Modulation of Inflammatory Responses by Select Plant-Derived Ingredients

June 14, 2017
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Training Objective

• Understand the science behind select plant-derived ingredients
  • Bioavailability
  • Biologic mechanisms of action (MOA)
  • Potential clinical applications
Scientific Takeaways

These plant-derived ingredients are:

- Highly bioavailable
  - Well-absorbed and reaches target tissues
- Exceptionally well-characterized
  - Have defined biologic mechanisms of action (MOA)
- Known to reduce systemic inflammation and pain
  - Via multiple MOAs
Ingredient Overview

Curcumin
Xanthohumol
*Boswellia serrata*
Ginger
Curcuminoids: Isolated Constituents

- Primary active constituents in turmeric root (*Curcuma longa*)

- Turmeric has culinary and medicinal uses
Curcumin/Turmeric Root

- Family: Zingiberaceae (Ginger family)
- “Orally, turmeric is used for osteoarthritis, rheumatoid arthritis (RA), dyspepsia, abdominal pain, Crohn's disease and ulcerative colitis, coronary artery bypass graft (CABG) surgery, hemorrhage, diarrhea, flatulence, abdominal bloating, loss of appetite, jaundice, hepatitis, Helicobacter pylori (H pylori), peptic ulcers, irritable bowel syndrome, and liver and gallbladder conditions. It is also used for headaches, bronchitis, common cold, respiratory infections, hyperlipidemia, lichen planus, radiation mucositis, fibromyalgia, fatigue, leprosy, fever, amenorrhea, pruritus, surgical recovery, and cancer, including colorectal cancer and prostate cancer. Other uses include depression, Alzheimer's disease, anterior uveitis, diabetes, edema, worms, kidney inflammation, systemic lupus erythematosus (SLE), tuberculosis, cystitis, and joint pain.”

- Therapeutic Research Center (formerly Natural Medicines Comprehensive Database)
Curcumin/Turmeric Root Actions

- **Analgesic**: Reduces pain including neuropathic pain
- **Anti-arthritic**: Reduces joint inflammation, reduces MMPs (involved in joint destruction)
- **Anti-inflammatory**
- **Antioxidant**

- Other:
  - Gastrointestinal, Respiratory effects, Anti-Alzheimer's, Antidepressant, Anticancer, Antidiabetic, Cardiovascular, Antithrombotic

Source: Therapeutic Research Center
Standard Curcumin Preparations

- Poorly bioavailable
  - Not well absorbed
  - Animal studies have shown that the majority of curcumin (up to 85%) passes through the GI tract

- Absorption improves slightly when consumed with lipids/fat or piperine (in peppercorns)
Curcumin as “CGM”

- Curcumagalactomannoside (CGM)
- Combines curcumin with galactomannan fibers (from fenugreek seeds)
- Patented (but *not* an exclusive ingredient)
- Bioavailability
  - Enhanced absorption of curcuminoids into the bloodstream
  - Exceptional delivery to target tissues
CGM: Human Plasma Levels

- Studies have shown that CGM is exceptionally well-absorbed compared to standard curcumin preparations.
- Plasma curcuminoids were assayed after a single 500mg dosage.

CGM: Human Plasma

- Plasma curcuminoids were also assayed after 30 days of twice daily 500mg administrations

Fig. 2 – Plasma concentration – time curve of total free curcuminoids and individual curcuminoids (curcumin, DMC and BDMC) of Wistar rats orally administered with standard curcumin or CGM. The values are presented as mean ± SD.

IM K., J of Functional Foods. 2015;14:215-225
CGM: Rat Tissue Levels

Table 1 – Pharmacokinetic parameters of CGM and standard curcumin in various biomatrices of rats up on oral administration.

<table>
<thead>
<tr>
<th>Sample</th>
<th>Dose (mg/kg)</th>
<th>Tissue</th>
<th>Parameters</th>
<th>Cmax (ng/g)</th>
<th>T1/2 (h)</th>
<th>C12 (ng/g)</th>
<th>C24 (ng/g)</th>
<th>AUC (ng/g-h)</th>
<th>Folds increase to standard curcumin</th>
<th>Tissue/plasma ratio</th>
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</thead>
<tbody>
<tr>
<td>Standard curcumin</td>
<td>200</td>
<td>Plasma</td>
<td>0.5</td>
<td>12.52 ± 4.16</td>
<td>0.80</td>
<td>n.d.</td>
<td>n.d.</td>
<td>70.18</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Liver</td>
<td>1.0</td>
<td>9.65 ± 5.08</td>
<td>1.50</td>
<td>n.d.</td>
<td>n.d.</td>
<td>7.77</td>
<td>–</td>
<td>0.77</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Kidney</td>
<td>1.0</td>
<td>6.89 ± 3.13</td>
<td>1.00</td>
<td>n.d.</td>
<td>n.d.</td>
<td>12.21</td>
<td>–</td>
<td>0.55</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Heart</td>
<td>0.5</td>
<td>5.58 ± 2.21</td>
<td>1.40</td>
<td>n.d.</td>
<td>n.d.</td>
<td>8.70</td>
<td>–</td>
<td>0.44</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Spleen</td>
<td>0.5</td>
<td>5.70 ± 2.62</td>
<td>1.50</td>
<td>n.d.</td>
<td>n.d.</td>
<td>9.87</td>
<td>–</td>
<td>0.45</td>
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<tr>
<td></td>
<td></td>
<td>Brain</td>
<td>1.0</td>
<td>1.40 ± 0.80</td>
<td>1.50</td>
<td>n.d.</td>
<td>n.d.</td>
<td>2.41</td>
<td>–</td>
<td>0.11</td>
</tr>
<tr>
<td>Intestine</td>
<td>0.5</td>
<td>Plasma</td>
<td>0.5</td>
<td>140,045.32 ± 56,000</td>
<td>2.00</td>
<td>1343.00 ± 210.00</td>
<td>54.00 ± 11.00</td>
<td>351,277</td>
<td>25.05</td>
<td>11,185.73</td>
</tr>
<tr>
<td>Intestine</td>
<td>200</td>
<td>Plasma</td>
<td>2.0</td>
<td>341.57 ± 30.88*</td>
<td>3.70</td>
<td>47.61 ± 11.00*</td>
<td>18.02 ± 0.10*</td>
<td>1758.00*</td>
<td>111.66</td>
<td>–</td>
</tr>
<tr>
<td>Intestine</td>
<td>200</td>
<td>Liver</td>
<td>2.0</td>
<td>445.52 ± 83.00*</td>
<td>3.00</td>
<td>n.d.</td>
<td>n.d.</td>
<td>857.60*</td>
<td>72.25</td>
<td>1.30*</td>
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<tr>
<td>Intestine</td>
<td>200</td>
<td>Kidney</td>
<td>2.0</td>
<td>240.10 ± 47.25*</td>
<td>2.75</td>
<td>n.d.</td>
<td>n.d.</td>
<td>882.20*</td>
<td>54.82</td>
<td>0.70*</td>
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<tr>
<td>Intestine</td>
<td>200</td>
<td>Heart</td>
<td>2.0</td>
<td>391.76 ± 102.50*</td>
<td>3.3</td>
<td>n.d.</td>
<td>n.d.</td>
<td>476.90*</td>
<td>55.02</td>
<td>1.14*</td>
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<tr>
<td>Intestine</td>
<td>200</td>
<td>Spleen</td>
<td>2.0</td>
<td>229.72 ± 42.20*</td>
<td>3.25</td>
<td>n.d.</td>
<td>n.d.</td>
<td>543.00*</td>
<td>347.93</td>
<td>0.67*</td>
</tr>
<tr>
<td>Intestine</td>
<td>200</td>
<td>Brain</td>
<td>2.0</td>
<td>343.00 ± 64.70*</td>
<td>3.40</td>
<td>n.d.</td>
<td>n.d.</td>
<td>838.50*</td>
<td>1.00*</td>
<td>1353.79*</td>
</tr>
</tbody>
</table>

AUC, area under the concentration-time curve; Cmax, maximum tissue concentration; Tmax; time to reach Cmax; T1/2, half-life; the fold increase is calculated as AUC_{Curcumin}/AUC_{Standard curcumin}. The values are given as mean ± SD (n = 3), where * denotes p < 0.001, when values of CGM are compared with the values of standard curcumin.

IM K., J of Functional Foods. 2015;14:215-225
CGM: Rat Brain Levels

- CGM effectively crosses the blood-brain barrier (BBB)

IM K., J of Functional Foods. 2015;14:215-225
Curcumin/CGM Key Takeaways

- Most pertinent therapeutic actions:
  - Analgesic
  - Anti-arthritic
  - Anti-inflammatory
  - Antioxidant

- CGM is highly bioavailable
  - Readily enters the blood and tissues
Xanthohumol: An Isolated Constituent

- Xanthohumol is one of many active constituents in hops flowers (Humulus lupulus)

- Hops flowers have commercial (used to flavor and preserve beer) and medicinal uses
Hops Flowers

- Family: Cannabaceae (same family as Cannabis)
- “Orally, hops are used for anxiety, insomnia and other sleep disorders, restlessness, tension, excitability, attention deficit-hyperactivity disorder (ADHD), nervousness, and irritability. They are also used orally as an appetite stimulant, diuretic, a bitter tonic, to stimulate lactation, and for indigestion. Other oral uses include prostate cancer, breast cancer, ovarian cancer, menopausal symptoms, hyperlipidemia, tuberculosis, cystitis, intestinal cramps, mucous colitis, neuralgia, and priapism."

- Source: Therapeutic Research Center
Hops Flower Actions

• Anti-arthritic
• Anti-inflammatory
• Antioxidant

• Other:
  • Anticancer, Cardiovascular risk reduction, Sedative, Nervine, Treats menopausal symptoms

• Source: Therapeutic Research Center
Xanthohumol as “XNTPM”

• Xanthohumol bound to a protein matrix to increase bioavailability and stability

• *Is* an exclusive ingredient

• Is a Hops extract standardized to 2.5% xanthohumol
Xanthohumol Bioavailability

- Xanthohumol is generally not well-absorbed.
- However, a study conducted at the FMRC showed that XNTPM had 81% higher bioavailability compared to a standard xanthohumol.
Xanthohumol/XNTPM Key Takeaways

• Most pertinent therapeutic actions:
  • Anti-arthritic
  • Anti-inflammatory
  • Antioxidant

• XNTPM
  • Standardized to 2.5% xanthohumol
  • Better bioavailability
Boswellia serrata Extract

- Also known as Indian Frankincense
- Is a “gum resin” from the *Boswellia serrata* tree

- Extract contains a few active constituents
  - Beta boswellic acid (#1)
  - Alpha boswellic acids
  - Essential oils
  - Flavonoids - Quercetin
Boswellia serrata Extract

• “Orally, boswellia is used for brain injury, osteoarthritis, rheumatoid arthritis (RA), rheumatism, bursitis, and tendonitis. Other uses include ulcerative colitis, collagenous colitis, Crohn's disease, and abdominal pain. It is used for asthma, allergic rhinitis, sore throat, syphilis, painful menstruation, pimples, bruises, headache, diabetes, and cancer. It is also used as a stimulant, respiratory antiseptic, diuretic, and for stimulating menstrual flow.”

• Source: Therapeutic Research Center
**Boswellia serrata Extract Actions**

- **Analgesic**: Reduces pain
- **Anti-arthritic**: Inhibits 5-LOX; Decreases cartilage damage
- **Anti-inflammatory/Immunomodulatory effects**
- **Antioxidant**

- **Other**:
  - Anticancer, Anti-asthma effects, Anti-microbial

- Sources: Therapeutic Research Center, Herbal Medicine from the Heart of the Earth
Ginger Root Extract

- Contains several constituents
  - Gingerol
  - Gingerdione
  - Shogaol
  - Sesquiterpene and monoterpene volatile oils

- Culinary and medicinal uses
Ginger Root

- Family: Zingiberaceae (Ginger family)
- “Orally, ginger is used for motion sickness, morning sickness, colic, diarrhea, dyspepsia, flatulence, irritable bowel syndrome, chemotherapy-induced nausea, antiretroviral-induced nausea and vomiting, rheumatoid arthritis (RA), osteoarthritis, loss of appetite, post-surgical nausea and vomiting, dysmenorrhea, migraine headache, and for discontinuing selective serotonin reuptake inhibitor (SSRI) drug therapy. It is also used orally for anorexia, upper respiratory tract infections, cough, respiratory distress, bronchitis, diabetes, as a galactagogue, diaphoretic, and diuretic; and for treating stomachache, nausea, cholera, and bleeding. Fresh ginger is used orally for treating acute bacterial dysentery, baldness, malaria, orchitis, poisonous snake bites, and toothaches. Dried ginger is used for chest pain, low back pain, and stomach pain.”

- Source: Therapeutic Research Center
Ginger Root Actions

- Analgesic
- Anti-arthritis
- Anti-inflammatory
- Antioxidant

- Other:
  - Anti-emetic, Anti-diabetic, Antibacterial, Antifungal, Cardiovascular

- Source: Therapeutic Research Center
Boswellia serrata & Ginger Key Takeaways

- Most pertinent therapeutic actions:
  - Analgesic
  - Anti-arthritic
  - Anti-inflammatory
  - Anti-oxidant
Biochemistry & Pharmacology Conventions
(Agonists and Antagonists)
Basic Biochemical Reaction

For example:

Substrate: Arachidonic acid
Enzyme: COX-2
Product: PGE$_2$
Pharmacology Basics

• Pharmacologic actions
  • **Agonists** – *Cause* an action
    • Activate receptors to produce a biological response
  • **Antagonists** – *Block/Inhibit/Reduce* an action
    • Reduce biological responses often by binding to receptors

• These actions can be produced by
  • Synthetic or natural compounds
  • Pharmaceuticals, nutraceuticals, vitamins, plant-derived constituents (including many that are found in foods and culinary herbs)
Antagonists

• Antagonist example:

Arachidonic acid \rightarrow^{COX-2} PGE_2

Ibuprofen

Ibuprofen, an NSAID, is well-known COX-2 inhibitor
Antagonists

Arachidonic acid \( \rightarrow \) COX-2 \( \rightarrow \) PGE\(_2\)

Ibuprofen
Aspirin
Celecoxib
Rofecoxib
Antagonists

Arachidonic acid → COX-2 → PGE$_2$

- Ibuprofen
- Aspirin
- Celecoxib
- Rofecoxib
- Curcumin
- Xanthohumol
- Boswellic acids
- Ginger extract
Inflammation & Pain Pathways

Mechanisms of Action (MOAs)
Key Mediators of Inflammation & Pain

- **Enzymes**
  - Phospholipase A2 (PLA2)
  - Cyclooxygenase (COX-1 and COX-2)
  - Lipoxygenase (LOX)

- **Gene Expression Regulators**
  - Nuclear factor-kappa B (NFkB)

- **Pro-inflammatory cytokines**
  - TNFα
  - IL-1β
  - IL-6
  - IL-12

- **Chemokines**
  - Neutrophil chemotactic factor (CXCL8, aka IL-8)
  - Monocyte chemoattractant protein 1 (MCP-1)
  - Interferon-γ activated protein (IP-10)
Key Mediators of Inflammation & Pain *Modulated by* Curcumin, Xanthohumol, Boswellic acids, and Ginger

- **Enzymes**
  - Phospholipase A2 (PLA2)
  - Cyclooxygenase (COX-1 and COX-2)
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  - Neutrophil chemotactic factor (CXCL8, aka IL-8)
  - Monocyte chemoattractant protein 1 (MCP-1)
  - Interferon-γ activated protein (IP-10)

ALL are interfered with by: Curcumin, Xanthohumol, Boswellic acids, Ginger
# Mechanism of Action (MOA) Summary

<table>
<thead>
<tr>
<th></th>
<th>Curcumin</th>
<th>Xanthohumol</th>
<th><em>Boswellia serrata</em></th>
<th>Ginger</th>
</tr>
</thead>
<tbody>
<tr>
<td>**Inhibition of pro-</td>
<td>✓ Inhibits NFκB</td>
<td>✓ Inhibits NFκB</td>
<td>✓ Inhibits NFκB</td>
<td>✓ Inhibits NFκB</td>
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<tr>
<td>inflammatory cytokines,</td>
<td>✓ Reduces serum levels</td>
<td>✓ Reduces WBC production</td>
<td></td>
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<tr>
<td>chemokines, and</td>
<td>of:</td>
<td>of:</td>
<td></td>
<td></td>
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<tr>
<td>transcription factors</td>
<td>- TNFα</td>
<td>- TNFα</td>
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<td>associated with</td>
<td>- IL-1β&lt;sup&gt;2&lt;/sup&gt;</td>
<td>- IL-12</td>
<td></td>
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<tr>
<td>inflammation and pain</td>
<td>- IL-6</td>
<td>- MCP-1</td>
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<tr>
<td></td>
<td>✓ Diminishes</td>
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<td></td>
<td>chondrocyte production</td>
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<td></td>
<td>of CXCL8 (IL-8)</td>
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</tr>
<tr>
<td>**Inhibition of</td>
<td>✓ Inhibits PLA2</td>
<td>✓ Inhibits COX-1 &amp;</td>
<td>✓ Inhibits COX-1 &amp; COX-2</td>
<td>✓ Inhibits PLA2</td>
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<td>enzymes and</td>
<td>✓ Inhibits COX-2</td>
<td>COX-2</td>
<td>✓ Inhibits COX-1 &amp; COX-2</td>
<td>✓ Inhibits COX-1 &amp; COX-2</td>
</tr>
<tr>
<td>prostaglandins</td>
<td>✓ Inhibits 5-LOX</td>
<td>✓ Inhibits 5-LOX</td>
<td>✓ Inhibits 5-LOX</td>
<td>✓ Inhibits LOX</td>
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<tr>
<td>associated with</td>
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</tr>
<tr>
<td>inflammation and pain</td>
<td></td>
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</tr>
</tbody>
</table>

*Note: The ✓ indicates the action is associated with inflammation and pain.*
Inflammation & Pain: Key Enzymes

• Phospholipase A2 (PLA2)
  • Liberates arachidonic acid (ARA) from the cell membrane

  • ARA is then available as a substrate for COX-1, COX-2, and LOX (as well as other enzymes)
Inflammation & Pain: Key Enzymes

- **Cyclooxygenase (COX-1 and COX-2)**
  - Converts arachidonic acid (AA) to prostaglandins (including PGE$_2$)

- **PGE$_2$**
  - Increases *pain perception*
  - Contributes to the *destruction of cartilage* in arthritic joints in both *rheumatoid arthritis (RA)* and *osteoarthritis (OA)*
Inflammation & Pain: Key Enzymes

- **Lipoxygenase (LOX)**
  - Converts arachidonic acid (AA) to leukotrienes (including LTB4)
  - Overproduction of leukotrienes plays a role in inflammatory conditions like asthma and allergic rhinitis
  - Commonly used LOX inhibitors include medications used as analgesics for OA and RA, and treatments for asthma
Inflammation & Pain: Key Enzymes

Arachidonic Acid (ARA)

- Phospholipase A2 (PLA₂)
  - Cycooxygenase-1 & 2 (COX-1, COX-2)
    - Prostaglandins: PGE₂
  - Lipoxygenase (5-LOX)
    - Leukotrienes: LTB₄
Inflammation & Pain: Key Enzymes

Arachidonic Acid (ARA)

- Phospholipase A2 (PLA2)
- Curcumin
- Ginger

- Cyclooxygenase-1 & 2 (COX-1, COX-2)
- Curcumin
- Xanthohumol
- Boswellic acids
- Ginger

- Lipoxygenase (5-LOX)
- Curcumin
- Boswellic acids
- Ginger

- Prostaglandins
  - PGE₂

- Leukotrienes
  - LTB₄
Inflammation & Pain: Key Regulator of Gene Expression

- **Nuclear factor-kappa B (NFkB)**
  - Protein complex that controls DNA transcription/genetic expression
  - When activated, controls/regulates the expression of ~500 genes including:
    - Pro-inflammatory enzymes - PLA2, COX-1, COX-2, LOX
    - Pro-inflammatory cytokines - IL-1β, IL-6, IL-12, TNFα
    - Chemokines – CXCL8 (aka IL-8), MCP-1

- For more go to: [http://www.bu.edu/nf-kb/gene-resources/target-genes/](http://www.bu.edu/nf-kb/gene-resources/target-genes/)
Nuclear factor-kappa B (NFkB)

**Upstream**
- NFkB (Inactive)
- NFkB (Activated)

**Downstream**
- Increased Expression of:
  - PLA2
  - COX-1
  - COX-2
  - LOX
  - TNFα, IL-1β, IL-6, IL-12
  - CXCL8 (IL-8)
  - MCP-1

Cytosol
- NFkB (Inactive)
- NFkB (Activated)

Nucleus
Nuclear factor-kappa B (NFkB)

**Upstream**
- NFkB (Inactive)
- NFkB (Activated)

**Downstream**
- Increased Expression of:
  - PLA2
  - COX-1
  - COX-2
  - LOX
  - TNFα, IL-1β, IL-6, IL-12
  - CXCL8 (IL-8)
  - MCP-1

**Cytosol**
- Curcumin
- Xanthohumol
- Boswellic acids
- Ginger

**Nucleus**
- NFkB (Inactive)
- NFkB (Activated)
Inflammation & Pain: NFkB & Pro-inflammatory Cytokines

- Not only does NFkB increase the *expression* of pro-inflammatory cytokines.

- Some pro-inflammatory cytokines increase the *activation* of NFkB.
  - TNFα, IL-1β
TNFα Activates NFkB

**Upstream**
- TNFα

**NFκB (Inactive)**

**NFκB (Activated)**

**Downstream**
- Increased Expression of:
  - PLA2
  - COX-1
  - COX-2
  - LOX
  - TNFα, IL-1β, IL-6, IL-12
  - CXCL8 (IL-8)
  - MCP-1

**Cytosol**

**Nucleus**
Curcumin and Xanthohumol Reduce TNFα Expression

**Upstream**
- TNFα
- NFkB (Inactive)
  - Curcumin
  - Xanthohumol

**Downstream**
- Increased Expression of:
  - PLA2
  - COX-1
  - COX-2
  - LOX
  - TNFα, MCP-1, IL-6, IL-12
  - CXCL8 (IL-8)
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**Cytosol**
- Curcumin
- Xanthohumol
- Boswellic acids
- Ginger

**Nucleus**
- NFkB (Inactive)
- NFkB (Activated)
Curcumin and Xanthohumol Reduce TNFα Expression

Upstream

- TNFα

- NFkB (Inactive)

- NFkB (Activated)

Curcumin
Xanthohumol
Boswellic acids
Ginger

Downstream

Increased Expression of:
- PLA2
- COX-1
- COX-2
- LOX
- TNFα, IL-1β, IL-6, IL-12
- CXCL8 (IL-8)
- MCP-1

Pro-inflammatory Cytokine Expression

NFkB Activation

TNFα
Inflammation & Pain: Chemokines

- Inflammatory chemokines
  - Chemokine ligand 8 (CXCL8, aka IL-8)
  - Monocyte chemoattractant protein 1 (MCP-1)
  - Interferon-γ activated protein (IP-10)

- Recruit white blood cells to local sites of inflammation
  - Promote *joint pathology* in patients with arthritis
Inflammation & Pain: Chemokines

- **Curcumin**
  - Reduces serum levels of MCP-1
  - Reduces chondrocyte production of CXCL8

- **Xanthohumol**
  - Reduces macrophage production of MCP-1

- **Ginger**
  - Reduces IP-10, specifically in activated human synoviocytes
Immune Response Causing the *Initiation* of Inflammation & Pain

**Tissue Affected (Injury)**

- ARA
- COX
- 5-LOX

- **PGE$_2$**
- **LTB$_4$**

**VASODILATION**

- CXCL8 (IL-8) released *into* the bloodstream which attracts Neutrophils to the local area

**PAIN**

- Tissue Affected
- Prostaglandins & Leukotrienes Produced
- Vasodilation
- Chemokines Released
- Neutrophils Converge
This Combination of Ingredients Acts *Upstream* of SPMs
Mechanistic Takeaways

• Curcumin + Xanthohumol + *Boswellia serrata* + Ginger:
  • Inhibit several key mediators of inflammation & pain
    • NFkB – Upregulates cytokines, chemokines, pro-inflammatory enzymes
    • Pro-inflammatory cytokines
    • Chemokines – WBC recruitment
    • Enzymes involved in prostaglandin and leukotriene production

• Act upstream and downstream on inflammation & pain pathways
# Mechanism of Action (MOA) Summary

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<thead>
<tr>
<th>Inhibition of pro-inflammatory cytokines, chemokines, and transcription factors associated with inflammation and pain</th>
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<td>✓ Inhibits NFkB</td>
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<td>✓ Inhibits NFkB</td>
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</tr>
<tr>
<td>✓ Reduces serum levels of: TNFα</td>
<td>✓ Reduces WBC production of: TNFα</td>
<td>✓ Inhibits NFkB</td>
<td>✓ Inhibits NFkB</td>
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</tr>
<tr>
<td>IL-1β²</td>
<td>IL-12</td>
<td>IL-12</td>
<td>IL-12</td>
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<tr>
<td>IL-6</td>
<td>MCP-1</td>
<td>MCP-1</td>
<td>MCP-1</td>
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</tr>
<tr>
<td>✓ Diminishes chondrocyte production of CXCL8 (IL-8)</td>
<td>✓ Diminishes synoviocyte production of IP-10</td>
<td></td>
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</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Inhibition of enzymes and prostaglandins associated with inflammation and pain</th>
<th>Curcumin</th>
<th>Xanthohumol</th>
<th>Boswellia serrata</th>
<th>Ginger</th>
</tr>
</thead>
<tbody>
<tr>
<td>✓ Inhibits PLA2</td>
<td>✓ Inhibits COX-1 &amp; COX-2</td>
<td>✓ Inhibits COX-1 &amp; COX-2</td>
<td>✓ Inhibits PLA2</td>
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</tr>
<tr>
<td>✓ Inhibits COX-2</td>
<td>✓ Inhibits COX-2</td>
<td>✓ Inhibits COX-1 &amp; COX-2</td>
<td>✓ Inhibits COX-1 &amp; COX-2</td>
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<tr>
<td>✓ Inhibits 5-LOX</td>
<td>✓ Inhibits 5-LOX</td>
<td>✓ Inhibits 5-LOX</td>
<td>✓ Inhibits LOX</td>
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Clinical Applications
## Clinical Applications

<table>
<thead>
<tr>
<th>Target</th>
<th>Pharmaceutical Antagonist</th>
<th>Botanical Antagonist</th>
<th>Clinical Relevance</th>
</tr>
</thead>
<tbody>
<tr>
<td>COX-1 &amp; COX-2</td>
<td>NSAIDs</td>
<td>Curcumin, Xanthohumol, Ginger</td>
<td>• Arthritis (OA, RA, JRA, AS, psoriatic, gout)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• Musculoskeletal pain (back, etc.)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• Tendonitis and bursitis</td>
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<td></td>
<td></td>
<td></td>
<td>• Menstrual cramps</td>
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<td></td>
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<td>• Postoperative pain</td>
</tr>
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<td>• Headache and migraine</td>
</tr>
<tr>
<td>LOX</td>
<td>Leukotriene inhibitors</td>
<td>Curcumin, <em>Boswellia serrata</em>, Ginger</td>
<td>• Arthritis (OA, RA, JRA, AS, gout)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Musculoskeletal pain</td>
</tr>
<tr>
<td></td>
<td></td>
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<td>• Tendonitis and bursitis</td>
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<td></td>
<td></td>
<td>• Menstrual cramps</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Asthma prevention and treatment</td>
</tr>
<tr>
<td>NFκB</td>
<td>Glucocorticoids</td>
<td>Curcumin, Xanthohumol, <em>Boswellia serrata</em>, Ginger</td>
<td>• Inflammatory, autoimmune and allergic disorders (including asthma)</td>
</tr>
<tr>
<td>TNFα</td>
<td>TNFα inhibitors</td>
<td>Curcumin</td>
<td>• Arthritis (RA)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Psoriasis</td>
</tr>
</tbody>
</table>
Scientific Takeaways

- CGM and XNTPM are highly bioavailable.

- Curcumin, Xanthohumol, *Boswellia serrata*, and Ginger reduce systemic inflammation and pain via several well-defined mechanisms.

- These ingredients could potentially be used as an alternative to or in conjunction with other treatments for inflammation and pain.