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RESEARCH ARTICLE

Influence of a low-dose supplementation of curcumagalactomannoside complex (CurQfen) in knee osteoarthritis: A randomized, open-labeled, active-controlled clinical trial

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A 6-week, randomized, open-label, active-controlled clinical trial was conducted to evaluate the influence of a low-dose curcumagalactomannosides (CGM) (400 mg once daily) in OA subjects. The treatment was compared with a standard combination of 500 mg glucosamine hydrochloride (GLN) and 415 mg chondroitin sulphate (CHN), supplied as a single oral dose twice a day. Out of 84 subjects randomized, 72 subjects who have completed the study were evaluated for the safety and efficacy of the treatments at baseline and subsequent visits (day 28 and 42), by measuring walking performance, VAS, KPS, and WOMAC scores. CGM exhibited 47.02, 21.43, and 206% improvement in VAS, KPS, and walking performance, respectively, compared to the baseline. Similarly, there was 31.17, 32.93, 36.44, and 35% improvement in the pain, stiffness, physical function, and total WOMAC scores. CGM also caused a substantial reduction in the serum inflammatory marker levels. The results indicate that a short-term supplementation of a low dosage CGM exerted superior beneficial effects than a high-dosage CHN–GLN combination in alleviating the pain and symptoms of OA subjects. Further clinical trials of extended duration in a larger population is required to substantiate the efficacy of CGM in the long-term management of OA.

KEYWORDS
chondrotin sulphate, curcumagalactomannoside, curcumin, glucosamine, osteoarthritis, phytotherapy

1 | INTRODUCTION

Osteoarthritis (OA) is a chronic inflammatory condition of joints that affects the quality of life of mid to elderly population worldwide, subsequently leading to the impairment of function. Even though obesity and age play a major role in the prevalence of OA, there is a mounting recognition that OA affects individuals at a relatively younger age, indicating the necessity of early diagnosis as well as preventive measures (Losina et al., 2013). Currently, available clinical management approaches for OA include analgesics, steroids, and other non-pharmacological options such as physical/occupational therapies and exercise programs (Persson et al., 2020; Yusuf, 2016). Analgesics and steroids are not advisable for frequent or long-term use owing to their potential side effects such as liver injury, cardiovascular issues, gastrointestinal tract disturbances, low blood cell count, and immunodeficiency disorders (Laev & Salakhutdinov, 2015). Recently, there is an urge among clinicians to suggest dietary supplements like chondroitin sulphate, glucosamine, fish oil, and antiinflammatory botanical extracts

to relieve pain and improve physical activities among OA subjects (Laev & Salakhutdinov, 2015).

Curcuminoids, the natural yellow pigments isolated from the rhizomes of turmeric (*Curcuma longa* L.), are quite popular among Asian spices for its various therapeutic effects (Akbar et al., 2018; Azhdari, Karandish, & Mansoori, 2019). Natural curcuminoids [curcumin, demethoxycurcumin, and bisdemethoxycurcumin, commonly referred to as "curcumin"] are extremely safe and well known for their antioxidant, antiinflammatory, and immunomodulatory properties (Ahmad et al., 2020; Chainani-Wu, 2003; Jurenka, 2009; Soleimani, Sahebkar, & Hosseinzadeh, 2018). A recent randomized, active-controlled study conducted by Shep, Khanwelkar, Gade, and Karad (2019) in patients with knee osteoarthritis reported that curcumin possesses equivalent efficacy and higher tolerance compared to diclofenac (Shep et al., 2019). Another multicentre study also reported the better tolerability and effectiveness of curcuma extracts compared to ibuprofen (Kuptniratsaikul et al., 2014). This superior efficacy and less toxicity of curcumin, comparable with the standard antiinflammatory drugs, make it a potential therapeutic candidate for the treatment of OA. However, poor oral bioavailability contributed by hydrophobicity or insolubility and in vivo instability due to rapid biotransformation to inactive metabolites limit the clinical application of this potential herbal component (Cas & Ghidoni, 2019; Liu et al., 2016).

Several published clinical trials are available in OA subjects reporting the efficacy of improved bioavailable formulations of curcumin, that are commercially presented as nutraceuticals (Table 1) (Belcaro et al., 2010a; Belcaro et al., 2010b; Gupte et al., 2019; Haroyan et al., 2018; Nakagawa et al., 2014; Panahi et al., 2014; Shep et al., 2019; Shin et al., 2017; Srivastava et al., 2016). Many of these formulations claim huge "number of folds of bioavailability" ranging from 10- to 285-folds. However, most of these studies have used a relatively higher dosage of intervention (1.5–3 g/day) for a longer duration (3–6 months). A careful examination of the pharmacokinetics of these formulations revealed that the expressed "number of folds" represents the bioavailability of conjugated metabolites of curcumin and not that of "free or unconjugated curcuminoids." Curcumin glucuronides, the primary metabolites of curcumin, exhibited very weak antioxidant, antiinflammatory, and antiproliferative effects compared to the free curcuminoids (Choudhury, Raja, Mahapatra, Nagabhushanam, & Majeed, 2015; Shoji et al., 2014). Thus, it is rational to assume that the poor oral bioavailability of the bioactive "free curcuminoids" from these formulations demanded their supplementation at high dosage for longer duration in clinical trials.

Curcumagalactomannosides (CGM), a novel oral delivery form of curcumin prepared using a noncovalent complex formation between curcumin and fenugreek galactomannans, have been identified as the only commercially available natural formulation with significant "free curcuminoids" bioavailability. Detailed pharmacokinetics study of CGM revealed an enhanced bioavailability of "free curcuminoids" over the "conjugated curcumin metabolites" in the plasma of tested subjects. This "free curcuminoid" bioavailability was 45.5-fold higher than that provided by the unformulated standard curcumin (Kumar et al., 2016). CGM was also reported to exhibit a better tissue distribution and blood–brain barrier permeability compared to the native curcumin, with extended elimination half-life of 3–4 hr (Krishnakumar et al., 2015). Thus, it was hypothesized that the supplementation of a relatively low dose of CGM (400 mg/day) for a short duration of 6 weeks would be sufficient enough to show the benefits in OA subjects. In this randomized, active-controlled study, 84 subjects supplemented with either CGM (400 mg) or GLN/CHN [a standard drug combination of 1,000 mg glucosamine hydrochloride (GLN) and 830 mg chondroitin sulphate (CHN) per day] for 42 days were assessed for the improvement in pain, joint flexibility, physical activity, and quality of life. The mechanism of their action was also assessed by monitoring the influence on associated serum inflammatory markers.

2 | MATERIALS AND METHODS

2.1 | Intervention

Hard-shell two-piece gelatin capsules of CGM (400 mg) were prepared using a modified method of Krishnakumar, Ravi, Kumar, Kuttan, and Maliakel (2012), by avoiding emulsifiers and employing high-pressure-mediated gel-phase homogenization technique. CGM comprised of curcuminoids (126.2 mg curcumin, 23.6 mg demethoxycurcumin, and 4.3 mg bisdemethoxycurcumin) encapsulated in fenugreek galactomannans (35:65 w/w ratio), as a novel amorphous, water dispersible, powder of curcumagalactomannoside complex. Standard drug capsules, CHN and GLN, were prepared as identical to the intervention capsules and consisted of 415 mg chondroitin sulphate (CHN) and 500 mg glucosamine hydrochloride (GLN), respectively. The intervention and standard drug capsules were provided, in high-density polyethylene (HDPE) containers labeled with separate codes and dosages, by M/s Akay Natural Ingredients, Cochin, India.

2.2 | Study design and ethical consent

The study was designed as a randomized, open label clinical trial with a parallel standard drug control group. The 6-week, single-centred study was conducted at Aman Hospital & Research Center, Vadodara, Gujarat, India, and the subjects were enrolled from the outpatient treatment facility of the hospital between March 2019 and January 2020. All the procedures performed in the study were in strict accordance with the clinical research guidelines of the Government of India, following the protocol approved by the registered ethical committee (Ref. ID. LCBS-OA-31/01/2019). The study was registered in the clinical trial registry of India (CTRI/2019/03/017954 dated 07/03/2019), and written informed consent was acquired from all the study participants in agreement with the principles of the Declaration of Helsinki.

TABLE 1 Comparison of efficacy of CGM against other curcuminoid formulations in alleviating the symptoms of OA

Reference and study material (reported bioavailability in folds)	No. of subjects recruited	Study design	Concomitant medications	Dosage and study duration	Clinical outcomes in curcumin group						
					Treadmill walking performance	Clinical outcomes in curcumin group					
						Total	Pain	Stiffness	Difficulty in physical function	KPS	VAS
Haroyan et al. (2018), CuraMed 500 mg (333 mg curcuminoids) (7X)	66	DB, PC, RCT	NIL	500 mg x 3 per day for 12 weeks	NR	B = 28.94 ± 13.20; A = 21.86 ± 14.36; AVD = 6.34 ± 11.4; *p* = 21.91%	B = 5.91 ± 2.77; A = 3.84 ± 2.88; AVD = 1.86 ± 2.95; *p* = 31.47%	B = 1.98 ± 1.29; AVD = 0.40 ± 1.54; *p* = 20.20%	B = 8.20 ± 9.91; AVD = 3.83 ± 7.56; *p* = 46.71%	NR	NR
Srivastava, Saksena, Khattri, Kumar, and Dagur (2016) Haridra 500 mg (95% total curcuminoids)	78	DB, PC, RCT	Diclofenac (50 mg x 1 per day)	500 mg x 2 per day for 4 months	NR	NR	B = 15.10 ± 0.31; A = 9.48 ± 0.17; AVD = 5.61 ± 0.34; *p* = 37.15%	B = 5.55 ± 0.21; A = 4.08 ± 0.17; AVD = 1.32 ± 0.21; *p* = 23.78%	B = 54.03 ± 0.68; A = 32.14 ± 0.40; AVD = 21.88 ± 0.8; *p* = 40.50%	NR	B = 7.94 ± 0.13; A = 4.03 ± 0.08; AVD = 3.91 ± 0.14; *p* = 49.24%
Belcaro et al. (2010b), Meriva 1,000 mg (200 mg curcuminoids) (29X)	25	—	Best available treatment	1,000 mg x 1 per day for 3 months	B = 76; A = 331; AVD = 255; *p* = 335.53%	B = 83.4; A = 34.8; AVD = 48.6; *p* = 58.27%	B = 16.9; A = 8.5; AVD = 8.4; *p* = 49.7%	B = 7.4; A = 3.3; AVD = 4.1; *p* = 55.41%	B = 59.1; A = 22.98; AVD = 36.12; *p* = 61.12%	NR	NR
Belcaro et al. (2010a), Meriva 500 mg (100 mg curcuminoids) (29X)	50	—	Best available treatment	500 mg x 2 per day for 8 months	B = 77.3; A = 344.4; AVD = 267; *p* = 345.53%	B = 80.6; A = 33.3; AVD = 47.3; *p* = 58.68%	B = 16.6; A = 7.3; AVD = 9.3; *p* = 56.02%	B = 7.4; A = 3.2; AVD = 4.2; *p* = 56.76%	B = 56.6; A = 22.8; AVD = 33.8; *p* = 59.72%	B = 73.3; A = 92.2; AVD = 18.9; *p* = 25.78%	NR
Nakagawa et al. (2014), Theracurmin 700 mg (30 mg curcumin) (27X)	18	DB, PC, RCT	Celecoxib (100 mg x 2 per day)	700 mg x 3 x 2 per day for 8 weeks	NR	NR	NR	NR	NR	NR	B = 0.52 ± 0.24; A = 0.20; AVD = 0.32; *p* = 61.54%
Shin, Suk, Jang, and Choi (2017) Theracurmin 700 mg (30 mg curcumin)(27X)	13	—	NIL	700 mg x 3 per day for 4 week	NR	B = 24.92 ± 10.21; A = 19.08 ± 12.38; AVD = 5.84; *p* = 23.43%	B = 5.25 ± 2.18; A = 3.17 ± 2.41; AVD = 2.08; *p* = 39.62%	B = 2.25 ± 1.28; A = 2.25 ± 1.48; AVD = 0; P = 0%	B = 17.42 ± 7.76; A = 13.67 ± 9.49; AVD = 3.75; *p* = 21.53%	NR	B = 4.42 ± 1.16; A = 2.75 ± 1.76; AVD = 1.67; *p* = 37.78%
Shep et al. (2019) BCM-95 (500 mg curcumin) (7X)	74	OP, AC, RCT	NIL	500 mg x 3 per day for 28 days	NR	NR	NR	NR	NR	NR	B = 7.84 ± 0.63; A = 2.20 ± 0.81; AVD = 5.64; *p* = 71.94%
Gupte et al. (2019), Longvida 400 mg (80 mg	23	DB, AC, RCT	NIL	400 mg x 2 per day for 90 days	NR	B = 39; A = 23; AVD = 16; *p* = 41.03%	NR	NR	NR	NR	B = 80; A = 30; AVD = 50; *p* = 62.5%

(Continues)

TABLE 1 (Continued)

Reference and study material (reported bioavailability in folds)	No. of subjects recruited	Study design	Concomitant medications	Dosage and study duration	Clinical outcomes in curcumin group						
					Treadmill walking performance	Clinical outcomes in curcumin group					
						Total	Pain	Stiffness	Difficulty in physical function	KPS	VAS
of curcumin) (65X)											
Panahi et al. (2014), C3 complex (500 mg curcuminoids +5 mg Bioperine) (20X)	27	DB, PC, RCT	NIL	500 mg x 3 per day for 6 weeks	NR	B = 42.4 ± 18.3; A = 25.0 ± 13; AVD = 17.4; p = 41.04%	B = 9.9 ± 4.1; A = 6.1 ± 2.9; AVD = 3.8; p = 38.38%	B = 1.05 ± 1.8; A = 0.15 ± 0.5; AVD = 0.9; p = 85.71%	B = 31.8 ± 14; A = 18.7 ± 10.3; AVD = 13.1; p = 41.19%	NR	B = 66.32 ± 4.22; A = 37; AVD = 29.32; p = 44.21%
CurQfen 400 mg (154.1 mg curcuminoids) (45X)	42	OP, AC, RCT	NIL	400 mg x 1 per day for 6 weeks	B = 106.43 ± 18.37; A = 325.86 ± 36.3; AVD = 219.43 ± 37; p = 206%	B = 68.8 ± 4.5; A = 44.73 ± 4.9; AVD = 24.1 ± 4.98; p = 35%	B = 13.12 ± 1.5; A = 9.03 ± 1.2; AVD = 4.09 ± 2.2; p = 31.18%	B = 4.97 ± 1.7; A = 3.34 ± 1.3; AVD = 1.64 ± 0.9; p = 32.93%	B = 50.73 ± 3.5; A = 32.24 ± 2.4; AVD = 18.49 ± 4; p = 36.44%	B = 64 ± 8.1; A = 77.71 ± 7; AVD = 13.71 ± 6.5; p = 21.43%	B = 6.87 ± 0.51; A = 3.64 ± 0.52; AVD = 3.23 ± 0.73; p = 47.02%

Abbreviations: A, end of the study value; AC, active controlled; AVD, average; B, baseline value; DB, double blind; OP, open label; PC, placebo controlled; RCT, randomized clinical trial.

2.3 | Patient recruitment, inclusion, and exclusion criteria

At visit 1 (screening day), a total of 100 subjects aged between 40 and 70 years, who were identified to have knee osteoarthritis, were screened for the study. Physical examination of the target knee was performed to identify subjects with class I-III osteoarthritis according to Kellgren and Lawrence system (Kellgren & Lawrence, 1958), followed by confirmation with radiographic (X-ray) image. Subjects with OA secondary to a known disorder such as rheumatoid arthritis, seronegative spondyloarthropathy, mixed connective tissue disease, collagen vascular disease, psoriasis, and any history of fracture involving the study joint, or any other type of arthritis, were excluded from the study. Individuals who had undergone surgery or arthroscopy within 3 months before the inclusion and those with severe bone or joint deformation or conditions other than OA, making the patient unable to walk, were also excluded from the study. Subjects with any concomitant critical illness in the previous 6 months like malignancies, hepatic injury, severe metabolic disorders including diabetes mellitus, diabetic or obstructive nephropathy, gastrointestinal disorders, history of cardiovascular or cerebrovascular diseases, pregnant, and breastfeeding women were excluded from the study. The subjects enrolled in the study were capable of performing the treadmill walking test and were able to understand the questions provided in the Western Ontario and McMaster Universities Arthritis Index (WOMAC) questionnaire. A 6-min treadmill walking test was performed to assess the WOMAC scores, and a cut-off point (total score ≥ 60) was enforced in patient selection as a means of standardizing the extent of pain and immobility (Frestedt, Walsh, Kuskowski, & Zenk, 2008).

2.4 | Randomization and dosage

At visit 2 (day 0), computer-generated randomization was employed, and the subjects were provided with a unique three-digit randomization code. After the baseline measurements, the CGM group subjects were provided with a bottle of 42 capsules (CGM 400 mg), and the standard drug treatment group subjects were provided with two bottles of 84 capsules each, one containing CHN (415 mg) and another containing GLN (500 mg). CGM group subjects were requested to consume one capsule per day (400 mg × 1/day) in the morning before breakfast, for 42 days. The standard group subjects were asked to consume one capsule from each bottle, as a single oral dose twice a day, once in the morning before breakfast and again in the evening before dinner (GLN 500 mg × 2/day and CHN 415 mg × 2/day), for 42 days. The subjects were recommended not to consume analgesics/steroids/NSAIDs, or any other antiinflammatory drugs unless it seems highly essential.

2.5 | Primary efficacy outcome measures

Primary outcome includes efficacy evaluation by measuring the improvement in pain intensity, performance, and other symptoms of

OA. For efficacy measures, all the participants were undergone an uphill treadmill walking protocol (Mangione, Axen, & Haas, 1996) to assess their walking performance, Visual Analogue Scale (VAS) scores (Katz & Melzack, 1999), Karnofsky Performance Scale (KPS) scores (Péus, Newcomb, & Hofer, 2013), and WOMAC scores (Bellamy, 2002). The performance in the uphill treadmill walking protocol was evaluated by analyzing the total distance that could be covered without pain. The VAS, KPS, and WOMAC scores were self-marked by the subjects based on their intensity of pain, stiffness, and functional limitations experienced during the uphill treadmill walking protocol. All the efficacy measurements were taken at baseline (visit 2—day 0) and repeated at every following visit till the end of the study (visit 3—day 28 and visit 4—day 42).

2.6 | Secondary safety outcome measures and mechanism study

Secondary outcome includes mechanism study and safety measurements. The mechanism of action of treated drugs was assessed by measuring the change in the levels of serum inflammatory markers [interleukin-1-beta (IL −1 β), interleukin-6(IL-6), soluble vascular cell adhesion molecule-1 (sVCAM), and high-sensitivity C-reactive protein (*hs-CRP*)], from baseline to end of the study. Vital signs, anthropometric, and demographic data were recorded at baseline (day 0) and at the end of the study (day 42). Blood samples were collected from all the subjects (in fasting state within 10 hr after the last meal) at baseline and at the end of the study for the analysis of hematological parameters (RBC, Hb, TLC, and platelet count). Serum samples were separated and used immediately for the measurement of toxicological parameters (SGOT, SGPT, creatinine, BUN) and lipid profile. A portion of the serum samples was stored at deep freezer (−80°C) till the end of the study, for the analysis of inflammatory markers. Any variation in the vital signs or any abnormality in hematological or clinical parameters was considered for safety evaluation. The subjects were asked to note down the requirement of analgesics and emergency instances or adverse events occurred during the study period. They were requested to contact the study coordinators for any events that necessitate an expert opinion. Subjects were also monitored for adverse effects weekly through regular telephonic follow-ups and short message services.

2.7 | Statistical analysis

Statistical analysis was performed using IBM SPSS Version 26 software. Mean and standard deviation for continuous variables and percentages for categorical variables were reported accordingly. Intergroup comparisons were done using independent sample *t*-test, and paired fed comparisons within the groups were performed by repeated-measures ANOVA. The "*p*" values <.05 were considered as statistically significant.

3 | RESULTS

The summary of the recruitment process and procedures performed by the subjects are provided in the CONSORT diagram (Figure 1). A total of 84 subjects (44 females and 40 males) who met the inclusion criteria, with conformed class I-III osteoarthritis according to Kellgren and Lawrence system, were enrolled for the study. Among the subjects who were randomized, 12 participants lost their follow-up due to various reasons. The performance and symptom score data of 72 subjects (35 from CGM and 37 from CHN–GLN group) who completed the study were analyzed for assessing the effectiveness of the treatments.

Anthropometric, demographic, and other clinical characteristics were well balanced between CGM and CHN–GLN groups at the time of randomization without exhibiting any statistical difference (Table 2). However, the average BMI of the CGM-treated group reduced to 24.12 ± 1.02 kg/m^2 by the end of the study, whereas there was no reduction observed in the BMI of the CHN–GLN group.

Both the CGM and standard drug treatments were well tolerated without exhibiting any serious adverse events. The number of subjects that required NSAIDs/analgesics during the study period was considerably low in CGM group (31.43%) compared to the CHN–GLN group (52.35%). All the hematological parameters measured remained within the normal limits. There were no significant differences observed in the clinical parameters including lipid profile, renal (creatinine and BUN), and hepatic function tests (SGOT and SGPT) from the baseline to end of the study, in both the study groups, indicating the safety of the supplements used at the particular dosage and duration (Table 2).

CGM group individuals showed a tremendous improvement (206%) in the walking performance when compared to the CHN–GLN-treated subjects (85.69%) (Figure 2). CGM treatment also exhibited a 47.02% reduction in VAS score, whereas there was only 24.67% reduction observed in the group treated with a high dose of CHN–GLN (Table 3). A similar trend was observed in the total and individual WOMAC scores of study subjects (Figure 3). There was a significant improvement observed in the total (35.01%), stiffness (32.93%), and physical function (36.44%) scores of CGM group when compared to the CHN–GLN group (16.46%, 25.97% and 12.56%, respectively) (Table 3). However, the changes in the WOMAC pain score (31.18%) of CGM subjects were nonsignificant compared to the double-dose treatment of CHN–GLN (26.62%). Correspondingly, CGM group indicated a 21.42% improvement in the KPS score, and the effect was almost equivalent to the 23.81% improvement expressed by the CHN–GLN group (Table 3).

The effects of CGM and CHN-GLN treatments in the serum inflammatory marker levels of OA subjects were measured using the ELISA method, and the observations were given in Figure 4. The treatments with CGM considerably reduced the concentration of hs-CRP and IL-1, IL-6, and sVCAM in the serum of treated subjects. hs-CRP levels decreased from 6.24 + 0.76 mg/dl to 2.59 + 0.94 mg/dl in CGM-treated group (58.49%), whereas the CHN-GLN group showed only a moderate reduction in hs-CRP from 5.97 + 0.42 mg/dl

to 4.34 + 0.65 mg/dl (27.3%) (p = .001). CGM-treated group showed a 29.61% decline in the levels of IL-1β on 42nd day, while the CHN-GLN group displayed only 18.38% reduction in the IL-1β concentration (p = .001). Comparable results were also observed in the case of IL-6 and sVCAM concentrations in the serum of treated subjects. There was a 39.88% and 12.97% reduction in the IL-6 and sVCAM levels in the serum of CGM-treated subjects, respectively, indicating its antiinflammatory effect. In contrast, there was only 19.1% (p = .000) and 6.72% (p = .051) reductions in the IL-6 and sVCAM levels observed in the CHN-GLN-treated group.

4 | DISCUSSION

Table 1 represents the summary of the clinical trials in OA using various bioavailable formulations of curcumin. It was observed that a relatively high dosage (1–3 g) of the formulations was generally used in all the studies, except for Longvida, which used 800 mg/day. A meta-analysis of the randomized clinical trials by Daily, Yang, and Park (2016) also confirmed the usage of 1,000 mg of curcumin/day as an effective dosage in the treatment of OA in most of the studies (Daily et al., 2016). The present study was designed based on the hypothesis that formulations of natural curcuminoids capable of delivering significantly high levels of bioactive "free" curcuminoids (unconjugated) into systemic circulation for a longer duration ($t_{1/2}$) would provide better results at a relatively low dosage and short duration. Earlier human pharmacokinetic studies have shown significantly high bioavailability, better absorption, longer duration ($t_{1/2}$), and systemic elimination of free curcuminoids from a relatively low dosage of CGM (250 mg) (Kumar et al., 2016). While 100 nM (36.8 ng) of free curcuminoids in the circulation has been suggested as the minimum for eliciting the bioactivities, 250 mg of CGM has provided a plasma concentration of more than 300 ng/ml (C_{max}) (Begum et al., 2008; Kumar et al., 2016). Moreover, the absorbed curcuminoids from CGM was found to remain in the circulation for a longer duration ($t_{1/2}$ = 3.7 ± 0.4 hr), with nearly 25 ng/ml sustained even after 7-hr post administration. Whereas the same dosage of unformulated standard curcumin degraded almost completely within 1 hr of ingestion. In view of this, the current study compared the efficacy of a low-dose CGM (400 mg/day) supplementation with a high-dosage standard treatment (CHN–GLN—1.83 g/day) in OA subjects. Forty-two days of CGM treatment offered a significant potential in the management of joint pain, stiffness, and physical function among OA patients, compared to the high-dosage standard treatment, validating the hypothesis.

Though the WOMAC questionnaire has been used as a validated tool for all the studies (Table 1), only a few studies have the detailed component scores indicating the influence on pain, stiffness, and physical function. Many of the studies have not used a secondary measure/questionnaires to confirm the correlation of WOMAC data with symptoms. Similarly, very few of them have used any standard

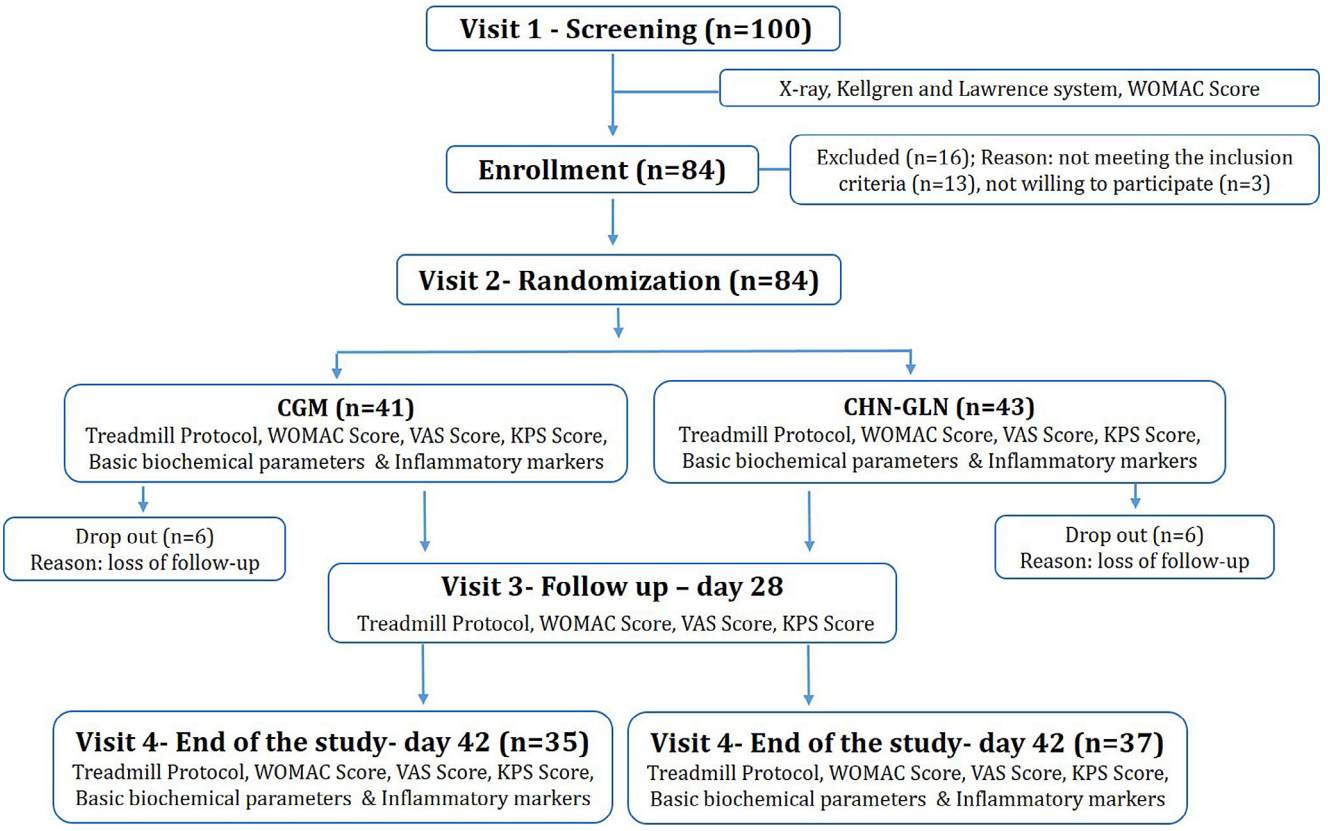

FIGURE 1 CONSORT flow diagram of the study [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 2 Demographic, anthropometric, and biochemical parameters of the study groups

	CGM (n = 35)		CHN–GLN (n = 37)	
Parameters	**Baseline**	**42th day**	**Baseline**	**42th day**
Age (years)	51.7 ± 5.52	–	52.3 ± 4.59	–
Male	19 (54.29%)	–	16 (43.24%)	–
Female	16 (45.71%)	–	21 (56.76%)	–
Duration (months)	42.14 ± 6.73	–	40.51 ± 8.67	–
BMI (kg/m^2)	25.65 ± 1.85	24.12 ± 1.02	25.58 ± 1.53	25.01 ± 1.72*
SGOT (U/L)	25.55 ± 3.38	25.68 ± 2.85	25.01 ± 4.7	26.62 ± 3.24
SGPT (U/L)	32.77 ± 6.57	31.59 ± 3.91	33.8 ± 4.5	32.84 ± 5.17
Serum Creatinine (mg/dl)	1.26 ± 0.05	1.23 ± 0.03	1.27 ± 0.21	1.25 ± 0.16
BUN (mg/dl)	13.15 ± 5.8	15.75 ± 3.7	12.56 ± 1.8	15.25 ± 1.5
TC (mg/dl)	164.66 ± 27.26	172.51 ± 18.15	167.77 ± 15.23	171.7 ± 18.43
TG (mg/dl)	120.15 ± 17.45	122.03 ± 25.51	128.02 ± 19.55	125.95 ± 17.02
LDL cholesterol (mg/dl)	111.64 ± 15.61	101.45 ± 18.22	107.52 ± 15.17	110.81 ± 17.67*
HDL cholesterol (mg/dl)	44.14 ± 1.85	45.7 ± 1.27	43.06 ± 3.3*	44.65 ± 2.95
VLDL (mg/dl)	35.72 ± 5.25	32.73 ± 4.52	34.20 ± 3.38	32.7 ± 3.10
TLC (cumm)	7,050 ± 1,182.08	7,155 ± 1,232.73	7,522 ± 1,442.85	7,455.50 ± 1,515.82
RBC (million/cumm)	5.95 ± 0.25	5.74 ± 0.85	5.96 ± 0.39	5.85 ± 0.35
Hb (g/dl)	14.54 ± 0.36	14.49 ± 0.35	13.95 ± 0.86**	13.76 ± 0.42***
Platelet count (lakhs/cumm)	2.85 ± 0.52	2.79 ± 0.63	2.73 ± 0.42	2.70 ± 0.16

Note: *p < .05, **p < .01, ***p < .001; CGM versus CHN–GLN group performed using paired sample t-test.
Abbreviations: BMI, body mass index; BUN, blood urea nitrogen; CGM, curcumagalactomannoside; CHN–GLN, chondroitin sulphate–glucosamine hydrochloride; Hb, hemoglobin; HDL, high-density lipoproteins; LDL, low-density lipoproteins; SGOT, serum glutamate-oxaloacetate transaminase; SGPT, serum glutamate-pyruvate transaminase; TC, total cholesterol; TG, triacylglycerol; TLC, total leucocyte count; VLDL, very low-density lipoproteins.

method to measure the improvements in functional performance like KPS. Moreover, most of these studies have not attempted to investigate the influence of supplementations on inflammatory or oxidative stress markers. Even though validated tools such as WOMAC or VAS scores have been used for the assessment of efficacy in these studies, their clinical measurements would be purely subjective. The variations in the inflammatory/oxidative stress markers are strongly correlating with the symptoms as well as the disease progression of OA. Therefore, analyzing the influence of treatments in the inflammatory markers levels is crucial in assessing their efficacy. Considering all these limitations, a well-validated treadmill uphill walking protocol was employed in the present study to measure the functional improvement along with a detailed analysis of the joint pain, flexibility and performance analysis using WOMAC, KPS, and VAS scores. Further, an analysis of critical serum markers of inflammation and oxidative stress was performed to correlate the influence of supplementation in the pathogenies of OA. Moreover, care has been taken not to include any concomitant medications like NSAIDs/analgesics, along with the intervention, in order to avoid the possible of misinterpretation of the observed results.

We have carefully examined the results of earlier clinical studies (Table 1) to learn the merits and demerits of the various curcumin formulations in joint health management. A solid–lipid nanoparticle formulation of curcumin using soy lecithin, stearic acid, and ascorbyl palmitate (Longvida, claimed to have 65-fold bioavailability), when supplemented at 400 mg × 2/day for 90 days, has been reported to exhibit similar effect as that of Ibuprofen (400 mg) (Gupte et al., 2019). Though this study has shown a significant reduction in WOMAC and VAS scores, in a relatively small number of subjects (n = 17) in 60 days, no positive correlation was observed between the reported benefits in symptoms and antiinflammatory markers. In another study using a water-dispersible nanocurcumin prepared by a nanogrinding technology using glycerin and gum gatti (Theracurmin, 27-fold bioavailability), supplementation of 2.1 g/day for 8 weeks reported no statistically significant improvement (p = .1) in either VAS or JKOM (Japanese Knee Osteoarthritis Measure, similar to WOMAC) scores as compared to the placebo (starch, dextrin, and maltose capsules), except for the subjects with initial VAS scores of 0.15 or less (Nakagawa et al., 2014). In a recent open-label study, the supplementation of BCM-95 (a blend of curcumin 85 and 10% turmeric oil with sevenfold bioavailability) at 1.5 g/day was shown to produce an effect similar to diclofenac (100 mg/day) when monitored by VAS score. However, the study did not attempt to follow the other key functionalities in OA, such as joint flexibility, physical motion, physical activities, and the influence on antiinflammatory markers (Shep et al., 2019). Contrary to this study, Haroyan et al. (2018) reported

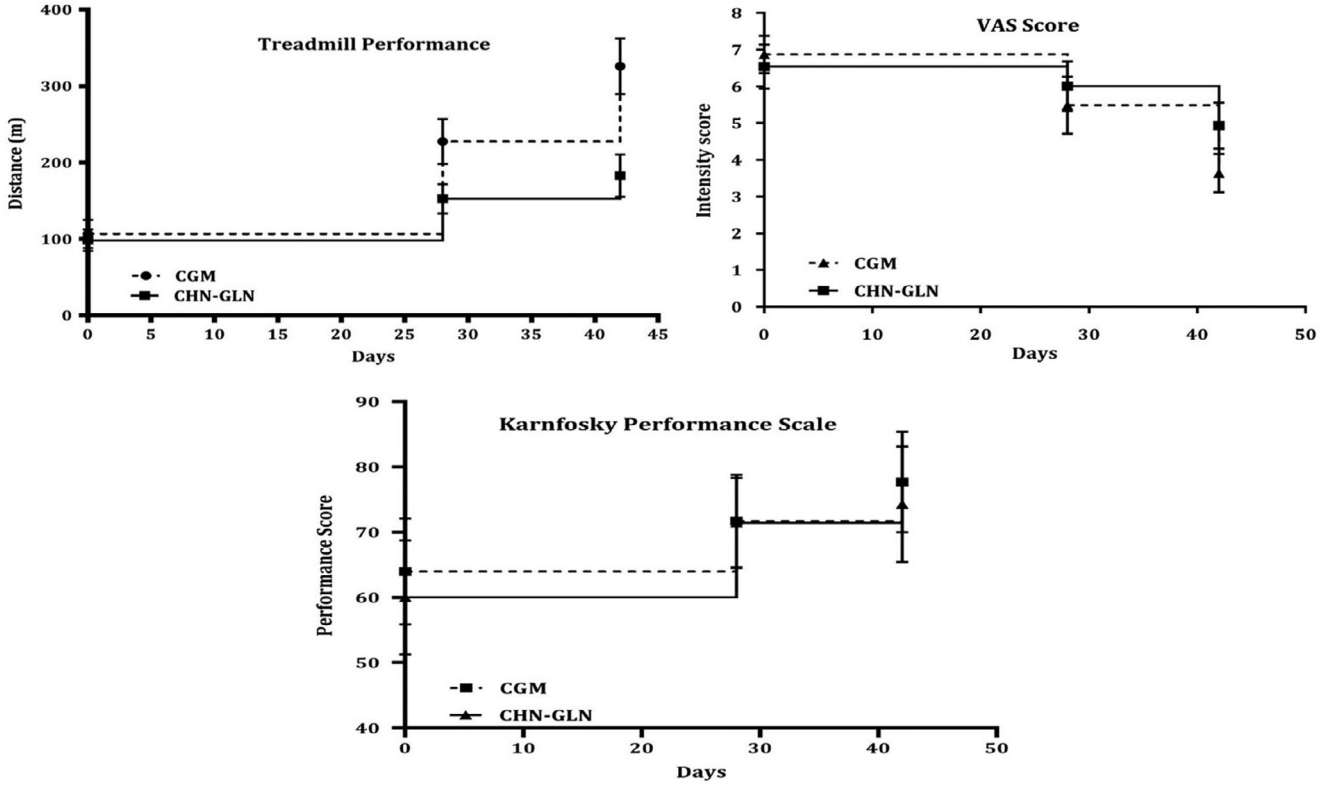

FIGURE 2 Difference in the walking performance and pain intensity scores of study groups

that the supplementation of BCM-95 (1.5 g/day) for 12 weeks indicated a superior efficacy over the maltodextrin placebo, only in the physical performance test. Other functionalities like pain and joint flexibility indicated significant improvement only up on the combination with Boswellia extract (Haroyan et al., 2018). The improved effects of BCM-95/Boswellic acid combination could be attributed to its enhanced "free curcuminoids" bioavailability contributed by the β-glucuronidase inhibitory effect of boswellic acid, indicating the significance of systemic absorption of free curcuminoids in biological activity (Sabina, Indu, & Rasool, 2012). Belcaro et al. (2010a) and Belcaro et al. (2010b) reported a significant improvement in WOMAC score and a corresponding decline in the antiinflammatory markers of OA subjects with the treatment of Meriva (1 g/day) (curcumin–lecithin complex with 29-fold bioavailability) in two separate studies of duration 3 and 8 months (Belcaro et al., 2010a; Belcaro et al., 2010b). In a randomized study using 1.5 g/day of C3 complex (95% curcuminoids along with 15 mg of piperine) for 6 weeks was found to offer a significant benefit in WOMAC pain and physical activity scores, with minimal improvement ($p > .05$) in stiffness score, compared to placebo (Panahi et al., 2014). Another study using curcumin 95% at 1 g/day along with 100 mg of diclofenac per day for 120 days produced significant changes in WOMAC and VAS score compared to the baseline. But the overall change was not as distinguishable with respect to the placebo, indicating the nonsignificant beneficial effects of unformulated curcumin 95% in alleviating OA symptoms, except its usefulness in reducing the gastrointestinal issues (Srivastava et al., 2016).

While considering the low dosage (400 mg) and short duration, CGM supplementation has been demonstrated to deliver superior efficiency in alleviating the potential problems of OA subjects, mainly the joint pain, stiffness, and physical activities than many other curcumin formulations as shown in Table 1 (Gupte et al., 2019; Haroyan et al., 2018; Nakagawa et al., 2014; Shep et al., 2019; Srivastava et al., 2016). From the comparative interpretation (Table 1), it is clear that CGM-alone treatment was more efficient in alleviating the pain and symptoms, even though few of the formulations were supplemented along with other treatment modalities like antiinflammatory drugs or aerobic training (Shin et al., 2017; Srivastava et al., 2016). However, treatment with a higher dosage or longer duration of curcumin products exhibited more effectiveness than CGM. Thus, it is postulated that supplementation of CGM for more extended period might produce better therapeutic results than the present, and further studies are necessitated to establish the efficacy associated with its long-term usage.

The significant analgesic effect and hence the improvement in physical functions exhibited by CGM subjects can be attributed to its antiinflammatory effects as evident from the modulation in IL-1β, IL-6 sVCAM, and hs-CRP. Serum hs-CRP can serve as a measure of systemic inflammation and its association with local synovitis, as well as the pain and muscle strength of OA patients is well established

TABLE 3 Changes in the walking performance, pain intensity, and symptom scores from baseline to 42nd day

Treatment/ groups		*Group II* (CGM)	*Group III* (CHN–GLN)	*p* value
Treadmill walking score (m)	Baseline	106.43 ± 18.37	98.4 ± 14.17	*.000*
	42nd day	325.86 ± 36.6	182.71 ± 27.80	
	Difference	219.43 ± 37.08	84.31 ± 18.24***	
VAS score	Baseline	6.87 ± 0.51	6.54 ± 0.6	*.000*
	42nd day	3.64 ± 0.52	4.93 ± 0.63	
	Difference	3.23 ± 0.73	1.61 ± 0.308***	
KPS score	Baseline	64 ± 8.12	60 ± 8.74	*.624*
	42nd day	77.71 ± 7.7	74.29 ± 8.84	
	Difference	13.71 ± 6.46	14.29 ± 5.02ns	
WOMAC total score	Baseline	68.82 ± 4.5	68.75 ± 3.71	.000
	42nd day	44.73 ± 4.9	57.44 ± 4.02	
	Difference	24.1 ± 4.98	11.3 ± 4.18***	
WOMAC pain score	Baseline	13.12 ± 1.48	14.44 ± 1.05	.764
	42nd day	9.03 ± 1.24	10.59 ± 1.43	
	Difference	4.09 ± 2.21	3.84 ± 1.69ns	
WOMAC stiffness score	Baseline	4.97 ± 1.67	4.81 ± 1.09	.091
	42nd day	3.33 ± 1.32	3. 56 ± 0.84	
	Difference	1.64 ± 0.9	1.25 ± 0.72*	
WOMAC difficulty in physical function score	Baseline	50.73 ± 3.47	49.50 ± 3.03	.000
	42nd day	32.32 ± 2.44	43.28 ± 3.25	
	Difference	18.48 ± 4.0	6.22 ± 3.1***	

Note: p values are measured using *two-way repeated-measures ANOVA* performed for CGM versus CHN–GLN; $^{*}p < .05$, $^{**}p < .01$, $^{***}p < .001$.
$^{ns}p > .05$ versus CGM group performed using independent sample *t*-test; $p < .05$ were considered as statistically significant.

(Babaei et al., 2019). CGM treatment for 42 days efficiently diminished the serum hs-CRP levels indicating its potential to attenuate local synovitis and inflammation in OA subjects. Since synovitis and joint inflammation have mainly been associated with the pathogenesis of OA, the measurement of proinflammatory cytokines can be considered as a useful index of OA severity (Scanzello & Goldring, 2012). IL-1β drives synovitis and acts as a potent instigator of cartilage degradation in OA via matrix metalloproteinase-3 (MMP-3) and MMP-13 induction in chondrocytes. It was demonstrated that the inhibition of IL-1β signal transduction could successfully reduce cartilage resorption by MMPs in arthritis (Liacini, Sylvester, Li, & Zafarullah, 2002). IL-6 is also an essential marker for cartilage loss in OA that can provide useful information in the prediction of disease outcomes, especially in obese and older individuals (Livshits et al., 2009). Soluble VCAM-1 is another biomarker strongly associated with the severity of cartilage loss and can be a good marker for synovial inflammation associated with OA progression. It can serve as a chemotactic stimulus for macrophages, routing it to the joint, thereby promoting cartilage degradation (Haraden, Huebner, Hsueh, Li, & Kraus, 2019). CGM could effectively reduce the IL-1β, IL-6, and sVCAM levels in the treated subjects indicating its potential to protect chondrocytes, thereby preventing cartilage degradation. Earlier studies have also established that curcumin protects human chondrocytes from the catabolic actions of IL-1β, including MMP-3 upregulation, inhibition of collagen type II, and downregulation of beta 1-integrin expression (Henrotin et al., 2010). Similarly, the effect of curcumin in downregulating the IL-6 (Derosa, Maffioli, Simental-Mendía, Bo, & Sahebkar, 2016) and sVCAM expression (Kim et al., 2012) was also established in various clinical experiments.

Additionally, CGM was also found to help overweight individuals to attain a healthy BMI. Obesity being one of the major risk factors in the progression of OA, maintaining ideal body weight is highly recommended for improving the quality of life. A 10% reduction in body weight has been found to offer a 28% reduction in the associated OA symptoms (Christensen, Astrup, & Bliddal, 2005). Earlier studies have demonstrated that dietary curcumin may have a potential benefit in preventing obesity by antiangiogenic activity in adipose tissue and also by inhibiting adipogenesis in 3T3-L1 adipocytes (Aggarwal, 2010; Ejaz, Wu, Kwan, & Meydani, 2009). The suppression of angiogenesis in adipose tissue by curcumin, together with its effect on lipid metabolism in adipocytes, contributed to the lower body fat and weight gain (Ejaz et al., 2009). Furthermore, CGM is a formulation using fenugreek dietary fiber rich in soluble fractions (galactomannans) (∼60% w/w). Fenugreek galactomannans is a prebiotic that was reported to have beneficial effects in regulating metabolic syndromes, including obesity. Fenugreek seed and fiber have

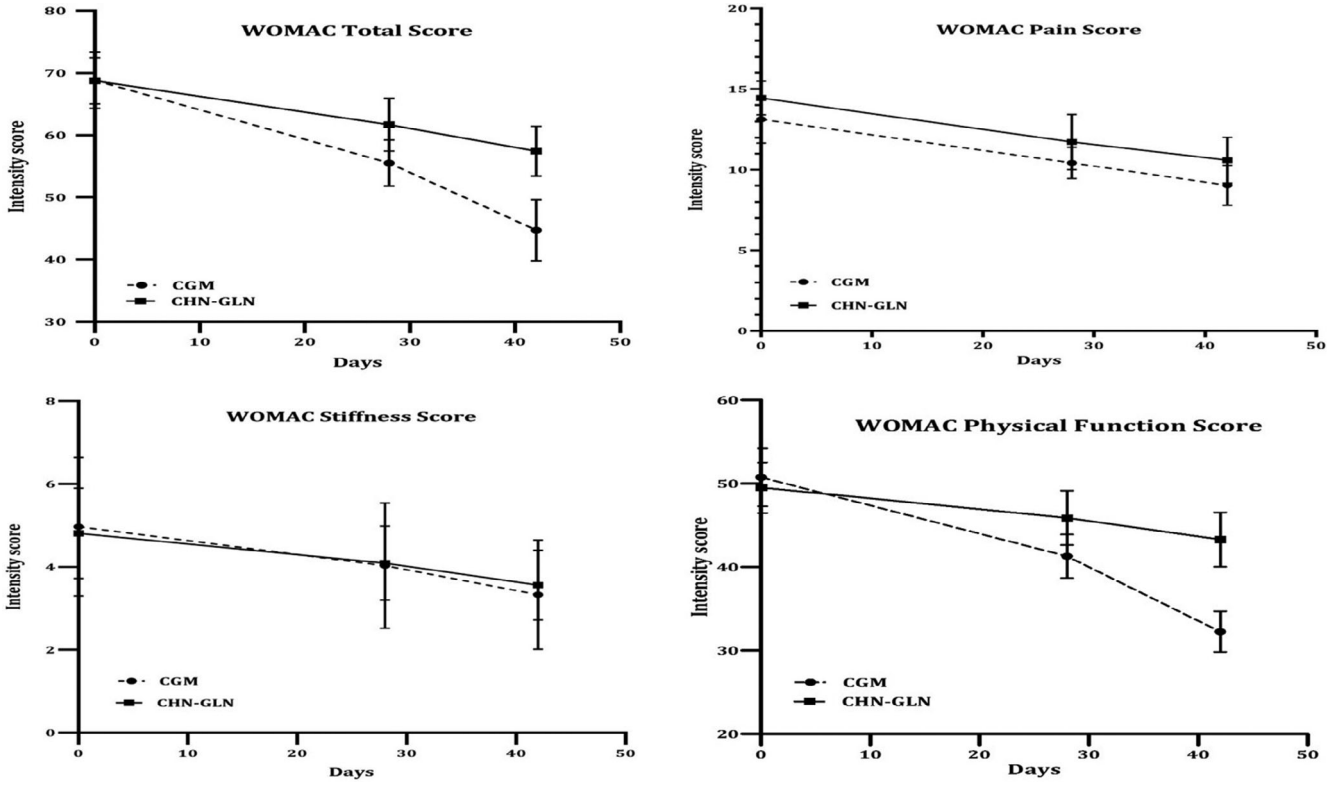

FIGURE 3 Improvement in the WOMAC scores of treated group during the study

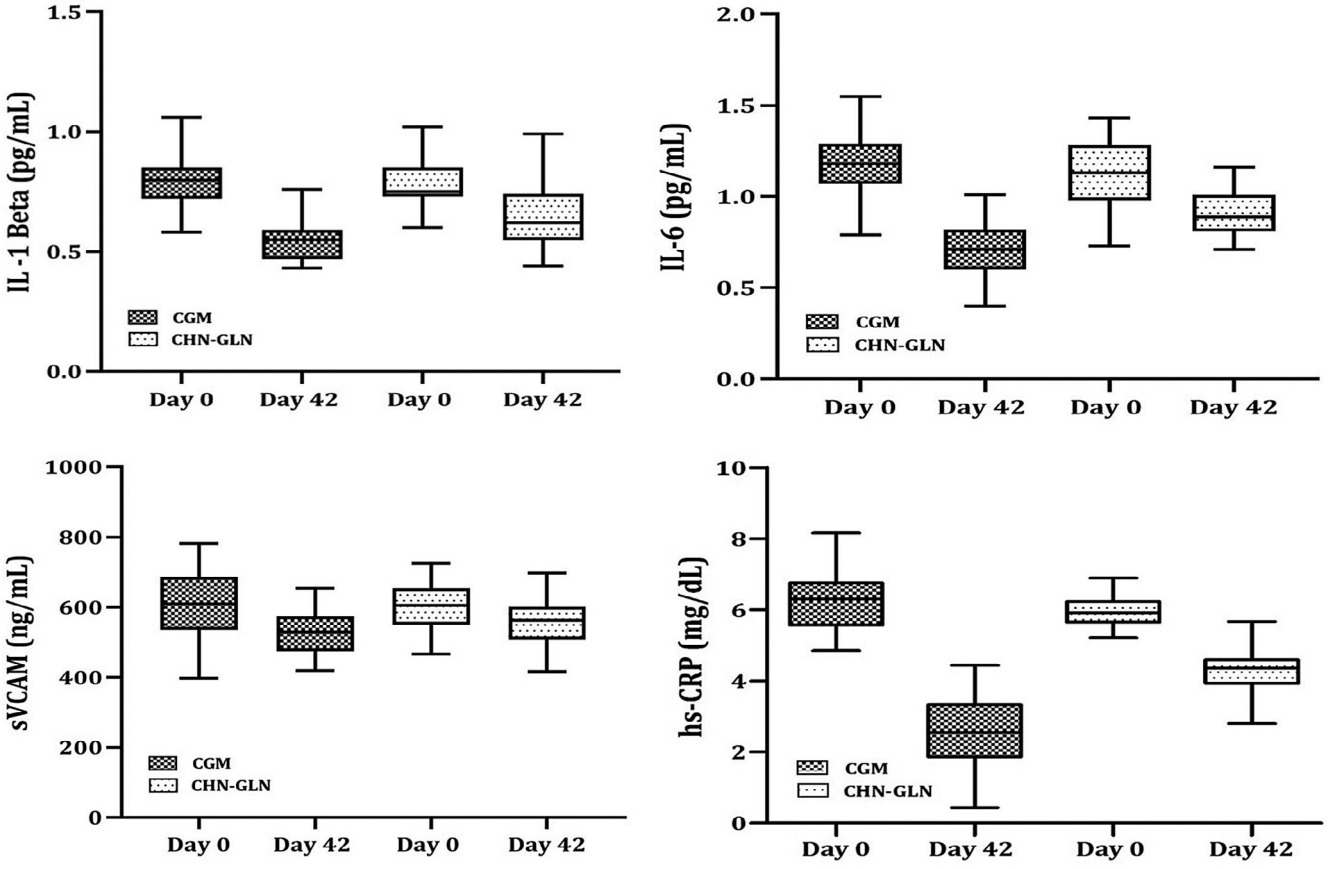

FIGURE 4 Effect on inflammatory markers levels in the serum of treated groups

been shown to regulate the intestinal microbiota and improve immunological responses in animals and consumption of diets containing fenugreek fiber resulted in gut microbiota comprising a healthier flora leading to positive effects on weight, glycemic control, and liver beta-oxidation (Shtriker et al., 2018; Zentek et al., 2013). Moreover, Fenugreek seed extract has been proven to inhibit fat accumulation and ameliorates dyslipidemia in high-fat diet–induced obese rats (Kumar, Bhandari, & Jamadagni, 2014). Thus, the presence of a good proportion of fenugreek fiber content in the CGM could have contributed to its beneficial effects among these obese individuals toward the improvement of their metabolic health, thereby helping them in weight reduction. However, further studies with an added emphasis on the metabolic and body weight regulating properties of CGM in a larger obese population are required to establish this ancillary finding.

CGM did not induce any adverse effects in the treated subjects during the study period that further support its earlier safety reports at dosages 500 –1,000 mg/day (Krishnareddy et al., 2018). Oral administration of CGM has already been proven as extremely safe and was validated to have no observable adverse effect level (NOAEL) up to 2000 mg/kg b. wt. in rats, when supplemented orally for 90 days (Liju et al., 2015). The observed safety of CGM can be attributed to the fact that CGM is just a combination of curcumin and fenugreek dietary fiber by a water-based process without having any synthetic excipients or additives. One more added advantage of the current invention is that CGM can provide a 100% vegetarian option for the treatment of OA and can be conveniently consumed by the vegetarian population. Standard supplements like chondroitin sulphate and glucosamine, being from animal origin, cause allergy in sensitive individuals when used in high doses (Zeng et al., 2015). CGM could serve as an excellent replacement for glucosamine/chondroitin combination in intolerant individuals to minimize the allergic reactions or adverse effects.

The present study has few limitations. Due to differences in the dosage as well as frequency of usage, the study was designed as an open label clinical trial. Considering the sample size, the minimum number of subjects required to acquire 80% power was 40 per arm. However, in the present study out of 100 subjects screened, 16 subjects did not meet the inclusion criteria. And among the 84 randomized subjects, 12 subjects lost their follow-up due to various reasons, leaving only 35 and 37 subjects in each study groups. Similarly, the duration of the treatment was comparatively smaller. Therefore, further studies in a larger population and extended duration are warranted to substantiate the proficiency of CGM in the long-term management of OA. Moreover, a follow-up of pain and symptom measurements was not done after the study duration to see whether the results were sustainable or the symptoms were recurring once the intervention medications were stopped. Additionally, the present study did not compare the efficacy of the tested drug with conventional remedies like NSAIDs, although there was a relative assessment of the intervention drug (CGM) treatment with the standard drug (CHN–GLN) often suggested by the physicians.

5 | CONCLUSION

In summary, CGM appears to be a safe pain reliever for the management of mild to moderate knee OA at a relatively low dosage. CGM, when supplemented at a low dose of 400 mg/day for 6 weeks, provided significant improvement in joint pain, stiffness, and physical functions of OA subjects than a high-dosage standard CHN–GLN treatment (1.83 g/day). The low dosage of CGM also allows potential synergistic combinations with other bioactive molecules. Osteoarthritis, a chronic degenerative disease that affects the functioning of the whole joint, demands prolonged treatment modalities. CGM did not cause any adverse effects in subjects during the study period indicating its safety. While considering the side effects associated with most common pharmacologic in practice such as NSAIDs, CGM may offer potential and safe therapeutic regime to achieve the major goals in OA treatment such as alleviating pain, boosting joint stability, and augmenting the movement and function, thereby improving the quality of life.

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CONFLICT OF INTEREST

The authors disclose the conflict of interest. “CurQfen” is the registered trademark of M/s Akay Natural Ingredients Pvt. Ltd. Cochin, India for CGM.

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REFERENCES

Aggarwal, B. B. (2010). Targeting inflammation-induced obesity and metabolic diseases by Curcumin and other Nutraceuticals. *Annual Review of Nutrition*, *30*(1), 173–199.

Ahmad, R. S., Hussain, M. B., Sultan, M. T., Arshad, M. S., Waheed, M., Shariati, M. A., … Hashempur, M. H. (2020). Biochemistry, safety, pharmacological activities, and clinical applications of turmeric: A mechanistic review. *Evidence-Based Complementary and Alternative Medicine*, *10*, 2020.

Akbar, M. U., Rehman, K., Zia, K. M., Qadir, M. I., Akash, M. S., & Ibrahim, M. (2018). Critical review on curcumin as a therapeutic agent: From traditional herbal medicine to an ideal therapeutic agent. *Critical Reviews in Eukaryotic Gene Expression*, *28*(1), 17–24.

Azhdari, M., Karandish, M., & Mansoori, A. (2019). Metabolic benefits of curcumin supplementation in patients with metabolic syndrome: A

systematic review and meta-analysis of randomized controlled trials. *Phytotherapy Research*, *33*(5), 1289–1301.

Babaei, M., Javadian, Y., Narimani, H., Ranaei, M., Heidari, B., Basereh, H., … Firouzjahi, A. (2019). Correlation between systemic markers of inflammation and local synovitis in knee osteoarthritis. *Caspian Journal of Internal Medicine*, *10*(4), 383–387.

Begum, A. N., Jones, M. R., Lim, G. P., Morihara, T., Kim, P., Heath, D. D., … Frautschy, S. A. (2008). Curcumin structure-function, bioavailability, and efficacy in models of neuroinflammation and Alzheimer's disease. *Journal of Pharmacology and Experimental Therapeutics*, *326*(1), 196–208.

Belcaro, G., Cesarone, M. R., Dugall, M., Pellegrini, L., Ledda, A., Grossi, M. G., & Appendino, G. (2010a). Efficacy and safety of Meriva, a Curcumin-Phosphatidylcholine complex, during extended administration in osteoarthritis patients. *Alternative Medicine Review*, *15*, 334–337.

Belcaro, G., Cesarone, M. R., Dugall, M., Pellegrini, L., Ledda, A., Grossi, M. G., & Appendino, G. (2010b). Product-evaluation registry of Meriva, a curcumin-phosphatidylcholine complex, for the complementary management of osteoarthritis. *Panminerva Medica*, *52*(2 Suppl 1), 55–62.

Bellamy. (2002). WOMAC: A 20-year experiential review of a patient-centered self-reported health status questionnaire. *The Journal Rheumatology*, *29*(12), 2473–2476.

Cas, M. D., & Ghidoni, R. (2019). Dietary curcumin: Correlation between bioavailability and health potential. *Nutrients*, *11*(9), 2147.

Chainani-Wu, N. (2003). Safety and anti-inflammatory activity of curcumin: A component of tumeric (*Curcuma longa*). *Journal of Alternative and Complementary Medicine*, *9*(1), 161–168.

Choudhury, A. K., Raja, S., Mahapatra, S., Nagabhushanam, K., & Majeed, M. (2015). Synthesis and evaluation of the anti-oxidant capacity of curcumin glucuronides, the major curcumin metabolites. *Antioxidants*, *4*(4), 750–767.

Christensen, R., Astrup, A., & Bliddal, H. (2005). Weight loss: The treatment of choice for knee osteoarthritis? A randomized trial. *Osteoarthritis and Cartilage*, *13*(1), 20–27.

Daily, J. W., Yang, M., & Park, S. (2016). Efficacy of turmeric extracts and curcumin for alleviating the symptoms of joint arthritis: A systematic review and meta-analysis of randomized clinical trials. *Journal of Medicinal Food*, *19*(8), 717–729.

Derosa, G., Maffioli, P., Simental-Mendía, L. E., Bo, S., & Sahebkar, A. (2016). Effect of curcumin on circulating interleukin-6 concentrations: A systematic review and meta-analysis of randomized controlled trials. *Pharmacological Research*, *111*, 394–404.

Ejaz, A., Wu, D., Kwan, P., & Meydani, M. (2009). Curcumin inhibits Adipogenesis in 3T3-L1 adipocytes and angiogenesis and obesity in C57/BL mice. *The Journal of Nutrition*, *139*(5), 919–925.

Frestedt, J. L., Walsh, M., Kuskowski, M. A., & Zenk, J. L. (2008). A natural mineral supplement provides relief from knee osteoarthritis symptoms: A randomized controlled pilot trial. *Nutrition Journal*, *7*, 9.

Gupte, P. A., Giramkar, S. A., Harke, S. M., Kulkarni, S. K., Deshmukh, A. P., Hingorani, L. L., … Bhalerao, S. S. (2019). Evaluation of the efficacy and safety of capsule Longvida optimized Curcumin (solid lipid curcumin particles) in knee osteoarthritis: A pilot clinical study. *Journal of Inflammation Research*, *12*, 145–152.

Haraden, C. A., Huebner, J. L., Hsueh, M. F., Li, Y. J., & Kraus, V. B. (2019). Synovial fluid biomarkers associated with osteoarthritis severity reflect macrophage and neutrophil related inflammation. *Arthritis Research and Therapy*, *21*(1), 146.

Haroyan, A., Mukuchyan, V., Mkrtchyan, N., Minasyan, N., Gasparyan, S., Sargsyan, A., … Hovhannisyan, A. (2018). Efficacy and safety of curcumin and its combination with boswellic acid in osteoarthritis: A comparative, randomized, double-blind, placebo-controlled study. *BMC Complementary and Alternative Medicine*, *18*(1), 7, 1–16.

Henrotin, Y., Clutterbuck, A. L., Allaway, D., Lodwig, E. M., Harris, P., Mathy-Hartert, M., … Mobasheri, A. (2010). Biological actions of curcumin on articular chondrocytes. *Osteoarthritis and Cartilage*, *18*(2), 141–149.

Jurenka, J. S. (2009). (PDF) anti-inflammatory properties of curcumin, a major constituent of *Curcuma longa*. A preclinical and clinical research. *Alternative Medicine Review: A Journal of Clinical Therapeutic*, *14*(2), 141–153.

Katz, J., & Melzack, R. (1999). Measurement of pain. *Surgical Clinics of North America*, *79*(2), 231–252.

Kellgren, J. H., & Lawrence, J. S. (1958). Osteo-arthrosis and disk degeneration in an urban population. *Annals of the Rheumatic Diseases*, *17*(4), 388–397.

Kim, K. H., Lee, E. N., Park, J. K., Lee, J. R., Kim, J. H., Choi, H. J., … Yoon, S. (2012). Curcumin attenuates TNF-α-induced expression of intercellular adhesion molecule-1, vascular cell adhesion molecule-1 and proinflammatory cytokines in human endometriotic stromal cells. *Phytotherapy Research*, *26*(7), 1037–1047.

Krishnakumar, I. M., Maliakel, A., Gopakumar, G., Kumar, D., Maliakel, B., & Kuttan, R. (2015). Improved blood-brain-barrier permeability and tissue distribution following the oral administration of a food-grade formulation of curcumin with fenugreek fibre. *Journal of Functional Foods*, *14*, 215–225.

Krishnakumar, I. M., Ravi, A., Kumar, D., Kuttan, R., & Maliakel, B. (2012). An enhanced bioavailable formulation of curcumin using fenugreek-derived soluble dietary fibre. *Journal of Functional Foods*, *4*(1), 348–357.

Krishnareddy, N. T., Thomas, J. V., Nair, S. S., Mulakal, J. N., Maliakel, B. P., & Krishnakumar, I. M. (2018). A novel curcumin-galactomannoside complex delivery system improves hepatic function markers in chronic alcoholics: A double-blinded, randomized, placebo-controlled study. *BioMed Research International*, *2018*, 9159281.

Kumar, D., Jacob, D., Subash, P. S., Maliakkal, A., Johannah, N. M., Kuttan, R., … Krishnakumar, I. M. (2016). Enhanced bioavailability and relative distribution of free (unconjugated) curcuminoids following the oral administration of a food-grade formulation with fenugreek dietary fibre: A randomised double-blind crossover study. *Journal of Functional Foods*, *22*, 578–587.

Kumar, P., Bhandari, U., & Jamadagni, S. (2014). Fenugreek seed extract inhibit fat accumulation and ameliorates dyslipidemia in high fat diet-induced obese rats. *BioMed Research International*, *2014*, 606021.

Kuptniratsaikul, V., Dajpratham, P., Taechaarpornkul, W., Buntragulpoontawee, M., Lukkanapichonchut, P., Chootip, C., … Laongpech, S. (2014). Efficacy and safety of *Curcuma domestica* extracts compared with ibuprofen in patients with knee osteoarthritis: A multicenter study. *Clinical Interventions in Aging*, *9*, 451–458.

Laev, S. S., & Salakhutdinov, N. F. (2015). Anti-arthritic agents: Progress and potential. *Bioorganic and Medicinal Chemistry*, *23*(13), 3059–3080.

Liacini, A., Sylvester, J., Li, W. Q., & Zafarullah, M. (2002). Inhibition of interleukin-1-stimulated MAP kinases, activating protein-1 (AP-1) and nuclear factor kappa B (NF-κB) transcription factors down-regulates matrix metalloproteinase gene expression in articular chondrocytes. *Matrix Biology*, *21*(3), 251–262.

Liju, V. B., Jeena, K., Kumar, D., Maliakel, B., Kuttan, R., & Im, K. (2015). Enhanced bioavailability and safety of curcumagalactomannosides as a dietary ingredient. *Food and Function*, *6*(1), 276–286.

Liu, W., Zhai, Y., Heng, X., Che, F. Y., Chen, W., Sun, D., & Zhai, G. (2016). Oral bioavailability of curcumin: problems and advancements. *Journal of Drug Targeting*, *24*(8), 694–702.

Livshits, G., Zhai, G., Hart, D. J., Kato, B. S., Wang, H., Williams, F. M. K., & Spector, T. D. (2009). Interleukin-6 is a significant predictor of radiographic knee osteoarthritis: The Chingford study. *Arthritis and Rheumatism*, *60*(7), 2037–2045.

Losina, E., Weinstein, A. M., Reichmann, W. M., Burbine, S. A., Solomon, D. H., Daigle, M. E., … Katz, J. N. (2013). Lifetime risk and age at diagnosis of symptomatic knee osteoarthritis in the US. *Arthritis Care and Research*, *65*(5), 703–711.

Mangione, K. K., Axen, K., & Haas, F. (1996). Mechanical unweighting effects on treadmill exercise and pain in elderly people with osteoarthritis of the knee. *Physical Therapy*, *76*(4), 387–394.

Nakagawa, Y., Mukai, S., Yamada, S., Matsuoka, M., Tarumi, E., Hashimoto, T., … Nakamura, T. (2014). Short-term effects of highly-bioavailable curcumin for treating knee osteoarthritis: A randomized, double-blind, placebo-controlled prospective study. *Journal of Orthopaedic Science*, *19*(6), 933–939.

Panahi, Y., Rahimnia, A. R., Sharafi, M., Alishiri, G., Saburi, A., & Sahebkar, A. (2014). Curcuminoid treatment for knee osteoarthritis: A randomized double-blind placebo-controlled trial. *Phytotherapy Research*, *28*(11), 1625–1631.

Persson, M. S. M., Stocks, J., Varadi, G., Hashempur, M. H., van Middelkoop, M., Bierma-Zeinstra, S., … Zhang, W. (2020). Predicting response to topical non-steroidal anti-inflammatory drugs in osteoarthritis: An individual patient data meta-analysis of randomized controlled trials. *Rheumatology*, *0*, 1–10.

Péus, D., Newcomb, N., & Hofer, S. (2013). Appraisal of the Karnofsky performance status and proposal of a simple algorithmic system for its evaluation. *BMC Medical Informatics and Decision Making*, *13*, 72.

Sabina, E. P., Indu, H., & Rasool, M. (2012). Efficacy of boswellic acid on lysosomal acid hydrolases, lipid peroxidation and anti-oxidant status in gouty arthritic mice. *Asian Pacific Journal of Tropical Biomedicine*, *2*(2), 128–133.

Scanzello, C. R., & Goldring, S. R. (2012). The role of synovitis in osteoarthritis pathogenesis. *Bone*, *51*(2), 249–257.

Shep, D., Khanwelkar, C., Gade, P., & Karad, S. (2019). Safety and efficacy of curcumin versus diclofenac in knee osteoarthritis: A randomized open-label parallel-arm study. *Trials*, *20*(1), 214, 1–11.

Shin, Y. A., Suk, M. H., Jang, H. S., & Choi, H. J. (2017). Short-term effects of Theracurmin dose and exercise type on pain, walking ability, and muscle function in patients with knee osteoarthritis. *Journal of Exercise Rehabilitation*, *13*(6), 684–692.

Shoji, M., Nakagawa, K., Watanabe, A., Tsuduki, T., Yamada, T., Kuwahara, S., … Miyazawa, T. (2014). Comparison of the effects of curcumin and curcumin glucuronide in human hepatocellular carcinoma HepG2 cells. *Food Chemistry*, *151*, 126–132.

Shtriker, M. G., Hahn, M., Taieb, E., Nyska, A., Moallem, U., Tirosh, O., & Madar, Z. (2018). Fenugreek galactomannan and citrus pectin improve several parameters associated with glucose metabolism and modulate gut microbiota in mice. *Nutrition*, *46*, 134–142.e3.

Soleimani, V., Sahebkar, A., & Hosseinzadeh, H. (2018). Turmeric (*Curcuma longa*) and its major constituent (curcumin) as nontoxic and safe substances. *Phytotherapy Research*, *32*(6), 985–995.

Srivastava, S., Saksena, A. K., Khattri, S., Kumar, S., & Dagur, R. S. (2016). *Curcuma longa* extract reduces inflammatory and oxidative stress biomarkers in osteoarthritis of knee: A four-month, double-blind, randomized, placebo-controlled trial. *Inflammopharmacology*, *24*(6), 377–388.

Yusuf, E. (2016). Pharmacologic and non-pharmacologic treatment of osteoarthritis. *Current Treatment Options in Rheumatology*, *2*(2), 111–125.

Zeng, C., Wei, J., Li, H., Wang, Y. L., Xie, D. X., Yang, T., … Lei, G. H. (2015). Effectiveness and safety of glucosamine, chondroitin, the two in combination, or celecoxib in the treatment of osteoarthritis of the knee. *Scientific Reports*, *5*, 16827.

Zentek, J., Gärtner, S., Tedin, L., Männer, K., Mader, A., & Vahjen, W. (2013). Fenugreek seed affects intestinal microbiota and immunological variables in piglets after weaning. *British Journal of Nutrition*, *109*(5), 859–866.

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