Jaja-Chimedza *et al.*
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The effects of an SPM-enriched marine oil and bioavailable curcumin combination on inflammation-associated discomfort in generally healthy individuals: a virtual open-label pilot study

Asha Jaja-Chimedza[1*], Steven Hirsh[1,2], Dainian Bruce[2], Tony Bou-Sliman[2], Steven Joyal[1] and Andrew G. Swick[1]

Abstract

Background: Acute inflammation is the body's immediate and well-coordinated response to injury, which if not resolved can lead to a state of chronic inflammation and is an important component of aging-associated pathologies and chronic diseases. Resolution of inflammation has been shown to be highly regulated by several endogenous specialized pro-resolving mediators which are metabolized from dietary omega-3 and -6 fatty acids. The aim of this pilot study was to validate the use of a combination of a specialized pro-resolving (SPM) enriched marine oil supplement and a highly bioavailable curcumin supplement to reduce pain/discomfort in healthy adults.

Methods: This was a virtual (remote), single-arm open-label study in healthy adults with mild to moderate pain. Twenty-nine individuals were provided with an SPM-enriched marine oil supplement (enriched for three SPM precursors) and a highly bioavailable curcumin supplement to be taken daily for 60 days. The Short-Form McGill Pain Questionnaire (SF-MPQ), Short-Form 36 (SF-36) Health Survey and Medical Symptoms Questionnaire (MSQ) were used to evaluate safety, tolerability and efficacy in reducing pain/discomfort of inflammation.

Results: The SF-MPQ showed significant improvement in all aspects of the questionnaire, especially in total pain, pain intensity and pain severity within 30 days of supplementation. Significant improvements were also observed in the physical health domain of the SF-36 health survey, particularly in the areas of pain and physical functioning at both days 30 and 60. No adverse events related to the study materials were reported during the study.

Conclusion: In conclusion, the combination of anti-inflammatory and pro-resolving supplements may provide a complementary approach for targeting pain/discomfort associated with inflammation.

Trial registration: ClinicalTrials.gov, NCT04819646. Registered 29 March 2021 – Retrospectively registered.

Keywords: Inflammation, Pro-resolving mediators, Curcumin, Pain/discomfort

Background

Acute inflammation is the initial process by which the human body responds to injury or pathogenic invasion, resulting in a cascade of reactions that mobilize defensive cells to target and remove the insult. This coordinated

*Correspondence: ajaja@lifeextension.com

[1] Life Extension, 3600 West Commercial Blvd, Fort Lauderdale, FL 33309, USA
Full list of author information is available at the end of the article

process involves the activation of inflammatory pathways, stimulating the production of pro-inflammatory mediators and the recruitment of neutrophils, which act to destroy the pathogens. Once the injury or infection is cleared, the process of "resolution" begins, turning off the inflammatory response and returning the injured site to a state of homeostasis for prevention of further damage. This is an active and highly coordinated process that involves halting the infiltration of neutrophils and clearing up inflammatory debris through several mediated processes [1, 2]. Unresolved or uncontrolled inflammation can lead to a state of chronic and excessive inflammation which is a primary component of chronic diseases and aging-associated pathologies. Many of these age-associated inflammatory diseases include arthritis, metabolic syndrome, vascular diseases and neurological diseases [3, 4].

Resolution of inflammation is an active process, involving a class of endogenous lipid mediators known as specialized pro-resolving mediators (SPMs) that are generated during the acute inflammatory process [5]. They are produced through the enzymatic conversion of long-chain polyunsaturated fatty acids, namely arachidonic acid (AA), eicosapentaenoic acid (EPA) and docoahexaenoic acid (DHA). The primary classes of these compounds are lipoxins which are derived from AA, E-series resolvins which are derived from EPA, and maresins, protectins and D-series resolvins which are all synthesized from DHA. SPMs act not by blocking the inflammatory process, but by promoting the termination of the inflammatory process and facilitating the healing process [5, 6]. Clinical studies have demonstrated that supplementation with omega-3 fatty acids increase plasma levels of SPMs and may hasten the resolution of acute inflammation [7–10]. In a preclinical model of inflammation, supplementation with omega-3 fatty acids in a concentrated fish oil reduced inflammatory pain likely through increased levels of resolvins and modulation of tumour necrosis factor-alpha (TNF-α), suggesting that omega-3s could potentially be used for treating pain associated with inflammatory conditions [11].

Curcumin, along with demethoxycurcumin and bisdemethoxycurcumin (collectively termed curcuminoids) are the primary bioactive constituents found in the culinary herb turmeric, which has been used in traditional medicine in several Asian countries [12, 13]. Curcumin, the most abundant of the curcuminoids, has been well-studied for its many benefits including anti-inflammatory and antioxidant properties, leading to the development of several supplements. Despite the extensive anti-inflammatory benefits observed in preclinical and clinical studies, one major challenge of curcumin is its poor bioavailability caused by rapid metabolism and elimination [14, 15]. Several successful technologies have been developed to improve the bioavailability and ultimately the therapeutic efficacy of curcumin and its curcuminoids [14, 16, 17]. A food-grade technology, with curcuminoids encapsulated in a fenugreek dietary fiber, showed enhanced bioavailability of free curcuminoids as well as safety in healthy individuals [18, 19]. This bioavailable form also showed that supplementation using a low dose (400 mg once daily) significantly reduced pain and stiffness, and improved physical function in individuals with knee osteoarthritis [20].

The purpose of this study was to validate the use of the combination of the anti-inflammatory benefits of a highly bioavailable curcumin supplement and the pro-resolving benefits of an SPM enriched marine oil in reducing pain/discomfort associated with inflammation in healthy individuals. This combination of ingredients aims to provide a complementary mechanism by targeting the different stages of the inflammatory process: reduction of inflammation via the anti-inflammatory effects of curcumin and the resolution of inflammation via the pro-resolving effects of the SPMs, thereby relieving some discomfort and/or pain associated with inflammation. This study was a completely virtual (remote) study, with individuals taking both supplements for 60 days and reporting how they felt via questionnaires administered by e-mail throughout the study.

Methods

Study supplements

The study used a combination of two retail supplements Pro-Resolving Mediators (#02223) and Curcumin Elite™ Turmeric Extract (#02467), provided by Life Extension®. The Pro-Resolving Mediators softgels each contain 500 mg of a marine lipid concentrate, providing 300 µg of SPM precursors including 18-hydroxyeicosapentaenoic acid (18-HEPE), 17-hydroxydocosahexaenoic acid (17-HDHA), & 14-hydroxydocosahexaenoic acid (14-HDHA). 18-HEPE is an E-series resolvin precursor that is converted to resolvins RvE1-E3, 17-HDHA is a D-series resolvin precursor that is converted to resolvins RvD1-D6, and 14-HDHA is a maresin precursor, derived from DHA. The Curcumin Elite™ Turmeric Extract capsules each contain 500 mg Curcumin Elite™ Proprietary CGM Blend, providing 40% curcuminoids (200 mg) and 3% turmerones (15 mg) [from turmeric (rhizome)], 30% galactomannans (150 mg) [from fenugreek (seed)].

Participants

Thirty-one (31) healthy individuals (18 females and 13 males; age range 35–72 yrs) were enrolled to receive the marine oil and curcumin supplements for a 60-day treatment period. Participants were recruited based on the

following inclusion criteria: both males and females, 35–75 years old with very mild to moderate body pain [based on the Short Form-36 (SF-36) Health Survey] during the previous 4 weeks and who have not taken any nutritional supplements containing components of the study products for at least 14 days prior to baseline and for the duration of the study. Individuals were excluded from the study if they were taking any medication or dietary supplement for pain or inflammation, or were diagnosed with a pain related disorder or any other clinically significant condition such as diabetes mellitus, eating disorder, cardiovascular disease or gastrointestinal disease. During the study, participants were asked to maintain their regular activity and usual diet.

Study design and outcome measures

This was a virtual, open-label, single-arm study to evaluate the effects of a combination of marine oil and curcumin on inflammation/discomfort and overall well-being in individuals who are generally healthy. As a virtual study, all visits with participants were remote (at-home), occurring via videoconference at screening/baseline, Day 1, Day 30 and Day 60, and all questionnaires were administered by e-mail. This study was conducted to also assess the feasibility of running an all-virtual study. The study was registered under ClinicalTrials.gov identifier: NCT04819646 (https://clinicaltrials.gov/ct2/show/NCT04819646). The study protocol was conducted with approval by IntegReview IRB and in conformity with International Conference on Harmonization E6 Good Clinical Practice (GCP) guidelines and the FDA Guidance for GCP in clinical trials. A signed informed consent was obtained from all participants prior to the start of the study.

Participants were enrolled based on the inclusion/exclusion criteria and provided the supplements, with subjective measurements taken over a 60-day period as shown in the flowchart (Fig. 1). Participants were assigned to take one softgel/capsule of each supplement (Pro-Resolving Mediators and Curcumin Elite™ Turmeric Extract) once daily with 8 oz. of water for 60 days, according to the packaging information for each product. The primary assessments included three questionnaires: Quality of Health Assessment (SF-36 Health Survey), Short-Form McGill Pain Questionnaire (SF-MPQ) and Medical Symptoms Questionnaire (MSQ). All questionnaires were completed via e-mail at screening/baseline, Day 30 and Day 60. SF-36 Health Survey is a validated questionnaire that measures health-related quality of life, covering eight domains: physical functioning, bodily

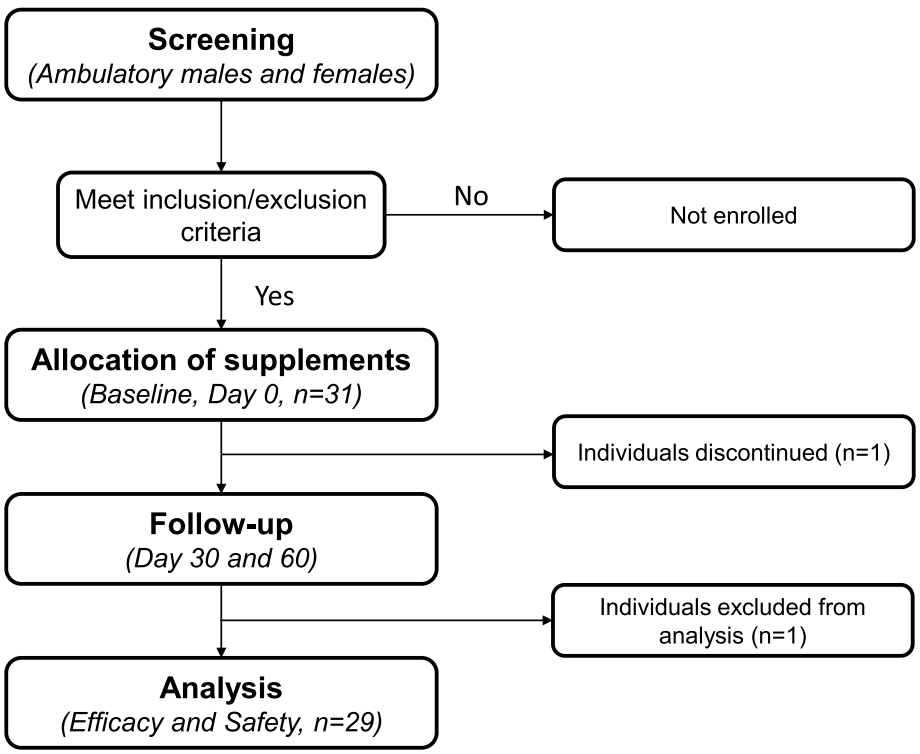

Fig. 1 Flow diagram for the study design of supplementation with Pro-Resolving Mediators and Curcumin Elite™ Turmeric Extract in healthy men and women. 29 individuals were included for the safety and efficacy analyses

pain, role limitations due to physical health problems, emotional well-being, role limitations due to personal and emotional problems, social functioning, energy/fatigue, and general health perceptions. It also includes a single item question for perceived change in health. SF-MPQ is a shorter version of the McGill Pain Questionnaire that is a measure of perceived pain with 2 subscales (sensory and affective) as well as overall intensity of pain [21]. The MSQ is an essential functional medicine tool to help to identify underlying causes of illnesses and monitor the progress over time, constituting several areas of health.

Safety and tolerability were also assessed through evaluation of changes from baseline based on interim telephone/e-mail contacts. All reports of adverse events were continuously monitored and documented throughout the study.

Statistical analysis

The number of participants used in the study were selected based on a previous unpublished multi-center, open-case series study, titled "Supplementation with Specialized Pro-resolving Mediators Reduces Inflammatory Biomarkers and Improves Reported Clinical Symptomology in Subjects with Chronic Inflammatory Conditions." The study evaluated the effect of a supplement containing fractionated lipid concentrate standardized to 18-HEPE and 17-HDHA on select circulating inflammatory biomarkers and overall well-being, in which thirty-four (34) subjects completed the study. Based on the results from the study, it was determined that thirty (30) participants were needed for this current study with a 10% dropout rate.

The statistical analyses were performed using Graph Pad Prism 9 (version 9.2.0). Changes from baseline to Day 30 and Day 60 were analyzed with one-way repeated measures ANOVA followed by Bonferroni's multiple comparison post-test for the numerical data sets following a normal distribution [i.e. body weight and body mass index (BMI)] and the non-parametric Friedman test followed by Dunn's multiple comparisons post-test for ordinal, categorical data sets (i.e. SF-MPQ, SF-36 Health Survey and MSQ).

Results

Demographics of participants

Thirty-one (31) participants were recruited in the study. Two participants dropped out of the study, one for unrelated medical condition and the other for non-compliance, resulting in 29 participants for which the final analyses were performed. Baseline measures and demographics of all 29 participants are presented in Table 1.

Table 1 Demographics and baseline measures of participants included in the final analyses

Number of participants	29
Gender, n (%)	
Females	17 (59%)
Males	12 (41%)
Age (years)	55.4 ± 10.3
Weight (kg)	73.3 ± 15.0
Height (m)	1.7 ± 0.1
BMI (kg/m^2)	26.1 ± 4.5

Data is represented as means ± standard deviation

Short-form McGill pain questionnaire

The SF-MPQ comprises of fifteen descriptors covering the 11 sensory (descriptors 1–11) and 4 affective (descriptors 12–15) dimensions of pain, rated on the following intensity scale: 0 – none, 1 – mild, 2 – moderate, or 3 – severe. The range for the total pain rating index score is 0–45, with a higher score indicating more pain. The questionnaire also includes a visual analogue scale (VAS) question for pain severity and a question for present pain intensity. There is no established critical cut point, with a higher score indicating worse pain. Results from the questionnaire and statistical analysis are detailed in Table 2. The participants in the study showed a significant reduction in all aspects of the questionnaire at all time points, with the exception of the affective subscore which showed a non-significant reduction only at day 60 (Fig. 2). There was a significant reduction from baseline in the median total pain score at day 30 (−2[5], $p = 0.008$) and day 60 (−4 [6], $p = 0.001$). There was also a significant reduction in the median score of the sensory (−2 [4], $p = 0.02$) and affective (0 [1], $p = 0.04$) subscore at day 30 and a significant reduction in the sensory subscore (−3 [5], $p = 0.003$) at day 60. There was a significant reduction in the median VAS score for pain severity at day 30 (−1 [2], $p = 0.002$) and day 60 (−2 [2.5], $p < 0.0001$). There was also a significant reduction in the median score for the present pain intensity at day 30 (0 [1], $p = 0.02$) and day 60 (−1 [1], $p = 0.0004$).

SF-36 health survey

The SF-36 Health Survey comprises of 36 items divided into 8 categories, each scored on a range of 0–100 for an overall minimum score of 0 and overall maximum score of 100 in each of the 8 categories. It also includes

Table 2 Short-Form McGill Pain Scores

	Baseline	Day 30			Day 60		
	Median (IQR)	Median (IQR)	Δ median (IQR)	*Adjusted p value*	Median (IQR)	Δ median (IQR)	*Adjusted p value*
Total McGill Pain Score	**6 (6.5)**	**3 (7.5)**	**−2 (5)**	***0.008***	**2 (3.5)**	**−4 (6)**	***0.001***
Sensory Subscore	**5 (6)**	**3 (7)**	**−2 (4)**	***0.02***	**2 (4)**	**−3 (5)**	***0.003***
Affective Subscore	**1 (2)**	**0 (0)**	**0 (1)**	***0.04***	0 (1)	0 (1)	*0.08*
Visual Analogue Scale (Pain Severity)	**4 (3)**	**3 (2.5)**	**−1 (2)**	***0.002***	**2 (2)**	**−2 (2.5)**	***< 0.0001***
Present Pain Intensity	**2 (1.5)**	**1 (1)**	**0 (1)**	***0.02***	**1 (1.5)**	**−1 (1)**	***0.0004***

Data is represented by the median (interquartile range, IQR) and Δ median is the change from baseline, $n = 29$. Statistical analysis was performed using the non-parametric Friedman test followed by Dunn's multiple comparisons test, showing the rank sum difference from baseline. *p*-value represents the significance of the treatment compared to baseline

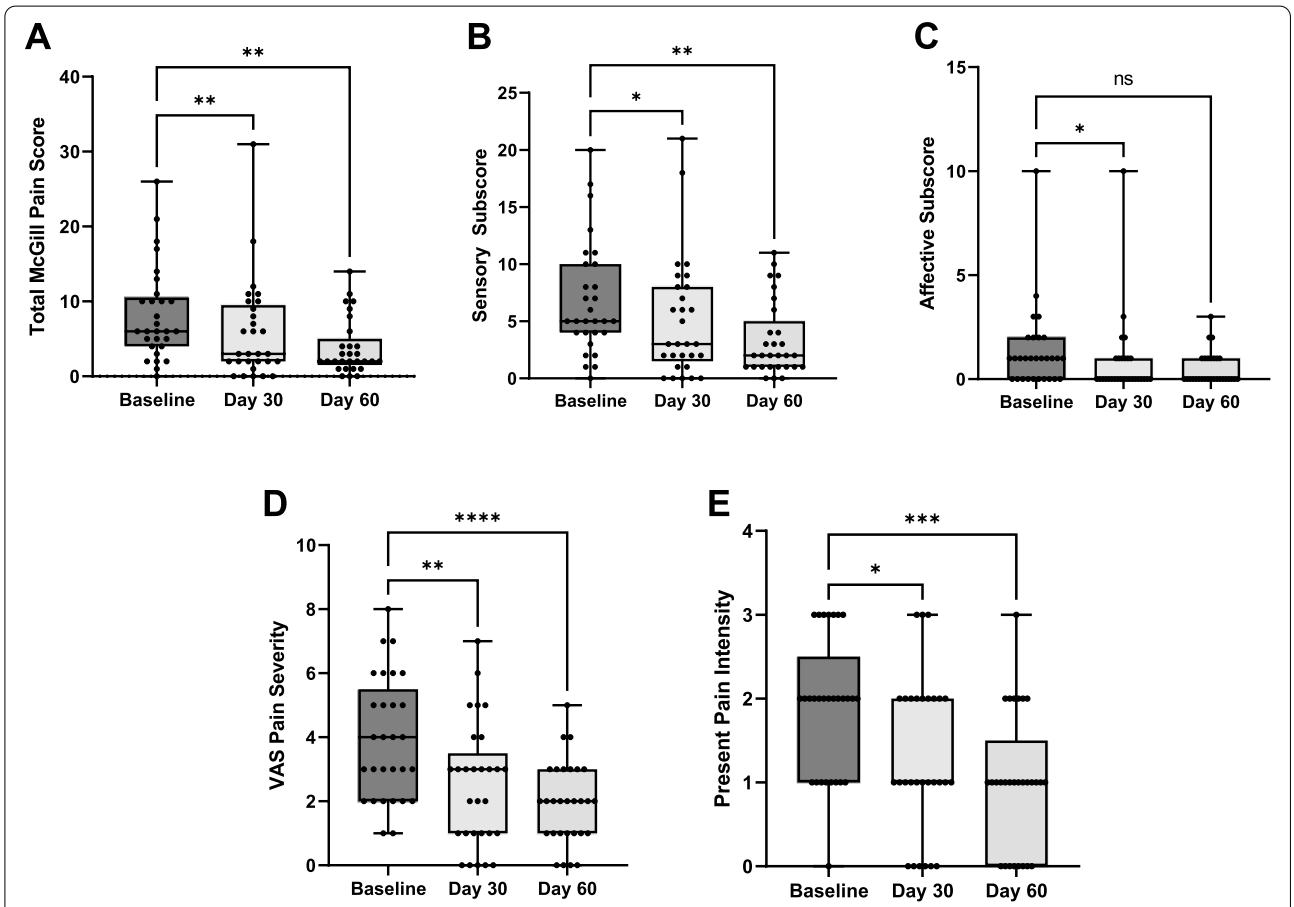

Fig. 2 Box and whisker plots of the Short-Form McGill Pain Scores: **A** Total McGill Pain Score, **B** Sensory subscore, **C** Affective subscore, **D** VAS pain severity and **E** Present pain intensity. Statistical analyses were performed using the non-parametric Friedman test followed by the Dunn's multiple comparison post-hoc test to identify changes from baseline. The following indicates the level of statistical significance; $^{ns}p > 0.05$, $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$, $^{****}p < 0.0001$ ($n = 29$)

a single item question for perceived change in health also scored on a range from 0 to 100. A higher score represents a more favorable health state. Table 3 shows the complete scores and statistical analyses for the 8 categories, grouped based on the physical and emotional health aspects, and the perceived health change. The participants indicated significant improvements in four of the physical aspects, especially that of bodily

Table 3 Short Form Health Survey (SF-36)

	Baseline	Day 30			Day 60		
	Median (IQR)	Median (IQR)	Δ median (IQR)	*Adjusted p-value*	Median (IQR)	Δ median (IQR)	*Adjusted p-value*
Physical Health							
Physical Functioning	**85 (25)**	**95 (17.5)**	**5 (12.5)**	***0.02***	**95 (15)**	**10 (15)**	***0.002***
Role Limitations Physical Health	**75 (75)**	**100 (25)**	**0 (50)**	***0.04***	100 (25)	0 (50)	*0.08*
Energy/Fatigue	**65 (30)**	70 (32.5)	5 (17.5)	*0.4*	**75 (25)**	**5 (15)**	***0.005***
Pain	**67.5 (20)**	**77.5 (22.5)**	**12.5 (22.5)**	***0.0002***	**80 (22.5)**	**20 (27.5)**	***< 0.0001***
General Health	80 (22.5)	80 (17.5)	5 (10)	*0.07*	80 (20)	0 (10)	*0.1*
Emotional Health							
Role Limitations Emotional Problems	100 (0)	100 (0)	0 (0)	*> 0.99*	100 (0)	0 (0)	*> 0.99*
Emotional Well-Being	88 (16)	84 (20)	0 (8)	*> 0.99*	88 (12)	0 (8)	*0.3*
Social Functioning	100 (31.25)	100 (12.5)	0 (12.5)	*0.6*	100 (6.25)	0 (18.75)	*0.4*
Single Item Question							
Perceived Health Change	**50 (0)**	50 (25)	0 (25)	*0.2*	**75 (25)**	**0 (25)**	***0.03***

Data is represented by the median (interquartile range, IQR), $n = 29$. Statistical analysis was performed using the non-parametric Friedman test followed by Dunn's multiple comparisons post-hoc test. $p < 0.05$ indicates statistical significance of the treatment from baseline

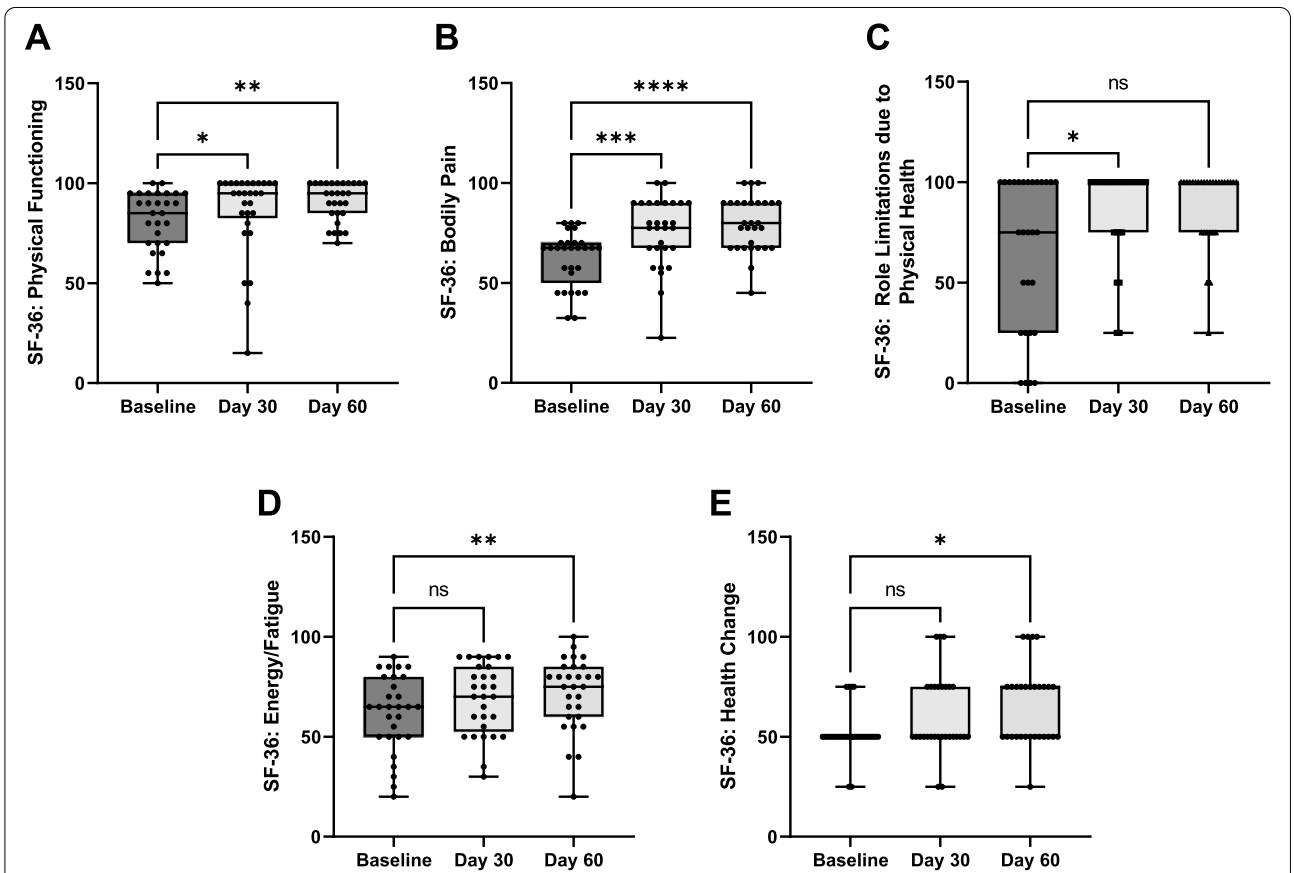

Fig. 3 Box and whisker plots of the SF-36 Health Survey categories showing significant changes during the study: **A** Physical functioning, **B** Bodily pain, **C** Role limitations due to physical health, **D** Energy/fatigue and **E** Health change. Statistical analyses were performed using the non-parametric Friedman test followed by the Dunn's multiple comparison post-hoc test to identify changes from baseline. The following denotes the level of statistical significance; $^{ns}p > 0.05$, $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$, $^{****}p < 0.0001$ ($n = 29$)

pain, and also the perceived health change during the study as shown in Fig. 3, but no significant difference in the emotional health aspects.

Medical symptoms questionnaire

The MSQ score is determined from individuals ranking the different areas on a scale of 0 ('never or almost never have the symptom') to 4 ('frequently have it, effect is severe'). The higher the symptom score, the more severe the condition. Figure 4 shows the areas with significant changes from baseline and the total results can be seen in the supplemental data (Table S1). There was a significant reduction of −5 (11.5) in the median (interquartile range: IQR) total score only at day 60 from baseline. The only parameter that showed a significant reduction was the joint/muscle at Day 60 [−1 (5.5)]. No other parameters showed a significant change from baseline at any of the time points.

Safety and tolerability

The combination of the supplements was safe and well tolerated with no reports of adverse events related to the study product, except for one individual reporting eructation. There were no changes in body weight or BMI over the course of the study.

Discussion

Non-resolving inflammation can lead to a state of chronic inflammation, causing deleterious effects as we age, including joint pain among many other age-related pathologies. This virtual study evaluated the impact of using a combination of the well-known anti-inflammatory phytochemical, curcumin, with a marine lipid SPM concentrate on inflammation/discomfort in healthy middle-aged individuals. The combination of these two ingredients should target the different stages of the acute inflammatory process: reduction of inflammation via the anti-inflammatory effects of curcumin and the resolution of inflammation via the pro-resolving effects of the SPMs, with the goal of relieving some discomfort and/or pain associated with inflammation.

Based on the questionnaires, the participants observed a significant improvement in parameters that were associated with pain and discomfort. This was especially pronounced in the SF-MPQ where there were significant improvements in the total pain score, pain severity score and the present pain intensity score at all the time points. The improvement in the sensory subscore, which comprises pain location, intensity, quality and pattern was the primary driver for the improvement in the total pain score. The median improvement of the total pain score observed among the participants was 4, which is slightly below what is considered to be a clinically relevant change based on the 0–45 Norwegian SF-MPQ scale [22]. However, 31% ($n=9$) and 41% ($n=12$) of the participants showed a reduction in the total pain score of 5 or greater at days 30 and 60, respectively, which is considered to be clinically meaningful. Additionally, 62% ($n=18$) and 79% ($n=23$) of the participants showed an improvement in the total pain score at days 30 and 60, respectively. Participants in the study had mild to moderate pain with a median baseline score of 6, which was probably too mild to observe a clinically relevant reduction.

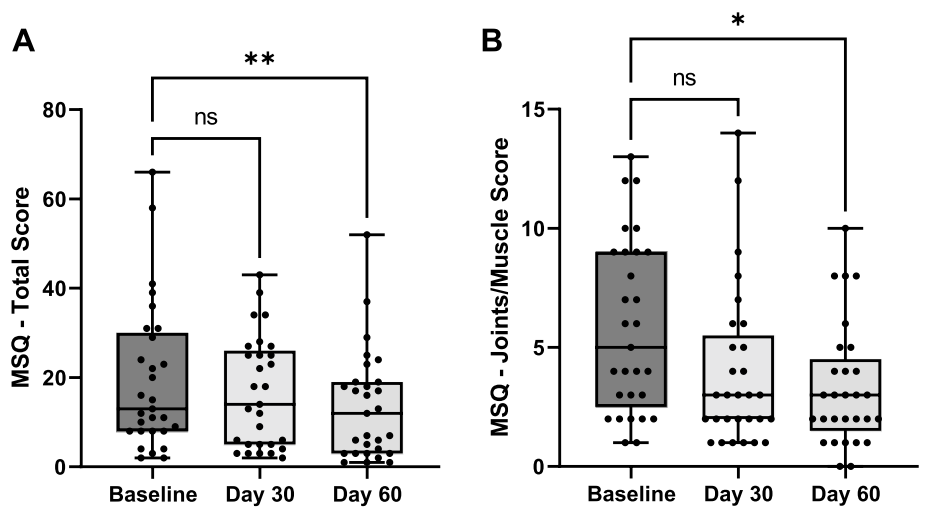

Fig. 4 Medical Symptoms Questionnaire represented as box and whisker plots. Statistical analyses were performed using the non-parametric Friedman test followed by the Dunn's multiple comparison post-hoc test to identify changes from baseline. The following denotes the level of statistical significance; $^{ns}p>0.05$, $^{*}p<0.05$, $^{**}p<0.01$ ($n=29$)

Similar improvements in pain/discomfort were observed in the SF-36 health survey, where the only significant changes observed were associated with the physical health such as pain, physical functioning and general health. The participants also showed improvement in the individual item question of perceived health change indicating that they could feel the improvement. This was further supported by the MSQ, with an improvement in the total symptoms scores. The only area from the MSQ to show improvement was the joint/muscle category, and this was primarily driven by a reduction in the 'pain/aches in muscle' subcategory (data not shown). All these improvements support the role of the supplements in reducing inflammation and the associated pain.

To our knowledge, there are no known studies that have evaluated the combination of curcumin and SPMs in reducing pain associated with inflammation however, there have been some studies with the individual components. There have been extensive reviews discussing how SPMs stimulate the resolution of inflammation, and the role they play in various inflammatory-related pathologies, including that of pain [6, 23, 24]. As such, it's suggested that supplementation may provide a new therapeutic approach to target human diseases with uncontrolled or non-resolving inflammation. Resolvins are the best characterized of the SPMs for resolution of inflammation with several preclinical models showing analgesic benefits, however clinical studies involving interventions with various resolvins and other SPMs are limited, in part due to their chemical instability [23, 25]. As such, most studies have used precursors of SPMs, primarily as omega-3 fatty acids, with very promising results in pain reduction associated with arthritis, joint pain, chronic pain, headaches/migraines and diabetic neuropathy [23, 26–28]. In a previous study, researchers indicated that the D- and E-series resolvins are not directly associated with pain, but the resolvin precursor, 17-HDHA is associated with heat pain sensitivity and chronic pain intensity in humans [29]. A recently published open-label study was performed in adults with chronic pain, orally supplemented with a marine lipid concentrate standardized to two resolvin precursors (17-HDHA and 18-HEPE) for 4 weeks. The results showed a reduction in pain intensity and interference as well as an improvement in the quality of life of the participants [26]. Currently this is the only known published clinical study with oral supplementation of the precursor resolvins for pain. These results are in support of our results that also utilized an SPM-enriched marine lipid containing the 17-HDHA and 18-HEPE (two resolvin precursors), and 14-HDHA (a maresin precursor) showing benefits in the reduction of bodily and joint/muscle pain.

Clinical studies have previously shown that supplementation with curcumin improves several inflammatory conditions, with most studies involving high doses because of the low bioavailability of the curcuminoids [14, 15]. In a non-inferiority trial, researchers demonstrated that an extract from *Curcuma domestica*, standardized to 75–85% curcuminoids (daily dose of 1500 mg for 4 weeks) was as effective as ibuprofen in reducing pain in individuals with knee osteoarthritis [30]. Improvements in the bioavailability have resulted in clinical trials with lower doses. The curcumin provided in this study was a highly bioavailable curcumin supplement (CGM), which was developed through the encapsulation of the curcuminoids in a fenugreek galactomannan fiber, resulting in a higher bioavailability and relative distribution of free (unconjugated) curcuminoids [18, 31]. These free curcuminoids are understood to be driver for the biological activity and this was demonstrated using a low dose of the highly bioavailable CGM in subsequent clinical studies [32, 33]. In an open-label, randomized, active-controlled clinical trial, this CGM was further studied in individuals with knee osteoarthritis at a low dose of 400 mg (containing 154 mg curcuminoids) per day for 6 weeks, showing significant improvement in pain, stiffness and physical function, which was more effective than the glucosamine hydrochloride/chondroitin sulfate active control [20].

The combination of these two supplements were safe and well-tolerated and no adverse events associated with the study materials were reported during the study. At the end of the study, 92% of the participants who complete the satisfaction survey indicated that the benefit received from taking the study product was 'great' or 'good' (Fig. S1).

As with all studies, there were several limitations with this current study. This was a virtual pilot study with an open-label study design. All outcome measures were subjective and based only on questionnaires. Since it was open-label and there was no placebo, it is unclear how much of the improvement was due to a placebo effect. Additionally, there were no measures of inflammatory biomarkers to obtain a better understanding of the impact of the supplements on the biochemical changes associated with the perceived improvements in pain.

Conclusions

Dysregulation in the resolution stage of inflammation can lead to the development of various chronic diseases and age-related pathologies, and new therapeutic approaches are always valuable in targeting the reduction and resolution of inflammation. This virtual study showed that supplementation with the anti-inflammatory curcumin and pro-resolving lipid mediators from the marine oil may help

to relieve pain in healthy individuals with mild to moderate pain, supporting previous research in this area. As this was a pilot study, future randomized placebo-controlled studies are needed to further explore and validate the potential health benefits of the combination of these supplements in reducing pain associated with inflammation.

Author details
[1]Life Extension, 3600 West Commercial Blvd, Fort Lauderdale, FL 33309, USA. [2]Life Extension Clinical Research, 900 North Federal Hwy, Fort Lauderdale, FL 33304, USA.

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Abbreviations
14-HDHA: 14-hydroxydocosahexaenoic acid; 17-HDHA: 17-hydroxydocosahexaenoic acid; 18-HEPE: 18-hydroxyeicosapentaenoic acid; AA: Arachidonic acid; BMI: Body mass index; DHA: Docoahexaenoic acid; EPA: Eicosapentaenoic acid; GCP: Good Clinical Practice; IQR: Interquartile range; MSQ: Medical Symptoms Questionnaire; SF-36: Short Form-36 Health Survey; SF-MPQ: Short-Form McGill Pain Questionnaire; SPM: Specialized pro-resolving mediator; TNF-α: Tumour necrosis factor-alpha; VAS: Visual analogue scale.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s41231-022-00131-7.

Additional file 1: Table S1. Medical Symptoms Questionnaire. **Figure S1.** Response of participants to the satisfaction survey at the end of the study (*n*=12).

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Authors' contributions
AJC was the primary contributor in the analysis, interpretation of the data, and writing and editing the manuscript. SH contributed to the design of the project, acquisition of the data and editing the manuscript. DB and TB contributed to acquisition of the data. SJ contributed to the conception of the project and editing the manuscript. AGS was the primary investigator and was the major contributor to the conception and design of the project and contributed to editing the manuscript. All authors read and approved the final version of the manuscript.

Authors' information
All authors are employees of Life Extension Inc.

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Availability of data and materials
The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study was conducted in conformity with International Conference on Harmonization E6 Good Clinical Practice (GCP) guidelines and the FDA Guidance for GCP in clinical trials with prior approval by IntegReview IRB. A signed consent form was obtained from each participant.

Consent for publication
Not applicable.

Competing interests
Life Extension is a nutraceutical company based in USA who sells the Pro-Resolving Mediators and Curcumin Elite™ Turmeric Extract supplements used in the study.

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