

# Improved Joint Mobility Associated with Reduced Inflammation Related to Consumption of Nopal Cactus Fruit Juice: Results from a Placebo-Controlled Trial Using Digital Inclinometry to Objectively Document Mobility of All Major Joints

This article was published in the following Dove Press journal:  
*Clinical Interventions in Aging*

Gitte S Jensen 

Natural Products Research, NIS Labs,  
Klamath Falls, Oregon, 97601, USA

**Objective:** To evaluate the effects of daily consumption of Nopal cactus fruit juice (NFJ) on joint mobility in a population experiencing chronic pain but otherwise in good health.

**Study Design:** A double-blind, placebo-controlled study design was used to enroll 40 people after written informed consent, randomized to consume 3 oz/day of NFJ versus placebo. At baseline and 8 weeks, joint range of motion (ROM) was examined by digital inclinometry along the vertical weight-bearing axis of the body from neck to knees and the shoulders. Blood samples were tested for cytokines and C-reactive protein (CRP). Questionnaires addressed wellness, pain, and reliance on pain medications.

**Results:** After 8 weeks of consuming NFJ, participants showed improved ROM beyond that of participants consuming placebo. Cervical and thoracic/lumbar ROM for the NFJ group was significantly improved when compared to placebo (cervical:  $P < 0.03$ , thoracic/lumbar:  $P < 0.04$ ). People consuming NFJ relied less on pain medication to complete daily activities ( $P < 0.1$ ) and experienced reduced interference from pain and breathing issues (not significant). Serum levels of Eotaxin, involved in airway inflammation, showed significant differences between placebo and NFJ groups after 8 weeks ( $P < 0.048$ ). Changes in CRP levels showed a larger reduction in the NFJ group ( $-13\%$ ) than in the placebo group ( $-4\%$ ) (not significant). In the subgroup with CRP levels between 1 and 9.9 mg/L at baseline, CRP levels decreased in the NFJ group ( $-30\%$ ) but increased in the placebo group ( $31\%$ ) ( $P < 0.015$ ).

**Conclusion:** Consumption of NFJ for 8 weeks was associated with statistically significant improvements in joint mobility and physical functioning compared to the placebo group, allowing participants in the NFJ group to be more physically active; daily activities were easier, including walking, sitting, and lying. This was associated with reduced use of pain medication, possibly associated with anti-inflammatory properties of NFJ, as suggested by reduced Eotaxin and CRP levels.

**Keywords:** activities of daily living, C-reactive protein, pain, range of motion, wellness

## Introduction

As we age, physical activity plays a major role in staying healthy. Maintaining a physically active lifestyle has been associated with lower risk of osteoporosis, prevention of loss of muscle mass, improved cardiovascular health, and delayed onset of cognitive decline and dementia.<sup>1</sup> Being able to stay active prolongs the time

Correspondence: Gitte S Jensen  
Natural Products Research, NIS Labs,  
1437 Esplanade, Klamath Falls, Oregon  
97601, USA  
Tel +1 541 884-0112  
Email gitte@nislabs.com

an individual can maintain independent living, and not only does this benefit personal wellness, but also has major economic impacts on personal and societal costs of assisted living and caring for the elderly.<sup>2,3</sup>

Mobility is a key component in maintaining a physically active lifestyle. It is a recognized factor and subject for clinical trials in programs to improve mobility and delay risk of frailty in the ageing population,<sup>4</sup> whether by walking<sup>5</sup> or stationary resistance strength exercises.<sup>6</sup> In a 14-year longitudinal study of over 4000 non-institutionalized elderly participants, it was shown that physical activity reduced total and cardiovascular death rates.<sup>7</sup> In participants in poor health, there is an association between reduced joint mobility and obesity.<sup>8</sup> Reduced body weight changes stress on various joints, and has impacts on gait and general mobility.<sup>9</sup> At the cellular level, it has been suggested that exercise training increases the mitochondrial bioenergetics, thereby supporting cellular energy production.<sup>10</sup> However, painful musculoskeletal ailments limit the ability of people to make necessary lifestyle changes.<sup>11</sup>

Joint function and mobility are negatively affected by inflammation. Chronic pain in joints and muscles is associated with low-grade inflammation and sets the stage for declining cardiovascular health. Monitoring acute and chronic inflammation often includes testing for C-reactive protein levels as a non-specific marker for inflammation. Elevated blood level of C-reactive protein is an indication of inflammation, either as an indication of chronic inflammatory illness or as a risk marker for cardiovascular disease, and is also associated with increased risk for stroke, diabetes, and neurodegenerative diseases.<sup>12</sup> People experiencing long-term chronic inflammatory problems frequently consume over-the-counter or prescription pain medications to be able to complete daily physical activities. Managing pain with pharmaceutical intervention is not ideal and carries risks of side effects, including gastrointestinal discomfort and bleeding<sup>13</sup> and kidney damage.<sup>14</sup>

There is an urgent and global need for effective evidence-based interventions for healthy aging,<sup>15</sup> including effective, low-cost nutritional strategies. Research has shown that consuming certain spices such as curcumin helps reduce joint pain.<sup>16,17</sup> Fermented fruits, such as papaya, have shown strong antioxidant effects, with anti-inflammatory and anti-ageing effects, including increased telomerase activity and telomere length in an animal model.<sup>18</sup> Consuming algae-based extracts rich in the light-harvesting pigment Phycocyanin has been shown to be a safe food-based method to achieve significant pain

reduction both when at rest and when physically active.<sup>19</sup> Plant-based anti-inflammatory compounds have been studied for their effects on joint mobility, including the anthocyanin-rich juice from Acai berries,<sup>20</sup> ergothioneine extracted from mushrooms,<sup>21</sup> and polyphenol-rich apple peel powder.<sup>22</sup>

A unique type of anti-inflammatory compounds are the red plant pigments betalains, which are different from anthocyanins and never found in the same plants.<sup>23</sup> A source of betalains is beet root, known to support healthy blood pressure levels,<sup>24</sup> via reduction of oxidative stress and inflammation.<sup>25</sup> Another source of betalains is the lesser-studied fruit of the Nopal cactus, responsible for the pink and red colors of the fruit. The fruit also contains the fibers and other anti-inflammatory compounds present in the cactus stems, also called cladodes. The Nopal cactus has been used in traditional folk medicine throughout millennia,<sup>26</sup> and is currently being researched for metabolic<sup>27,28</sup> and anti-inflammatory benefits when added to common foods.<sup>29,30</sup>

In a previous clinical study, we reported preliminary evidence for anti-inflammatory effects of consuming Nopal fruit juice.<sup>31</sup> The placebo-controlled nutritional intervention study reported here was performed to evaluate the potential benefits of consuming the betalain-rich Nopal fruit juice on objective measures of joint mobility and C-reactive protein, as well as questionnaire-based data collection on pain, physical functioning, and daily activities. It was of particular importance to evaluate objective joint mobility across the vertical weight-bearing axis of the body, since the functionality of neck and back plays a major role in the ability to perform daily activities and retain an active lifestyle.

## Materials and Methods

### Clinical Study Design

#### Study Design

A double-blinded, randomized, placebo-controlled, parallel-arm clinical study design was used, performed in accordance with the principles stated in the Declaration of Helsinki (trial registration number NCT03619265). The study involved 40 people, enrolled after screening for moderate levels of chronic pain (a minimum score of 4 out of 20, lasting at least 6 months prior to the study) and signing written informed consent. Each study participant was randomized to one of the two groups to consume one of the following test products: Nopal fruit juice or placebo juice. Questionnaire-based data collection was performed

at baseline, after 2 weeks, and after 8 weeks. Blood draws were performed at the baseline visit and at the 8-week visit. Range of motion assessments of joint mobility were performed at baseline and week 8.

### Study Population

People were enrolled in the study, based on the following criteria: healthy adults of either gender, age 35–75 years old, body mass index (BMI) at or below 34.9 kg/m<sup>2</sup> with chronic joint/muscle related pain for at least the previous 6 months. People were excluded from participating if they had bariatric surgery, were diagnosed with diabetes Type I or taking medication for diabetes Type II, had a known serious chronic health condition, major surgery or trauma during the previous 3 months, serious active illness during the previous 12 months. People were also excluded if they took anti-inflammatory medications (81 mg aspirin was allowed), if they had used oral, injected or inhaled steroids during the previous 6 months (nasal sprays for allergies were allowed), or if they had used anti-inflammatory nutritional supplements, including the daily consumption of Nopal cactus fruit juice or similar products.

Forty-two people were enrolled after written informed consent (as approved by the registered Institutional Review Board Sky Lakes Medical Center Institutional Review Board FWA 2603), an IRB board that broadly serves the Klamath Falls medical research community. However, the data presented here focuses on the analysis of 40 people (20 per group) (Table 1). Two people were not included in the data analysis for the following reasons: 1) one person dropped out almost immediately after study start. Prior to her 2-week appointment, we learned that she had shingles and had not felt well enough to participate. It is unknown whether she consumed the test product before dropping out. She was in the Placebo group. Her data is not included in the tables and data graphs in this report. 2) One person completed study participation, but a critical review of her data revealed that her responses were deemed unreliable. Prior to the study she failed to report exclusionary conditions including chronic physical and mental health conditions. She was in the Nopalea group. Her data is not included in the tables and data graphs.

### Randomization

The study participants were randomized to one of two groups, where one group consumed 3 ounces placebo daily, and the other group consumed 3 ounces NFJ daily.

**Table 1** Demographics of the Study Population

	Placebo	NFJ	P-value
Females	12	12	
Age, average <sup>a</sup>	56.2 ± 7.8	60.8 ± 7.5	0.16
Age range	45.8–74.4	48.8–70.7	
BMI, average <sup>a</sup>	30 ± 4.3	27.1 ± 3.7	0.09
BMI range	23.2–34.9	22.1–33.3	
Males	8	8	
Age, average <sup>a</sup>	57.1 ± 11.9	54.9 ± 7.9	0.67
Age range	37–69.1	42.7–69.3	
BMI, average <sup>a</sup>	30.7 ± 3.5	28.9 ± 4.0	0.36
BMI range	25–34.8	23.4–33.5	

**Note:** <sup>a</sup>The group average ± standard deviation

**Abbreviation:** BMI, body mass index (kg/m<sup>2</sup>).

For pilot studies of this nature, it is important to have similar numbers of females in each group, and also similar numbers of males in each group, but not necessary to have the same number of females and males in the study. Female and male study participants were randomized separately, aiming for a similar gender distribution in the two groups. The first female was randomly assigned to a group by tossing a coin. The next female was assigned to the other group, and the group assignment alternated from here onwards. The first male was assigned to the opposite group as the first female, and the group assignment for males alternated from here onward. The study coordinator and clinic staff, as well as data analyst and auditor, were blinded until all analysis was completed and audited.

### Consumable Test Products

The study involved 2 consumables: Nopalea™ Nopal fruit juice (NFJ) and a placebo juice, matched to NFJ for viscosity, color, and taste. The placebo juice had no active ingredients, was sweetened with 0.028% sucralose, thickened by guar gum and xanthan gum, colored by artificial colors, and flavored by artificial prickly pear flavor. The two juice products have similar viscosity, color, and flavor, and were bottled in identical containers with identical labels, except for different lot numbers. Instructions included taking a dose of 3 oz/day for 8 weeks. Study participants were provided with 3 oz measuring glasses.

### Compliance

All bottles of juice were weighed before the beginning of the study. Study participants were instructed to return bottles containing any remaining juice at the 8-week visits, and the bottles were weighed to estimate the amount of

juice consumed. The weight of 3 ounces daily for 8 weeks (56 days) was used to calculate 100% compliance. Table 2 summarizes the percent compliance

## Joint Range of Motion Assessment

The range of motion assessment was performed along the entire weight-bearing axis from the neck to the knees, as well as shoulder range of motion. Participants were instructed to abstain from the use of over-the-counter pain medication, such as Naproxen, for at least 18 hours, and aspirin and ibuprofen for at least 8 hours prior to the visits. The evaluation of ROM was conducted in a detailed manner using the J-Tech Tracker Freedom dual digital inclinometry (J-Tech Medical, Midvale, UT, USA), where not only a person's major area of discomfort was evaluated but also the entire vertical weight-bearing axis of the body was studied, from the neck to the knees. In addition, shoulder ROM was also evaluated. Each ROM measurement was performed at least 2 consecutive times during each evaluation. The rationale behind this detailed assessment is that often a person's primary complaint (eg, right hip) would lead to a compensated posture and compensated ROM of other anatomical areas as the person strived to put less pressure on a painful area, as previously described in studies for natural products.<sup>19–21</sup>

## Questionnaire-Based Data Collection

At each study visit, 3 questionnaires were administered where the study participant would answer the questionnaires by use of a tablet computer in the presence of clinic staff available to answer any questions or provide clarifications. 1) A Wellness questionnaire contained questions regarding general health and wellness, designed and validated by our team to specifically capture changes in a person's perception of health and wellness, based on the World Health Organization's definition of "Health": "Physical, mental, and social well-being, and not merely the absence of disease and infirmity".<sup>32</sup> Our research

team has used the Wellness questionnaire for 10 years in clinical trials focusing on fairly healthy individuals and documenting health improvements when consuming natural products, foods, juices, alkaline waters, and botanical extracts. 2) At the time of enrollment, study participants identified their primary and secondary areas of chronic pain complaints. The pain assessments for these areas, when at rest and when physically active, were performed at baseline, 2 weeks, and 8 weeks, where the scores were measured using scales from 0–10, following previously published processes for data collection on pain in studies on natural products and dietary supplements.<sup>19–22,33</sup> 3) In addition, questions were asked as to what degree pain interfered with daily activities.<sup>20,21,33</sup>

## Blood Draws

During the clinical trial, blood draws were performed at baseline and at the 8-week visit for all study participants, where 1 serum separator tube was filled, and the blood allowed to coagulate at room temperature for 30–60 minutes. The serum separator tube was centrifuged at 500 g for 15 minutes and the serum was harvested into Eppendorf tubes and frozen at  $-80^{\circ}\text{C}$ .

## Serum Cytokines

Serum levels of the following cytokines were tested: IL-1beta, IL-1ra, IL-6, IL-9, IL-32, RANTES, Eotaxin, IP-10, MIP-1-beta, MCP-1, and Tumor Necrosis Factor-alpha (TNF- $\alpha$ ), using Bio-Plex Pro™ multiplex Luminex immunoassays (Bio-Rad Laboratories, Hercules, CA, USA). Testing of these biomarkers was performed at NIS Labs using xMAP technology (Luminex, Austin, TX, USA).

## C-Reactive Protein

Serum samples were shipped to Interpath Laboratories, Redmond, Oregon, USA, for testing using the high sensitivity CRP test.

## Data Analysis

Statistical significance of changes from baseline to later assessments when consuming a test product was evaluated by the within-subject analysis using the two-tailed paired *t*-test. Statistical significance of differences between groups at baseline and at later assessments was evaluated by the between-groups analysis using the two-tailed unpaired *t*-test. Statistical trends are indicated if  $P < 0.1$ , statistical significance is indicated if  $P < 0.05$ , and a high level of significance is indicated if  $P < 0.01$ .

**Table 2** Compliance

Product	Average <sup>a</sup>	Range	Number of Participants
Placebo	89.3%	68.8–100%	20
Nopal fruit juice	91.8%	64.9–100%	20

**Note:** <sup>a</sup>The group average  $\pm$  standard deviation

## Results

### Joint Range of Motion (ROM)

Joint range of motion (ROM) was measured at baseline and after 8 weeks for the vertical weight-bearing axis from the neck to the knees and for the shoulders (Table 3). Analysis of the inclinometry data showed improvements in the NFJ group that were not seen in the placebo group. The specific improvements in joint range of motion were most robust for the cervical, thoracic, and lumbar regions, where the improvements were statistically significant

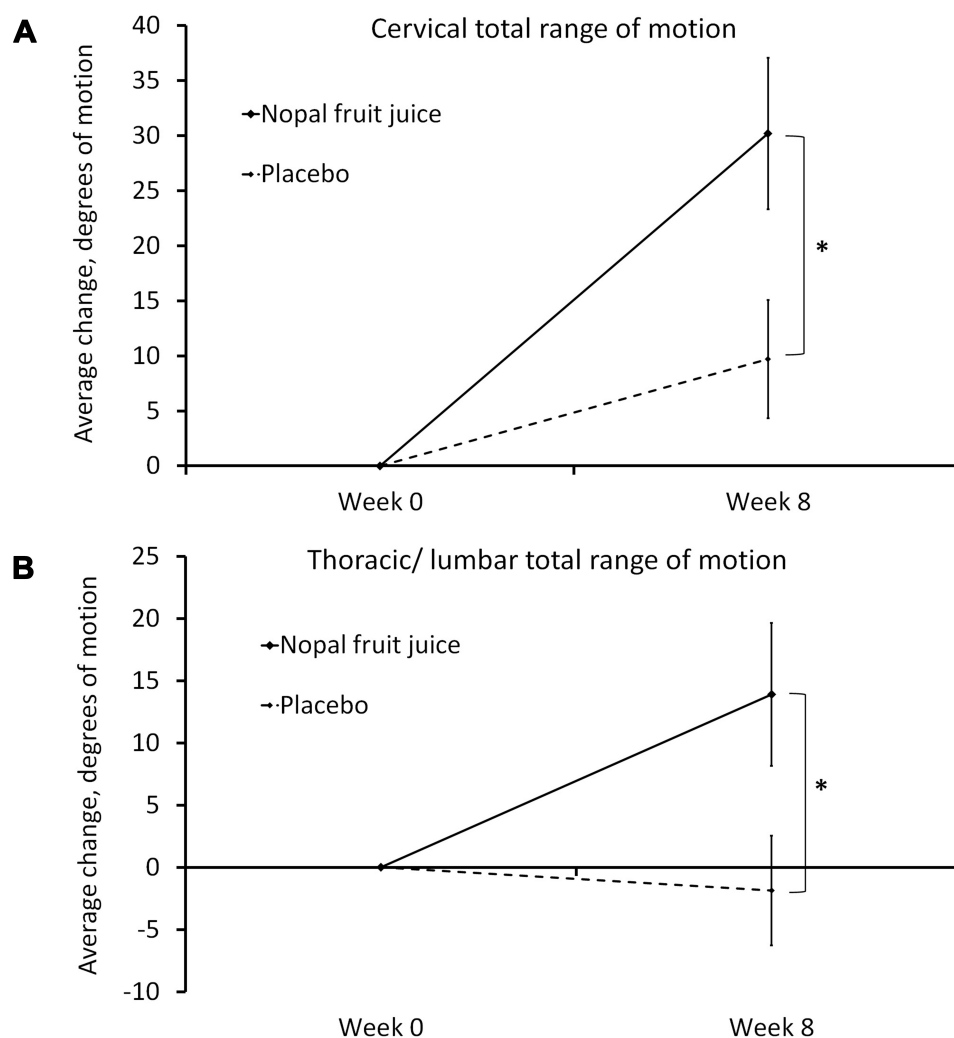
between the two groups (Figure 1). For mobility in the cervical region, improvements were seen in the NFJ group for all 3 measures: lateral ROM, flexion/extension, and rotation. The difference in cervical lateral motion between the two groups reached a high level of statistical significance ( $P<0.006$ ). The difference in total cervical ROM between the two groups was statistically significant ( $P<0.03$ , Figure 2A). Thoracic and lumbar ranges of motion were improved in the NFJ group, where the difference in total thoracic/lumbar range of motion reached

**Table 3** Joint Range of Motion (ROM)

Motion	Product	Baseline <sup>a</sup>	Week 8 <sup>a</sup>	P-value Within Group <sup>b</sup>	P-value Between Groups <sup>c</sup>
Cervical Flexion/Extension	Placebo	96.1 ± 3.11	98.9 ± 2.93	NS	NS
	Nopalea	85.3 ± 3.65	92.8 ± 3.89	*	
Cervical Lateral Motion	Placebo	59.9 ± 4.28	60.4 ± 4.09	NS	##
	Nopalea	52.4 ± 3.13	62.8 ± 3.37	**	
Cervical Rotation	Placebo	143.4 ± 3.41	149.7 ± 4.20	(*)	NS
	Nopalea	124.2 ± 4.63	136.5 ± 4.27	**	
Thoracic Rotation	Placebo	36.5 ± 2.54	37.5 ± 2.57	NS	(#)
	Nopalea	34.7 ± 3.01	41.7 ± 3.57	*	
Lumbar Rotation	Placebo	27.6 ± 2.98	26.3 ± 2.56	NS	NS
	Nopalea	21.7 ± 2.65	24.9 ± 2.88	NS	
Lumbar Flexion/Extension	Placebo	72.3 ± 4.01	70.7 ± 4.57	NS	NS
	Nopalea	62.9 ± 2.90	68.2 ± 3.79	NS	
Sacral Hip Flexion/Extension	Placebo	51.7 ± 3.35	55.2 ± 2.76	NS	NS
	Nopalea	50.2 ± 4.88	56.2 ± 5.96	(*)	
Left Shoulder Flexion/Extension	Placebo	229.3 ± 6.61	234.2 ± 4.96	NS	NS
	Nopalea	212.6 ± 4.66	219.9 ± 5.77	NS	
Right Shoulder Flexion/Extension	Placebo	224.3 ± 6.55	231.2 ± 5.48	NS	NS
	Nopalea	207.4 ± 5.40	221.9 ± 6.04	*	
Left Shoulder Abduction/Adduction	Placebo	175.9 ± 3.13	184.3 ± 4.15	*	NS
	Nopalea	169.4 ± 4.92	176.9 ± 5.41	*	
Right Shoulder Abduction/Adduction	Placebo	167.4 ± 6.09	185.9 ± 6.23	*	NS
	Nopalea	170.4 ± 4.64	177.9 ± 5.36	(*)	
Left Hip Flexion/Extension	Placebo	112.2 ± 3.16	114.3 ± 3.46	NS	NS
	Nopalea	99.6 ± 4.07	104.0 ± 4.40	NS	
Right Hip Flexion/Extension	Placebo	114.6 ± 3.37	115.7 ± 3.63	NS	NS
	Nopalea	100.4 ± 3.66	105.2 ± 4.60	NS	
Left Knee Flexion/Extension	Placebo	125.2 ± 2.97	128.3 ± 2.74	(*)	NS
	Nopalea	124.0 ± 2.48	123.5 ± 3.47	NS	
Right Knee Flexion/Extension	Placebo	121.9 ± 3.99	126.9 ± 2.64	NS	(#)
	Nopalea	121.4 ± 3.21	118.4 ± 5.48	NS	

**Notes:** <sup>a</sup>The average ± standard deviation of degrees of motion was recorded by dual digital inclinometry at baseline and after 8 weeks. <sup>b</sup>This column shows within-subject statistical analysis, where NS: Not significant, (\*)  $P<0.1$ , \*  $P<0.05$ , and \*\* $P<0.01$ . <sup>c</sup>This column shows between-group statistical analysis, where NS: Not significant, (#)  $P<0.1$ , #  $P<0.05$ ; ## $P<0.01$ .





**Figure 1** Change in joint mobility.

**Notes:** Data reflects the physical degrees of motion and is shown as the group averages  $\pm$  standard error of mean for the Nopal fruit juice group (solid lines) and the placebo group (dashed lines), for the sum of the range of motion for the three cervical motions flexion/extension, lateral motion and rotation (**A**) and the sum of the range of motions for thoracic and lumbar rotation and lumbar flexion/extension (**B**). The average improvement in the Nopal fruit juice group was statistically significant when compared to the placebo group, as indicated by \* ( $P < 0.05$ ).

statistical significance between the two groups ( $P < 0.04$ , Figure 2B). Changes to the mobility of the hips, knees and shoulders did not reveal a significant benefit from NFJ consumption; however, it is possible that a longer study duration, or a higher dose of NFJ may have showed a difference.

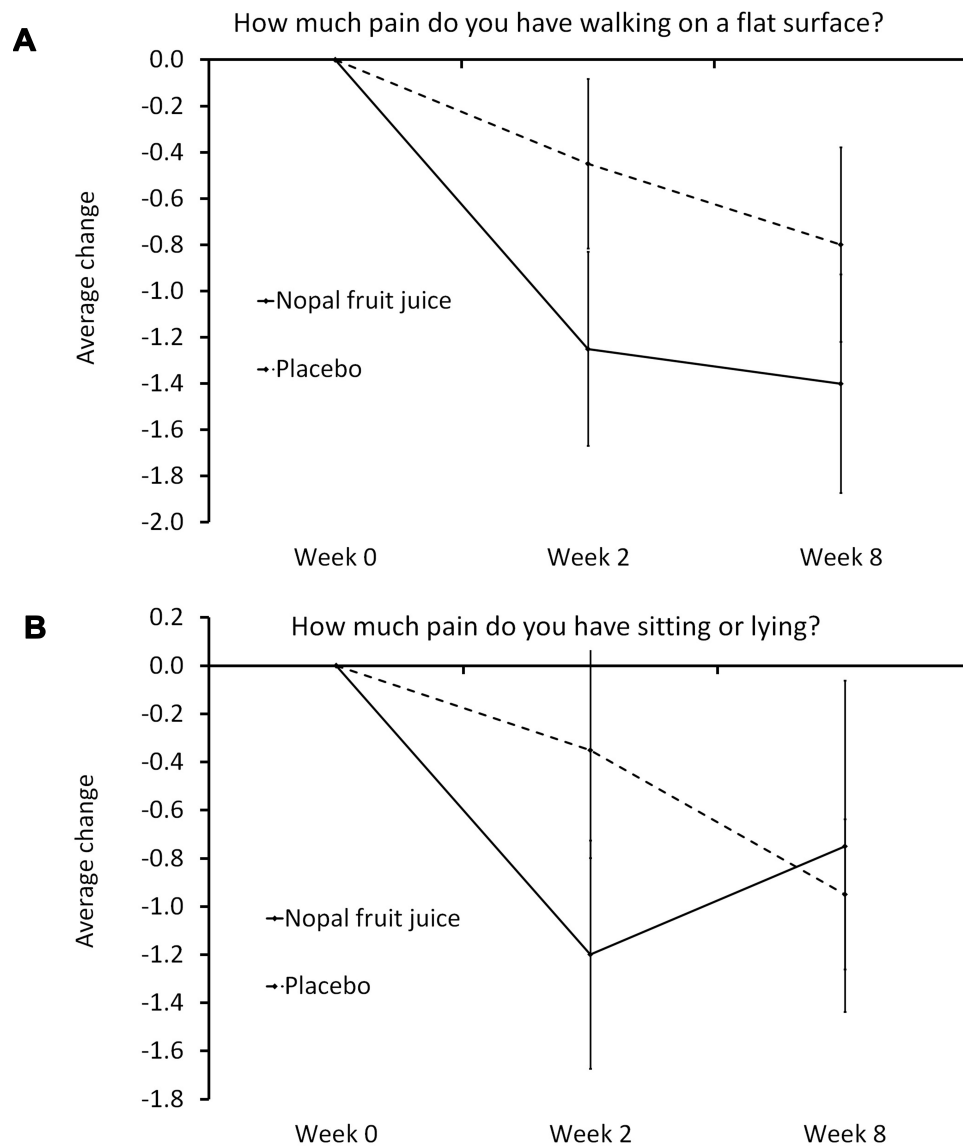
## Pain

The questionnaire-based data collection included several questions pertaining to pain interfering with physical functioning (Figure 2). The average change in scores for the NFJ group showed that pain interfered less with walking on a flat surface (Figure 2A) as well as sitting or lying (Figure 2B) than the average change in the placebo group.

The differences between the NFJ and placebo groups were not statistically significant.

## Improved Wellness Scores

Consumption of NFJ was associated with several specific, though not statistically significant, improvements in different aspects of wellness (Figure 3). Pain interfered less with daily activities for people in the NFJ group than people in the placebo group; the change was not significant ( $P < 0.4$ , Figure 3A). People in the NFJ group relied less on medications than in the placebo group, reaching a statistical trend ( $P < 0.06$ , Figure 3B). Breathing placed less strain on people in the NFJ group (Figure 3C).



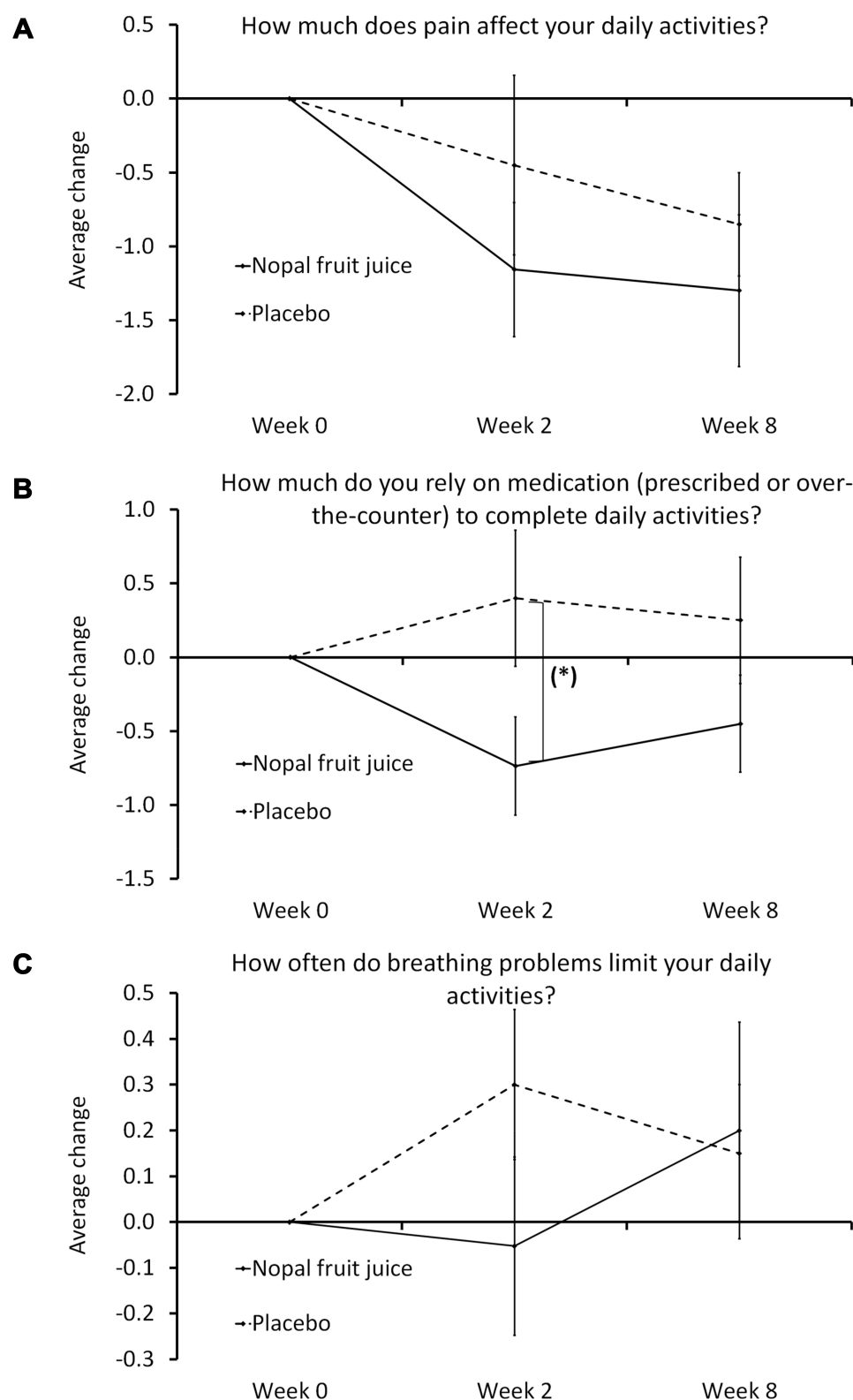
**Figure 2** Change in pain interfering with physical functioning.

**Notes:** Data is shown as the group averages  $\pm$  standard error of mean for the Nopal fruit juice group (solid lines) and the placebo group (dashed lines), for the questions “pain when walking on flat surface” (A) and “pain when sitting or lying” (B). The average change in the Nopal fruit juice group was larger at 2 weeks than the placebo group, and was further reduced at 8 weeks for “pain when walking on flat surface”. The differences between the two groups did not reach statistical significance.

## Change in Serum Cytokine Levels

Serum levels for 11 pro- and anti-inflammatory cytokines were tested. As expected in a fairly healthy population only 5 of the 11 cytokines were detectable in serum (Table 4). Six cytokines were below levels of detection, including Interleukin-1 receptor antagonist-a (IL-1ra), Interleukin-1 beta (IL-1 $\beta$ ), Interleukin-6 (IL-6), Interleukin-9 (IL-9), Interleukin-32, and Tumor Necrosis Factor-alpha (TNF- $\alpha$ ). Two cytokines, namely Macrophage Inflammatory Protein-1 beta (MIP-1 $\beta$ ) and Regulated on Activation, Normal T cell Expressed and Secreted (RANTES, CCL5), showed similar

mild increases over the 8-week study in both the Nopal fruit juice group and the placebo group, with no significant differences between the Nopal fruit juice group and the placebo group. Two cytokines showed decreases in both groups, namely Monocyte Chemoattractant Protein-1 (MCP-1) and Interferon gamma-induced protein 10 (IP-10). The exception was the eosinophil chemotactic cytokine Eotaxin (CCL11), where a decrease was seen over the 8 weeks in the Nopal fruit juice group, in contrast to a mild increase in the placebo group. The difference reached statistical significance at 8 weeks ( $P < 0.048$ , Figure 4).



**Figure 3** Daily activities.

**Notes:** Data is shown as the group averages  $\pm$  standard error of mean for the Nopal fruit juice group (solid lines) and the placebo group (dashed lines), for the questions "pain affecting daily activities" (A), "rely on medications to complete daily activities" (B), and "breathing problems limiting daily activities" (C). Regarding pain (A), the average change in the NFJ group was larger at 2 weeks than the placebo group and was further reduced at 8 weeks; the difference between the two groups did not reach statistical significance. Regarding use of medication (B), the average change at 2 weeks reached a statistical trend ( $P < 0.06$ , indicated by (\*)), and the average change for breathing problems also reached a statistical trend at 2 weeks ( $P < 0.1$ , indicated by (\*)).



**Table 4** Serum Cytokine Levels (Pg/mL)

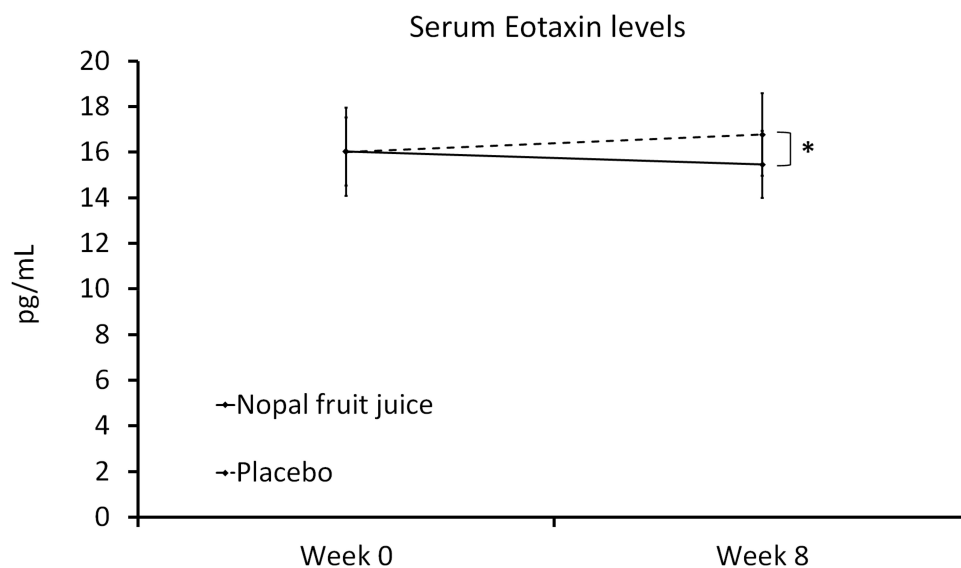
	Placebo			Nopal Fruit Juice			P-value <sup>a</sup>
	N	Baseline	8 Weeks	N	Baseline	8 Weeks	
MIP-1 $\beta$	20	4.37 $\pm$ 0.35	5.27 $\pm$ 0.37	20	4.89 $\pm$ 0.38	6.15 $\pm$ 0.37	NS
RANTES	20	2210 $\pm$ 98	4021 $\pm$ 316	20	2079 $\pm$ 166	3640 $\pm$ 346	NS
MCP-1	20	3.16 $\pm$ 0.48	2.45 $\pm$ 0.46	20	3.23 $\pm$ 0.45	2.38 $\pm$ 0.31	NS
IP-10	20	126.2 $\pm$ 28.6	103.0 $\pm$ 14.2	20	87.67 $\pm$ 10.29	87.48 $\pm$ 14.37	NS
Eotaxin	19 <sup>b</sup>	16.01 $\pm$ 1.94	16.77 $\pm$ 1.81	20	16.04 $\pm$ 1.49	15.46 $\pm$ 1.47	0.047

**Notes:** <sup>a</sup>P-value between the groups, using 2-tailed unpaired t-test. NS: Not significant, P>0.05. <sup>b</sup>One study participant was removed from this analysis due to lack of compliance during the 8-week study with respect to medication that may have influenced this biomarker.

## Change in C-Reactive Protein

Serum levels for C-reactive protein (CRP) was tested (Table 5). The group averages were comparable for the two groups at study start. After 8 weeks, there was a mild difference in CRP levels between the placebo and NFJ groups, with an average lower level in the NFJ group, but it did not reach statistical significance. Based on our previous study on NFJ,<sup>30</sup> we performed a sub-group analysis of the CRP levels for study participants with CRP levels below 3.0 mg/L at study start. This sub-group analysis did not show a difference between the two groups. Based on the interpretive guide for CRP levels in cardiovascular health, where people with CRP levels below 1.0 mg/L have a low risk of heart disease, sub-group analysis was performed to remove data from

participants with CRP levels at or below 1.0 mg/L. In the sub-group of study participants with CRP levels above 1.0 mg/L at baseline, there was an average decrease in the NFJ group, where the difference between placebo and NFJ reached a statistical trend (P=0.06). Finally, based on the interpretive guide for the CRP levels in cardiovascular health, where people with CRP levels above 9.9 mg/L have a very high risk of heart disease, analysis of the CRP levels for study participants with CRP levels at baseline above 1.0, and those with CRP levels at baseline below 10, was performed. This showed a reduction in CRP levels in the NFJ group, in contrast to an increase in the placebo group, where the difference reached statistical significance (P<0.015).

**Figure 4** Serum Eotaxin levels.

**Notes:** Data is shown as the group averages  $\pm$  standard error of mean for the Nopal fruit juice group (solid line) and the placebo group (dashed line), for the serum level of Eotaxin, provided in picogram/milliliter (pg/mL). A decrease in serum Eotaxin levels was seen for the Nopal fruit juice group over the 8 weeks of study participation, in contrast to a mild increase in serum Eotaxin levels seen for the placebo group. The difference in the change in Eotaxin levels between the two groups reached statistical significance (P<0.047, indicated by \* on the graph).

**Table 5** Serum C-Reactive Protein Levels (Mg/L)

	Placebo			Nopal Fruit Juice			P-value <sup>a</sup>
	N	Baseline	8 Weeks	N	Baseline	8 Weeks	
All study participants	20	2.84 ± 0.92	2.72 ± 0.72	20	2.41 ± 0.64	2.09 ± 0.55	0.494
CRP <3.0 mg/L at baseline	16	1.18 ± 0.18	1.57 ± 0.23	14	0.93 ± 0.18	1.04 ± 0.15	0.831
CRP >1.0 mg/L at baseline	13	4.08 ± 1.29	3.72 ± 1.00	11	3.96 ± 0.93	3.11 ± 0.90	0.060
1.0 mg/L < CRP at baseline <10.0 mg/L	12	2.95 ± 0.68	3.86 ± 1.08	10	3.26 ± 0.68	2.29 ± 0.39	0.013

**Note:** <sup>a</sup>P-value between the groups, using 2-tailed unpaired t-test.

## Discussion

Preserving the ability to function and complete daily activities is important in healthy ageing and prolongs the time a person can maintain non-institutionalized independence, as well as reduces comorbid factors of declining health. Physical mobility plays a pivotal role for quality of life and has a preventive role in delaying the process of ageing. Declining mobility is often associated with chronic muscle and joint pain, and pharmaceutical pain management is associated with unwanted side effects. In contrast, natural food-based compounds offer methods to not only reduce pain but also to improve functionality, through reducing inflammation and supporting regenerative functions.

In the study reported here, we observed improved joint mobility in the group consuming Nopal cactus fruit juice (NFJ), when compared to the placebo group, most noticeably improved range of motion of neck, upper back, and lower back including the hips. The method we used for the measurements of joint mobility allowed evaluation of multiple areas of the body, especially the vertical weight-bearing axis from the neck to the knees, as well as the shoulders. This is different from a traditional study of osteoarthritis of the knee or hip where only one joint is evaluated, typically by simple goniometry. Our chosen methodology evaluates general mobility as a combination of joint and muscle function, as a study participant is instructed to perform complex movements, which are then recorded digitally. The results have provided objective data on improvements when consuming NFJ, compared to placebo.

The consumption of NFJ did not have a significant effect on pain scores beyond the changes seen in the placebo group, but noticeably, in the NFJ group pain interfered less with the ability to perform multiple daily activities. Furthermore, people consuming NFJ reported reduced reliance on pain medication to complete daily activities, which taken in combination supports the association of NFJ consumption with improved physical functioning and

wellbeing. The results suggest that people consuming NFJ were able to be more physically active and may have increased their activity levels until they reached a similar pain level they were used to before consuming NFJ; therefore, a future follow-up study will need to track activity levels. An additional observation was that breathing problems interfered less with daily activities in the NFJ group than in the placebo group. This warrants further study, for example in a population that frequently use inhalers to complete physical activities, combined with markers associated with airway inflammation. This was further emphasized by the statistically significant change in serum levels of Eotaxin, a biomarker associated with eosinophil recruitment to inflamed tissue, including lung tissue during asthma and bronchitis,<sup>34</sup> and related to severity during treatment.<sup>35</sup>

The serum levels of C-reactive protein (CRP) were analyzed and showed a greater reduction in the NFJ group than in the placebo group, however the difference between the two groups did not reach statistical significance. When subgroup analysis was performed, focusing on people with baseline CRP levels above 1.0 mg/L, a statistical trend was seen. When also removing data from people with very high CRP levels of 10 mg/L and higher, suggestive of a passing infection or recent injury irrelevant to the chronic pain and limited activity levels, and focusing on people with mild-to-moderate elevation of CRP at baseline (1.0–9.9 mg/L), the difference between the changes in CRP for the NFJ group and the placebo group was statistically significant. This suggests that in a population with mild to moderate inflammation, direct anti-inflammatory properties of NFJ may have helped improve the CRP levels and possibly contributed to the improved joint function and mobility.

Whereas the questionnaire-based data collection showed some interesting trends, the objective data for joint mobility and CRP levels showed definitive improvements associated with NFJ consumption, that were not seen in the placebo group. One limitation from the study

reported here is that the screening criteria focused on moderate chronic pain, rather than limited mobility. Further work is needed to document modes of action involved in improved joint function and should also include tracking of physical activity for example by a fitness tracker (wrist or phone) to help evaluate whether the improvements translate to increased physical activity and intensity.

## Conclusion

Consumption of Nopal fruit juice (NFJ) for 8 weeks was associated with statistically significant improvements in neck and back mobility and range of motion when compared to the placebo group, allowing participants in the NFJ group to be more physically active. In the NFJ group pain placed less limitations on daily activities, and several daily activities became easier, including walking, sitting, and lying. In the subgroup with CRP levels between 1 and 10 mg/L at baseline a reduction in CRP levels was significantly more reduced in the NFJ group than the placebo group. Taken together, the results suggest that NFJ provided support of joint mobility and physical functioning, likely via antioxidant protection and anti-inflammatory properties of NFJ.

## Acknowledgments

The study was conducted at NIS Labs, an independent contract research laboratory specializing in natural-product research. I thank Dina Cruickshank, Allison Young, and Nathan Mendoza-Connell for conscientious study management. The study was sponsored by Trivita LLC.

## Disclosure

Gitte Jensen reports that Trivita sponsored the work. The author reports no other potential conflicts of interest in this work.

## References

- Wu W, Ding D, Zhao Q, et al. Medium-to-High Late-Life Physical Activity Is Associated with Lower Risk of Incident Dementia: the Shanghai Aging Study. *J Alzheimers Dis*. 2019. doi:10.3233/JAD-190937
- Hajek A, Brettschneider C, Scherer M, et al. Needs and health care costs in old age: a longitudinal perspective: results from the AgeMooDe study. *Aging Ment Health*. 2019;8:1–6.
- Alwin J, Karlson BW, Husberg M, Carlsson P, Ekerstad N. Societal costs of informal care of community-dwelling frail elderly people. *Scand J Public Health*. 2019;11:1403494819844354.
- Ignasiak Z, Sebastjan A, Kaczorowska A, Skrzek A. Estimation of the risk of the frailty syndrome in the independent-living population of older people. *Aging Clin Exp Res*. 2020;1. doi:10.1007/s40520-019-01439-5
- Brach JS, VanSwearingen JM, Gil A, et al. Program to improve mobility in aging (PRIMA) study: methods and rationale of a task-oriented motor learning exercise program. *Contemp Clin Trials*. 2019;Dec:105912.
- de Mello RGB, Dalla Corte RR, Gioscia J, Moriguchi EH. Effects of Physical Exercise Programs on Sarcopenia Management, Dynapenia, and Physical Performance in the Elderly: A Systematic Review of Randomized Clinical Trials. *J Aging Res*. 2019;20(2019):1959486.
- Higueras-Fresnillo S, Cabanas-Sánchez V, García-Esquinas E, Rodríguez-Artalejo F, Martínez-Gómez D. Physical activity attenuates the impact of poor physical, mental, and social health on total and cardiovascular mortality in older adults: a population-based prospective cohort study. *Qual Life Res*. 2018;27(12):3293–3302. doi:10.1007/s11136-018-1974-5
- Belczak CE, de Godoy JM, Belzack SQ, Ramos RN, Caffaro RA. Obesity and worsening of chronic venous disease and joint mobility. *Phlebology*. 2014;29(8):500–504. doi:10.1177/0268355513492510
- Li JS, Tsai TY, Clancy MM, Li G, Lewis CL, Felson DT. Weight loss changed gait kinematics in individuals with obesity and knee pain. *Gait Posture*. 2019;68:461–465. doi:10.1016/j.gaitpost.2018.12.031
- Hsu CC, Tsai HH, Fu TC, Wang JS. Exercise Training Enhances Platelet Mitochondrial Bioenergetics in Stroke Patients: A Randomized Controlled Trial. *J Clin Med*. 2019;11(12):8.
- Briggs AM, Cross MJ, Hoy DG. Musculoskeletal Health Conditions Represent a Global Threat to Healthy Aging: A Report for the 2015 World Health Organization World Report on Ageing and Health. *Gerontologist*. 2016;56(Suppl 2):S243–S255.
- Luan YY, Yao YM. The Clinical Significance and Potential Role of C-Reactive Protein in Chronic Inflammatory and Neurodegenerative Diseases. *Front Immunol*. 2018;9:1302. doi:10.3389/fimmu.2018.01302
- Han MH, Nam JH, Noh E, Lee EK. Gastrointestinal risk of non-steroidal anti-inflammatory drugs and gastroprotective agents used in the treatment of osteoarthritis in elderly patients: A nationwide retrospective cohort study. *Int J Clin Pharmacol Ther*. 2019;57(11):531–541. doi:10.5414/CP203377
- Bakhriansyah M, Souverein PC, van den Hoogen MWF, de Boer A, Klungel OH. Risk of Nephrotic Syndrome for Non-Steroidal Anti-Inflammatory Drug Users. *Clin J Am Soc Nephrol*. 2019;14(9):1355–1362. doi:10.2215/CJN.14331218
- Briggs AM, Cross MJ, Hoy DG. Musculoskeletal Health Conditions Represent a Global Threat to Healthy Aging: A Report for the 2015 World Health Organization World Report on Ageing and Health. *Gerontologist*. 2016;56(Suppl 2):S243–S255. doi:10.1093/geront/gnw002
- Henrotin Y, Malaise M, Wittoek R, et al. Curcuma longa extract is efficient on knee osteoarthritis pain: a double-blind multicenter randomized placebo controlled three-arm study. *Arthritis Res Ther*. 2019;21(1):179. doi:10.1186/s13075-019-1960-5
- Hashemzadeh K, Davoudian N, Jaafari MR, Mirfeizi Z. The Effect of Nanocurcumin on the Improvement Symptoms of Knee Osteoarthritis: A Randomized Clinical Trial. *Curr Rheumatol Rev*. 2019;23.
- Logozzi M, Di Raimo R, Mizzone D, Fais S. Anti-aging and anti-tumor effect of FPP® supplementation. *Eur J Transl Myol*. 2020;30(1):8905. doi:10.4081/ejtm.2019.8905
- Jensen GS, Drapeau C, Lenninger M, Benson KF. Clinical Safety of a High Dose of Phycocyanin-Enriched Aqueous Extract from *Arthrospira (Spirulina) platensis*: results from a Randomized, Double-Blind, Placebo-Controlled Study with a Focus on Anticoagulant Activity and Platelet Activation. *J Med Food*. 2016;19(7):645–653. doi:10.1089/jmf.2015.0143
- Jensen GS, Ager DM, Redman KA, Mitzner MA, Benson KF, Schauss AG. Pain reduction and improvement in range of motion after daily consumption of an Acai (*Euterpe oleracea* Mart.) pulp-fortified polyphenolic-rich fruit and berry juice blend. *J Med*. 2011;2(7–8):702–711.

21. Benson\* KF, Ager\* DM, Landes B, Aruoma OI, Jensen GS. Improvement of joint Range of Motion (ROM) and reduction of chronic pain after consumption of an ergothioneine-containing nutritional supplement. *Prev Med.* **2012**;54:S83–S89. doi:10.1016/j.ypmed.2012.02.001
22. Jensen GS, Attridge VA, Benson KF, Beaman JL, Carter SG, Ager D. Consumption of dried apple peel powder increases joint function and range of motion. *J Med Food.* **2014**;17(11):1204–1213. doi:10.1089/jmf.2014.0037
23. Li G, Meng X, Zhu M, Li Z. Research Progress of Betalain in Response to Adverse Stresses and Evolutionary Relationship Compared with Anthocyanin. *Molecules.* **2019**;24(17):pii: E3078. doi:10.3390/molecules24173078
24. Rahimi P, Mesbah-Namin SA, Ostadrahimi A, Abedimanesh S, Separham A, Asghary Jafarabadi M. Effects of betalains on atherogenic risk factors in patients with atherosclerotic cardiovascular disease. *Food Funct.* **2019**;10(12):8286–8297. doi:10.1039/C9FO02020A
25. Raish M, Ahmad A, Ansari MA, et al. Beetroot juice alleviates isoproterenol-induced myocardial damage by reducing oxidative stress, inflammation, and apoptosis in rats. *Biotech.* **2019**;9(4):147. doi:10.1007/s13205-019-1677-9
26. Ríos-Hoyo A, Romo-Araiza A, Meneses-Mayo M, Prehispanic Functional G-SG. Foods and Nutraceuticals in the Treatment of Dyslipidemia Associated to Cardiovascular Disease: a Mini-Review. *Int J Vitam Nutr Res.* **2017**;87(1–2):58–98. doi:10.1024/0300-9831/a000290
27. Angulo-Bejarano PI, Mdr G-G, Valverde ME, Paredes-López O. Nopal (*Opuntia* spp.) and its Effects on Metabolic Syndrome: new Insights for the Use of a Millenary Plant. *Curr Pharm Des.* **2019**;25(32):3457–3477. doi:10.2174/1381612825666191010171819
28. Sánchez-Tapia M, Aguilar-López M, Pérez-Cruz C, et al. Nopal (*Opuntia ficus indica*) protects from metabolic endotoxemia by modifying gut microbiota in obese rats fed high fat/sucrose diet. *Sci Rep.* **2017**;7(1):4716. doi:10.1038/s41598-017-05096-4
29. Guevara-Arauz JC, Órnelas Paz JDJ, Mendoza SR, Guerra RES, Paz Maldonado LMT, González DJP. Biofunctional activity of tortillas and bars enhanced with nopal. Preliminary assessment of functional effect after intake on the oxidative status in healthy volunteers. *Chem Cent J.* **2011**;5(1):10. doi:10.1186/1752-153X-5-10
30. Guevara-Cruz M, Tovar AR, Aguilar-Salinas CA, et al. A dietary pattern including nopal, chia seed, soy protein, and oat reduces serum triglycerides and glucose intolerance in patients with metabolic syndrome. *J Nutr.* **2012**;142(1):64–69.
31. Jensen GS. The Effect of Consumption of a Nopal Cactus Fruit Juice on C-Reactive Protein Levels in Healthy Adults: results from a Randomized, Double-Blind, Controlled Clinical Pilot Study. *Eur J Nutrition Food Safety.* **2015**;6(1):1–9. doi:10.9734/EJNFS/2016/18218
32. Preamble to the Constitution of the World Health Organization as adopted by the International Health Conference, New York: World Health Organization, 19-22 June, 1946 Available from: <http://www.who.int/suggestions/faq/en/>. Accessed November 18, 2020.
33. Hamilton DE, Jensen GS. Pain reduction and improved vascular health associated with daily consumption of an anti-inflammatory dietary supplement blend. *J Pain Res.* **2019**;12:1497–1508. doi:10.2147/JPR.S189064
34. Pease JE, Williams TJ. Eotaxin and asthma. *Curr Opin Pharmacol.* **2001**;1(3):248–253. doi:10.1016/S1471-4892(01)00044-3
35. Tateno H, Nakamura H, Minematsu N, et al. Plasma eotaxin level and severity of asthma treated with corticosteroid. *Respir Med.* **2004**;98(8):782–790. doi:10.1016/j.rmed.2004.01.005

## Clinical Interventions in Aging

Dovepress

## Publish your work in this journal

Clinical Interventions in Aging is an international, peer-reviewed journal focusing on evidence-based reports on the value or lack thereof of treatments intended to prevent or delay the onset of maladaptive correlates of aging in human beings. This journal is indexed on PubMed Central, MedLine, CAS, Scopus and the Elsevier

Bibliographic databases. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <https://www.dovepress.com/clinical-interventions-in-aging-journal>