Inflammation and Targeted Nutrition

Nutrition Masters Course

Anu Desai, PhD

Metagenics Institute

Learning Objectives

01

Understand normal and chronic inflammation including phases of inflammation: initiation and resolution.

02

Review the advantages of nutritional bioactives that modulate inflammation initiation.

03

Review the science behind specialized pro-resolving mediators (SPMs), their biosynthesis, and the essential role they play in inflammation resolution.

04

Discuss an integrated view of up-to-date research supporting the clinical management of inflammation in practice.

05

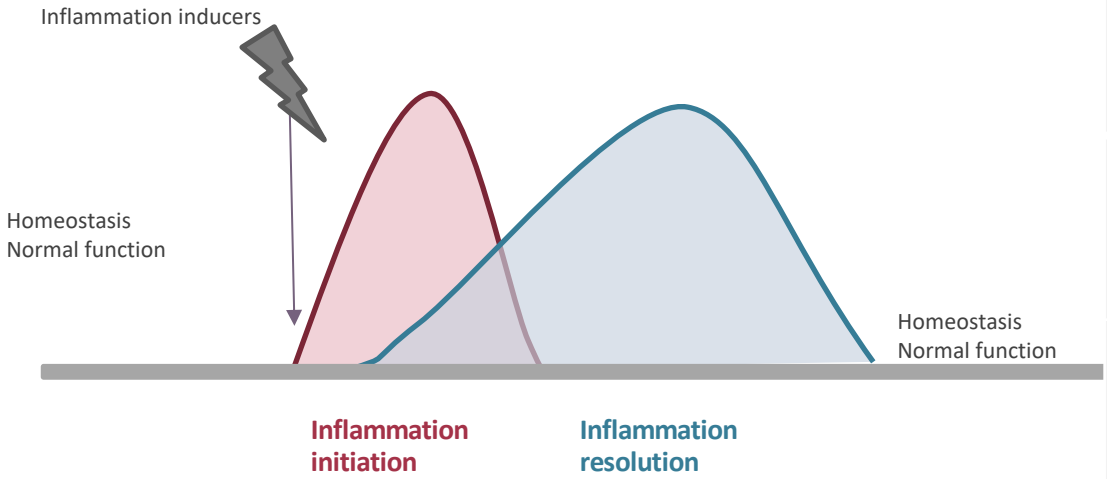
Discuss how to talk to patients about targeted nutrients and their role in inflammation and the rationale for supplementation.

Metagenics Institute

Inflammation Overview

Metagenics Institute

Normal Inflammatory Process



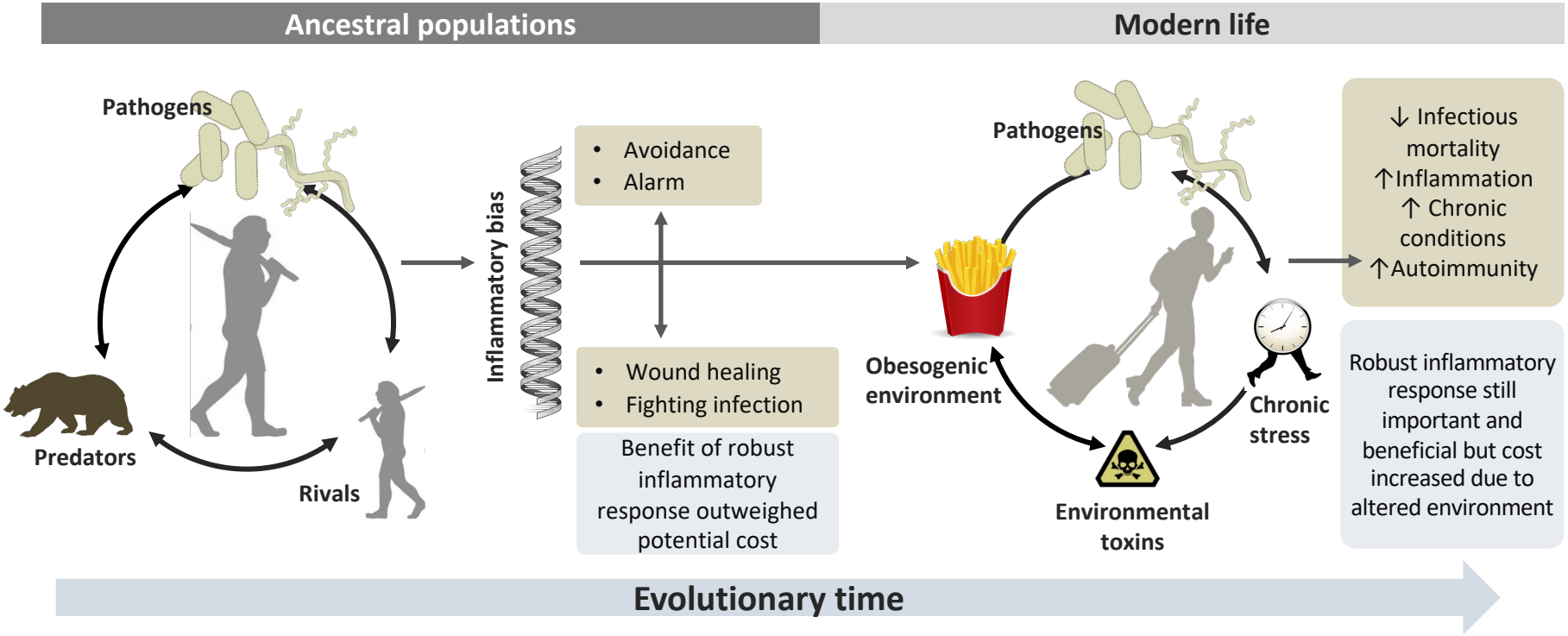
Goal	Localize and eliminate trigger of inflammation	Counter-regulate initiation; subsidence of inflammation, tissue regeneration, and return to normal function
Predominant immune cells	Neutrophils, monocytes, polymorphonuclear leukocytes (PMNs)	Resolving macrophages
Chemical mediators	Proinflammatory lipid mediators—e.g., PGs, LTs, chemokines, and proinflammatory cytokines)	Specialized pro-resolving mediators (SPMs)

Serhan CN. *Nature*. 2014;510:92-101.

Metagenics Institute

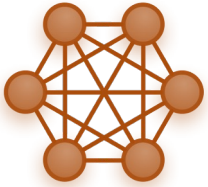
Inflammation: Friend or Foe?

Inflammation is critical for survival, but excessive inflammation is linked with disease.



Adapted from: Miller AH et al. *Nat Rev Immunol*. 2016;16(1):22–34.
Okin D et al. *Curr Biol.* 2012;22(17):R733-R740.

Metagenics Institute



Stressors of the Modern World

Dietary

- “Fast” food
- Ultraprocessed food
- Extra sugars
- Artificial ingredients

Lifestyle

- Bright gadgets at night
- Driving everywhere
- Sedentary routine
- Smoking

Psychological

- Dependence on pharmaceuticals
- Money
- Relationships

Agricultural

- Unhealthy soil
- Mass production
- Loss of biodiversity

Environmental

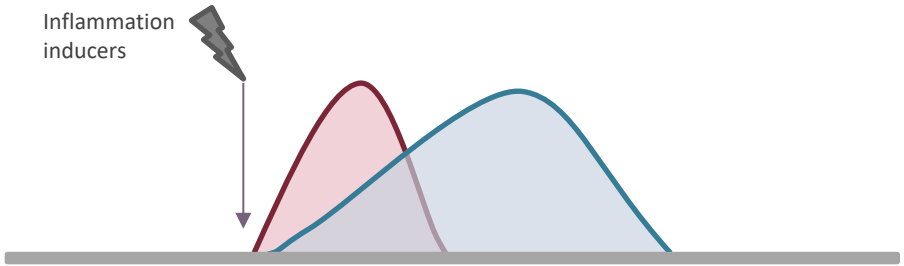
- Industrial pollutants
- Chemical products

How about COVID-19?

- Worry and fear
- Social isolation

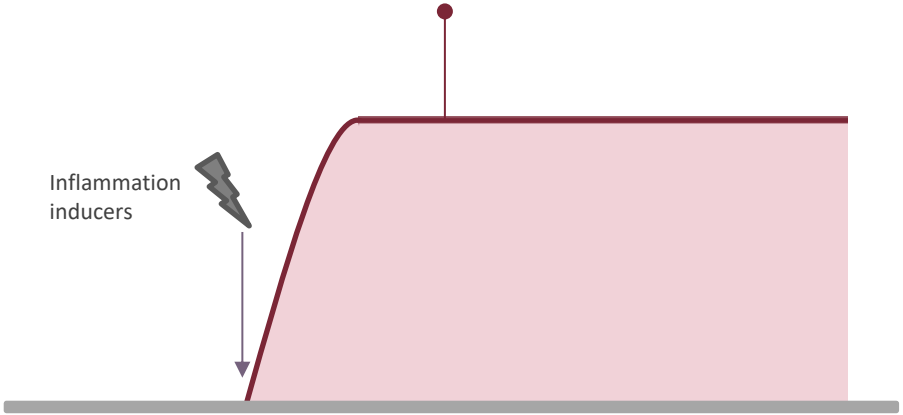
Metagenics Institute

No Resolution = Chronic Inflammation



Balanced response with active and complete resolution

Without counter-regulatory force of resolution, the inflammation response can be excessive and persistent



Impaired resolution response

Serhan CN. *Nature*. 2014;510:92-101.

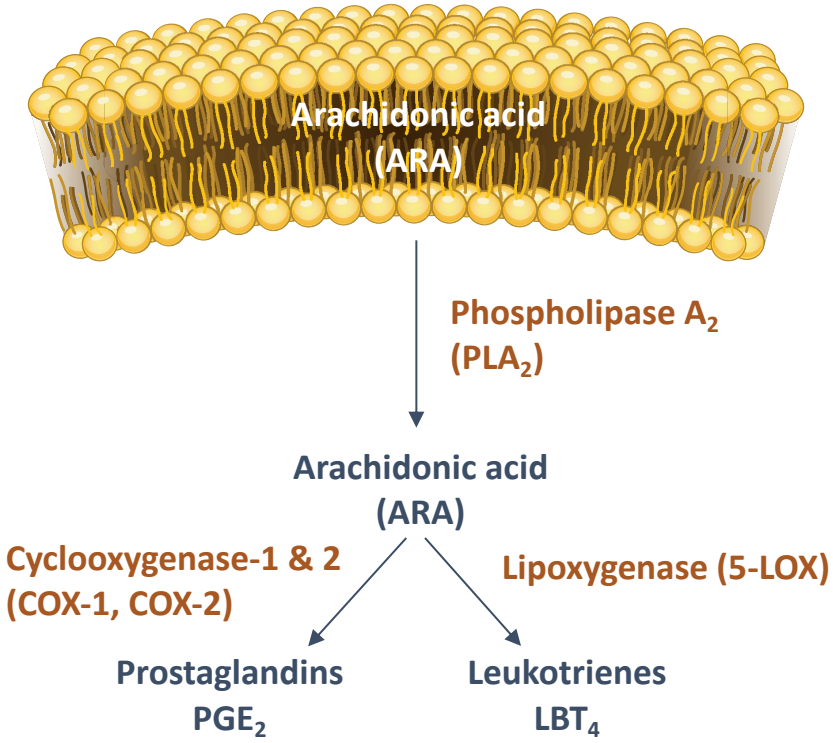
Metagenics Institute

Inflammation Initiation

Metagenics Institute

Inflammation Initiation

1. ARA is released from the cell membrane through the action of PLA_2.
2. Through the actions of COX and LOX enzymes, ARA is converted to the proinflammatory lipid mediators such as prostaglandins and leukotrienes.
3. These proinflammatory lipid mediators are key drivers of inflammation initiation, and they enhance vasodilation, attract proinflammatory immune cells to the affected tissue, and—in the case of prostaglandins—contribute to pain.



Dennis EA et al. *Chem Rev*. 2011;111(10):6130-6185.

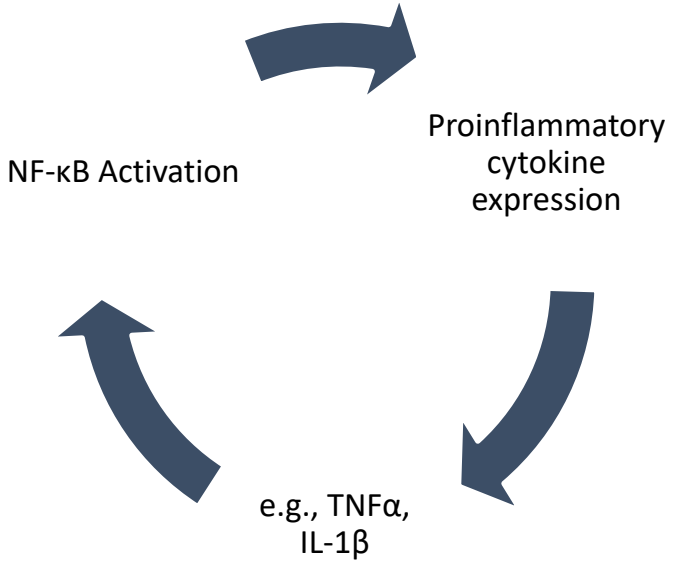
Metagenics Institute

Inflammation & Pain:
NF-κB & Proinflammatory Cytokines

Not only does NF-κB increase the **expression** of proinflammatory cytokines, some proinflammatory cytokines increase the **activation** of NF-κB

e.g., TNFα, IL-1β

Chronic inflammation persists



Hayden MS, Ghosh S. *Semin Immunol.* 2014;26(3):253-266.

Metagenics Institute

TNFα Activates NF-κB

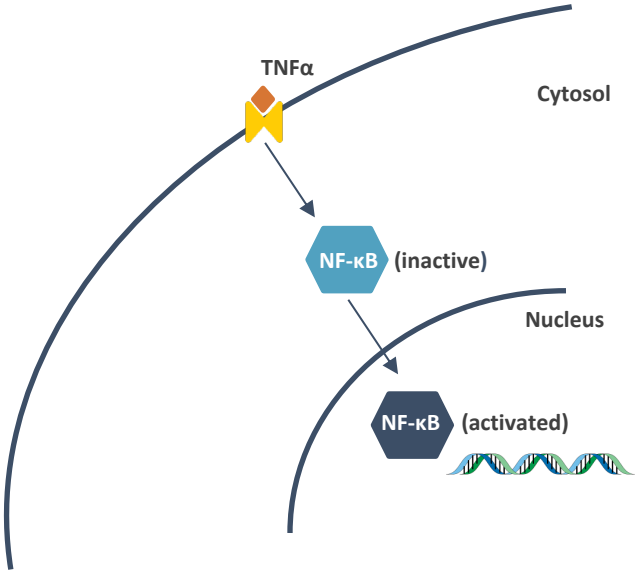
Upstream **TNFα**

NF-κB (inactive)

NF-κB (activated)

Downstream **Increased expression of:**

- **PLA_2**
- **COX-1**
- **COX-2**
- **LOX**
- **TNFα, IL-1β, IL-6, IL-12**
- **CXCL8 (IL-8)**
- **MCP-1**



Hayden MS, Ghosh S. *Semin Immunol.* 2014;26(3):253-266.
Shih R et al. *Front Mol Neurosci.* 2015;8:77.

Metagenics Institute

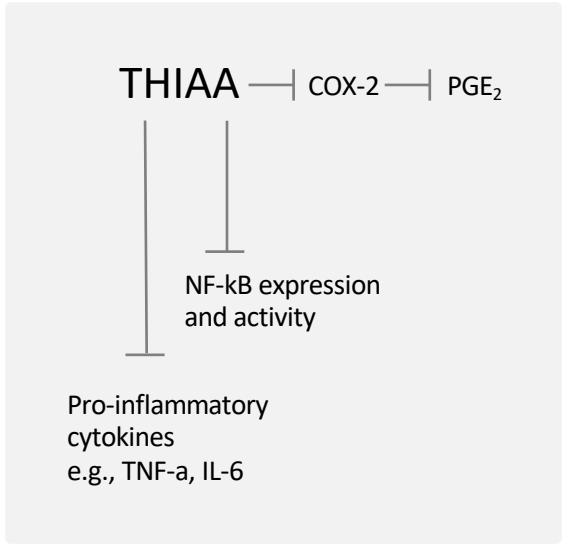
Key Nutritional Bioactives for Modulation of Inflammation Initiation

- Tetrahydro-iso-α acids (THIAA)
- Curcumin
- Xanthohumol
- *Boswellia serrata*
- Ginger
- Palmitoylethanolamide (PEA)
- Omega-3 fatty acids EPA and DHA

Metagenics Institute

Tetrahydro-iso-α acids (THIAA) from Hops Have Anti-Inflammatory Properties

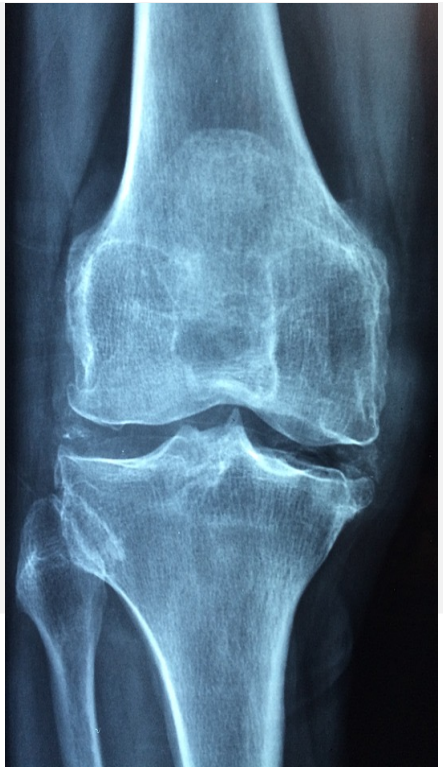
Mechanistic studies in endothelial cells, monocytes, macrophages, and human rheumatoid arthritis synovial fibroblasts indicate anti-inflammatory activities of THIAA.



Desai A et al. *Inflamm Res.* 2009;58(5):229-34.
Konda VR et al. *Arthritis Rheum.* 2010;62(6):1683-1692.
Desai A et al. *Atherosclerosis.* 2012;223:130-136.

Metagenics Institute

Tetrahydro-iso-α acids (THIAA) from Hops Have Anti-Inflammatory Properties



In a mouse model of induced arthritis, treatment with THIAA

- ✓ Reduced paw swelling
- ✓ Reduced arthritis index
- ✓ Reduced extent of joint damage
- ✓ Reduced cartilage degradation
- ✓ Reduced bone erosion
- ✓ Reduced IL-6 levels

Konda VR et al. *Arthritis Rheum.* 2010;62(6):1683-1692.

Metagenics Institute

Curcuminoids: Isolated Constituents

- Primary active constituents in turmeric root (*Curcuma longa*)
- Turmeric has culinary and potential therapeutic uses

Properties

- **Analgesic**: Reduces pain including neuropathic pain [1-2]
- **Antiarthritic**: Safe and effective in reducing joint inflammation, pain, function, and stiffness in osteoarthritis patients[3]
- **Anti-inflammatory**[1-3]
- **Antioxidant**[4]
- Other: Inflammatory bowel disease (animal models and pilot human data),[5] antidepressant (clinical data),[6,7] antidiabetic (clinical data),[8-10] cardiovascular risk markers (clinical data)[11,12]

1. Caillaud M et al. *Antioxidants.* 2020; 9(10): 950.
2. Wang Z et al. *Curr Rheumatol Rep.* 2021;23(2):11.
3. Zeng L et al. *Biosci Rep.* 2021;41(6):BSR20.
4. Shezhad A et al. *J Food Sci.* 2017;82(9):2006-2015.
5. Vecchi Brumatti L et al. *Molecules.* 2014;19(12):21127-21153.
6. Sanmukhani J et al. *Phytother Res.* 2014;28(4):579-585.
7. Lopresti AL et al. *J Affect Disord.* 2014;167:368-375.
8. Maradana MR et al. *Mol Nutr Food Res.* 2013;57(9):1550-1556.
9. Na LX et al. *Mol Nutr Food Res.* 2013;57(9):1569-1577.
10. Chuengsamarn S et al. *Diabetes Care.* 2012;35(11):2121-2127.
11. Khurana S et al. *Nutrients.* 2013;5(10):3779-3827.
12. Chuengsamarn S et al. *J Nutr Biochem.* 2014;25(2):144-150.

Metagenics Institute

Boswellia Serrata

- Also known as Indian frankincense
- A “gum resin” from the *Boswellia serrata* tree
- Contains a few active constituents:
  - 3-Acetyl-11-keto-β-boswellic acid
  - Beta-boswellic acids
  - Alpha-boswellic acids
  - Essential oils
  - Flavonoids—quercetin
- **Properties**
  - **Analgesic** (increased pain threshold in healthy subjects)[1]
  - **Antiarthritic** (reduced inflammatory markers and reduced knee pain in subjects with OA)[2-4]
  - **Anti-inflammatory and anti-oxidant signaling**[5]

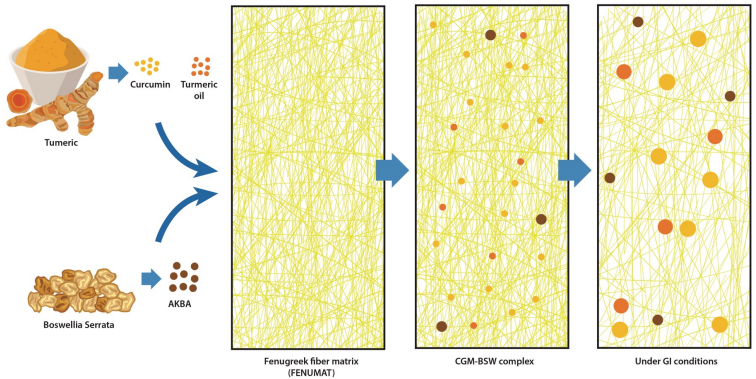
1. Prabhavathi K et al. *Indian J Pharmacol.* 2014;46(5):475-479.
2. Umar S et al. *Phytomedicine.* 2014;21(6):847-856.
3. Bannuru R et al. *Semin Arthritis Rheum*. 2018; 48(3):416–429.
4. Majeed M et al. *Phytother Res*. 2019;33(5):1457-1468.
5. Du Z et al. *Planta Med.* 2015;81(4):259-267.

Metagenics Institute

FENUMAT Technology

Curcumin and Boswellia as CGM-BSW

- Enhanced absorption of poorly bioavailable lipophilic nutrients—curcuminoids and AKBA from fenugreek galactomannan hydrogel beadlets—**fenugreek dietary fiber-mediated technology** (FENUMAT technology)
- Curcumagalactomannoside-Boswellia (CGM-BSW)
- Combines curcumin and Boswellia with galactomannan fibers (from fenugreek seeds)
- Bioavailability[1-3]
  - Enhanced absorption of curcuminoids and AKBA into the bloodstream
  - Exceptional delivery to target tissues



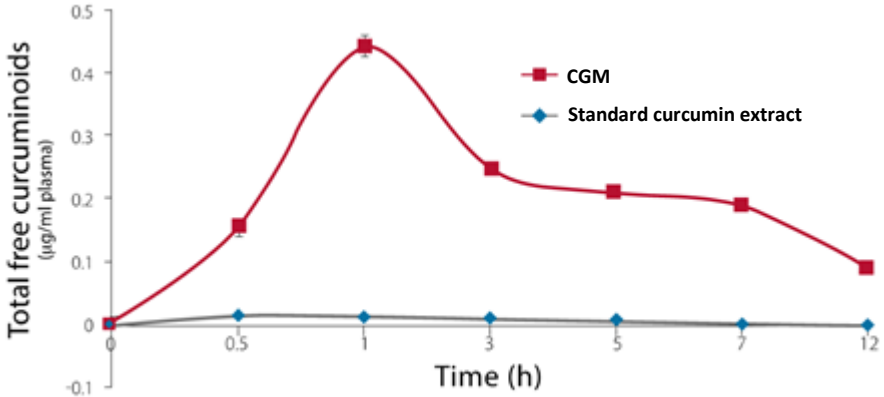
Adapted from: Abhilash MB et al. *J Funct Foods*. 2021;79:104405

1. Abhilash MB et al. *J Funct Foods*. 2021;79:104405
2. Kumar D et al. *J Funct Foods.* 2016; 22:578-587.
3. IM K et al. *J Funct Foods*. 2015;14:215-225.

Metagenics Institute

Circulating Free Curcuminoids in Human Plasma Are Higher with CGM Compared to Standard Curcumin Extract

- Studies have shown that CGM is exceptionally well-absorbed compared to standard curcumin
- Plasma curcuminoids were assayed after a single 1,000 mg dosage



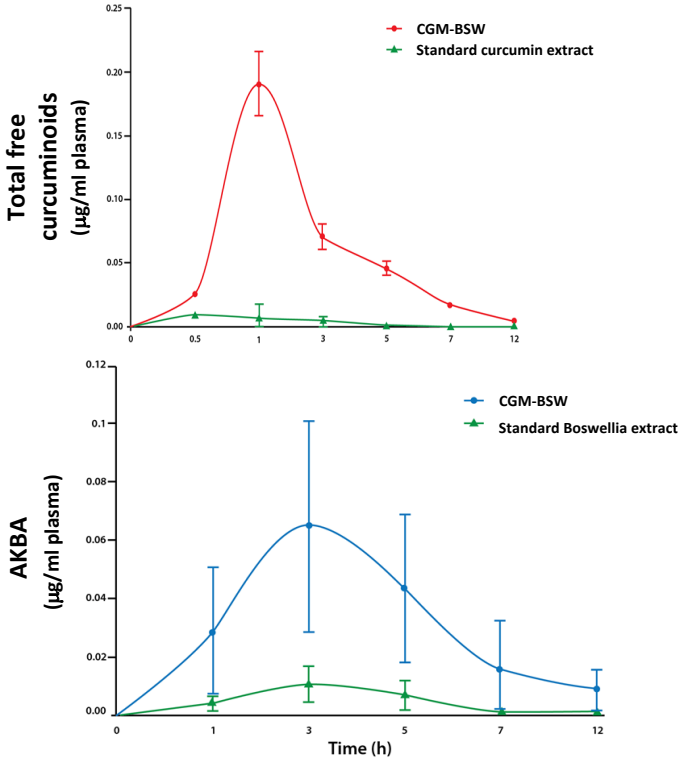
In a randomized, crossover study of 50 subjects, the CGM group demonstrated 45.5-fold more bioavailability of free curcuminoids in plasma (AUC) as per UPLC-MS/MS detection method. Subjects were given a single dose of 1000 mg of CGM in each group, and curcumin levels were measured over 12 hours. No glucuronidase enzyme was used for the treatment of blood to convert the glucuronides to free curcumin; therefore, the quantification is mainly for the free curcuminoids (curcumin, demethoxycurcumin, and bisdemethoxycurcumin). Data represented as mean±SEM.

Adapted from: Kumar D et al. *J Functional Foods.* 2016; 22:578-587.

Metagenics Institute

Circulating Free Curcuminoids and AKBA in Human Plasma Are Higher with CGM-BSW Compared to Standard Curcumin and Boswellia Extracts

- CGM-BSW beadlets
  - Capable of extensive swelling
  - Sustained release of self-emulsified colloidal particles containing curcuminoids and AKBA
- CGM-BSW well-absorbed compared to standard curcumin and Boswellia extracts
- Plasma curcuminoids and AKBA were assayed after a single 250 mg dosage



In a randomized, crossover study of 14 subjects, the CGM-BSW group demonstrated 24.8-fold more bioavailability of free curcuminoids and 6.9-fold more bioavailability of AKBA in plasma (AUC) as per UPLC-MS/MS detection method. Subjects were given a single dose of 250 mg of CGM-BSW in each group, and curcumin and AKBA levels were measured over 12 hours. No glucuronidase enzyme was used for the treatment of blood to convert the glucuronides to free curcumin; therefore, the quantification is mainly for the free curcuminoids (curcumin, demethoxycurcumin, and bisdemethoxycurcumin). Data represented as mean±SEM.

Adapted from: Abhilash MB et al. *J Funct Foods*. 2021;79:104405

Metagenics Institute

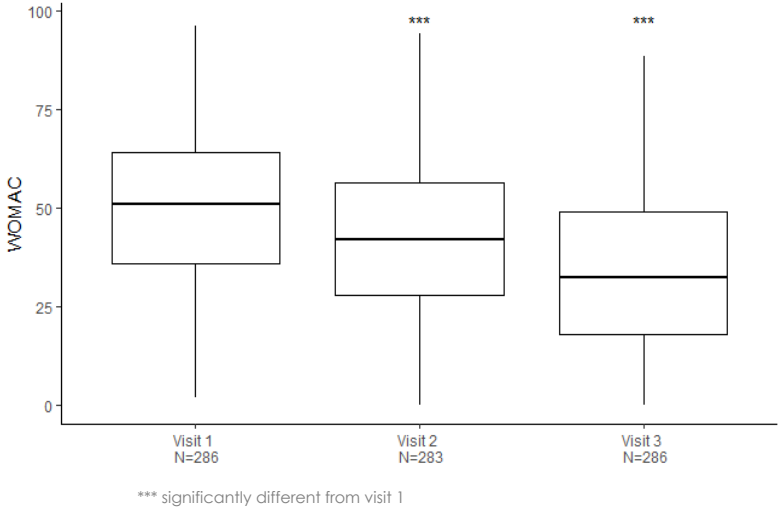
CGM-BSW Improved Joint Pain and Stiffness in Osteoarthritis Patients

Treatment:

- 30 days for 286 osteoarthritis patients

Outcomes:

- Statistically significant reduction in the WOMAC score
- Improvement in chronic pain and stiffness conditions as early as 14 days
- Clinically significant improvement at 30 days
- Improvement in physical functioning
- No significant side effect linked to intake



WOMAC—Western Ontario and McMaster Universities Arthritis Index

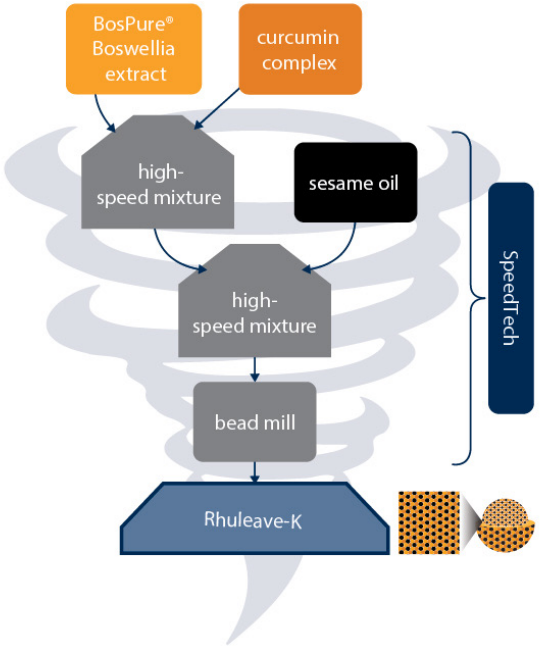
Adapted from: Salamone M et al. *L'Integratore Nutrizionale*. 2020; 23:10-16.

Metagenics Institute

SpeedTech™ Technology Designed to Enhance Curcumin and Boswellia Absorption

The combination of curcumin and Boswellia extracts, Rhuleave-K™, features SpeedTech technology.

SpeedTech is a micronization technology that combines herbal actives like curcumin and Boswellia in a lipid matrix (black sesame oil) using a proprietary process, creating a specialized formula with smaller particle sizes for increased absorbability.

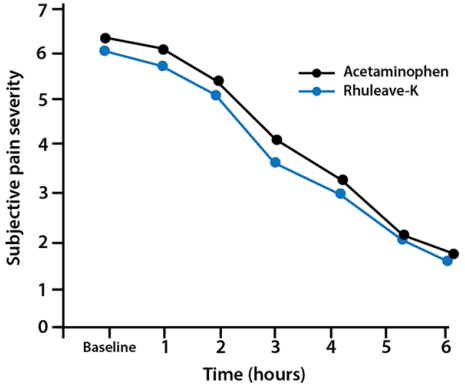


Rudrappa G et al. *Medicine (Baltimore).* 2020;99(28):e20373.

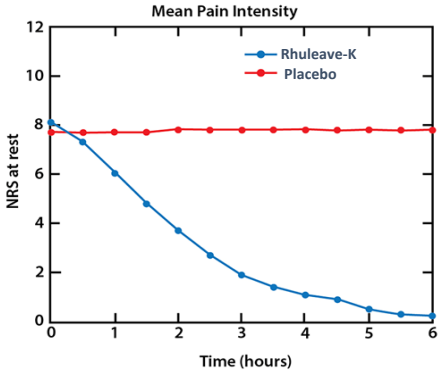
Metagenics Institute

Rhuleave-K—Effective Pain Relief for Short-Term (Acute) Episodes of Musculoskeletal Pain and Soreness

Suitable as an alternative to over-the-counter analgesics: A recent randomized controlled trial concluded Rhuleave-K provides meaningful acute musculoskeletal pain intensity and relief, comparable to acetaminophen (paracetamol) as fast-acting, safe, and efficient, with the average onset being 1 hour.[1]



Analgesic: Research shows that Rhuleave-K provides over 96% reduction in pain intensity, irrespective of location of pain, compared to placebo (p=0.004), as shown in a randomized clinical trial in > 230 healthy adults aged 18 to 65 with acute musculoskeletal pain.[2]



1. Adapted from: Rudrappa G et al. *Medicine (Baltimore).* 2020;99(28):e20373.
2. Adapted from: Murthy M et al. *Sch J App Med Sci.* 2022; 10(3): 311-326.

Metagenics Institute

Xanthohumol: An Isolated Constituent

- Xanthohumol is one of many active constituents in hops flowers (*Humulus lupulus*)
- Hops flowers have commercial uses (to flavor and preserve beer) and medicinal uses
- Xanthohumol is safe and well-tolerated in human study [1]

Properties[2]

- **Anti-inflammatory**
- **Antioxidant**

Evidence:

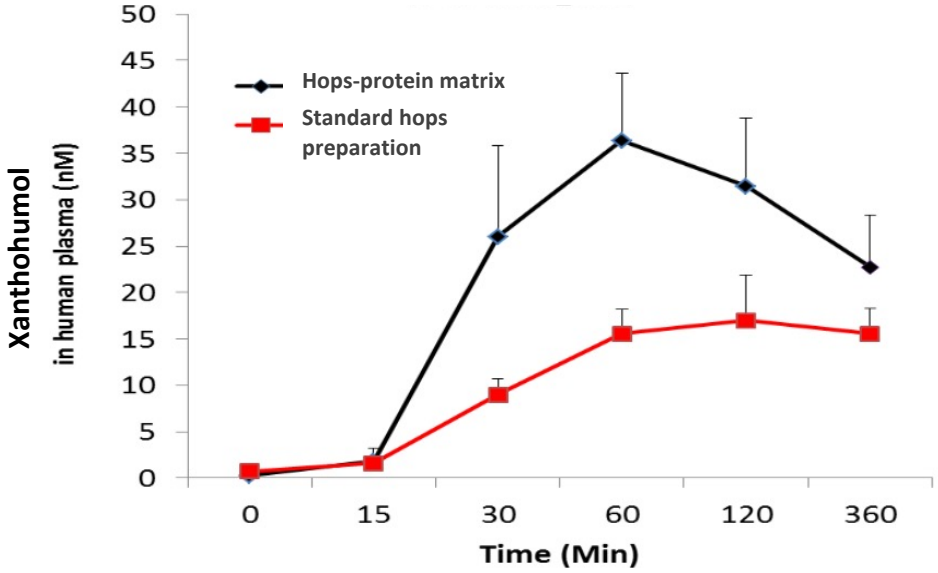
- Antiarrhythmic and antiatherosclerotic properties in animal models,[2-4] reduced platelet activation (human *ex vivo*),[5] antiobesity and glucose-lowering effect in animal models,[6] reduced DNA damage (clinical study)[7]

1. Langley BO et al. *Mol Nutr Food Res.* 2021; 65(8): e2001170.
2. Liu M et al. *Molecules.* 2015;20(1):754-779.
3. Arnaiz-Cot JJ et al. *J Pharmacol Exp Ther.* 2017;360(1):239-248.
4. Liu et al. *J Nat Prod.* 2017;80(7):2146-2150.
5. Hirata et al. *PLoS One.* 2012;7(11):e49415.
6. Lee YM et al. *Evid Based Complement Alternat Med.* 2012;2012:852362.
7. Legette LL et al. *Phytochemistry.* 2013;91:236-241.

Metagenics Institute

Xanthohumol Availability Is Enhanced by Delivery Through a Hops-Protein Matrix

- Xanthohumol is generally not well absorbed
- Xanthohumol given as part of a hops-protein matrix shows enhanced bioavailability compared to standard hops-xanthohumol preparations



Adapted from: O'Connor A. *Mol Nutr Food Res*. 2018;62(6):e1700692.

Metagenics Institute

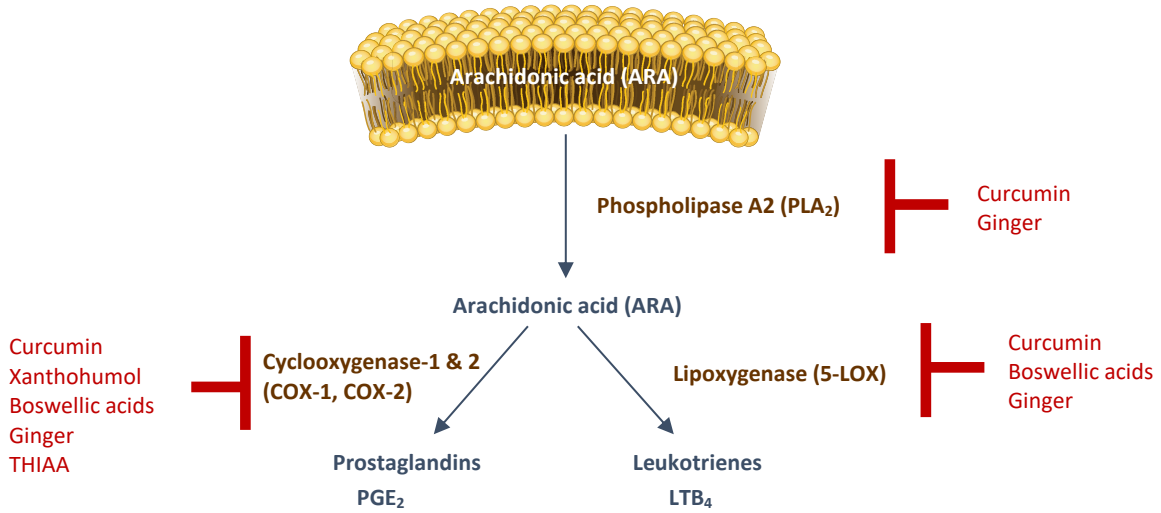
Ginger Root

- Contains several constituents:
  - Gingerol
  - Gingerdione
  - Shogaol
  - Sesquiterpene and monoterpene volatile oils
- Properties[1-4]
  - **Analgesic**
  - **Anti-inflammatory**
  - **Antioxidant**

1. Araya-Quintanilla F et al. *Pain Physician*. 2020;23(2):E151-E161.
2. Rondanelli M et al. *Phytother Res*. 2020;34(11):2843-2856.
3. Semwal RB et al. *Phytochemistry.* 2015;117:554-568.
4. Rayati F et al. *Dent Res J.* 2017;14(1):1-7.

Metagenics Institute

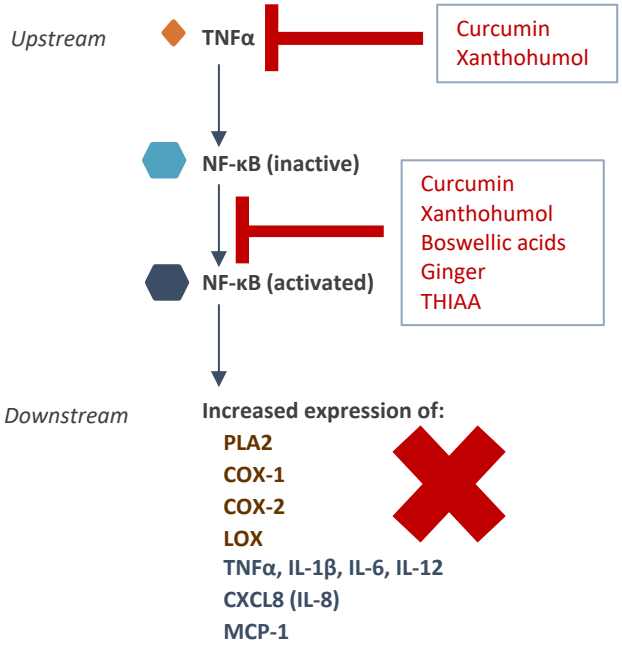
Inflammation & Pain: Key Enzymes

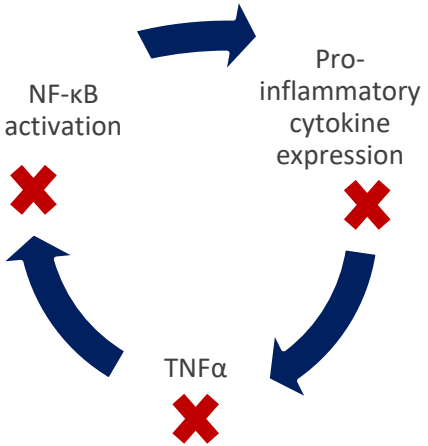


Perrone D et al. *Exp Ther Med.* 2015;10(5):1615-1623.
Zhou H et al. *Curr Drug Targets*. 2011;12(3):332-347.
Nievergelt A et al. *J Immunol.* 2011;187(8):4140-4150.
Kunnumakkara AB et al. *Br J Pharmacol.* 2017;174(11)1325-1348.
Weiskirchen R et al. *Front Physiol.* 2015;6:140.
Abdel-tawab M et al. *Clin Pharmacokinet*. 2011;50(6):349-369.
Grzanna R et al. *J Med Food*. 2005;8(2):125-132.
Desai A et al. *Inflamm Res.* 2009;58:1-6.
Konda VR et al. *Arthritis Rheum.* 2010;62(6):1683-1692.
Desai A et al. *Atherosclerosis.* 2012;223:130-136.

Metagenics Institute

Phytonutrients Shown to Modulate Inflammatory Cascade





Panahi Y et al. *Biomed Pharmacother*. 2016;82:578-582.
Lupinacci EL et al. *J Agric Food Chem*. 2009;57(16):7274-7281.
Kunnumakkara AB et al. *Br J Pharmacol.* 2017;174(11)1325-1348.
Weiskirchen R et al. *Front Physiol.* 2015;6:140.
Liu M et al. *Molecules*. 2015;20(1):754-779.
Khan MA et al. *Molecules*. 2015;20(1):754-779.
Desai A et al. *Inflamm Res.* 2009;58:1-6.
Konda VR et al. *Arthritis Rheum.* 2010;62(6):1683-1692.
Desai A et al. *Atherosclerosis.* 2012;223:130-136.

Metagenics Institute

Palmitoylethanolamide (PEA)

- Naturally occurring lipid in plants and animals
- PEA is an endogenous endocannabinoid receptor agonist[1]
- Possess physiological activities including[1-3]
  - Neuroprotective
  - Antiepileptic
  - Antinociceptive
  - Anti-inflammation

Example natural sources of PEA[1]

Soy lecithin	Soybean	Peanut	Cotton
950 µg/g fw	6.7 µg/g fw	3.73 µg/g fw	0.35 µg/g fw
			
Corn	**Alfalfa**	**Garden pea**	**Tomato**
0.2 µg/g fw	1.1 µg/g fw	0.1 µg/g fw	0.1 µg/g fw
			
Edible bivalve mollusks	**Yeast**	**Human breast milk**	**Human muscle**
20–60 ng/g ww	650 pmol/g of protein	8.98 ± 3.35 nmol/l	0.53 nM
			
Human eye tissues	**Human colon**	**Human blood**	**Human knee joint**
95–637 pmol/g	109 pmol/g (range 28–401)	14 pmol/ml	1,000–2,300 pmol/g
			

fw, fresh weight; ww, wet weight

1. Esposito E et al. *Mini RevMed Chem.* 2013;13:237–255.
2. Couch DG et al. *Clin Sci.* 2017;131:2611–2626.
3. Keppel Hesselink JM et al. *PharmaNutrition*. 2014;2:19–25.

Metagenics Institute

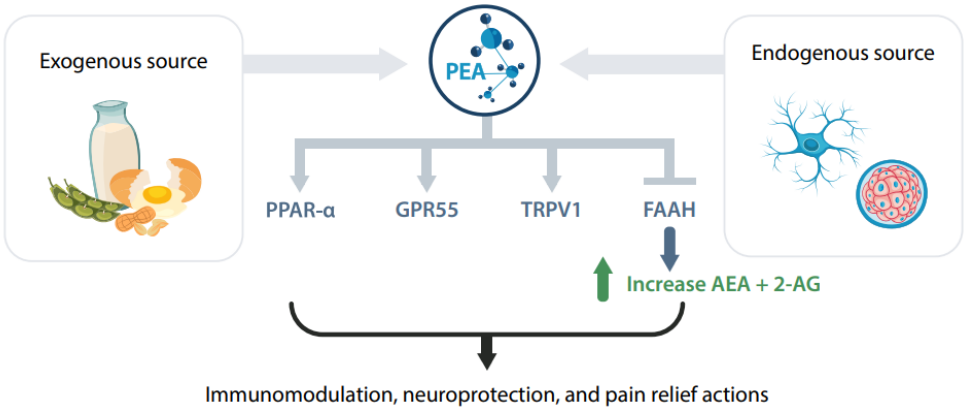
PEA Exerts an Entourage Effect by Interacting with Endocannabinoid System (ECS)

Entourage effect on ECS[1–4]

- Enhances actions/levels of eCBs AEA and 2-AG by:
  - Inhibiting FAAH-mediated AEA breakdown
  - Increasing their affinity for receptors CB1, CB2, and TRPV1 channels

Direct receptor-mediated mechanism[1,5]

- Agonist of PPARα
  - Anti-inflammatory and analgesic effects
  - TRPV1 receptor activation via PPARα in sensory neurons
- GRP55 and GR119 receptors—expressed primarily in the gut



2-AG, 2-arachidonoyl-glycerol; CB1, cannabinoid receptor 1; CB2, cannabinoid receptor 2; GPR55, orphan GPCR 55; PPARα, peroxisome proliferator-activated receptor alpha; TRPV1, transient receptor potential vanilloid type-1

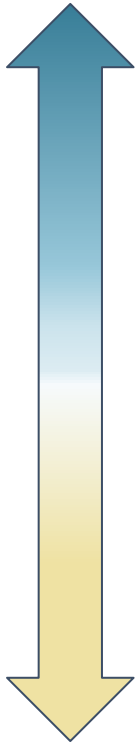
1. Iannotti FA et al. *Prog Lipid Res* 2016;62:107–128.
2. Garcia MD et al. *Eur J Pharmacol.* 2009;610:75–80.
3. Bisogno T et al. *J Biol Chem.* 1997;272:3315–3323.
4. Jonsson KO et al. *Br J Pharmacol.* 2001;133:1263–1275
5. Keppel Hesselink JM et al. *PharmaNutrition.* 2014;2:19–25.

Metagenics Institute

Changes in PEA Levels as a Response to Cellular Injury

Decreased PEA levels may contribute to cell damage in **chronic conditions**:

- Huntington's disease (animal model)
- Obesity (human)
- Chronic inflammation e.g. osteoarthritis (human)



PEA levels increase in response to injury and pain contributes as an adaptive protective mechanism to cell protection in **acute conditions:***

- Stroke (animal model)
- Migraine (human)
- Ulcerative colitis (human)
- Spinal cord injury (animal model)

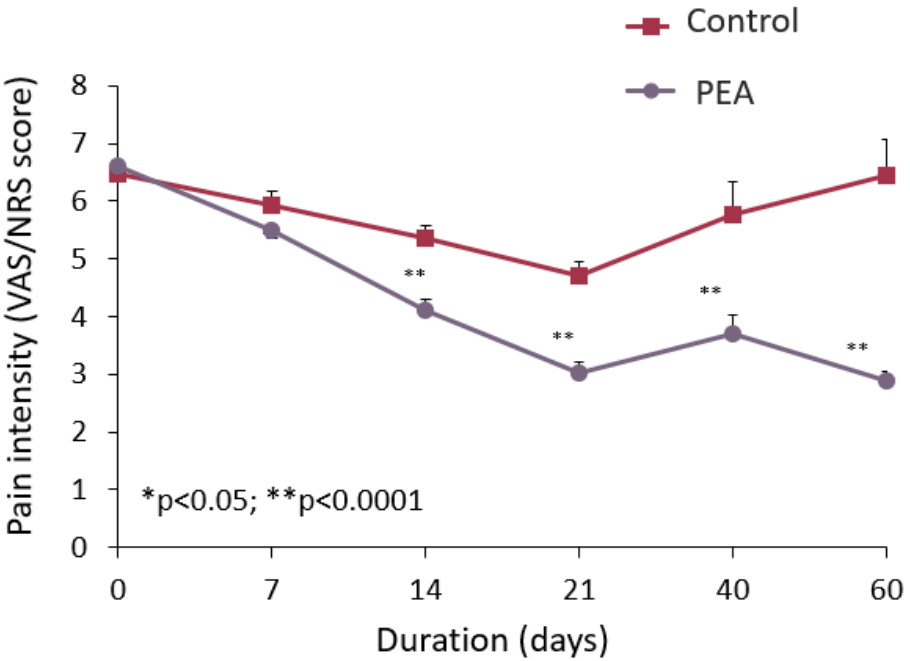
*Even though the endogenous levels of PEA are upregulated during some neurological diseases, its production may not always be sufficient to exert neuroprotection and anti-inflammatory actions

Esposito E et al. *Mini Rev Med Chem.* 2013;13:237–255.
Petrosino et al. *Br J Pharmacol*. 2017;174(11):1349–1365.

Metagenics Institute

PEA in Chronic Pain Management; Meta-Analysis

- Pooled data of 12 trials
- 300–1,200 mg/day for 21–60 days
- Significantly reduced pain intensity over time
- Benefits of PEA were independent of age, sex, or pain type



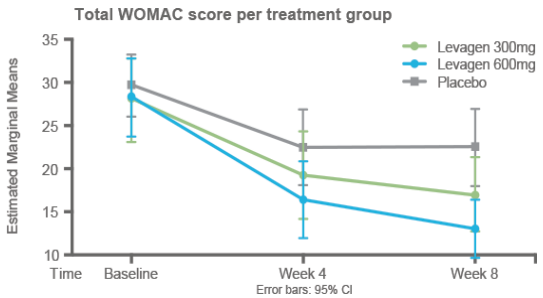
Adapted from Paladini A et al. *Pain Physician*. 2016;19:11–24.

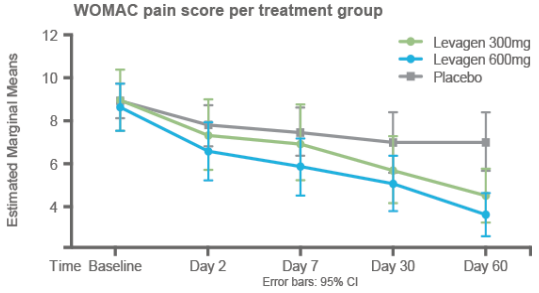
Paladini A et al. *Pain Physician*. 2016;19:11–24.

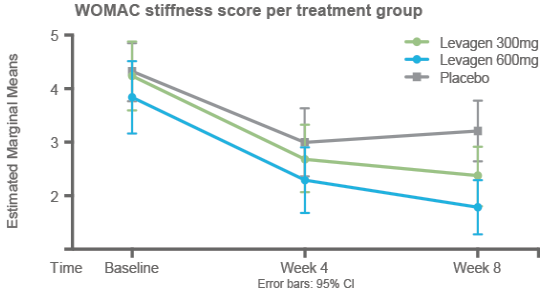
Metagenics Institute

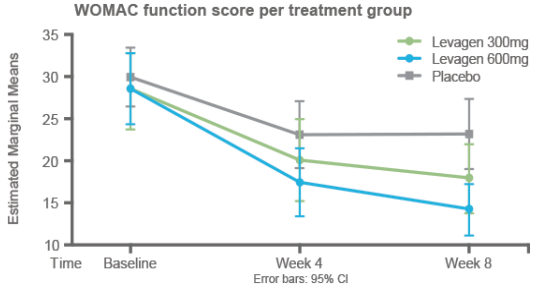
Levagen® PEA for Symptoms of Knee Osteoarthritis

- DouPEA in Chronic Pain Management; Meta-Analysable-blind placebo-controlled study in adults with mild to moderate knee osteoarthritis
- 300 mg PEA, 600 mg PEA or placebo for 8 weeks
- Significant reduction in total, pain, stiffness, and function scores









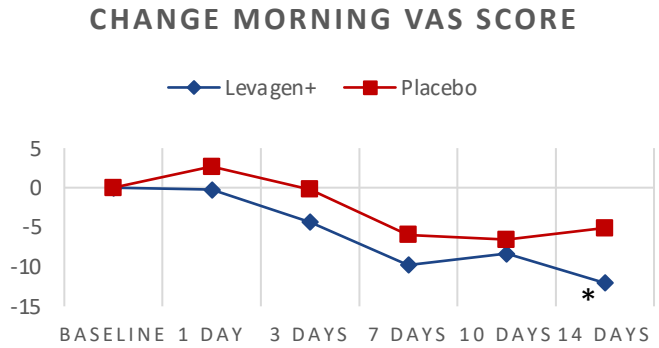
Steels E et al. *Inflammopharmacology*. 2019;27(3):475-485

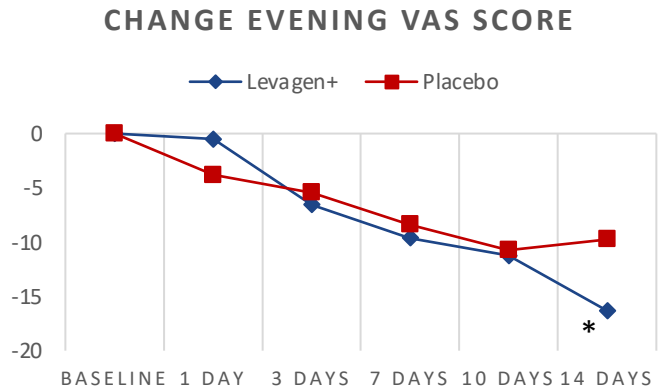
Metagenics Institute

Levagen+ PEA Alleviating Joint Pain and Improving Quality of Life in Adults

2-week double-blind, randomized, placebo-controlled study:

- 350 mg of Levagen+ for reducing joint pain in healthy adults
- Significant reduction in joint pain score after Day 3
- Improvement in QOL





Brisky D et al. *Inter J Nutr and Food Scien* 2021;10(1):9-13.

Metagenics Institute

Levagen+ PEA for Pain Severity and Duration of Headaches

Double-blind, randomized controlled study:

- Levagen+ containing 475 mg PEA compared with 400 mg ibuprofen (NSAID)
- Levagen+ was equivalent to ibuprofen across the whole spectrum of headache resolutions
- Levagen+ acted faster than ibuprofen in resolving severe headaches

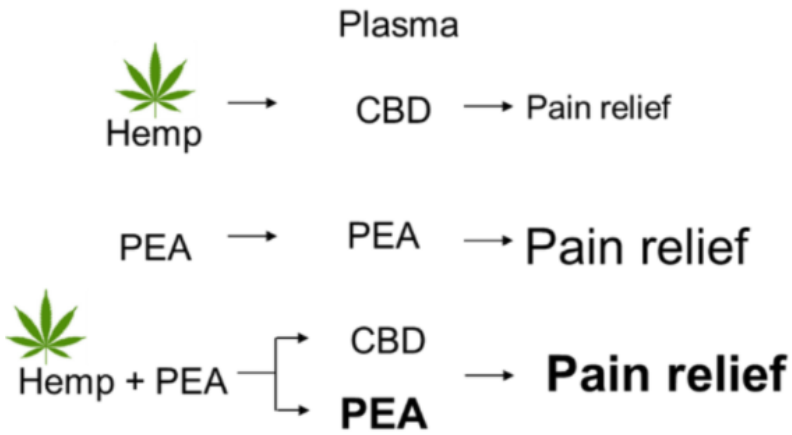
Briskey D et al. *Food and Nutr Sci*. 2022; 13: 690-701.

Metagenics Institute

Palmitoylethanolamide and Hemp Oil Extract Exert Synergistic Antinociceptive Effects

Mouse models of acute and chronic pain:

- A proprietary, organic, full-spectrum hemp oil extract alone modestly effective in treating acute and chronic pain
- PEA alone showed a dose-dependent effect in reducing acute and chronic pain
- Hemp oil extract strongly enhanced the analgesic effects of PEA such that the combination of the two compounds exerted greater-than-additive alleviation of pain-related behaviors
- The synergism was partially supported by hemp oil extract's extending the life of PEA in the blood circulation and therefore prolonging its actions



Tange AM et al. *Pharmacol Res*. 2021;167:105545.

Metagenics Institute

Clinical Evidence Supporting the Therapeutic Application of PEA in Pain Management

Lower back pain[1–4]

- ☐ Reduced pain
- ☐ Improved physical function/reduced disability
- ☐ Effective add-on therapy to standard treatments
- ☐ May act on neuropathic compartment of sciatica
- ☐ Reduced need for analgesia

Chronic pain[5–11]

- ☐ Reduced pain in various chronic conditions, particularly pelvic pain
- ☐ Reduced pelvic pain incl. postoperative pain vs. PBO (endometriosis)
- ☐ Reduced need for analgesia (endometriosis)
- ☐ Reduced pain, swelling, and disability (CRPS-T1 + topical ketamine)
- ☐ Reduced pain in CP/CPPS in combination with ALA

Neuropathic pain (NP)[12–19]

- ☐ Improvement in NP associated with diabetes, trauma, and chemotherapy but not spinal cord injury
- ☐ Reduced symptoms of diabetic NP, improved QoL
- ☐ Reduced pain and need for acupuncture in MS
- ☐ Reduced NP after stopping pregabalin due to AEs
- ☐ Effective as monotherapy or in combination with analgesics
- ☐ May reduce mast cell hyperactivity and restore nerve function

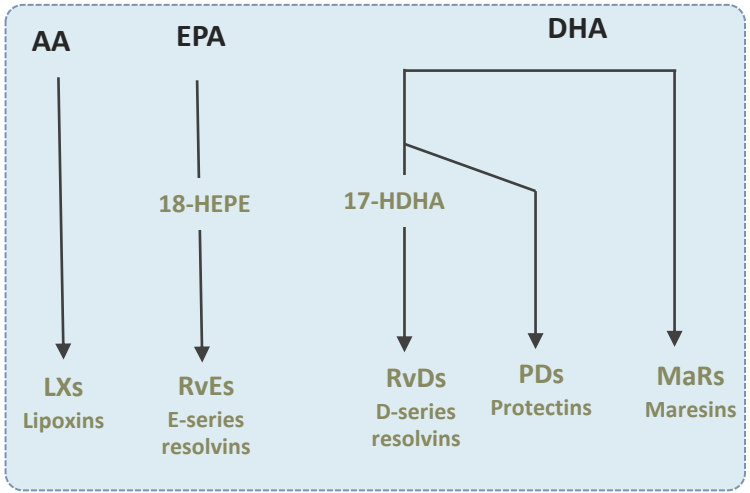
Pain—other[20–26]

- ☐ Reduced pain across range of conditions
- ☐ Reduced number of tender points (fibromyalgia)
- ☐ Reduced need for NSAIDs
- ☐ Reduced pain; improved nerve function and sleep quality (CTS)*
- ☐ Reduced abdominal pain (IBS)
- ☐ Improved pain relief vs. TENS alone (recent-onset vestibulodynia)

1. Dominguez VM et al. *Pain Manag*. 2012;2:119–124.
2. Cruccu G et al. *CNS Neurol Disord Drug Targets*. 2019;18:491-495.
3. Passavanti MB et al. *BMC Anesthesiol*. 2017;17:171.
4. Chirchiglia D et al. *Neurol Neurochir Pol*. 2018;52:44–47.
5. Gatti A et al. *Pain Med*. 2012;9:1121–1130.
6. Cobellis L et al. *Eur J Obstet Gynecol Reprod Biol*. 2011;158: 82–86.
7. Giugliano E et al. *Eur J Obstet Gynecol Reprod Biol*. 2013;168:209–213.
8. Indraccolo U et al. *Ann Ist Super Sanita*. 2017;53:125–134.
9. Indraccolo U et al. *Eur J Obstet Gynecol Reprod Biol*. 2010;1:76–79.
10. Keppel Hesselink JM et al. *J Pain Res*. 2013;6:239–245.
11. Giammusso B et al. *Arch Ital Urol Androl*. 2017;89:17-21.
12. Cocito D et al. *Pain Res Treat*. 2014;2014:854560.
13. Schifilliti C et al. *Pain Res Treat*. 2014;2014:849623.
14. Truini A et al. *CNS Neurol Disord Drug Targets*. 2011;10:916–920.
15. Andresen SR et al. *Pain*. 2016;157(9):2097-103.
16. Keppel Hesselink JM et al. *Int Med Case Rep J*. 2013;6:49–53.
17. Kopsky DJ et al. *Acupunct Med*. 2012;1:53–55.
18. Calabro RS et al. *Pain Med*. 2010;11:781–784.
19. Semprini R et al. *Minerva Med*. 2018;109:358-362.
20. Marini I et al. *J Orofac Pain*. 2012;26:99–104.
21. Del Giorno R et al. *Pain Ther*. 2015;4:169–178.
22. Bacci C et al. *ISRN Surg*. 2011;2011:917350.
23. Murina F et al. *ISRN Surg*. 2011;2011:917350.
24. Conigliaro R et al. *Minerva Med*. 2011;102:141–147.
25. Cremon C et al. *Aliment Pharmacol Ther*. 2017;45:909-922.
26. Evangelista M et al. *CNS Neurol Disord Drug Targets*. 2018;17:291-298.

Metagenics Institute

Specialized Pro-Resolving Mediators



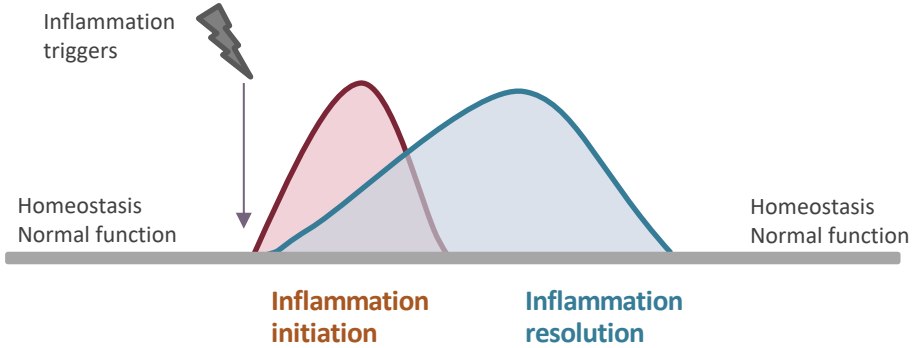
Specialized Pro-Resolving Mediators

Adapted from: Serhan CN. *FASEB J.* 2017;31(4):1273-1288.

1. Specialized pro-resolving mediators (SPMs) are a group of lipid mediators that drive the resolution of inflammation.
2. SPMs can be produced endogenously in the body from precursor polyunsaturated fatty acids (AA, EPA, and DHA).
3. SPMs are required for inflammation resolution to occur and for effective return to homeostasis or previously normal conditions.
4. There are several classes of SPMs (lipoxins, resolvins, protectins and neuro-protectins, maresins) that all work together to resolve inflammation.
5. Key hydroxylated precursor SPMs such as 18-HEPE and 17-HDHA can give rise to an array of downstream SPMs that have been identified to date. 18-HEPE can be converted into 4 distinct E-series resolvins (RvE_{1-4}) and 17-HDHA can be converted into 6 distinct D-series resolvins (RvD_{1-6}).

Metagenics Institute

Hallmarks of SPM Activity and Inflammation Resolution



SPMs actively promote inflammation resolution

- Enhance macrophage phagocytosis and efferocytosis, which clears up dead or dying cells and cellular debris
- Shorten the time to resolution
- Increase the production of anti-inflammatory mediators
- Increase the killing and clearance of microbes
- Enhance tissue regeneration

SPMs act to curtail excessive inflammatory response

- Limit further proinflammatory PMN cells coming to the site of inflammation
- Counter-regulate proinflammatory mediators
- Limit tissue damage from excessive or persistent inflammation

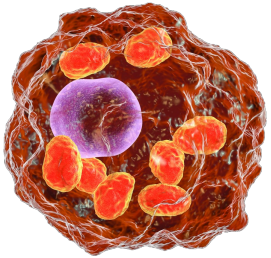
Adapted from: Serhan CN. *FASEB J.* 2017;31(4):1273-1288.

Metagenics Institute

Macrophages: Inflammatory vs. Resolving

Inflammatory (M1)

Classically activated macrophages



Functions:

- Antimicrobial activity
- ROS production
- Engulfs pathogens

Free radicals
Proinflammatory cytokines e.g. TNF-α, IL-6
MHC-II

End result = inflammation

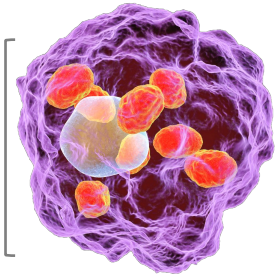
SPMs shift phenotype

Resolving (M2)

Alternatively activated macrophages

Functions:

- Anti-inflammatory
- Engulfs dead/dying cells and other cell debris



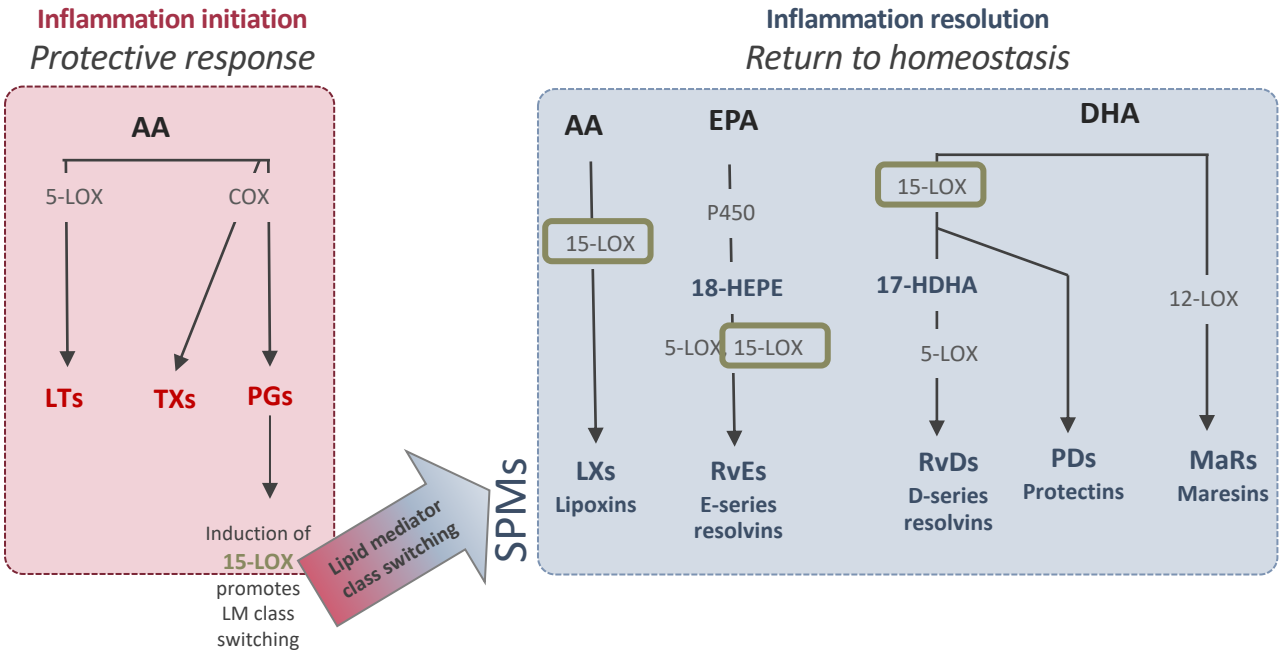
IL-10 TGF-β
VEGF PDGF

Resolution of inflammation and tissue regeneration

Das A et al. *Am J Pathol.* 2015;185(10):2596-2606.

Metagenics Institute

Lipid Mediator Biosynthesis



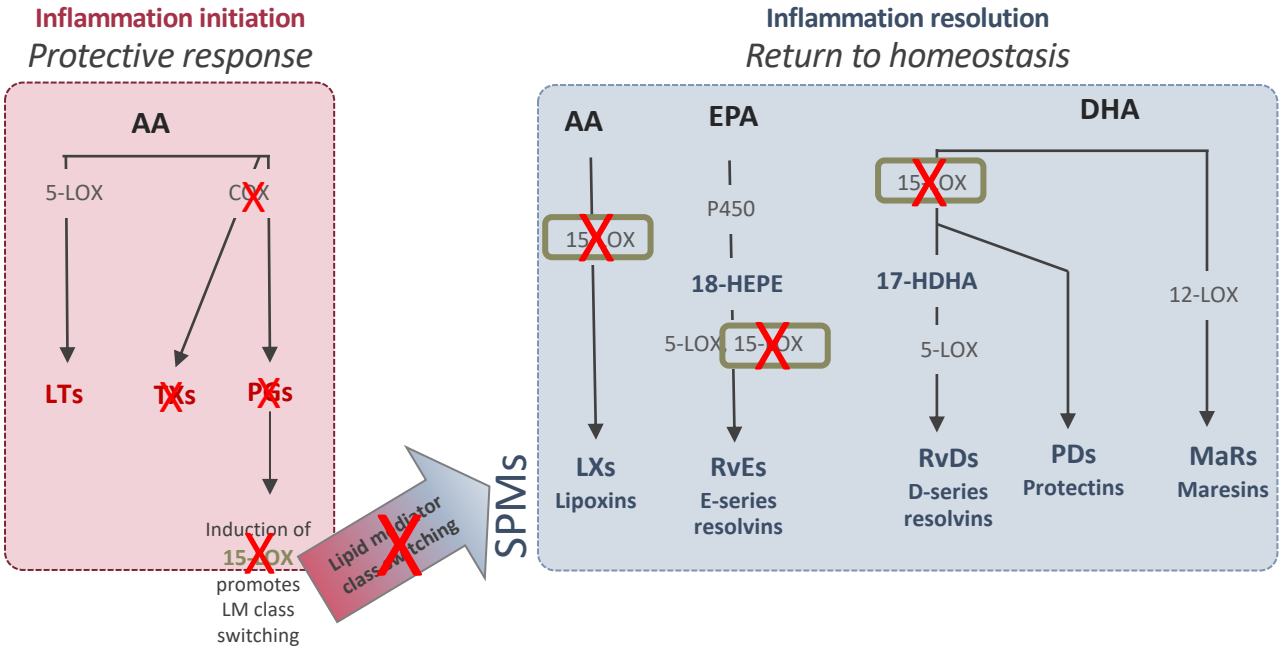
1. During initiation, proinflammatory lipid mediators such as LTs and PGs are predominant.
2. PGs promote 15-LOX induction. 15-LOX is an enzyme important for SPM production.
3. Lipid mediator class switching occurs when SPM synthesis increases. SPMs promote inflammation resolution.
4. During resolution, SPMs are predominant.

Lipid mediators involved in inflammation initiation
Lipid mediators involved in inflammation resolution

Adapted from: Serhan CN. *FASEB J.* 2017;31(4):1273-1288.

Metagenics Institute

Impact of COX-2 Inhibitors on Lipid Mediator Biosynthesis



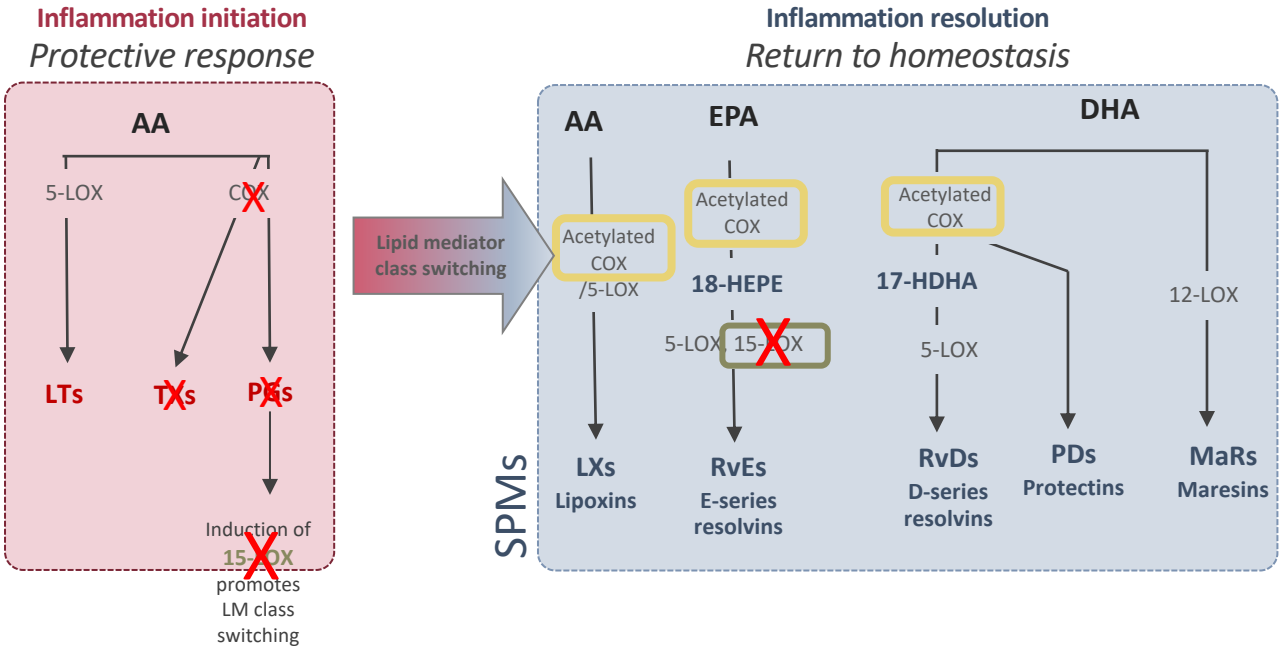
1. COX-2 inhibitors block the production of PGs.
2. Because PGs promote the induction of 15-LOX needed for production of SPMs, SPM production can be reduced.
3. Lipid mediator class switching is impaired.
4. COX-2 inhibitors are considered "resolution toxic."

Lipid mediators involved in inflammation initiation
Lipid mediators involved in inflammation resolution

Adapted from: Serhan CN. *FASEB J.* 2017;31(4):1273-1288.

Metagenics Institute

Impact of Low-Dose Aspirin on Lipid Mediator Biosynthesis



1. Low-dose aspirin blocks the activity of COX that leads to PG production.
2. But low-dose aspirin changes the COX catalytic domain. Acetylated COX is involved in the production of aspirin-triggered SPMs.
3. Lipid mediator class switching can occur.
4. Low-dose aspirin is considered "resolution friendly."

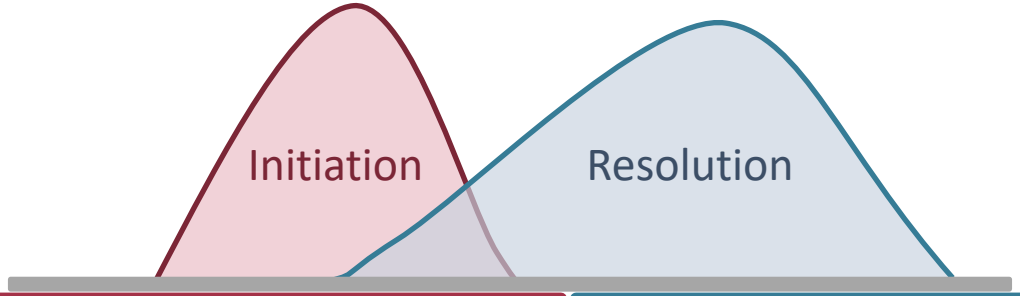
Catalytic domain: the region where the chemical reaction takes place

Lipid mediators involved in inflammation initiation
Lipid mediators involved in inflammation resolution

Adapted from: Serhan CN. *FASEB J.* 2017;31(4):1273-1288.

Metagenics Institute

Talking to Patients About SPMs



Initiator: leak

Initiation: open wall

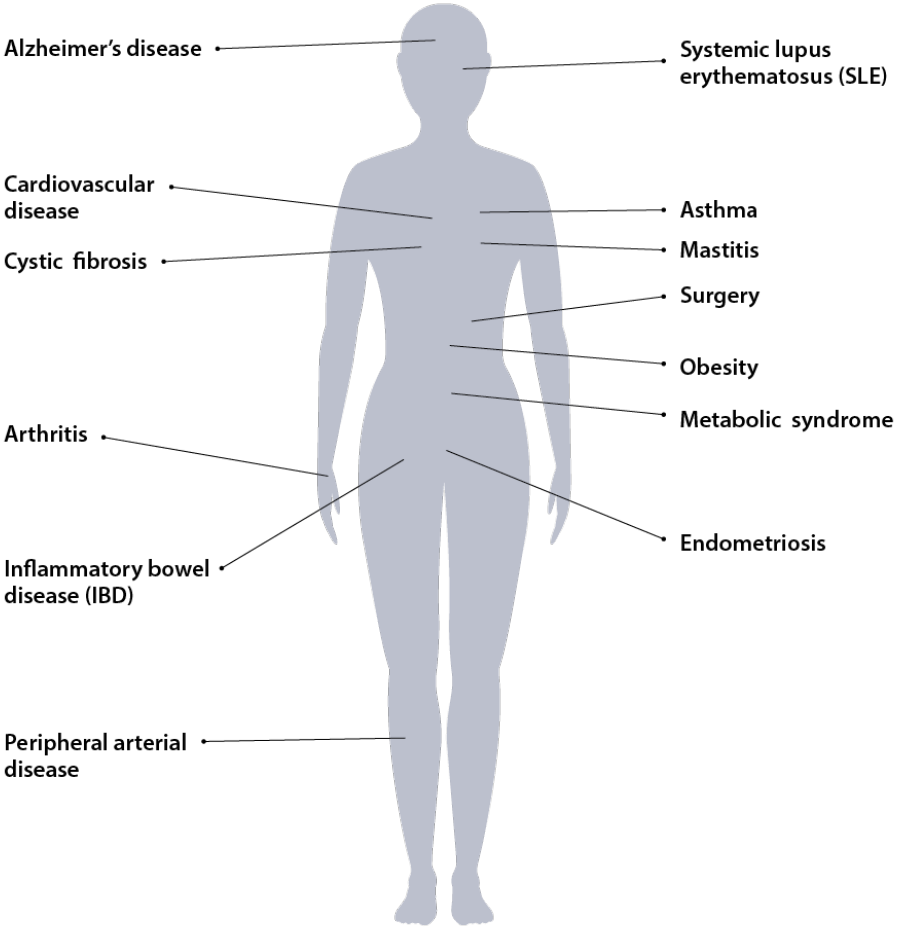
Initiation: cut out affected structures

Resolution: clear the mess

Resolution: repair and patch

Resolution: paint to match original wall

Metagenics Institute



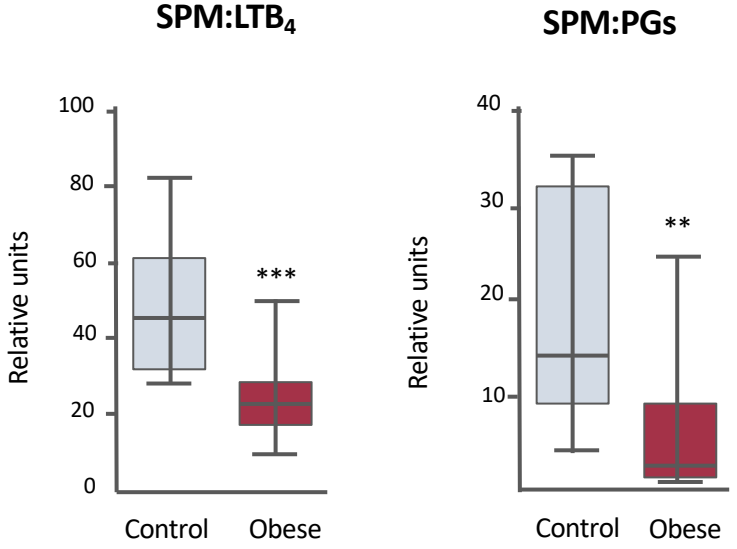
Conditions with Reduced Endogenous SPMs[1-35]

References

1. Serhan CN. *Nature.* 2014;510(7503):92-101.
2. Arnardottir H et al. *Mucosal Immunol.* 2016;9(3):757-766.
3. Wang X et al. *Alzheimers Dement.* 2015;11(1):40-50.e1-2.
4. Lukiw WJ et al. *J Clin Invest.* 2005;115(10):2774-2783.
5. Zhu M et al. *Mol Neurobiol.* 2016;53(4):2733-2749.
6. Barden AE et al. *Prostaglandins Leukot Essent Fatty Acids.* 2016;107:24-29.
7. Arnardottir HH et al. *J Immunol.* 2016;197(6):2362-2368.
8. Fredman G et al. *Nat Commun.* 2016;7:12859.
9. Elajami TK et al. *FASEB J.* 2016;30(8):2792-2801.
10. Bazan HA et al. *Prostaglandins Leukot Essent Fatty Acids.* 2017;125:43-47.
11. Thul S et al. *Eur J Prev Cardiol.* 2017;24(9):903-906.
12. Claria J et al. *Am J Physiol Cell Physiol.* 2013;304(12):C1141-1149.
13. Schaller MS et al. *Arterioscler Thromb Vasc Biol.* 2017;37:A20.
14. Sorrentino TA et al. *Circulation.* 2018;138:A12919.
15. Barden AE et al. *Am J Clin Nutr.* 2015;102(6):1357-1364.
16. López-Vicario C et al. *FASEB J.* 2019;33(6):7072-7083.
17. Titos E et al. J *Immunol.* 2016;197(8):3360-3370.
18. Eickmeier O et al. *PLoS One.* 2017;12(2):e0171249.
19. Yang J et al. *Free Radic Biol Med.* 2012;53(1):160-171.
20. Flitter BA et al. *Proc Natl Acad Sci U S A.* 2017;114(1):136-141.
21. Cata JP et al. *World J Surg Oncol.* 2017;15(1):152.
22. Chen S et al. *Fertil Steril.* 2014;102(1):264-271.
23. Wu R et al. *Br J Pharmacol.* 2014;171(21):4927-4940.
24. Mangino MJ et al. *Prostaglandins Other Lipid Mediat.* 2006;79(1-2):84-92.
25. Vong L et al. *PLoS One.* 2012;7(6):e39244.
26. Gobbetti T et al. *Proc Natl Acad Sci U S A.* 2017;114(15):3963-3968.
27. Bhavsar PK et al. *Respir Res.* 2010;11:71.
28. Kazani S et al. *J Allergy Clin Immunol.* 2013;132(3):547-553.
29. Levy BD et al. *J Immunol.* 2007;178(1):496-502.
30. Levy BD et al. *Am J Respir Crit Care Med.* 2005;172(7):824-830.
31. Wu SH et al. *Pediatr Pulmonol.* 2010;45(4):333-340.
32. Miyata J et al. *J Allergy Clin Immunol.* 2013;131(2):353-360 e351-352.
33. Planaguma A et al. *Am J Respir Crit Care Med.* 2008;178(6):574-582.
34. Yamaguchi H et al. *Clin Exp Allergy.* 2011;41(12):1711-1718.
35. Navarini L et al. *J Immunol Res.* 2018;2018:5264195.

Metagenics Institute

Obesity: Imbalanced Lipid Mediators in Adipose Tissue



Data are mean ± SEM. **p<0.005, ***p<0.001 versus CT subjects

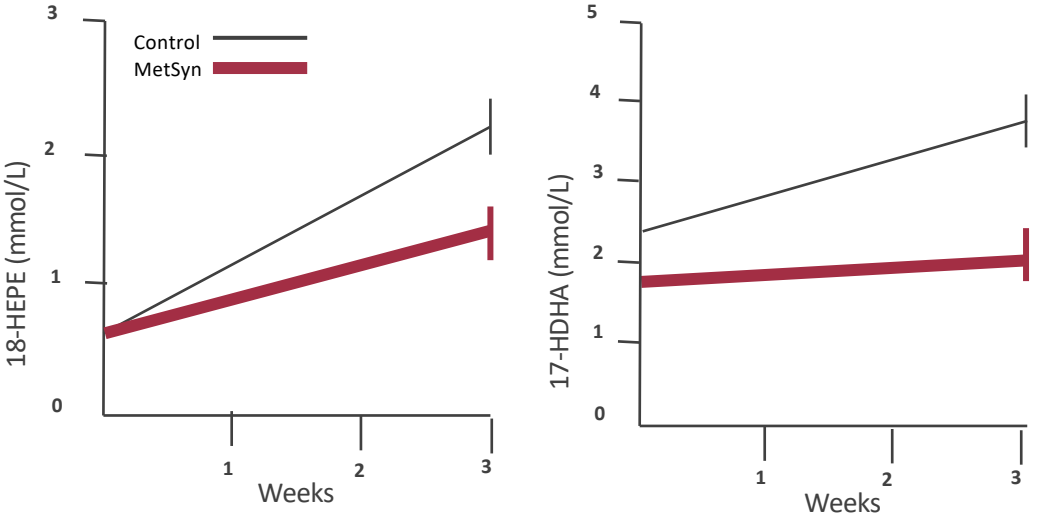
Obese patients exhibited a **lower ratio of SPMs: proinflammatory markers** (LTB_4 and PGs)

This suggests the presence of **SPM deficit** and an impaired capacity for the adipose tissue to resolve uncontrolled inflammation

Adapted from: Titos E et al. *J Immunol.* 2016;197:3360-3370.

Metagenics Institute

Metabolic Syndrome: Reduced SPM Precursors from Fish Oil



Metabolic syndrome (MetSyn) **blunts increase in SPM precursors** following 2.4 g/d EPA+DHA supplementation

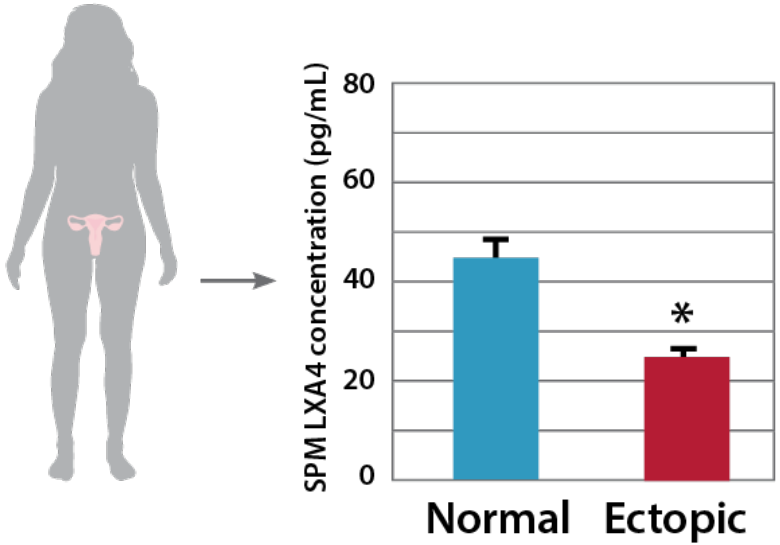
This suggests the biosynthetic pathways may be dysregulated

1. Barden AE et al. *Am J Clin Nutr.* 2015;102:1357-1364.

Adapted from: Barden AE et al. *Am J Clin Nutr.* 2015;102:1357-1364.

Metagenics Institute

Endometriosis: Reduced SPM in Endometrial Tissue



*p<0.001. Figure: Chen S et al. *Fertil Steril*. 2014;102(1):264-271.

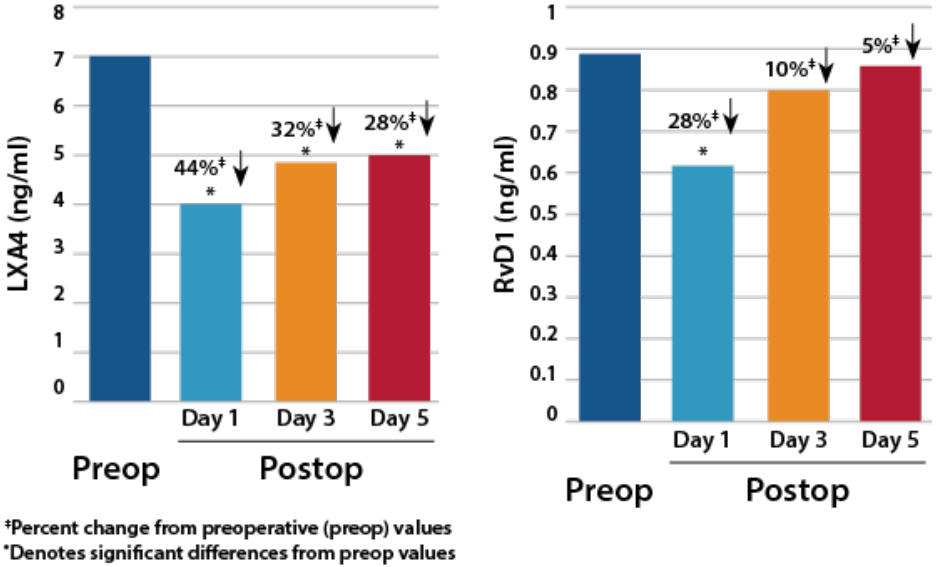
Endometrial lesions secrete proinflammatory cytokines and chemokines, major drivers of inflammation[1]

Compared with endometrial tissue of healthy women, endometrial tissue of women with endometriosis exhibits **significantly lower levels of specific SPM (LXA4)**[2,3]

1. Giudice LC. *N Eng J Med.* 2010;362(25):2389-2398.
2. Chen S et al. *Fertil Steril*. 2014;102(1):264-271.
3. Wu R et al. *Br J Pharmacol.* 2014;171(21):4927-4940.

Metagenics Institute

Surgery: Reduced SPMs Seen Postoperatively



‡Percent change from preoperative (preop) values
*Denotes significant differences from preop values

Adapted from: Cata JP et al. *World J Surg Oncol*. 2017;15(1):152.

Circulating levels of SPMs (LXA4 and RvD1) **significantly reduced immediately postsurgery**[1]

Surgery elicits inflammatory response[2]

Managing perioperative inflammation may have benefits[2]

1. Cata JP et al. *World J Surg Oncol*. 2017;15(1):152.
2. Alazawi W et al. *Ann Surg*. 2016;264(1):73-80.

Metagenics Institute

Recent Human Clinical Studies

- Healthy volunteers
- Subjects with peripheral artery disease (PAD)
- Subjects with chronic pain
- Patients with fibromyalgia
- Subject with obesity

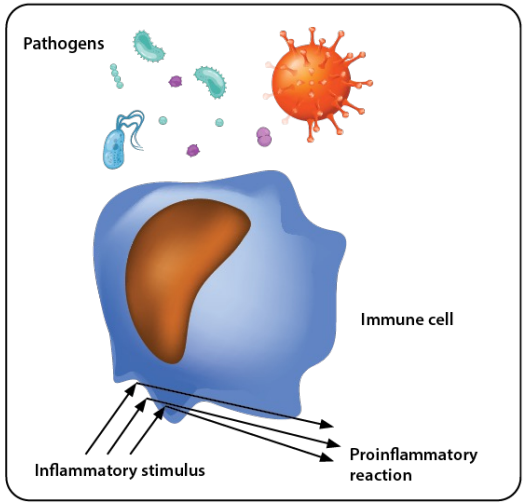
Disclosure/limitation: These clinical studies utilized the same supplier/manufacturer for their proprietary SPM supplement. This information may not be representative of all SPM products available on the market.

Metagenics Institute

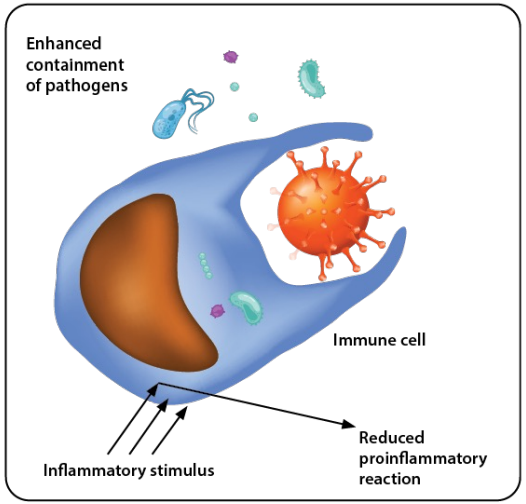
SPMs and Healthy Volunteers:

More protective and resilient immune cells within 24 hours

Placebo



SPM supplementation



Supplementing SPMs:

- Reprograms white blood cell (WBC) behaviors
- Enhances WBC phagocytosis of pathogens (*S. aureus, E. coli*)
- Reduces inflammation reaction from WBCs
- Results occur within 24 hours

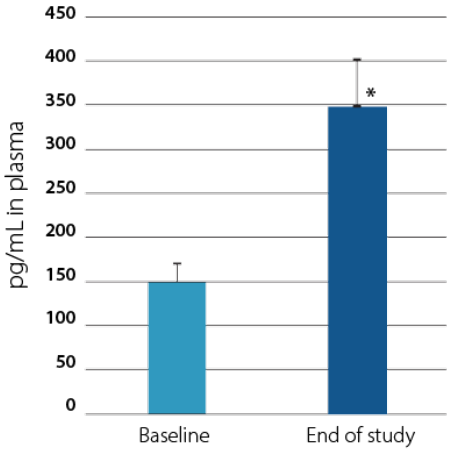
Souza PR et al. *Circ Res.* 2020;126(1):75-90.

Metagenics Institute

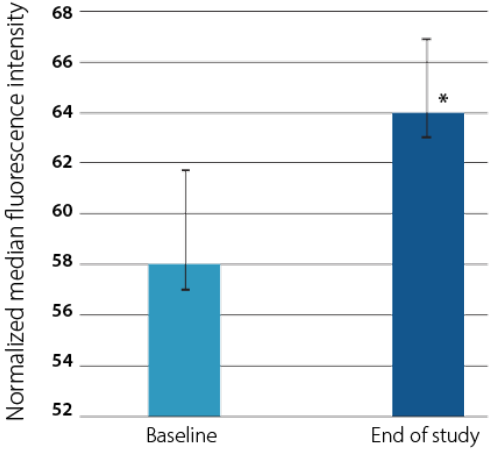
SPMs and Patients with Peripheral Artery Disease (PAD):

A more proresolving phenotype in immune cells

Increase in circulating SPMs in PAD cohort



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



*** statistically significant vs. baseline**

Supplementing SPMs:

- Increases SPM in plasma and HDL particles
- Reduces M1 (inflammatory) markers
- Increases M2 (resolving) markers
- Reduces adhesion molecule expression on WBCs

Schaller MS et al. *J Am Heart Assoc*. 2020,9(15):e016113.

Metagenics Institute

SPMs and Adults with Chronic Pain:

An improved quality of life and reduced pain in 4 weeks

PROMIS-43 profile

(% change 4 weeks vs baseline):

Social functioning
+8.1%**

Fatigue
-4.8%*

Sleep disturbance
-6.2%**

Physical function
+9.6%**

Depression
-4.1%*

Anxiety
-6.5%**

Pain intensity
-28.8%**

Pain interference
-6.5%**

*p<0.05, **p<0.001

Supplementing with SPMs:

- Improves quality of life measures
- Reduces pain intensity and interference
- Improves mood
- Results seen in 4 weeks

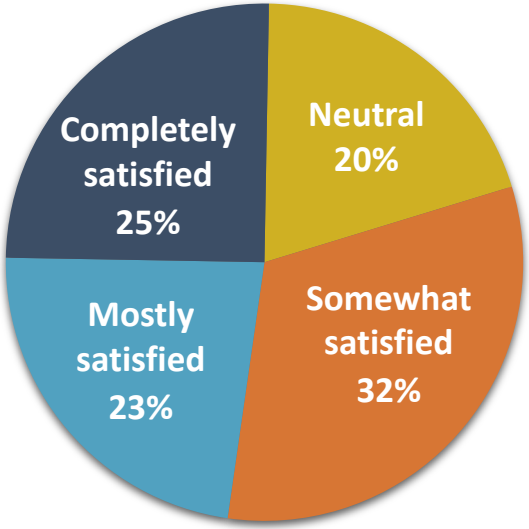
Callan N et al. *J Transl Med*. 2020;18(1):401.

Metagenics Institute

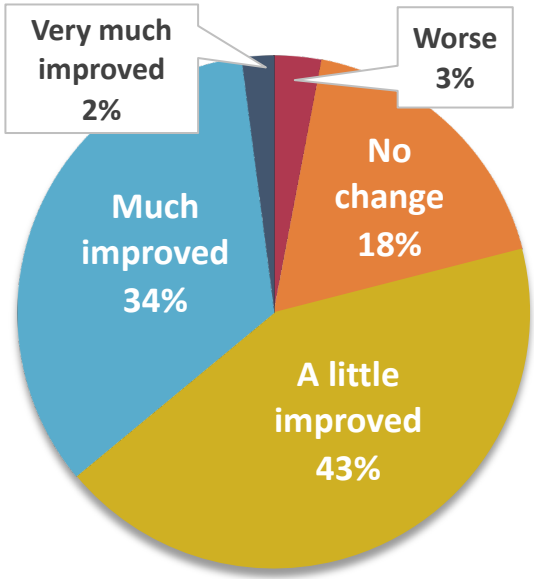
SPMs and Adults with Chronic Pain (cont.):

Patients expressed satisfaction and improvement at 4 weeks

Participant satisfaction

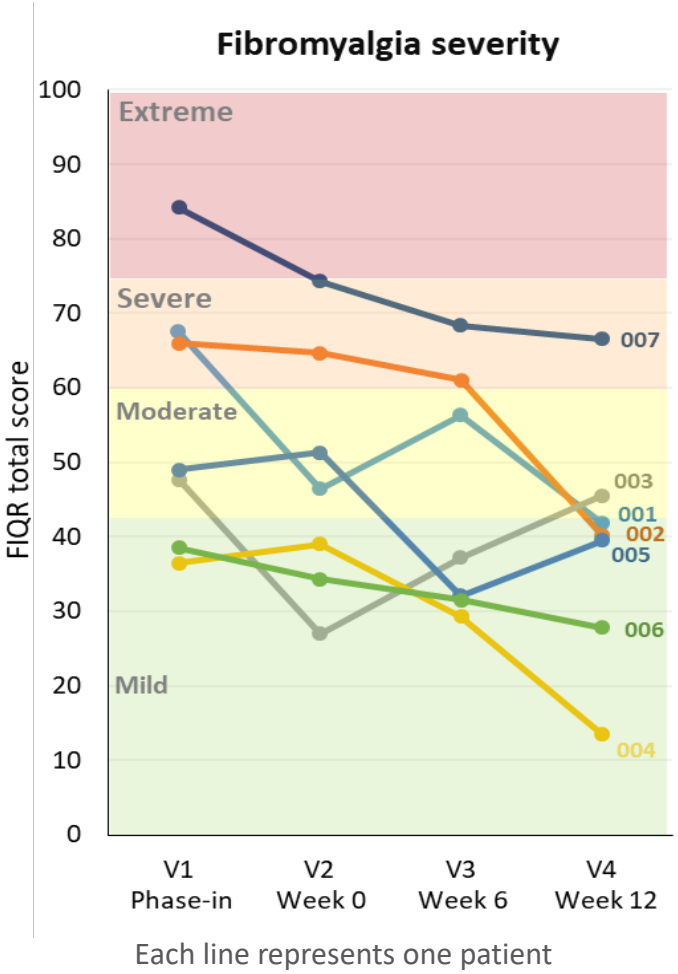


Participant-assessed improvement



Callan N et al. *J Transl Med*. 2020;18(1):401.

Metagenics Institute



Each line represents one patient

Effect of Supplement of SPMs on the Wellbeing and QOL in Patients with Fibromyalgia

Results of SPM supplementation:

- 87% response rate
- Improvements in physical function
- Symptoms worsened after supplements stopped in some patients
- Lower CIRS score indicative of better outcomes (subject 004)
- No reported side effects

O'Connor A et al. Poster presented at the 10th Linus Pauling Institute International Conference, Corvallis, RA. August 2019.

Metagenics Institute

SPMs and Adults with Obesity

- Supplement is enriched with 18-HEPE, 14-HDHA, and 17-HDHA
- Supplementation with marine oils, several circulating SPMs and other intermediates increased in obese individuals
- Resolvin E1 increased by 3.5-fold from baseline; RvE1 is made from 18-HEPE and is associated with better insulin sensitivity and glucose control
- 3 different HETEs were reduced from baseline (11-HETE, 15-HETE, 12-HETE); HETEs are generally associated with reduced insulin sensitivity and other metabolic risk factors
- B-cells isolated from blood produced less proinflammatory antibodies (IgG) upon cytokine stimulation (e.g., IL-4); this suggests that SPMs reduced the magnitude of immune cells' antibody production as part of the resolution response
- Docosapentaenoic acid–derived maresin 1 concentrations increased by 4.7-fold; maresin 1 is associated with improved insulin sensitivity and attenuates adipose tissue inflammation

Al-Shaer A et al. *J Nutr*. 2022;152(7):1783-1791.

Patients to Consider SPM Support

Chronic inflammation such as:

- Cardiovascular diseases
- Arthritis
- Obesity/metabolic syndrome

Acute inflammation such as:

- Infections
- Surgery
- Musculoskeletal injuries/exercise recovery

Metagenics Institute

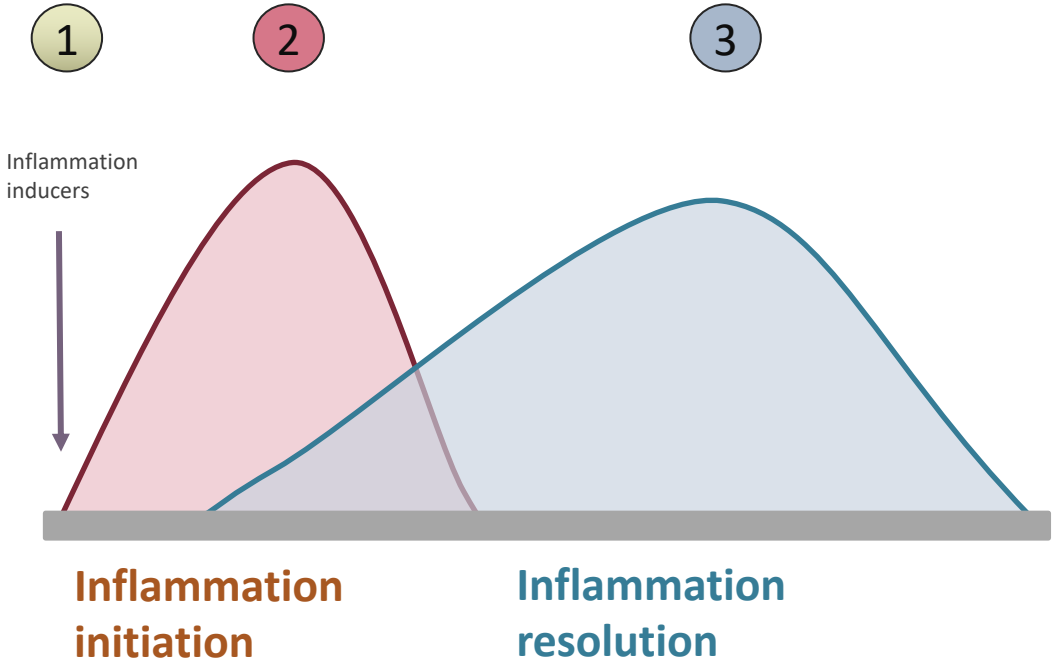
Takeaway Messages

Clinical management of inflammation: a question of balance

1. **Reduce inflammatory predisposition**

2. **Modulate initiation**
   Utilize nutrients like curcumin, Boswellia, xanthohumol, ginger, PEA, and long-chain omega-3 fatty acids that act on intercellular inflammatory signals that impact NF-κB, oxidative stress, and proinflammatory eicosanoid production

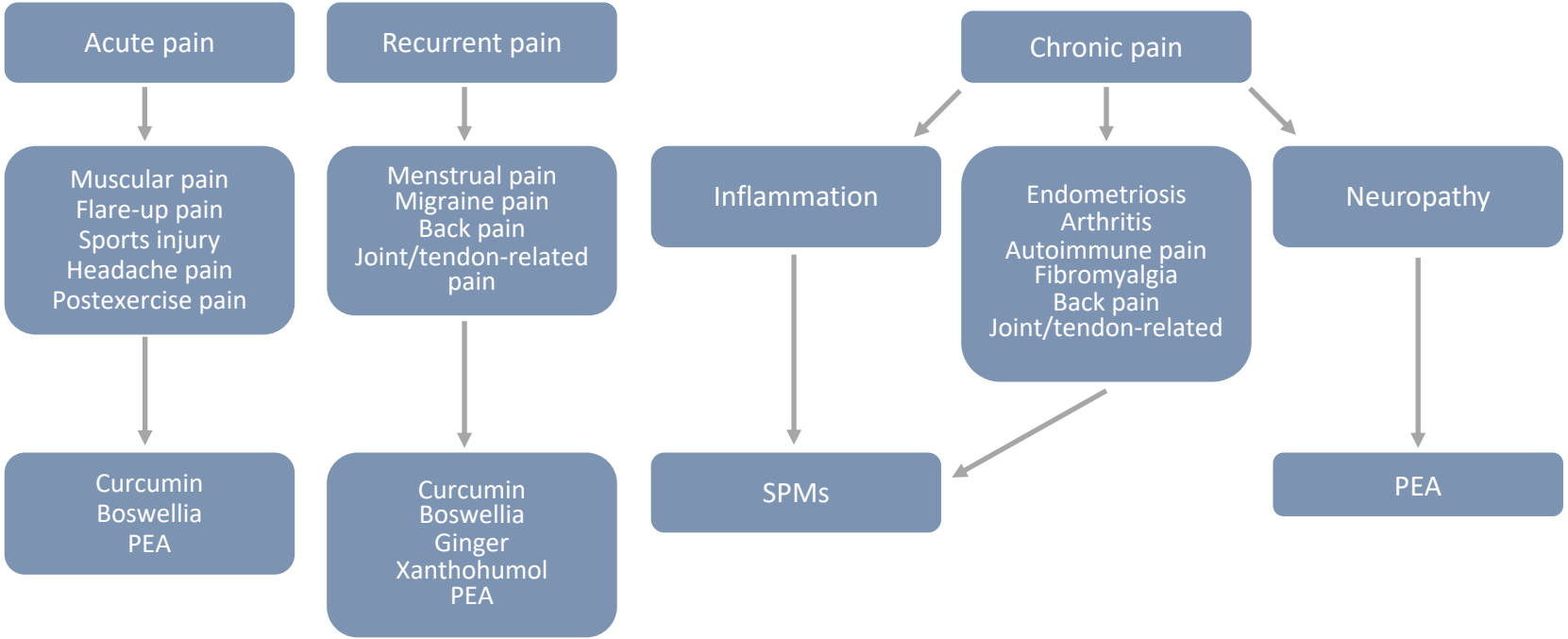
3. **Push for resolution**
   Utilize specialized pro-resolving mediators and emerging science of inflammation resolution



Serhan CN. *Nature*. 2014;510:92-101.

Metagenics Institute

Pain Is Complex; for Effective Pain Solutions, Bioavailability Can Speed Time to Relief or Provide Sustained Relief



Metagenics Institute

Thank you.

Metagenics Institute