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Potential of Astaxanthin in the Treatment of Knee Osteoarthritis: A Randomized, Double-Blind, Placebo-Controlled Trial

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Abstract

Background: Osteoarthritis (OA) is a major disabling disorder of the elderly population worldwide. Pharmacotherapy focuses on symptomatic relief through nonsteroidal anti-inflammatory drugs (NSAIDs) or intra articular steroids, which are associated with significant adverse effects. Astaxanthin, a marine carotenoid, is a strong antioxidant with anti-inflammatory properties which may be a safe and effective alternative treatment.

Objectives: The purpose of the research was to look into how a commercially available astaxanthin supplement affected knee pain, stiffness, physical function and inflammatory markers in persons with moderate to severe knee osteoarthritis.

Methods: Adults with knee pain (n = 71, >40 years old), radiologically diagnosed with moderate to severe knee OA, participated in the 8-weeks double-blind, randomized, placebo-controlled trial. Participants consumed either 12 mg astaxanthin capsule each day or placebo identical to astaxanthin capsule. Knee outcomes were assessed using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) visual analog scale (normalized to scores of 0–100), serum hsCRP and IL-6 were measured. Outcomes were assessed at baseline, and at the end of 8th week.

Results: Knee pain and physical function score improved in both groups with greater improvements for astaxanthin ($p<0.05$) than for placebo ($p>0.05$) group. Total WOMAC score improved significantly in the astaxanthin (177.36 ± 12.6 to 166.95 ± 12.96) group than for placebo group (177.24 ± 12.45 to 175.09 ± 12.21). Serum hsCRP and IL-6 also reduced significantly in the astaxanthin group.

Conclusions: Astaxanthin consumption resulted in modest subjective improvements in knee pain, stiffness, and physical function in adults with moderate to severe knee OA with improvements in inflammatory markers.

Keywords: Osteoarthritis; Knee pain; Astaxanthin; IL-6; High-sensitivity C-reactive protein

Introduction

Osteoarthritis (OA) is a chronic progressive disabling disorder of the elderly population that causes structural changes in the joints [1]. Over 595 million people are suffering from OA around the globe [2]. The quality of life of the affected individuals is greatly compromised by chronic pain, stiffness and physical impairment [3]. OA has a significant financial impact, from

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direct medical expenses to reduced productivity at work [4,5]. Treatment for this disease remains unsatisfactory as there are no disease-modifying drugs to date, non-steroidal anti-inflammatory drugs constitute the cornerstone of OA pain management, but they have substantial gastrointestinal, renal, and hepatic adverse effects and increased cardiovascular risks which restricted their usage to the shortest possible duration and have a little positive effect on joint structures [6,7]. Intra-articular corticosteroid therapy has been found to give short-term symptomatic relief but their long-term detrimental effects on articular cartilage remains a major concern [8]. Various nutrients and nutraceuticals were trialed in OA management with inconsistent outcomes [9]. Total knee replacement is considered as a last resort when nonsurgical treatment is ineffective which is associated with high complication and revision rate [10]. Hence the search for a safe and effective treatment option for slowing disease progression and improving symptoms continues.

Astaxanthin, commonly known as a "marine carotenoid," is a natural lipid-soluble and red-orange oxycarotenoid pigment that belongs to the xanthophyll group of carotenoids [11]. It is widely found in a variety of aquatic animals including shrimp, lobster, salmon, trout, red seabream and fish eggs [12]. The richest source of natural astaxanthin for human consumption is astaxanthin obtained from algae *Haematococcus pluvialis* [13]. Astaxanthin is a strong anti-oxidant with multiple health benefits for which it received significant attention and now it is a well-known neutraceutical [14]. Oxidative stress is regarded as a significant contributor to the etiology and disease progression in OA [15]. Anti-oxidant activity of astaxanthin is 10 fold higher than of other carotenoids and 100 times higher than α tocopherol [16].

The Matrix Metalloproteinases family (MMPs) is well established to have significant roles in cartilage breakdown [17]. It was reported that astaxanthin reduce MMP expression in chondrocytes and improve loss of cartilage [18]. which was confirmed by morphological and histological evaluation on the articular cartilage in experimental OA in rabbits [19]. Though once considered as a simple disease of wear and tear in recent years' low grade chronic inflammation was linked with OA evidenced by increased levels of pro-inflammatory cytokines IL-1β, IL-6 and tumor necrosis factor-α (TNF-α) [20]. Astaxanthin can reduce critical mediators of inflammation including CRP, IL-1β, IL-6, NF-κB and nitric oxide (NO) [21].

All of this scientific evidence highlights astaxanthin's enormous potential to improve disease progression and symptoms in OA patients, implying that it could be a promising therapeutic option for the treatment of OA. The goal of this trial was to evaluate the efficacy of 12 mg of commercially available astaxanthin supplement daily on pain, stiffness and physical function in patients with moderate to severe knee OA compared with a placebo over an 8-weeks period. Changes in serum inflammatory markers-high-sensitivity C-reactive protein (hsCRP) and IL-6 level was also evaluated.

Methods

This study was a randomized, double-blind, placebo-controlled trial conducted in the Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh in collaboration with the Department of Pharmacology, the Department of Physical Medicine and Rehabilitation and the Department of Microbiology and Immunology. Before the study's conduct, the research protocol was submitted to the Institutional Review Board (IRB) of BSMMU to review the scientific and ethical issues related to the research to obtain the required approval. The protocol was reviewed and the IRB of BSMMU issued a Clearance Letter (Memo No. BSMMU/2022/5680). The trial was registered on ClinicalTrials.gov (trial ID number NCT05437601) and conducted in accordance with the International Council on Harmonization Good Clinical Practice (ICH GCP) guidelines. The intervention phase was executed from June 2022 to January 2023.

Participants

All the patients (both male and female) with knee pain and above 40 years old attending the outpatient department and Osteoporosis, Osteoarthritis and Postmenopausal Muscle Bone Health Clinic of the Department of Physical Medicine and Rehabilitation, BSMMU were given X-ray of the affected knee joints in a standing position and were diagnosed according to the Kellgren-Lawrence radiographic grading scale. Those with Grade III and Grade IV knee OA were selected for the study by a competent Physiatrist. Patients with prior history of knee trauma or surgery, history of presence of systemic inflammatory conditions such as rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease, current smokers, known allergy to seafood, shellfish or astaxanthin, taking immunosuppressant, pregnant and nursing mothers, history of taking intra-articular steroid within 6 months of the study were excluded from the study. Patients with major comorbidities or inability to cooperate with study requirements were precluded entry. The study objectives were explained to each participant and they were informed about the potential benefits and risks associated with the intervention. Participants were also informed that they can participate in this study of their free will and also, they had every right to refuse to participate or to withdraw at any time without compromising their medical care. Patients who were convinced and agreed willingly after adequate understanding were enrolled in the study with written consent. Participants' confidentiality was rigorously protected. The participant's personal information regarding name, age, sex and other information was not disclosed anywhere and were used for research purpose only.

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Study design and procedure

Medicines and placebo were purchased from the manufacturer at the original market price so that there was no conflict of interest. Astaxanthin capsules (Astagen 4 mg) and placebo capsules were purchased from General Pharmaceuticals Limited, a leading Pharmaceutical company in Bangladesh. The capsule placebo was identical to the capsule astaxanthin 4mg in size, shape and color and was also supplied in an identical container.

Participants were randomly allocated in a double-blind manner in equal numbers to receive either astaxanthin 12 mg daily or placebo. Online GraphPad software was used to perform the randomization. The software automatically generated two distinct sets of random numbers after giving the necessary inputs (sample size, sets of numbers). Here every patient had an equal chance to be assigned to any one of the groups (Placebo and Intervention). The whole process of randomization was conducted by a competent third person who had no relationship with this research. Medicine was given to participants at the baseline after taking baseline blood sample and filling the WOMAC form. Compliance was assessed by returned capsule counts at the end of eight weeks (56±4 days) of treatment.

Patients were requested to avoid non-steroidal anti-inflammatory drugs (NSAIDs) for the next six weeks and any dietary supplement during the study period. Paracetamol was allowed for breakthrough pain <2000mg/day. If any patient required paracetamol after the initial two weeks of the treatment, the patients were instructed to stop medications 48 hours before the follow-up visit. They were allowed to withdraw from the study if their pain could not be relieved by paracetamol at a dose upto 2000 mg/day. Quadriceps strengthening exercises were advised to all the participants. Instruction for the activities of daily living (avoiding stairs, walking on flat surface, prohibiting weight carrying, using walking aid and kneecap during walking, avoiding kneeling and squatting, avoiding sitting for prolonged periods in with bent knees in one position, measures to reduce weight) was prescribed for all participants (both placebo and intervention group). They were in touch with the investigator over the phone during the study period.

Outcome measures

Knee pain, stiffness, and physical function of the index knee were assessed using the translated and validated Bangla version of WOMAC index version VA3.01 [22]. WOMAC is a 24 –item self-report questionnaire, that includes pain score (5 domain), stiffness score (2 domain) and physical function score (17 domain). Each domain in the visual analog scale VA3.01 is presented as a 0-100 mm line, where the patient will mark according to his/her severity perception. A higher score implies a deterioration in the condition.

Each domain score was converted into a scale of 0 to 100 for better representation. Finally, they were summed up for the total WOMAC score from 0 to 300. After ensuring that patients were free from any analgesic drugs in the last 48 hours they were assessed by the by the translated and validated Bangla version of WOMAC index version VA3.01 and after 8 weeks, the patients were again assessed by the WOMAC index. The total procedure took approximately 20-30 minutes for each patient in each visit.

Estimation of Laboratory Parameters

4 ml blood was collected from all the participants at baseline and after 8 weeks into clot activator test tubes for estimation of serum hsCRP and IL-6. The tubes were placed in the sampling rack for at least 30 minutes. Then the tubes were centrifuged for 10 minutes at 7000-8000 rpm. Serum hsCRP was measured by the nephelometric system at BN ProSpec automated analyzer and serum IL-6 was measured by chemiluminescence immunoassay at Snibe Maglumi in the department of Microbiology and Immunology, BSMMU.

Adverse events: After every 15 days over the telephone each participant was asked in a no leading manner about occurrence of any adverse events or discomfort. For each adverse events detailed information regarding onset, duration, action taken and outcome was recorded. To facilitate the use of computers a special spreadsheet prepared by the researcher was used in this study.

Statistical analysis

Statistical analysis was done by Microsoft Office Excel 2007. A Chi-square test was done to see the association between the intervention and the placebo arm. An unpaired t-test was done to compare a score between the two arms. Spearman's rank correlation test was done to see a correlation between changes in serum levels with changes in WOMAC scores. The significant p value is <0.05.

Result

A total of 300 participants were screened (Figure 1). Of these Eighty (80) patients were enrolled based on the study's eligibility criteria. They were randomly assigned to allocated interventions (astaxanthin group: n=40; placebo: n=40). 7 participants (8.75%) discontinued intervention or were lost to follow-up (astaxanthin group: n=4; placebo: n=5).

The baseline characteristics summarized in Table 1 reflect males and females, with moderate to severe knee OA involving unilateral or both knees. The majority of participants had Grade III or moderate knee OA.

Knee pain, stiffness and physical function:

Table 2 shows WOMAC knee outcome changes from baseline to after 8 weeks of treatment. In the intervention arm, compared to the placebo arm, WOMAC pain, physical

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Table 1: Baseline characteristics of participants at the time of enrollment (n=71).

Variables		Placebo (n=35) Mean ± SD	Astaxanthin (n=36) Mean ± SD	P value	Method
Age (years)		58.86 ± 7.63	59.89 ± 9.69	0.62	Unpaired t-test
BMI(kg/m²)		27.57 ± 2.7	27.29 ± 3.12	0.679	Unpaired t-test
Gender	Male	16	15	0.73	Chi-square test
	Female	19	21		
Radiological grading	Grade III	33	32	0.678	Fisher's exact test
	Grade IV	2	4		
Affected knee	Bilateral	18	22	0.659	Chi-square test
	Left	6	4		
	Right	11	10		
Duration of knee pain	≤5 year	14	13	0.93	Chi-square test
	6 - 9 year	16	17		
	≥10 year	5	6		

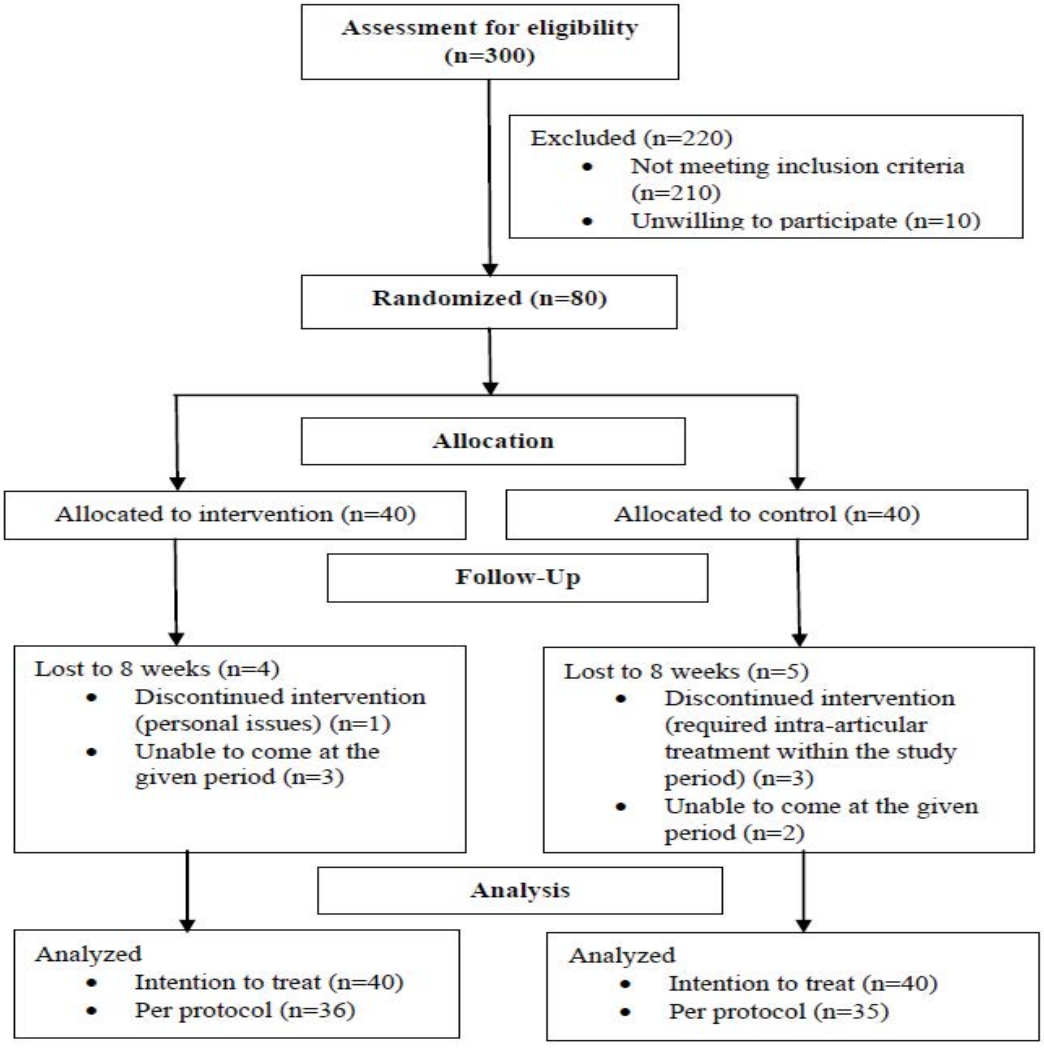

Figure 1: Flowchart of Consolidated Standards of Reporting Trials (CONSORT).

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function, and overall WOMAC ratings all significantly decreased. All 3 domains of the WOMAC index and total WOMAC scores also reduced significantly in the intervention arm compared to the baseline. But the reduction of stiffness score in intervention arm in comparison to the placebo arm is not statistically significant.

Serum inflammatory markers

Table 3 summarizes changes in inflammatory markers-serum hsCRP and IL-6 from baseline to the end of intervention. Serum hsCRP reduced from 3.61 ± 1.49 to 3.02 ± 1.44 mg/L in the intervention arm which was statistically significant compared to the placebo arm. Serum IL-6 level reduced in the intervention arm from 7.06 ± 2.09 to 6.21 ± 2.45 pg/ml which was statistically significant compared to the placebo arm. On the other hand, a rise of serum hsCRP and IL-6 was observed in the placebo arm after 8 weeks.

Statistically significant positive monotonic correlation was found when a correlation test was done between changes in serum hsCRP with total WOMAC scores changes (p=0.00) in Figure 2 and changes in serum IL-6 with total WOMAC scores changes (p=0.000) in Figure 3.

Table 2: Comparison of WOMAC Score between two arms (at baseline and after 8 weeks of treatment).

		Placebo (n=35) Mean ± SD	Astaxanthin (n=36) Mean ± SD	P value
WOMAC Pain Score	At Baseline	62.8 ± 5.58	61.88 ± 6.79	0.534
	After 8 weeks of treatment	62.29 ± 6.3	58.9 ± 7.2	0.039*
WOMAC Stiffness Score	At Baseline	49.13 ± 9.1	49.54 ± 8.53	0.843
	After 8 weeks of treatment	48.29 ± 8.2	47.68 ± 7.41	0.745
WOMAC Physical Function Score	At Baseline	65.22 ± 6.2	66.02 ± 6.08	0.586
	After 8 weeks of treatment	64.52 ± 8.68	60.44 ± 8.11	0.045*
Total WOMAC Score	At Baseline	177.24 ± 12.45	177.36 ± 12.6	0.969
	After 8 weeks of treatment	175.09 ± 12.21	166.95 ± 12.96	0.008*

*; p<0.05. Unpaired t-test was done between placebo and intervention arm

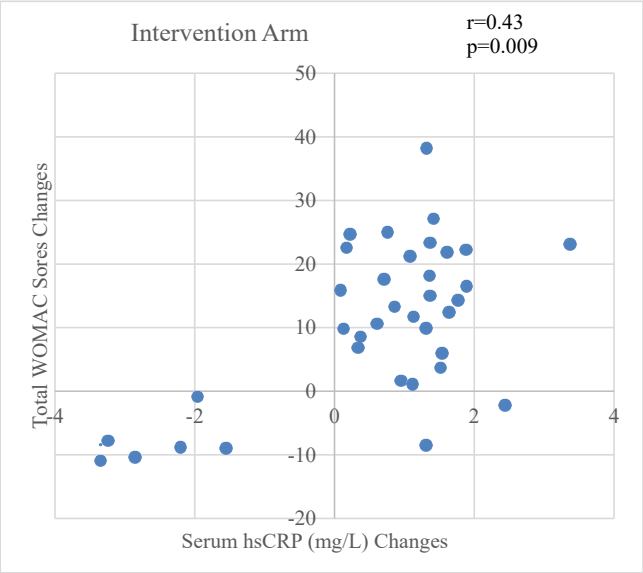

Figure 2: Scatter diagram showing positive monotonic correlation of serum hsCRP level changes with total WOMAC Score changes in intervention arm after 8 weeks. Spearman's rank correlation coefficient after 8 weeks was r= 0.43.

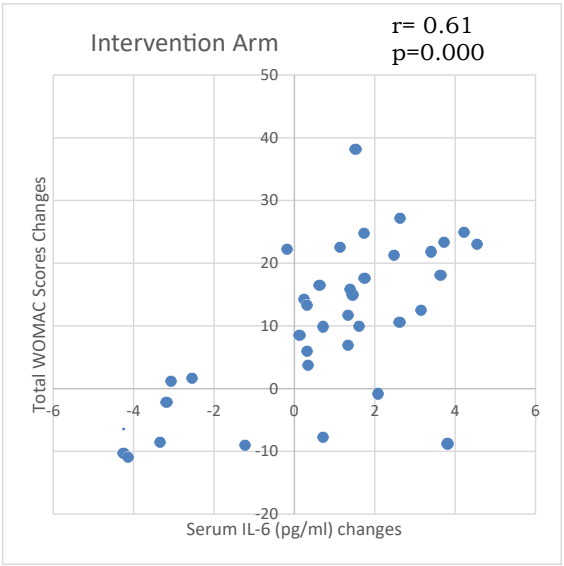

Figure 3: Scatter diagram showing positive monotonic correlation of serum IL-6 level changes with total WOMAC scores changes in intervention arm after 8 weeks. Spearman's rank correlation coefficient after 8 weeks was r= 0.61.

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Adverse events during treatment

Table 4 shows the adverse events in the placebo and intervention arms that occurred during the treatment period. There was no significant difference between adverse events of the placebo and intervention arm after 8 weeks of treatment (P=0.674). Adverse events in the intervention arm were - increased frequency of bowel movement (3) and anorexia (1). 3 participants had increase frequency with normal stool consistency around 3-5 times per day on first 2 days of treatment which resolved spontaneously on subsequent days. Whereas adverse events in the control arm were - insomnia (1) and nausea (1). All the events were mild in form and did not require discontinuation of treatment.

Table 3: Comparison of serum High-Sensitivity C-Reactive Protein (hsCRP) level (mg/L) and Interleukin-6 (IL-6) level (pg/ml) between two arms (at baseline and after 8 weeks of treatment).

Serum		Placebo (n=35) Mean ± SD	Astaxanthin (n=36) Mean ± SD	P value
hsCRP (mg/L)	At Baseline	3.55 ± 1.38	3.61 ± 1.49	0.303
	After 8 weeks of treatment	3.8 ± 1.16	3.02 ± 1.44	0.031*
IL-6 (pg/ml)	At Baseline	7.08 ± 2.06	7.06 ± 2.09	0.432
	After 8 weeks of treatment	7.41 ± 1.84	6.21 ± 2.45	0.034*

*; p<0.05. Unpaired t-test was done between placebo and intervention arm

Table 4: Comparison of adverse events between two arms.

Adverse Events	Placebo (n=35)	Intervention (n=36)	P value
Yes	2(5.71%)	4(11.11%)	0.674
No	33(94.29%)	32(88.89%)	

Fisher's exact test was done between placebo and intervention arm

Discussion

This study is so far the first RCT conducted to explore the effects of astaxanthin on knee symptoms and serum inflammatory markers. There was no significant difference between placebo and intervention arms in baseline clinical characteristics.

After 8 weeks of treatment, the WOMAC pain scores were significantly lower in the intervention arm (p<0.05) than in the placebo arm (p>0.05). It indicates that astaxanthin could effectively reduce pain in knee OA patients. Astaxanthin was found to be as effective as indomethacin in reducing inflammation-induced thermal and mechanical hyperalgesia in mice [23]. Anti-nociceptive function of astaxanthin was also found in experimentally induced pain in mice [24-26]. Intra-articular astaxanthin administration gave better outcomes than corticosteroid and hyaluronic acid in both dynamic gait parameters and histological examinations of articular structures in a rat osteoarthritis model [27]. This study further contributed to the evidence of the analgesic potential of astaxanthin.

The WOMAC stiffness scores decreased in the intervention arm after 8 weeks of treatment, however, this decrease was not statistically significant compared to the placebo arm (p>0.05). All of the study participants were given standard advice for symptomatic improvement including topical application of heat and quadriceps strengthening exercises, which might have contributed to the improvement of stiffness in both arms. As the exact mechanism of the effect of astaxanthin on joint stiffness is not yet known, further study warrants exploring the effect of astaxanthin on joint stiffness.

This study found, after 8 weeks of intervention, WOMAC physical function scores were significantly lower (p<0.05) in the intervention arm than the placebo arm (p>0.05). Reduction of pain might have contributed to the improvement of physical activities. Similar to this study, krill oil supplementation (a combination of astaxanthin and omega-3 fatty acids) resulted in significant improvement in the WOMAC index [28,29]. However, such a statistically significant improvement was not found in a study where 2g/day krill oil supplementation was given [30]. That study included participants with more severe disease (who had effusion synovitis and significant knee pain) whereas, such clinical severity was not in the inclusion criteria of others.

In this study, after 8 weeks of intervention, the total WOMAC scores were significantly lower (p<0.05) in the intervention arm than in the placebo arm (p>0.05). In this regard, we must mention that the WOMAC index is widely used in the clinical trials of knee and hip osteoarthritis and its improvement is considered as a significant therapeutic potential. Currently used NSAIDs and intra-articular steroids were also studied for their capacity in improving the WOMAC index [31-33]. So, the improvement in the WOMAC index

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indicates that astaxanthin has the potential to be an effective treatment option in OA and future studies should be directed to evaluate and include astaxanthin in OA treatment.

To explore how astaxanthin plays role in improving OA symptoms pathophysiology of OA was considered we observed astaxanthin's effect on serum hsCRP and IL-6 levels. After 8 weeks of treatment, hsCRP levels decreased significantly in the intervention arm whereas, an increase was observed in the placebo arm. A similar decrease in hsCRP level was observed in studies using 4mg [34] and 2mg of astaxanthin [35]. On the contrary, a high dose of astaxanthin (12mg), not a low dose (6mg) was found to reduce hsCRP significantly [36]. In gouty arthritis, 8mg/day astaxanthin administration was as potent as 100 mg celecoxib in reducing CRP levels [37]. A significant inhibitory effect of astaxanthin on COX-II activity found in that study might have contributed to the reduction of hsCRP by astaxanthin. However, statistically non-significant changes in hsCRP levels with astaxanthin was also reported in several studies [38-40]. Among them 2 studies were conducted in healthy volunteers whose hsCRP levels were within the normal limits with not much scope to improve [38,40]. In the other study, research was conducted in renal transplant patients who had high CRP levels at baseline [39]. It indicates that there might be a certain range of baseline CRP within which the effect of astaxanthin is more prominent which needs to be confirmed in further studies.

In this study, serum IL-6 levels decreased significantly ($p<0.05$) in the intervention arm after 8 weeks of treatment, whereas, a non-significant increase was observed in the placebo arm ($p>0.05$). Astaxanthin reduces the expression of different cytokines including IL-6, IL-1β and TNF-α [24,41,42], also downregulates IL-6 production by inhibiting the NF-κB signaling pathway [43] which might have contributed to the IL-6 reduction. This reduction of systemic IL-6 is supposed to be comparable and correspondingly reflect in synovial fluid as serum and synovial fluid IL-6 concentration correlates highly [44]. A similar significant reduction of serum IL-6 levels was found in other study also [36]. But an increase in serum IL-6 levels was found in another [35]. As the study included healthy and young females, the outcome might not be the same when pathology is present. A significant decrease in serum IL-6 levels with astaxanthin treatment was also showed in pre-clinical studies [45,46]. As IL-6 is known to decrease the production of type II collagen and increase the production of MMPs enzymes [47] the reduction of IL-6 seems to be beneficial in halting the OA progression.

A significant positive monotonic association was found between changes in serum hsCRP and serum IL-6 levels with changes in the total WOMAC scores. Changes in the hsCRP were noted to be positively and significantly associated with the change in knee pain [48]. A positive correlation was also observed between functional pain disability status and serum IL-6 levels [44]. A significant correlation between synovial fluid IL-6 with pain and total WOMAC sores was also found [49,50]. Regarding hsCRP, a significant association with WOMAC pain scores was also observed [50,51]. This indicates that the reduction of serum hsCRP and IL-6 might have contributed to the reduction of the WOMAC index in this study.

The incidence of treatment-related adverse events that were seen in the present trial was mild, did not require any treatment or discontinuation of treatment with astaxanthin and did not differ statistically between arms. This study contributes to the excellent safety profile of astaxanthin in knee OA patients.

To the best of our knowledge, this is the first study conducted on the effects of astaxanthin on adults with moderate to severe knee osteoarthritis. One of the strengths of the current study is its rigorous design, which hides the treatment assignment from all study participants and researchers and employs placebo capsules and containers that are identical to astaxanthin capsules. Another strength includes using a study population for whom the intervention is targeted, participants with appropriately diagnosed moderate to severe knee OA with room to improve knee pain and function were recruited. The use of a valid, reliable, and responsive standardized globalized measure (WOMAC Index) to assess knee pain, stiffness and function further contributed to the study's strength. Findings from this study could help millions of OA patients throughout the world by guiding future investigations into OA and possibly bolstering the usage of astaxanthin to treat it.

This study also has several limitations. It was a short duration study. Participants were given both naproxen/paracetamol and astaxanthin in the first 2 weeks of the study, so it is possible that there was a synergistic effect. The values of IL-6 and hsCRP measured after the intervention do not reflect the actual anti-inflammatory effect of astaxanthin as paracetamol was allowed as rescue medication for breakthrough pain. Number of days where rescue medication was needed was not possible to determine. Less than 10% of the study population had severe OA, so the effect of astaxanthin in severe knee OA patients was not clearly reflected.

Conclusion

The present study provides scientific evidence on the symptomatic improvement of knee osteoarthritis patients and reinforces the potential mechanism of action. Astaxanthin can also be an effective alternative treatment for mild to moderate inflammatory diseases where long-term treatment is necessary to slow the disease progression. A large-scale

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study is warranted to explore the required dose, effect duration and cost-effectiveness of astaxanthin in the treatment of OA knee joints. Change in joint morphology and effect on joints other than knee need to be determined in future studies. In conclusion, astaxanthin is safe and effective as an adjunct therapy to reduce symptoms and inflammation in patients with moderate to severe knee osteoarthritis.

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Conflicts of interest

There are no conflicts of interest declared by all authors.

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