical treatment modalities for arthritis has grown, particularly with the Food and Drug Administration (FDA) regarding COX-2 inhibitors.[3] These anti-inflammatory drugs (NSAIDs) not only carry cardiovascular risks but have suboptimal effectiveness.[4,5] However, there are insufficient reliable clinical data concerning the efficacy and safety of complementary and alternative antiarthritic remedies.[6] Moreover, the rational medicinal use of these natural treatments is further complicated by the fact that the composition of over-the-counter nutraceutical supplements is not strictly regulated.

This study was a randomized, double-blind, and placebo-controlled trial of a polyherbal supplement with methylsulfonylmethane (MSM) and vitamin C for 90 days in patients with moderate to severe OA of the knee. Its aims were to assess the supplement's specific efficacy and safety profile, and to develop more rigorous methodology for a definitive study.

Materials and Methods

Study Design: The study was a 3-month, multicenter, prospective, randomized, double-blind, placebo-controlled trial. The study protocol was conducted in accordance with the Declaration of Helsinki and was approved by the institutional board at each study site. All patients provided written informed consent.

Patients were screened at baseline visit that included a physical examination, a knee radiograph according to a standardized method, a symptom questionnaire, and routine safety laboratory tests. After enrollment, patients were randomly assigned to 1 of the 2 treatment groups; that is, supplements or placebo. Clinic visits were conducted at monthly intervals from the time of randomization until the end of the 3-month treatment course.

Patients: Eligible patients were at least 52 years of age and selected if they been diagnosed as having clinical evidence of knee pain (in 1 or both knees) according to the clinical and radiographic criteria of the American College of Rheumatology.[7] Disease stage was determined based on the Kellgren-Lawrence radiographic system (either grade II or III).[8] This radiographic disease system grades osteoarthritis on a severity scale from I to IV based on the assumed sequential appearance of osteophytes, loss of joint space, subchondral sclerosis, and cyst formation. Other inclusion criteria were a baseline functional assessment of overall pain of at least 50 mm on a 100 mm visual analog scale (VAS).

Subjects were excluded if they met any of the following criteria: (1) knee injection with hyaluronate in the previous 6 months or with corticosteroids in the previous 3 months; (2) surgical procedure on the affected knee; (3) narcotic analgesic use; (4) rheumatoid or seronegative arthritis; (5) patellofemoral pain syndrome; (6) concurrent trauma or surgery that could confound evaluation of the index joint; (7) evidence of renal or hematologic disease, cardiac insufficiency, neuropathy; (8) coexisting disease that could preclude successful completion of the study; (9) unwillingness to present to follow-up visits for the length of the study; (10) pregnancy or lactation; (11) body mass index (BMI calculated as weight in kilograms divided by the square of height in meters) greater than 30.

Randomization: A central computer-generated randomization code was maintained by individuals not affiliated with the trial who assigned patients to their randomized treatments. Permuted-block randomization was conducted with random

block sizes, stratified according to the 3 clinical centers. The randomization codes remained sealed until the blinded analysis had been carried out. Thus, allocation concealment was maintained, and the study investigators and patients were blinded throughout the trial.

Treatment Regimens: The duration of the treatment was 12 weeks. Eligible patients were randomly assigned with the use of a double-dummy scheme to one of 1 of 2 orally administered treatments:

Group A: 4 capsules of a polyherbal supplement (Flex-Connect Plus) and 8 capsules of MSM with vitamin C daily during meals.

Group B: Placebo

The Flex-Connect Plus and MSM with Vitamin C, and placebo capsules were supplied by Herbal Products & Development (Aptos, CA). Products were tested for purity, potency, and quality. Each Flex-Connect Plus capsule consisted of 500 mg of glucosamine sulfate; 100 mg of protease, amylase, lipase, serratia, bromelain, and papain; 50 mg of standardized turmeric extract; 50 mg of standardized boswellia extract; 50 mg of standardized horse chestnut extract; 25 mg of quercetin, rutin, and amla; and 10 mg of ginger. The MSM with Vitamin C capsule consisted of 700 mg of MSM and 100 mg of vitamin C. The placebo capsules were identical in appearance to the active supplements but contained inactive excipients. Uniformity was maintained in both treatment groups in terms of capsule weight, size, color, labeling, and packaging. Supplements were packaged in white gelatin capsules and placed in opaque bottles with screw caps in a clean room. Treatment compliance was checked at clinic visits by patient interview and by counting the number of unused doses of the study supplements.

Patients were permitted to take up to 4000 mg of acetaminophen daily as a rescue medication, except during the 24 hours before a clinical evaluation. To avoid confounding in the efficacy assessments, the use of the rescue medication in case of persistent pain was carefully standardized according to the following sequential instructions: Allow the painful joint to rest for at least 3 hours, and take one 500 mg tablet every 8 hours, but limit intake to a maximum of 4 per day. Patients were not allowed to consume NSAIDS or other agents that might affect the outcomes of the study other than the rescue medication. Patients were evaluated at baseline and at 4, 8, and 12 weeks after randomization. Each study visit included an evaluation of knee symptoms (joint warmth, effusion, crepitus, tenderness, and range of motion), review of medications, and adverse events. A radiological examination of the affected knee and laboratory tests (complete blood count, erythrocyte sedimentation rate) was conducted one 1 week before baseline and repeated at week 12. All events were coded according to the Medical Dictionary for Regulatory Activities, as required by all regulatory authorities including the FDA. All investigators were informed of ICH-GCP guidelines, and the quality of data and execution of the clinical trial were monitored by individuals independent of patient contact and treatment assessment.

A disease-specific index for osteoarthritis known as WOMAC (Western Ontario and McMaster Universities) was employed as a primary outcome measure. There are three sections to the WOMAC score (Table 1; p.70). Section A deals with the amount of pain (5 questions), section B addresses the magnitude of joint stiffness (2 questions), and section C addresses assessment of physical function (17 questions). Each question had a response on a scale of 0 to 4 with 0 representing none, 1 slight, 2, moderate, 3 severe, and 4 extreme. The total score in all 3 sections is summed to form a score ranging from 0 (best) to 96 (worst). We used a response-rate-to-treatment as a primary efficacy variable based on the WOMAC section A criteria.[9] Subjects had to report a 20% in their basal WOMAC pain score to be deemed responders (Table 2; p.70). Moreover, the investigators sought additional metrics based on reduction of WOMAC or VAS assessment of pain to determine if a patient responded to therapy. This included a combination of 10 mm reduction in VAS pain and 20% reduction in WOMAC pain assessments.

A VAS score of 0 mm to 100 mm was used as a secondary outcome measure to assess for pain status, with 0 representing no pain and 100 being unbearable pain. The relevant amount of pain that patients experienced was marked on a linear scale by the study investigators. Recovery was characterized by 5 categories: Excellent: complete relief of symptoms; Good: partial relief of symptoms; Fair: minimal relief of symptoms; Poor: no relief of symptoms; Very poor: worsening of symptoms. Tolerability was assessed by 3 categories: Good: no side effects; Fair: mild to moderate side effects; Poor: severe side effects and withdrawal of therapy. Measurements of recovery and tolerability were performed at the end of the protocol (week 8).

Statistical Analysis: A statistician blind to the treatment regimen was hired to analyze the study data. Results were expressed as the difference between final group means and 95% confidence level, with P values based on analysis of variance (ANOVA). To assess the differences between the active group (Flex-Connect Plus and MSM with Vitamin C) and placebo, a general linear model approach was applied in a one-way analysis of variance, with treatments as fixed effect and application of Dunnett's two-tailed test to adjust for multiple pairwise comparisons. The same analysis was conducted on the secondary efficacy outcome represented by the WOMAC, while the difference between the active group and placebo was analyzed by two-tailed chi-square test. The chi-square test was

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also performed to compare the active group with placebo for the additional efficacy metrics described in WACO. Results were expressed as the mean +/– SEM. All efficacy analysis were conducted on an intention-to treat basis. Additionally, the following tests were performed: Bonferroni, Dunnett's, and Tukey's. The following software was used: SPSS 11.5, PEPI, EPI INFO 2000, and MS Excel.

The use of the rescue analgesic medication was assessed in per-protocol completers over the 3-month treatment course. The mean number of days of use was tabulated for descriptive purposes with calculation of the daily average, while the proportion of patients with any use of the rescue analgesic was compared between the active treatment group and the placebo by using the chi-square test.

Results

Patients: A total of 138 patients were screened for the study (Figure 1). Of these, 60 met the inclusion and exclusion criteria and were randomized to receive the active supplement, Flex-Connect Plus and MSM with Vitamin C (29) or placebo (31). In total, 55 patients completed the study. Of the remaining 5 patients, 3 patients were lost to follow-up after week 12 in the Flex-Connect Plus and MSM Vitamin C group, and 2 discontinued from the study as a result of not being able to come to follow-up after week 4 in the placebo group. Disposition of subjects are described in Figure 1. No subsequent dropouts were due to lack of efficacy or adverse events.

The majority of the patients tested were female, reflecting the general demographic profile of the osteoarthritis (Table 3): Women made 68% of patients in the Flex-Connect Plus and MSM with Vitamin C, compared with 70% in the placebo group. Age was also comparable in both treatment groups (Flex-Connect Plus and MSM with Vitamin C 53.6 +/– 1.2 years, Placebo 52.3 +/– 1.8). Radiographic knee osteoarthritis Kellgren-Lawrence grade II was present in 82% of the Flex-Connect Plus and MSM with Vitamin C, and 76% in the placebo group. Chi-square analysis revealed no statistical difference in the entry of the disease status evident among the treatment groups using the Kellgren-Lawrence radiographic criteria.

Table 1
Modified WOMAC Questionnaire. Subjects responded with the following numerical assessment: 0 = none; 1 = slight; 2 = moderate; 3 = severe; 4 = extreme.

WOMAC A: Pain on
___ walking
___ stair climbing
___ nocturnal
___ rest
___ weight bearing

WOMAC B: Stiffness
___ morning
___ during the day

WOMAC C: Physical Functions
___ descending stairs
___ ascending stairs
___ rising from sitting
___ standing
___ bending to the floor
___ walking on flat
___ getting in/out of a car
___ going shopping
___ putting on socks
___ taking off socks
___ lying on bed
___ getting in/out of bath
___ sitting
___ getting out of toilet
___ heavy domestic duties
___ light domestic duties

Table 2
Response Rates of Patients to Treatments Based on Pain Assessments

	4 weeks		12 weeks	
Criteria	Flex Connect Plus/Placebo (n = 29)	(n = 31)	Flex Connect Plus/Placebo (n = 29)	(n = 31)
20% decrease in WOMAC pain	69.2%	28.6%	95.6%	29.8%

Percentage of patients meeting various criteria for response to treatment. Results between the placebo (n = 31) and Flex Connect Plus and MSM with Vitamin C were significantly different.

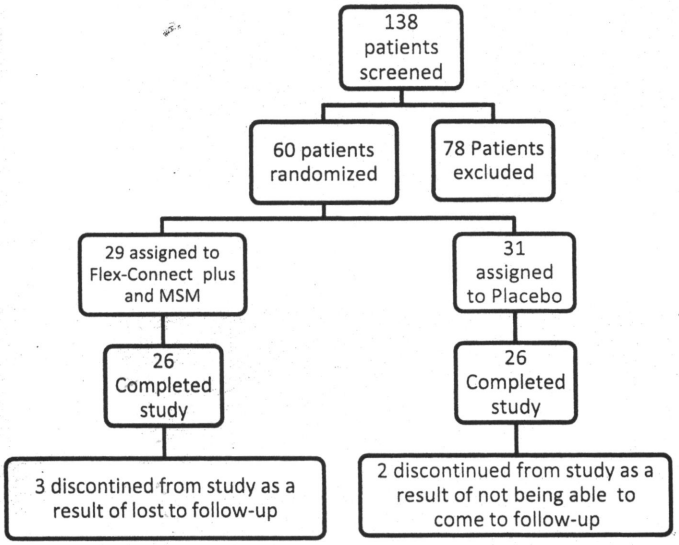
Table 3
Baseline Characteristics of Treatment Groups

	Flex Connect Plus MSM Vitamin C	Placebo
N started (completed)	29 (26)	31 (29)
Age (years)	53.6 +/– 1.2	52.3 +/– 1.8
Gender (F:M %)	58:32	70:30
Kellegren Lawrance Criteria Grade 2:3 %	82:18	76:24
WOMAC Pain	8.8 +/– 0.3	9.1 +/– 0.3
WOMAC Stiffness	42 +/– 0.3	44 +/– 0.5
WOMAC Function	29.6 +/– 3.1	33.1 +/– 0.3
WOMAC Total	80.40	86.20
VAS Pain	61.3 +/– 0.6	60.9 +/– 0.3

Data expressed as percentage of total mean +/– SEM. The entry assessments between the Flex Connect Plus and MSM with Vitamin C and placebo group were not significantly different.

Primary Efficacy Variable: The investigators calculated the response to treatment rate, a method that uses a 20% reduction in WOMAC pain as the primary assessment of response to treatment.[9] The proportions of responders within 1 week of treatment were as follows: 22.3% for placebo and 49.6% for the active supplement (Figure 2). Noteworthy is that after 4 weeks of treatment, the placebo group was still significantly lower from baseline for any of the WOMAC scores, compared with the group ingesting the active supplement. Response to treatment to the Flex-Connect and MSM with Vitamin C group continued to increase for the duration of the study protocol. The response rate at week 4 was significantly higher for the group ingesting the active supplement group (69.2%), compared with the placebo (28.6%; Table 2). At the conclusion of the study (week 12), the response rate for the active supplement group continued to increase compared with the placebo, 95.6% and 29.8%, respectively.

Figure 1
Disposition of Study Patients



Significant differences between the active supplement group and placebo were noted on the baseline disease activity as defined by WACO pain (Figure 3), stiffness (Figure 4), and function (Figure 5), or total WOMAC score (Figure 6). The Flex-Connect Plus and MSM with Vitamin C group revealed significant improvement 4 weeks of treatment for the individual components of WOMAC (pain, stiffness, function) when compared with placebo (Figures 3–5) or the total WOMAC assessment (Figure 6). It is of note that after 12 weeks of treatment, the placebo group was not significantly different from baseline for any of the WOMAC scores. However, there was marked improvement over baseline for the group treated with the active supplement.

Secondary efficacy variable: Pain status in both treatment groups was compared at recruitment (Table 3) and baseline. Significant reduction in VAS pain score was shown by the active treatment group at week 4, and reduction in pain was evident by the completion of the study at week 12.

Laboratory tests were unchanged from baseline to week 12 for both the active treated group and placebo with the following exception: the erythrocyte sedimentation rate (ESR) at week 12 in the actively treated group was mildly reduced from 33.2 +/− 4.2 to 30.6 +/− 3.0 ($p < .05$). A summary of all assessments is depicted in Table 4 (p.75).

Acetaminophen was used as a rescue medication with dosing limited to 4 × 500 mg per day. Though consumption was relatively consistent throughout the study, significantly

Figure 2
Responders % WOMAC Pain

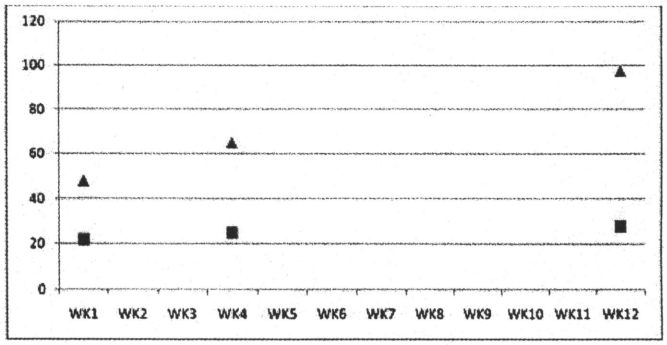


Figure 3
WOMAC: Pain

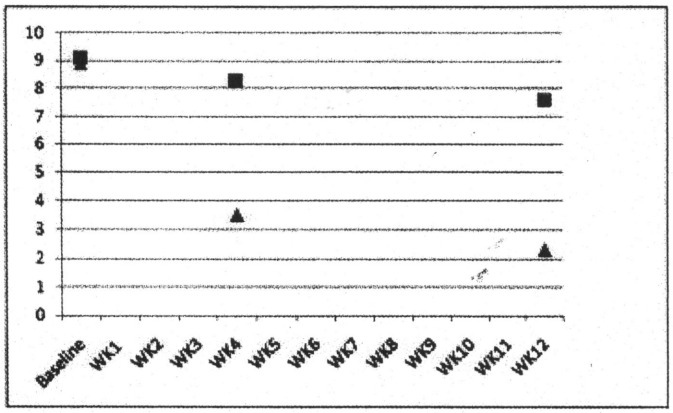
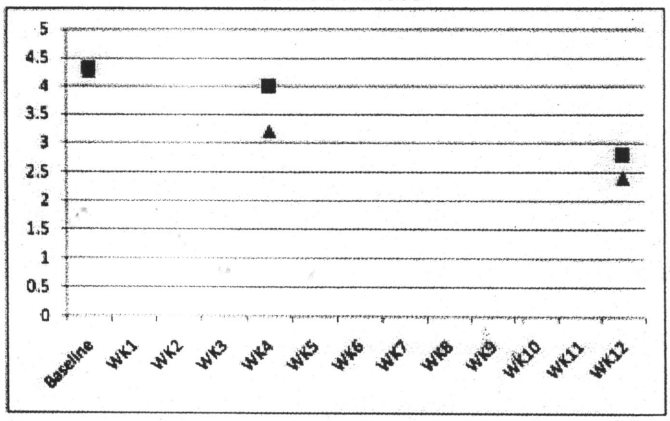


Figure 4
Joint Stiffness



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fewer acetaminophen tablets were consumed in the Flex-Connect Plus and MSM with Vitamin C group compared with placebo at each assessment period ($p < .02$).

Discussion

The purpose of this study was to determine the efficacy and safety of a new polyherbal supplement, Flex-Connect Plus and MSM with Vitamin C, in patients with symptomatic osteoarthritis of the knee. Results reveal that the polyherbal supplement was able to elicit significant reductions in pain, joint stiffness, and physical functional indices of osteoarthritis activity; these benefits were statistically evident within the first week of treatment using the WOMAC and VAS criteria compared with placebo. Trends for earlier symptomatic relief in the active treated subjects for all three WOMAC subsets,

Figure 5
WOMAC: Physical Function

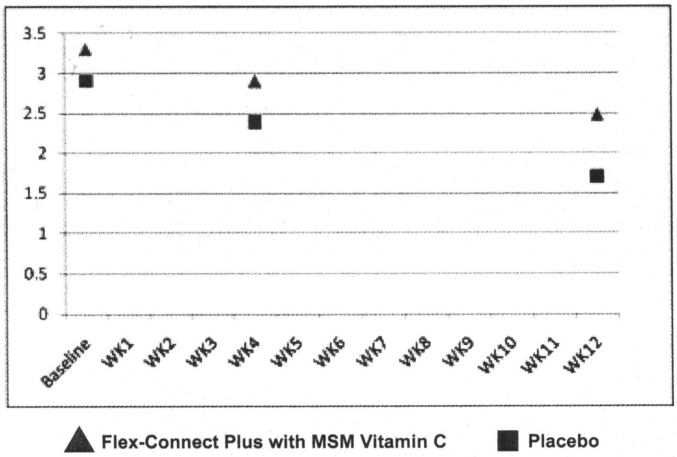
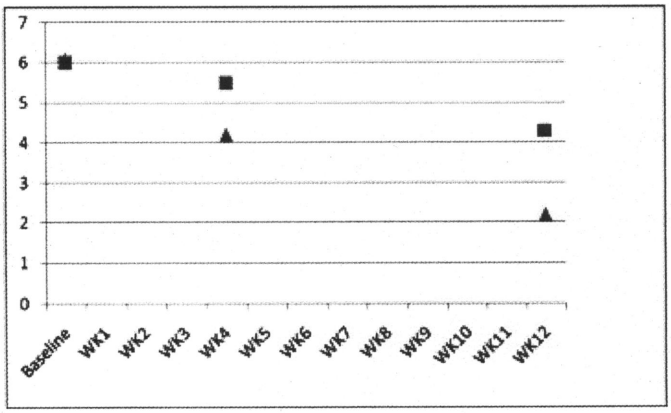


Figure 6
VSA Pain



as well as VAS pain was noticeable and readily distinguishable from the placebo treated group (Figures 3–6). Collectively, observations using the response rate as the primary efficacy variable (Figure 2), coupled with the secondary efficacy variable of reductions in baseline WOMAC score and VAS pain, highly suggest that Flex-Connect Plus and MSM with Vitamin C relieve moderate to severe osteoarthritis of the knee.

Symptom improvement with the placebo treated group at week 12 was limited to 29.81%, whereas subjects receiving the active polyherbal supplement reported an average 95.6% (Table 2) in pain assessment according to the per-protocol analysis and 20% by intent-to-treat approach adopted, which is in agreement with other studies.[10–12] Such results were confirmed for consistency using the WOMAC index (Table 1), the most widely used algofunctional indexes of the severity of knee osteoarthritis.[13] Similarly, other studies showed a significantly better effect than placebo therapy in the first 12 weeks, with improvement in pain and function between 40% to 50% relative to basal conditions.[14,15]

The focus of our study was on the synergistic effect of the Flex-Connect Plus and MSM with Vitamin C. A significant component of this polyherbal blend is the nutraceutical known as glucosamine sulfate. According to the definition of scientific organizations and regulatory agencies, glucosamine sulfate is the first agent that meets the current requirements to be classified as a symptom- and structure-modifying nutraceutical in osteoarthritis.[16–18]

Several experimental studies have now elucidated the mechanism of action of glucosamine sulfate on osteoarthritis. First, glucosamine sulfate is bioavailable and reaches the articular cartilage after oral administration.[19] Then, it is preferentially incorporated by the chondrocytes into the components of the glycosaminoglycan chains in the intact cartilage, thereby stimulating the synthesis of proteoglycans and decreasing the activity of catabolic enzymes, including metalloproteases.[20,21]

Several study trials have evaluated the efficacy of glucosamine.[22–25] Some have demonstrated efficacy but have been criticized as having flaws, such as the failure to adhere to the intention-to-treat principle, the enrollment of small numbers of patients, potential bias related to sponsorship of the study by the manufacturers of the dietary supplements, and inadequate masking of the study agent. In general, these studies have recruited patients with lower levels of knee pain and failed to show improvement in WOMAC pain scores. Clegg et al. reported indistinguishable results in treating osteoarthritis of the knee from glucosamine sulfate and the placebo group at 4 and 24 weeks.[9] In contrast, Herrero-Beaumont et al. demonstrated that glucosamine sulfate was significantly more effective than placebo.[26] The present trial does differ from both GUIDE and GAIT in the timing and distribution of the doses.[9,26] The daily dose in the GAIT study is divided into three doses, whereas the GUIDE used a once a day dosing regimen consistent with an approved prescription approach in Europe. We adopted a one-a-day dosing regimen to prevent breach of compliance among our study population. Nevertheless, it is clear that the variety of dosing regimen in these studies is not fully understood, suggesting that timing is a not a critical determinant of efficacy.[22–28]

In subsequent trials, glucosamine was predominantly administered orally to optimize long-term compliance of osteoarthritic patients. Noack et al. treated 252 patients with osteoarthritis of the knee with 1500 mg/day glucosamine sulfate for four weeks.[29] Their trial reported a significant reduction in Lequesne's index (an index assessing pain and joint function) than the placebo group. Assessed also by Lequesne's index, Rovati examined 319 patients randomized to 1500 mg/day.[30] Results suggested that glucosamine sulfate significantly improved the long-term symptomatic evolution of knee osteoarthritis. Muller-Fabender et al.

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Table 4
Laboratory Evaluation

Test	Flex Connect Plus & MSM with Vitamin C	Flex-Connect Wk 12	Placebo Wk 0	Placebo Wk 12
Neutrophils %	63.3 +/–1.7	63.12 +/– 1.2	62.16 +/– 1.9	62.46 +/– 1.2
Lymphocytes %	32.6 +/– 0.14	33.8 +/– 0.15	31.6 +/– 2.5	32.3 +/– 1.6
Monocytes %	1.16 +/– 0.3	1.21 +/– 0.14	1.11 +/– 0.11	1.12 +/– 1.6
Eosinophils %	3.44 +/– 0.41	3.21 +/– 0.26	3.46 +/– 0.11	3.11 +/– 1.6
WBC mm3	7932 +/– 231	8031 +/– 144	8026 +/– 645	8011 +/– 298
RBC mm3	3.96 +/– 0.08	4.11 +/– 0.11	3.96 +/– .11	3.98 +/– 0.08
Hemoglobin gm/dl	12.1 +/– 0.3	12.4 +/– 0.2	12.4 +/– 0.3	12.1 +/– 0.2
Erythrocyte Sedimentation Rate	33.2 +/– 4.2	30.6 +/– 3.0	29 +/– 3.6	31.2 +/– 1.2
SGPT Iu/l	28.7 +/– 1.8	27.6 +/– 2.3	29.1 +/– 1.3	29 +/– 1.6
Creatinine	0.98 +/– 0.03	.94 +/– 0.03	1.3 +/– 0.3	1.2 +/– 0.2

Data expressed as mean +/– SEM

compared the symptomatic action of glucosamine sulfate with nonsteroidal anti-inflammatory drugs in 200 hospitalized patients with osteoarthritis of the knee.[15] The investigators reported that glucosamine sulfate (1500 mg) and ibuprofen (1200) had the same success rate (48% versus 52% respectively) after 4 weeks of treatment. However, the number of adverse–events related dropouts differed between the two groups (7% ibuprofen versus 1% glucosamine sulfate).

Controversy on the efficacy of glucosamine in osteoarthritis continues, despite multiple clinical trials. Indeed, meta-analysis studies have produced conflicting results.[31–33] The Cochrane Database of Systemic Reviews on glucosamine included 20 studies with 2570 patients.[34] Pooled results from studies using a non-Rotta preparation or adequate allocation concealment failed to show reduction in pain and WOMAC function, while those trials evaluating the Rotta preparation revealed that glucosamine was more efficacious in the treatment of pain and functional impairment resulting from symptomatic osteoarthritis. Glucosamine was found to be superior for pain and function using the Lequesne index. Most of the negative clinical studies were conducted with glucosamine 500 mg three times daily, whereas most of the positive trials were performed with glucosamine sulfate 1500 mg once daily. This raises the question of the importance of sulfate and its contribution to the overall effects of glucosamine; sulfate may be clinically relevant in that it is readily hydrolyzed from the glucosamine in the gastrointestinal tract.[35,36]

Additionally, one of the components of the polyherbal blend in this study, turmeric, profoundly inhibited joint inflammation and periarticular joint destruction, suggesting that it may offer benefits in the treatment of osteoarthritis.[37,38] Consistent with these findings, turmeric extracts inhibited periarticular osteoclast formation, inflammatory cell influx, joint levels of prostaglandin E.[39] Turmeric, is also used as a spice and is part of curry. Curcumin, one of three major phenolic curcuminoids that constitute 3% to 5% of turmeric, is the active anti-inflammatory ingredient in turmeric.[40] Indeed, an antiarthritic effect of curcumin has been reported in one clinical study of rheumatoid arthritis and three descriptive studies of arthritis studies in animals.[41–44]

Evaluating the safety of this newly formulated polyherbal supplement was of paramount importance. In this 3-month trial, subjects being tested exhibited no adverse changes in clinical and laboratory measures.

As a possible limitation, we excluded obese patients (BMI > 32) and those with metabolic diseases that may be responsible for secondary osteoarthritis, though the patient population in our study is largely representative of the general population with knee osteoarthritis.

In summary, how should our results affect the treatment of symptomatic osteoarthritis of the knee? A critical issue is how to place this study's findings in a therapeutic perspective. With the life-threatening concern regarding increased risk of cardiovascular disease and stroke with COX-2 inhibitors, the need for alternatives has never been more dire.[45,46] That said, according to US arthritis studies, 42% of persons have reported the use of complementary and alternative medicine, including dietary supplements.[47] In contrast, since the passage of the Dietary Supplement Health and Education Act by Congress in 1994, scientific studies supporting dietary supplements have increased but still lack quality methodology and research design.

Finally, before Flex-Connect Plus and MSM with Vitamin C can be recommended for medicinal use, clinical trials are clearly needed to verify/determine whether treatment with adequate doses of this polyherbal formula can indeed prevent or suppress disease flares in osteoarthritis patients, as well as to explore any potential benefits of this formula in the prevention or treatment of other forms of arthritis in the general population.

Jack Haddad received his undergraduate degree in nutritional science from San Jose State University, and his medical degree in podiatric medicine from the California College of Podiatric Medicine. He is very active in clinical trial research involving neutraceuticals and polyherbal products. Moreover, his research in the past five years has focused on the effects of electromagnetic field stimulation on bone and cartilage in patients with osteoarthritis.

Phillip Shinnick received his PhD from the University of California at Berkeley and was a former assistant professor of Rutgers University and New York Medical College. He is associate editor of the *Journal of the Science of Healing Outcomes* and an ambassador of UNESCO. Dr. Shinnick combines occidental and Oriental approaches to medicine. He has a license in Chinese medicine and was at the Heart Disease Research Foundation for eight years.

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