Modulation of Inflammatory Responses by Select Plant-Derived Ingredients

Takeaways:

- ✓ Inflammation is a complex biological response involving several modifiable mechanisms.
- ✓ Curcumin, xanthohumol, *Boswellia serrata*, and ginger (*Zingiber officinale*) are well-researched plant-derived ingredients shown through research to modulate inflammation and pain pathways by modulating enzymes, prostaglandins, leukotrienes, pro-inflammatory cytokines, and chemokines.
- ✓ These well-characterized ingredients can be used in combination with, or as an alternative to, anti-inflammatory and analgesic agents including COX, LOX, or TNFα inhibitors.
- ✓ Human clinical studies have demonstrated the increased bioavailability of curcumagalactomannoside (CGM) and xanthohumol bound to a protein matrix (XNTPM). Standard curcumin and xanthohumol preparations are typically poorly absorbed in the GI tract.

Inflammatory Immune Responses

Inflammation is an essential biological response that may be triggered by a variety of stimuli, including tissue injury, pathogens, toxins, and oxidative stress. Inflammation underlies many normal physiologic processes, yet it also underlies many pathologic states—especially when inflammatory responses become excessive or chronic. Inflammation initiation pathways involve several enzymes, transcription factors, and signaling molecules (i.e., chemokines and cytokines) that can be modulated by a variety of agents, including select botanical ingredients.

Mechanisms of Immunomodulation by Curcumin, Xanthohumol, *Boswellia Serrata*, and Ginger

Inflammatory Chemokine Inhibition

Inflammatory chemokines—such as chemokine ligand 8 (CXCL8, aka IL-8), monocyte chemoattractant protein 1 (MCP-1), and interferon-γ activated protein (IP-10)—recruit white blood cells to local sites of inflammation during the initiation phase. Because these messengers promote joint pathology in patients with arthritis, they have been suggested as potential therapeutic targets in this population.[1,2] **Curcumin reduces chondrocyte production of CXCL8 and serum levels of MCP-1.**[3–5] **Xanthohumol diminishes macrophage production of MCP-1 while ginger decreases IP-10, specifically in activated human synoviocytes.**[6,7]

Phospholipase A2 Inhibition

Phospholipase A2 is an enzyme that liberates arachidonic acid (ARA), a pro-inflammatory omega-6 fatty acid, from the cell membrane. This makes ARA available to interact with cyclooxygenase (COX) and lipoxygenase (LOX) enzymes to produce inflammatory eicosanoids, including prostaglandins and leukotrienes. **Curcumin and ginger compounds inhibit phospholipase A2.**[8–10]

COX Inhibition

The cyclooxygenase enzymes COX-1 and COX-2 are responsible for the conversion of ARA to prostaglandins, including prostaglandin E2 (PGE_2). Prostaglandins are potent mediators that play central roles in the modulation of inflammatory responses.[11] PGE_2 increases pain perception and contributes to the destruction of cartilage in arthritic joints in both rheumatoid arthritis (RA) and osteoarthritis (OA).[11,12] Commonly used COX inhibitors include NSAIDs. **Curcumin, xanthohumol, boswellic acids, and ginger also inhibit the COX enzymes and thus may reduce the synthesis of PGE_2.**[13–16]

LOX Inhibition

Overproduction of leukotrienes plays a role in inflammatory conditions, particularly asthma and allergic rhinitis. LOX inhibitors work against this by decreasing the conversion of ARA to leukotrienes. Commonly used LOX inhibitors include medications used as analgesics for OA and RA and treatments for asthma. **Curcumin, boswellic acids, and ginger also inhibit LOX activity, thereby reducing leukotriene levels.**[9,15,16]

Nuclear Factor-Kappa B (NFkB) Inhibition

The nuclear factor-kappa B (NFkB) protein complex is a central regulator of DNA transcription, cell survival, and pro-inflammatory cytokine production.

Table I: Curcumin, Xanthohumol, *Boswellia serrata* & Ginger Mechanisms

	Curcumin	Xanthohumol	*Boswellia serrata*	Ginger
Inhibition of pro-inflammatory cytokines, chemokines, and transcription factors associated with inflammation and pain	✓ Inhibits NFkB[13] ✓ Reduces serum levels of: TNFα[5] IL-1β[25] IL-6[5] MCP-1[4,5] ✓ Diminishes chondrocyte production of CXCL8 (IL-8)[3]	✓ Inhibits NFkB[14,19] ✓ Reduces WBC production of: TNFα[6] IL-12[19] MCP-1[6]	✓ Inhibits NFkB[20]	✓ Inhibits NFkB[21,22] ✓ Diminishes synoviocyte production of IP-10[7]
Inhibition of enzymes and prostaglandins associated with inflammation and pain	✓ Inhibits PLA2[8,9] ✓ Inhibits COX-2[13] ✓ Inhibits 5-LOX[9]	✓ Inhibits COX-1 & COX-2[14]	✓ Inhibits COX-1 & COX-2[15] ✓ Inhibits 5-LOX[15]	✓ Inhibits PLA2[10] ✓ Inhibits COX-1 & COX-2[16] ✓ Inhibits LOX[16]

Chronic activation of NFkB is implicated in inflammatory and autoimmune diseases, including asthma, arthritis, and inflammatory bowel disease (IBD). NFkB activation leads to increased production of COX, LOX, and PLA2.[17] Glucocorticoids demonstrate immune-suppressing effects primarily by blocking NFkB activation.[18] **Curcumin, xanthohumol, boswellic acids, and ginger constituents have also been shown to inhibit NFkB.**[3,14,19–22]

Pro-inflammatory Cytokine Inhibition

Pro-inflammatory cytokines promote both local and systemic inflammation and pain. IL-1β, IL-6, and tumor necrosis factor alpha (TNFα) can initiate and promote the persistence of pain locally by directly activating nociceptive sensory neurons.[23] TNF-α also initiates several inflammatory pathways, including NFkB activation, which results in systemic inflammation.[24] TNFα can promote RA, ankylosing spondylitis, IBD, and refractory asthma; therefore, TNFα inhibitors are often used in their treatment. **Curcumin reduces serum levels of TNFα, IL-1β, and IL-6.**[5,25] **Xanthohumol diminishes the production of TNFα and IL-12 in white blood cells (WBCs).**[6,19]

Enhancing Bioavailability of Key Constituents

Curcumin and xanthohumol are key medicinal constituents of turmeric root and hops flowers. Both have robust anti-inflammatory and analgesic properties. While their use had previously been limited due to poor absorption in the GI tract, recent technologic advances have resulted in cutting-edge, highly bioavailable forms of curcumin and xanthohumol. These ingredients are now clinically shown to have much higher oral bioavailability than standard preparations.

Curcumagalactomannoside (CGM) is a novel, highly bioavailable curcumin preparation formulated to provide enhanced absorption of curcuminoids into the bloodstream. CGM combines curcumin from turmeric with galactomannan fibers from fenugreek seeds. Studies have shown that CGM is more stable than standard curcumin preparations and demonstrates exceptional delivery to target tissues. Randomized clinical research studies have shown that oral CGM—an unconjugated (free) curcumin preparation—results in 40 to 45 times higher levels of free curcuminoids and a prolonged half-life in human plasma compared to standard curcumin.[26,27]

Supporting previously published human subject data, a rodent study showed that CGM was significantly more bioavailable in blood plasma than standard curcumin. In addition, it was shown that levels of free curcuminoids were at least 13 times higher in all tested target tissues (including the intestines, liver, spleen, kidney, and heart). Furthermore, levels of free curcuminoids in brain tissue were over 300 times higher in the CGM group, indicating that CGM has an exceptional ability to cross the blood-brain barrier.[28]

Xanthohumol bound to a protein matrix (XNTPM) is a novel form of the potent anti-inflammatory flavonoid xanthohumol, which is found in hops flowers. A potent antioxidant, human studies have shown that xanthohumol protects DNA from damage caused by reactive oxygen species, as well as dietary carcinogens.[29,30] Unfortunately, xanthohumol demonstrates poor bioavailability.[31]

Developed by scientists at Rutgers and North Carolina State Universities, new technology now combines protein with phytonutrients.[32–34] XNTPM utilizes this proprietary protein matrix technology to enhance the delivery of xanthohumol for increased bioavailability and stability. In a randomized, double-blind, crossover study, plasma levels of xanthohumol and its metabolites were increased by 81%.[35]

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