# Clinical Studies of Proprietary Specialized Pro-Resolving Mediators (SPM) Formula at a Glance

| Collaborators/ Researchers | Key Takeaways | Page | Associated External Info |
|---|---|---|---|
| **Jesmond Dalli, PhD** (Queen Mary University of London) | • Subjects: healthy volunteers<br>• Study type: randomized trial aimed to increase understanding of SPM actions in humans<br>• **Findings: SPM supplementation increases circulating SPM levels and enhances immune cell function and resilience** | 2-3 | • Study abstract<br>• Link to journal *Circulation Research* |
| **Jen Stagg, DO**<br>**Bridget Briggs, MD**<br>**Taz Bhatia, MD**<br>**Cory Rice, DO**<br>**Robert Bonakdar, MD**<br>**Andrew Heyman, MD** | • Subjects: patients with chronic inflammatory conditions<br>• Study type: practice-based case series<br>• **Findings: reductions in proinflammatory markers, pain scores, and improvements in pain-related quality of life** | 4 | • Lecture by Dr. Stagg<br>• Lecture by Dr. Rice<br>• Webinar<br>• Full report |
| **Erik Lundquist, MD** | • Subjects: patients with fibromyalgia and CIRS<br>• Study type: N-of-1 type case reports in real-life setting<br>• **Findings: improvements in physical functions without flare-ups** | 5 | • Dr. Fitzgerald podcast |
| **Ryan Lazarus, DC** | • Subjects: two competitive athletes<br>• Study type: case studies<br>•**Findings: reductions in pain after physical activity; improvements in fatigue and mood** | 6 | • MAPS talk (SPMs overview) |
| **Michael Conte, MD** (UCSF Heart and Vascular Center) | • Subjects: patients with peripheral arterial disease vs. healthy volunteers<br>• Study type: short-term dose escalation study<br>• **Findings: increases in the levels of SPMs and SPM-to-prostaglandin ratio in plasma, increases in SPMs in HDL particles, and changes in immune cell resolution phenotype** | 7 | • Abstract published in *Circulation*<br>• Study summary<br>• Vascular Discovery 2018 abstracts #120 and #121 |
| **Ryan Bradley, ND** (National University of Natural Medicine) | • Subjects: patients with a history of chronic pain lasting at least 3 months<br>• Study type: single-arm observational study<br>• **Findings: reductions in pain and improvements in quality of life** | 8 | |
| **GRAS expert panel** | • Study type: safety review<br>• **Findings: expert panel unanimously concluded the proprietary SPM formula is GRAS** | 9-10 | |

Detailed evidence of these studies is summarized in a table at the end of the document (see page 11-13).

## SPM supplementation increases circulating SPMs and enhances immune cell function and resilience: a placebo-controlled, double-blind, randomized-controlled trial

**Collaborators:** Jesmond Dalli, PhD (Queen Mary University of London) et al.

**Study objective:** To determine the impact of different doses of SPM supplementation on circulating SPM concentrations in plasma as well as immune cell response to bacterial and proinflammatory challenges over a 24-hour time-frame.

**Study participants:** 22 healthy participants (59% women). Average age was 26.4 ± 4.0 years. Average BMI was 23.5 ± 4.7 kg/m$^2$.

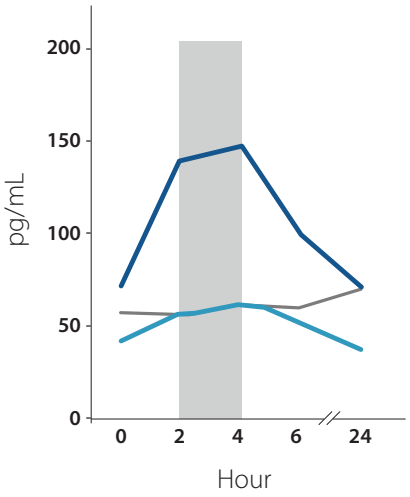
## Results:

**Increase in plasma SPMs within 2 hours:** Plasma SPMs increased acutely within 2 hours. Peak increase occurred within 2-4 hours (Figure 1). Increases in certain resolvins, maresins, and protectins were seen.

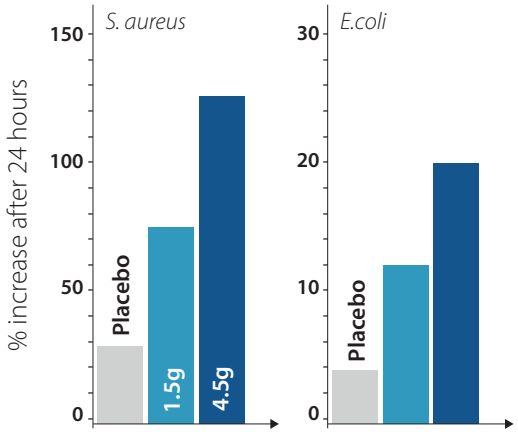
**More protective immune cell behavior:** The ability of immune cells to phagocytose (engulf) pathogens was enhanced followed SPM supplementation. Monocytes more effectively engulfed *S. aureus*, and neutrophils more effectively engulfed *S. aureus* and *E. coli* 24 hours after consumption of SPM supplement (Figure 2, neutrophils data).

**Reduced proinflammatory response:** When immune cells from subjects supplemented with SPMs were treated with a proinflammatory challenge,† the expression of proinflammatory activation markers such as CD49d and CD11b was reduced (Figure 3, monocytes data).

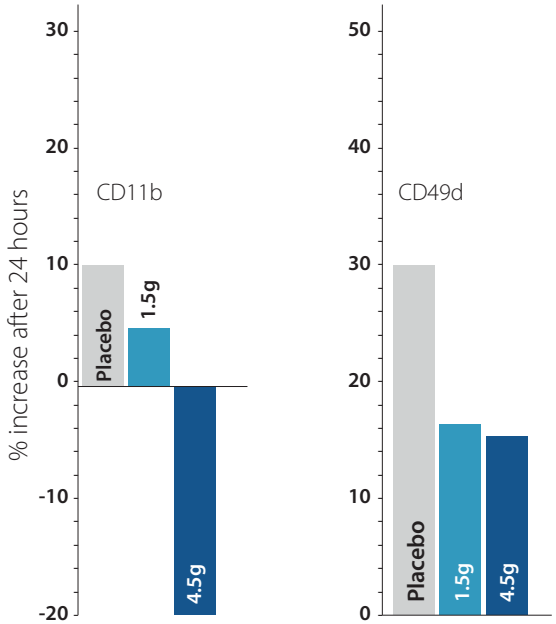
### Fig 1: Increased SPMs in circulation




### Fig 2: Enhanced containment of pathogens



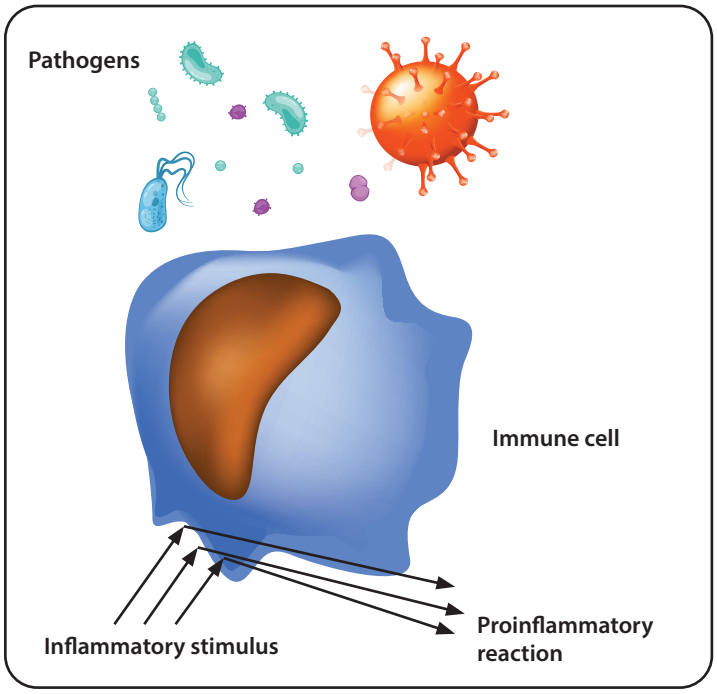

### Fig 3: Less proinflammatory reaction



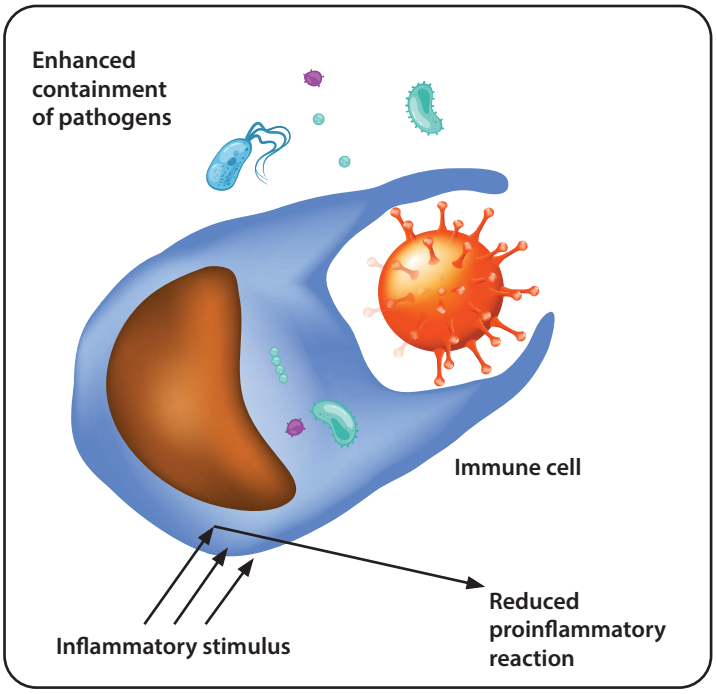

## Summary:

SPM supplementation results in a reprogramming of immune cell behavior representing enhanced resilience in the face of environmental challenges.

## Placebo




## SPM Supplementation




## Conclusions

- SPMs increase in plasma and can alter immune cell phenotype within 24 hours.
- SPM supplementation drove a more protective and potentially less damaging response when cells were faced with proinflammatory challenges. This change in cell behavior represents enhanced resilience in the face of environmental challenges.

## Why is this important?

- Immune cell response and reactivity drives inflammation at the tissue level and is implicated in the development of diseases such as atherosclerosis, diabetes, and osteoarthritis, among others.
- Changing immune cell behavior is how SPMs drive inflammation resolution. This study shows that consuming an SPM supplement can impact pathways relevant to inflammation resolution within 24 hours.

**Study design and methods:** This was a double-blind, placebo-controlled, randomized-controlled trial. All subjects completed 4 study days in random order. On each study day the subjects consumed either placebo or different doses (1.5 g, 3 g, or 4.5 g) of SPM supplementation (Active Fractionated Marine Lipid Concentrate standardized to proprietary SPMs*) made up to a 30-mL serving of a liquid emulsion. Blood was sampled at 0, 2, 4, 6, and 24 hours for analysis of SPMs. Immune cells (monocytes and neutrophils) were isolated at each time point, challenged with fluorescently labeled bacteria and phagocytosis activity measured by flow cytometry. Monocytes were isolated from blood at each time point, challenged with platelet aggregating factor (PAF), a proinflammatory stimulus implicated in the propagation of vascular inflammation, and the expression of cell-surface proinflammatory activation markers (CD11b and CD49d) measured. † PAF stimulation.

*Research was conducted on an earlier liquid emulsion version of a fractionated marine lipid concentrate which was standardized to a lower level of 17-HDHA and 18-HEPE than the current formula.

### Reference

Souza PR et al. *Circulation Research* 2020;126(1):75-90. PMID: 31829100

## SPM supplementation reduces pain scores and proinflammatory markers in patients with chronic inflammatory conditions: a multicenter observational study

**Collaborators:** : Jen Stagg, DO; Bridget Briggs, MD; Taz Bhatia, MD; Cory Rice, DO; Robert Bonakdar, MD; and Andrew Heyman, MD

**Study objective:** To determine the impact of SPM supplementation for 8 weeks on pain, quality of life, and proinflammatory markers in patients with conditions of chronic pain and inflammation.

**Study population:** 34 men and women diagnosed with fibromyalgia (n=6), arthritis (RA or OA, n=14), or chronic pain (n=14) were included in the study. The average age was 49.3 ± 10.8 years, and the average BMI was 29.4 ± 8.2 kg/m$^2$.

## Results:

### Improved inflammatory biomarkers

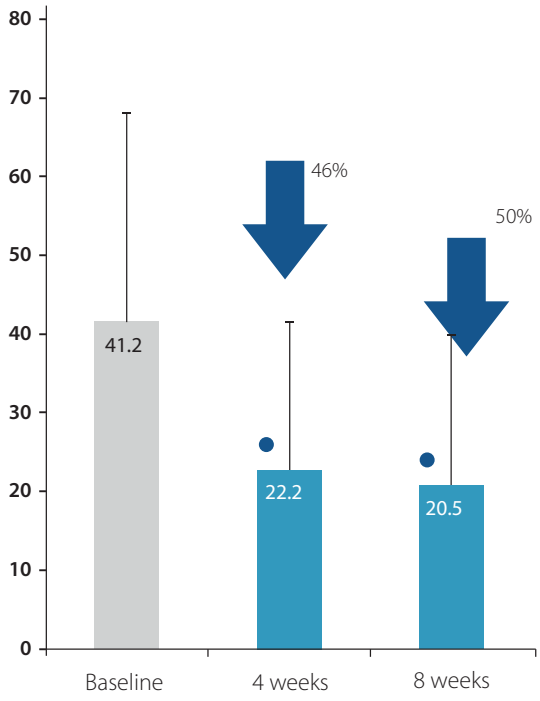
- hs-CRP: 43% reduction within 4 weeks
- $PGE_2$: Normalization within 4 weeks
- Fibrinogen: Significant reduction in 8 weeks

| Biomarker | Level | p value | Reference range |
|---|---|---|---|
| **hs-CRP** (mg/L) | Baseline: 9.2 ± 15.8<br>4 weeks: 5.2 ± 9.5<br>8 weeks: 6.3 ± 10.6 | 0.031*<br>0.007* | 0–3 |
| **$PGE_2$** (pg/mL) | Baseline: 590.6 ± 802.0<br>4 weeks: 486.5 ± 400.4<br>8 weeks: 350.6 ± 334.3 | 0.03<br>0.039* | 200–400 |
| **Fibrinogen** (mg/dL) | Baseline: 343.9 ± 93.3<br>4 weeks: 324.9 ± 114.0<br>8 weeks: 315.0 ± 74.2 | 0.11<br>0.007* | 193–504 |

Data are expressed as mean + SD. *Statistically significant from baseline as assessed by paired t-tests between time points. Smaple size for each factor may vary due to missing data. Missing values were not imputed for paired t-tests analyses.

### Significantly reduced pain

- 46% reduction in scores of the Brief Pain Inventory (BPI) within 4 weeks




- Significant reduction in pain scores at worst, at least, on average, within the last 24 hours, at time of assessment.
- Significantly reduction in pain interference with activities of daily living.
- Significantly improvement on scores of the American Pain Association Quality of Life Scale.

## Conclusions

- SPM supplementation reduced biomarkers of systemic inflammation that are easily trackable in the clinic.
- The patients reported a reduction in pain, reduced interference of pain with activities of daily living, and an increase in quality of life as measured by validated tools.

**Methods and study design:** This 8-week, open-label, case observation study was conducted by 6 independent practitioners across the US. (4 MDs, 1 DO, and 1 ND). Subjects consumed 6 x 250 mg SPM softgels (providing 1.5g of Active Fractionated Marine Lipid Concentrate standardized to proprietary SPMs*) for the first 4 weeks and increased to 8 x 250 mg SPM softgels (2 g total) for the final 4 weeks. Subjects were assessed at baseline (Week 1), Week 4, and Week 8. Fasting blood was measured at each time-point and assessed for hs-CRP, $PGE_2$, erythrocyte sedimentation rate (ESR), fibrinogen, B-type natriuretic peptide (BNP), serum ferritin, and the proinflammatory cytokines tumor necrosis factor alpha (TNF-α) and interleukin-6 (IL-6). Validated questionnaires (Brief Pain Inventory, American Chronic Pain Association Quality of Life Scale) at each visit. Data are reported as mean ± SD. A value of $p<0.05$ was considered statistically significant. The study was approved by the Western Independent Review Board (Seattle, WA). Informed written consent was obtained from all participants prior to enrollment. Metagenics. Data on File, 2016.

*Research was conducted on an earlier version of a fractionated marine lipid concentrate which was standardized to a lower level of 17-HDHA and 18-HEPE than the current formula.

## A SPM supplement improves physical function and quality of life in patients with fibromyalgia: an n-of-1 clinical evaluation

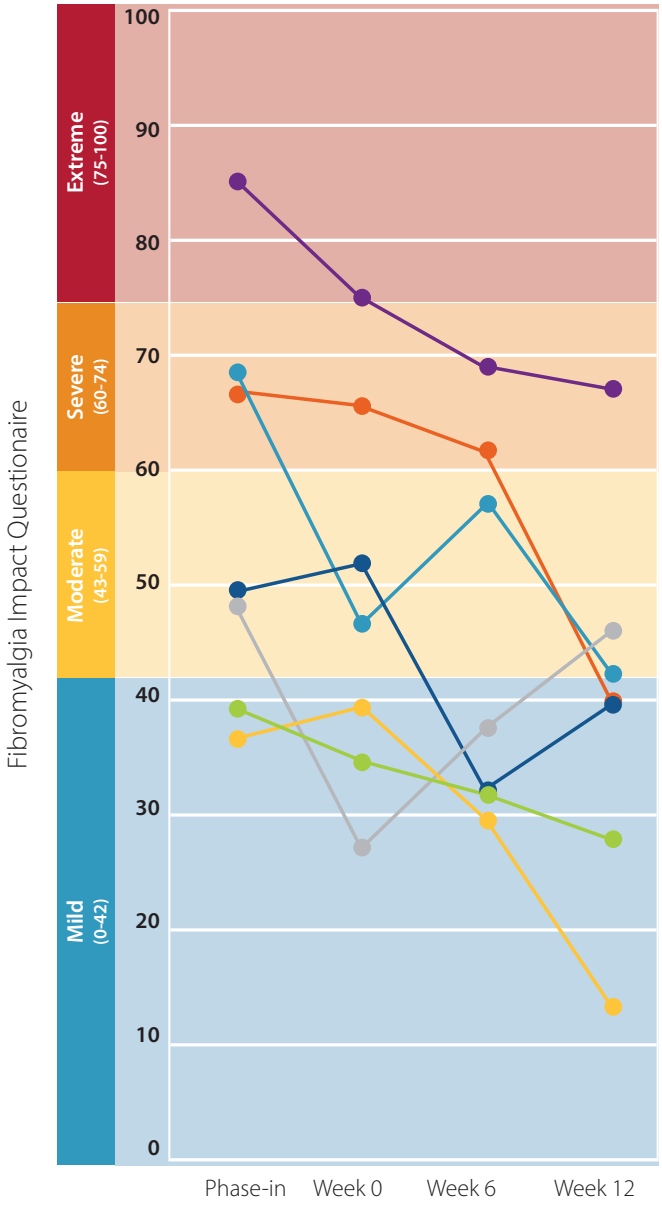
**Collaborators:** : Erik Lundquist, MD

**Study objective:** To evaluate the impact of a SPM supplement on the wellbeing and quality of life in patients with fibromyalgia (FM) over 12 weeks.

**Study participants:** Seven female patients with different severity and duration of FM who attended Temecula Center of Integrative Medicine (Temecula, CA).

## Results:

### Severity of Fibromyalgia




Each line above represents one patient's changes in fibromyalgia severity (as indicated by Fibromyalgia Impact Questionnaire total score) from baseline to end of study.

## Conclusions:

- Improvements were seen in patients' physical functions and activities after SPM supplementation without flare-ups.
- Physician considered 6 of the 7 patients of FM were responders to the supplement (S003 a nonresponder).
- In patients with FM, lower scores of the Chronic Inflammatory Response Syndrome (CIRS) questionnaire may be indicative of better outcomes with a SPM supplement.
- One patient indicated the supplement had a very positive impact in her life and wished the study were longer. Four patients (S001, S002, S006, and S007) noted a positive impact. Two patients (S003 and S005) reported experiencing less pronounced impact.
- Some patients with FM are highly sensitive to environmental triggers (e.g., mold exposure) and significant life events, by which the potential effects of a SPM supplement may sometimes be overshadowed.
- No patients experienced any side effects from taking the supplement.

**Study protocol:** Each patient received 2 x 500 mg softgels a SPM supplement (Active Fractionated Marine Lipid Concentrate standardized to proprietary SPMs) per day for 12 weeks. Changes in symptoms and quality of life over time were assessed via Revised Fibromyalgia Impact Questionnaire (FIQR), MOS SF-36, and PROMIS-43 Questionnaires as well as Chronic Inflammatory Response Syndrome (CIRS) Cluster Score Questionnaire. Metagenics, Data on File, 2019.

## SPM supplementation reduces pain after physical activity, improves mood, and reduces fatigue in highly active individuals: a case series

**Collaborators:** : Ryan Lazarus, DC

**Study objective:** To assess the impact of an SPM supplement on pain following a typical workout, as well as outcomes that can be impacted by high-intensity, frequently training schedules (including mood and quality of life) in individuals engaging in high-intensity, high-frequency physical activity.

**Study participants:**

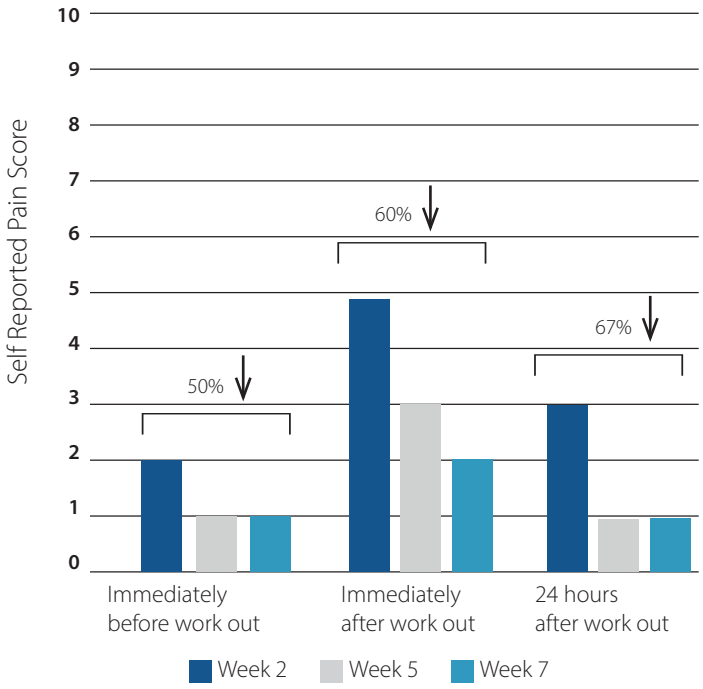
**Patient 1:** A 34-year-old male cross-fit competitive athlete who engaged in a high-intensity long-duration training schedule 6 days per week presented with mild bodily discomfort and intermittent periods of reduced mental focus.

**Patient 2:** A 48-year-old woman, who competes biannually in IFBB Pro Bikini Contest which requires frequent and intense training regimen, presented with fatigue, minimal recovery, compromised sleep patterns, bodily discomfort, intermittent reduced focus, and impatience.

## Results:

### Patient 1

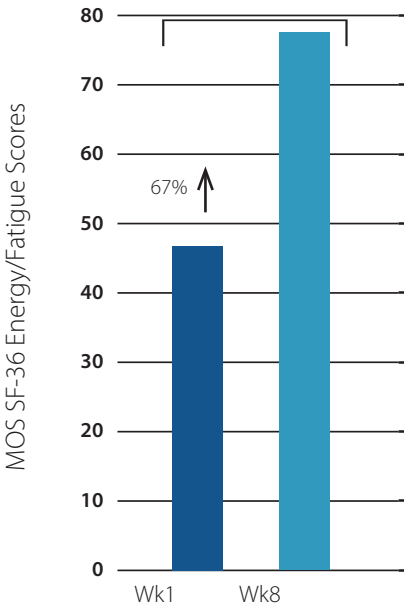
- Over 50% improvements in self-reported pain scores before and after a typical work-out. Subject was asked to rate pain on a scale of 0-10 with 0 being no pain and 10 being worst imaginable.




### Patient 2

- 87% reduction in fatigue as assessed by the BRUMS tool
- 67% increase in energy (MOS SF-36)

**Improvements in Energy/Fatigue Scores**




### Improvement in mood scores

- 67% reduction in confusion (confused, muddled, mixed up, incertain)
- 100% reduction in depression, depressed down-hearted, unhappy, miserable)
- 62.5% reduction in tension (panicky, nervous, worried, anxious)

## Conclusions:

The individuals who took part in this case series experienced improvements in mood, mental clarity, stress, and fatigue and reduction in bodily discomfort after a typical workout when taking SPM supplement

**Study design and methods:** Case studies conducted at Lazarus Wellness (Napa CA) under the care of a licensed health-care practitioner, Ryan Lazarus, DC. IRB Approval for this study was obtained (Aspire IRB, Santee, CA). Mood disturbances were assessed using the Brunel Mood Scale (BRUMS). Health-related quality of life was assessed using the MOS SF-36 instrument. Patients were instructed to consume 2 x 500 mg softgels of an SPM Supplement (Active Fractionated Marine Lipid Concentrate standardized to proprietary SPMs) for 8 weeks, while keeping dietary, lifestyle, and physical activity patterns consistent across the study. Metagenics. Data on File, 2019.

## SPM supplementation increases lipid mediator content of plasma and high-density lipoprotein (HDL) and changes immune cell resolution phenotype in patients with peripheral arterial disease (PAD)

**Collaborators:** : Michael Conte, MD (UCSF Heart and Vascular Center) et al.

**Study objective:** To determine the impact of an SPM supplement on lipid mediator levels in the blood and HDL and whether it influences immune cell resolution phenotype in patients with PAD.

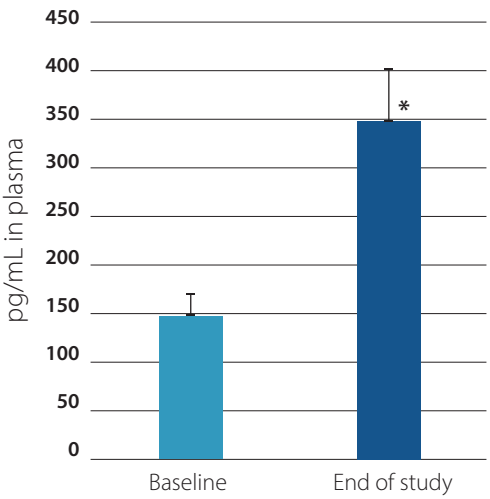
**Study population:** Short-term, dose-escalation study in 10 patients with PAD and 10 healthy volunteers.

### Results:

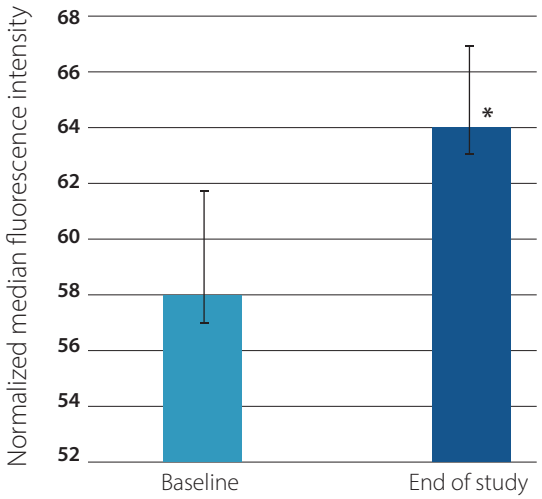
- The supplementation increased levels of pro-resolving mediators and SPM-to-prostaglandin ratio in the plasma
- The supplementation increased levels of pro-resolving mediators in the HDL particles
- The supplementation increased the phagocytic activity of monocytes and neutrophils and decreased the expression of monocyte surface markers associated with systemic inflammation and atherosclerosis

**Study design and methods:** 10 PAD subjects and 10 healthy subjects consumed escalating doses (1.5 g, 2.5 g, and 5 g/day) of SPM supplementation (Active Fractionated Marine Lipid Concentrate standardized to proprietary SPMs**) for 5-day periods separated by a 1-week washout period. Resolution phenotype was assessed by measurement of phagocytic activity of neutrophils and monocytes as well as monocyte cell surface markers. Phagocytosis of fluorescently labeled E. coli and expression of leukocyte surface markers were assessed by flow cytometry. HDL was isolated from serum isolated from a subset of the subjects (6 per group). LC-MS/MS was used to measure HDL lipid mediator levels, and multiplex array was used to evaluate HDL cytokine profiling.

**Increase in circulating SPMs in PAD cohort**




**Increase in monocyte phagocytosis of *E.coli* in PAD cohort**




*** statistically significant vs. baseline**

### Summary of changes in PAD cohort


- ↑ Circulating SPMs
- ↑ Engulfment of pathogens
- ↓ Proinflammatory and adhesion molecule expression on immune cells
- Shift toward ↓ expression of M1 macrophage proinflammatory markers, and ↑ in M2 macrophage antiinflammatory markers

**Research was conducted on an earlier version of a fractionated marine lipid concentrate which was standardized to a lower level of 17-HDHA and 18-HEPE than the current formula.

### References


1. Schaller MS et al. Short-term oral supplementation with a novel marine oil fraction alters resolution phenotype in healthy subjects and patients with peripheral arterial disease. Presented at Vascular Discovery: From Genes to Medicine 2018 Scientific Sessions (abstract #120).
2. Schaller MS et al. Inflammation and resolution phenotype is altered in peripheral arterial disease. Presented at Vascular Discovery: From Genes to Medicine 2018 Scientific Sessions (abstract #121).
3. Sorrentino TA et al. Effects of marine oil supplementation on cytokine and lipid mediator content of HDL in patients with peripheral arterial disease. *Circulation.* 2018;138:A12919.

## SPM supplementation improves quality of life and pain scores in patients suffering from chronic pain conditions

**Collaborator:** Ryan Bradley, ND (National University of Natural Medicine)

**Study objective:** To assess the impact of SPM supplementation for 4 weeks on health-related quality of life, inflammation, and pain in adults with chronic pain.

**Study participants:** 44 adults (31 women, 12 men, and 1 identified as transgender) with a history of chronic pain lasting as least 3 months as determined by the PROMIS-43 PROFILE—Pain Intensity subdomain of 4 or higher. The average age of the group was 45.5 years, and 31.5% of them were currently taking omega-3 fatty acids, fish oil, or krill oil.

## Results:

At 4 weeks, quality of life as measured by the PROMIS-43 was improved.

Significant changes in measures of pain intensity and pain interference were also seen, including the BPI items and PROMIS-43 subdomains.

| PROMIS-43 | Brief Pain Inventory (BPI) |
|---|---|
| ↓ Reduction in pain interference -3.99 points | ↓ Worst pain intensity in past week -1.05 points |
| ↓ Fatigue -2.61 points | ↓ Least pain intensity in past week -1.18 points |
| ↓ Sleep disturbance -3.35 point | ↓ Current pain -1.42 points |
| ↓ Depression/sadness -2.16 points | ↓ Average pain -1.45 points |
| ↓ Anxiety/fear -3.71 points | ↓ Pain interference -1.75 points |
| ↑ Physical function +3.4 points | |
| ↑ Social functioning +3.7 points | |

## Conclusions:

Supplementation with SPM may improve quality of life and significantly reduce measures of pain intensity and pain interference and increase physical function in adults with chronic pain.

**Study design and methods:** Single-arm, observational study with mid-study dose titration conducted by researchers at National University of Naturopathic Medicine (NUNM). IRB Approval for this study was obtained (NUNM, Portland, Oregon), and the trial was registered on ClinicalTrials.gov as NCT02683850. Patients were instructed to consume 6 x 250 mg softgels of an SPM supplement (Active Fractionated Marine Lipid Concentrate standardized to 17-HDHA and 18-HEPE*) for 2 weeks, and dose was titrated up or down by 2 softgels depending on whether or not their pain score improved by at least 2 points. Quality of life was measured by the PROMIS-43 validated questionnaire. Self-reported pain was measured by the PROMIS-43 tool as well as the Brief Pain Inventory (BPI). Metagenics Institute. Data on File, 2019. Metagenics. Data on File, 2019.

*Research was conducted on an earlier version of a fractionated marine lipid concentrate which was standardized to a lower level of 17-HDHA and 18-HEPE than the current formula.

## SPM Supplementation: SAFETY SUMMARY

**Introduction**

When clinical research is performed with nutritional supplements, it is imperative that these products are shown to be safe. In the case of the proprietary SPM supplementation used in the clinical work described in this brochure, the safety has been confirmed and documented by an independent expert panel qualified by scientific training and experience in the evaluation of the safety of food and food ingredients. An expert panel granted Generally Recognized as Safe (GRAS) status to this proprietary SPM Supplement. The expert scientific panel studying the proprietary SPM precursors with standardized content determined that the intended use of the SPM precursors has been determined to be safe through scientific procedures as set forth in 21 CFR§170.3(b). The panel determined the proprietary SPM-precursors with standardized content are appropriately characterized, meet product specifications, and have a proven stability profile.

**Safety determination**

The safety analysis included a detailed review of the existing scientific literature (through June 2018) on the safety of the pro-resolving mediators 17-hydroxy-docosahexaenoic acid (17-HDHA) and 18-hydroxy-eicosapentaenoic acid (18-HEPE) standardized in this supplement and their specific properties. Based on this independent, critical evaluation of all of the available information as well as discussions by the expert panel, they unanimously concluded that this proprietary SPM formula is GRAS. The SPM formula is a fraction of marine oil. The SPM-precursor products are shown to be manufactured following current Good Manufacturing Practices (cGMP). Analytical (chemical) results for the SPM products confirm that the finished product formulations meet the proposed specifications as demonstrated by the consistency of production, the lack of impurities/contaminants (e.g., heavy metals, polychlorinated dibenzo-p-dioxins (PCDDs), polycyclic aromatic hydrocarbons (PAHs), and polychlorinated biphenyls [PCBs]), and their stability over a 6-month period.

The expert scientific panel studying the proprietary SPM precursors with standardized content determined that the intended use of the SPM precursors has been determined to be safe through scientific procedures as set forth in 21 CFR§170.3(b). The panel determined the proprietary SPM precursors with standardized content are appropriately characterized, meet product specifications, and have a proven stability profile.

**Clinical experience**

The proprietary SPM supplement with proprietary SPM standardization has been clinically tested in multiple studies:

- 4 clinical evaluations with a total of 86 subjects at dosages ranging from 1.5 g to 6 g per day for up to 12 weeks
- 43 case studies at a dosage of 1-2 g per day for 8 to 12 weeks.

| Study Type | # Subjects | Dose SPM | Time frame |
|---|---|---|---|
| Randomized, placebo-controlled, double-blind study in healthy men and women | 22 | 1.5 g–4.5 g of SPM supplement | Single intake of each dose with monitoring over 24 hours after each dose |
| Case series in healthy individuals engaging in high-frequency, high-intensity physical activity training | 2 | 2 x 500 mg softgels per day | 8 weeks |
| Case series in women with fibromyalgia | 7 | 2 x 500 mg softgels per day | 12 weeks |
| Case series in individuals with conditions of chronic inflammation and pain | 34 | 6–8 x 250 mg softgels per day for 8 weeks | 8 weeks |
| Dose escalation study in healthy subjects and subjects with peripheral artery disease | 20 | 1.5 g–6 g of SPM supplement | 15 days |
| Single-arm observational study in patients with a history of chronic pain | 44 | 4–8 x 250 mg softgels | 2 weeks |
| **TOTALS** | 129 (43 cases and 86 clinical study subjects) | 1 g–6 g daily | 2–24 hours |

No adverse events were reported in these clinical studies related to product consumption.

| SPM Supplementation: Summary of Evidence Table | | | |
|---|---|---|---|
| **Study** | **Population** | **Study Design** | **Outcomes** |
| **SPM supplementation improves plasma SPM status and positively influences immune cell behavior in healthy men and women (Jesmond Dalli et al.)** | 22 healthy men and women | Randomized, placebo-controlled, crossover study. Each subject completed 4 study days investigating the impact of different doses (1.5, 3, 4.5 g) of SPM supplementation** on plasma SPM status and immune cell phenotype and behavior over 24 hours. | • Plasma SPM content increased within 2 hours.<br>• Immune cells exhibited a less proinflammatory response: Expression of proinflammatory activation markers (CD49d and CD11b) on monocytes in response to a pro-inflammatory challenge was reduced with SPM supplementation.<br>• The immune cells exhibited a more protective response: Monocyte phagocytosis of *S. aureus* and monocyte and neutrophil phagocytosis of *E. coli* were increased within 24 hours. |
| **SPM supplementation reduces pain and inflammatory markers in patients with chronic inflammatory conditions (Jen Stagg et al.)** | 34 men and women diagnosed with fibromyalgia (n=6), arthritis (RA or OA, n=14), or chronic pain (n=14) | Open-label observational study conducted at with 6 practitioners as across the US. 8-week intervention. 6 x 250 mg softgels* for first 4 weeks followed by 8 x 250 mg softgels for the final 4 weeks. | • Inflammatory biomarkers improved as follows: 43% reduction in hs-CRP, normalization of $PGE_2$ within 4 weeks, significantly reduction in fibrinogen levels.<br>• Scores on the Brief Pain Inventory reduced by 46% within 4 weeks and to 50% total reduction at 8 weeks. There was significantly reduced interference with activities of daily living compared with baseline.<br>• Scores on the American Pain Association Quality of Life Scale were significantly increased at 4 and 8 weeks. |
| **SPM supplementation improves SPM status and immune cell phenotype in healthy subjects and those with peripheral artery disease (PAD) (Michael Conte et al.)** | 10 healthy men and women and 10 subjects with PAD | Dose-escalation study. Subjects completed 3 x 5-day interventions of escalating doses (1.5 g, 3 g, 6 g) of SPM supplementation** each separated by 1 week. SPM plasma status and immune cell phagocytosis, and expression of proinflammatory markers was assessed before and after each intervention phase. | • SPM supplementation increased plasma SPMs and led to a shift toward a more pro-resolving lipid mediator profile in plasma with all doses.<br>• Over the course of the study, there was a significant reduction in classical monocytes (proinflammatory) and a significant increase in nonclassical monocytes (anti-inflammatory/pro-resolving).<br>• Proinflammatory activation markers on monocytes were reduced over the course of the study in the whole group (CD18, CD26) and PAD group (CD18, CD163, CD54/ICAM-1, CCR2, CD36).<br>• Macrophages differentiated from monocytes isolated from PAD subjects showed reduced expression of proinflammatory genes.<br>• Monocyte and neutrophil phagocytosis of *E. coli* was increased over the course of the study. |

| SPM Supplementation: Summary of Evidence Table cont. | | | |
|---|---|---|---|
| **Study** | **Population** | **Study Design** | **Outcomes** |
| **In subjects with a history of chronic pain, SPM supplementation reduced pain and improved condition-related outcomes (Ryan Bradley)** | 44 men and women with a history of chronic pain lasting at least 3 months | Single-arm observational study with midstudy dose titration. Subjects consumed 6 softgels of SPM supplement* for the first 2 weeks and titrated up or down by 2 softgels depending on whether or not their pain score improved by at least 2 points. | • Average pain significantly reduced in the whole group at 2 and 4 weeks. Pain in the subgroup of "nonresponders" (did not experience a reduction of > 2 points) saw reduction in pain when the dose was increased.<br>• The whole group experienced an improvement in questionnaire scores assessing sleep and ability to carry out social activities and physical function at both 2 and 4 weeks.<br>• At 4 weeks, the whole group experienced significant reduction in scores related to depression, anxiety, and quality of life.<br>• ESR and hs-CRP remained within normal limits during the study. |
| **SPM supplementation reduces pain and inflammatory markers in patients with chronic inflammatory conditions (Erik Lundquist)** | 7 women with different ages and severity and duration of fibromyalgia (FM) | Case series conducted at a physician clinic. Patients were instructed to take 2 softgels/day for 12 weeks. Symptoms and quality of life were assessed over 12 weeks using Revised Fibromyalgia Impact Questionnaire (FIQR), MOS SF-36, PROMIS-43, and Chronic Inflammatory Response Syndrome (CIRS) Cluster Score Questionnaire. | • Physician considered 6 of the 7 patients of FM were responders to the supplementation.<br>• Marked or modest improvements were seen in patients' physical functions and activities after supplementation without flare-ups.<br>• One patient with the lowest score in CIRS indicated the supplement had a very positive impact in her life and wished the study were longer. Four patients noted a positive impact. Two patients indicated the supplement had a small or no impact.<br>• Some patients with FM are highly sensitive to environmental triggers (e.g., mold exposure) and significant life events, by which the potential effects of an SPM supplement may sometimes be overshadowed.<br>• In patients with FM, a low CIRS score (absence of biotoxin illness) may be indicative of better treatment outcomes with an SPM supplement.<br>• No patients experienced any side effects from taking the supplement. |

| SPM Supplementation: Summary of Evidence Table cont. | | | |
|---|---|---|---|
| **Study** | **Population** | **Study Design** | **Outcomes** |
| **SPM supplementation reduces pain after physical activity, improves mood, and reduces fatigue in a short case series of highly active individuals (Ryan Lazarus)** | **Patient 1:** 34 y/o male competitive cross-fit athlete presenting with mild bodily discomfort and intermittent periods of reduced mental focus.<br><br>**Patient 2:** 48 y/o woman who competes biannually in IFBB Pro Bikini Contents presented with fatigue, minimal recovery, compromised sleep, bodily discomfort, and reduced focus. | Patients were instructed to continue SPM supplementation*** for 8 weeks. Mood and health related-quality of life were assessed at baseline (Wk0) and at Wk 4 and 8. Patients scored their pain before and immediately and 24 hours after a typical workout weekly during the 8-week study. | • Patient 1 experienced 50% reduction in reported pain immediately before workouts, a 60% reduction in pain immediately after, and a 67% reduction in pain 24 hours following a typical workout over the 8-week period. He also experienced a reduction in confusion, depression, and tension during the study.<br>• Patient 2 experienced an improvement in fatigue as assessed by two different instruments. The Brunel Mood Scale (BRUMS) indicated an 87% reduction in fatigue over 8 weeks. The MOS SF-36 questionnaire indicated a 67% increase in Energy scores over 8 weeks. |

*SPM supplementation (250 mg softgel containing Active Fractionated Marine Lipid Concentrate with proprietary SPM standardization)

**Active fractionated marine lipid concentrate standardized to SPM content made up to a 30ml serving of liquid emulsion

***SPM supplementation (500 mg softgel containing Active Fractionated Marine Lipid Concentrate with proprietary SPM standardization)