Inflammation + Root Health Summary

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Inflammation occurs when cells of the immune system become activated by the presence of infections or ‘sterile’ agents (physical, chemical or metabolic stimuli released in response to cellular damage or stress) (1). The immune system has a wide response spectrum and can thus execute local and systemic inflammatory responses to eliminate threats. When activated, the immune system induces metabolic and neuroendocrine changes to divert nutrients towards the activated immune cells while conserving energy in non-immune cells (1, 2). Further, these changes can lead to biobehavioral alterations, often referred to as “sickness behaviors”, (i.e. sadness, fatigue, social-behavioral withdrawal, altered food intake, altered sleep, increased blood pressure, dyslipidemia and insulin resistance), which, during infections or cellular injury, can be advantageous (1-5).

Generally, the immune system activates acute (short-term) inflammatory processes in response to microbial infections or cellular damage. During acute infections, the immune system temporarily upregulates inflammatory activity and subsequently downregulates these processes after the threat is cleared (1, 4). Immune cells express receptors which are used to bind to structures on foreign molecules called pathogen-associated molecular patterns (PAMPs) (1, 6). These cells can also be activated by signaling molecules called damage-associated molecular patterns (DAMPs) that are released during cellular damage or stress (1). Thus, immune cells can very quickly identify and terminate foreign molecules, effectively clearing most infections. Immune cell activation stimulates proinflammatory pathways, the release of cytokines, and further stimulation of the immune response (6). Amongst these events, the release of soluble proteins from immune cells known as cytokines plays a key role in regulating the acute inflammatory response and contributes to the initiation of other inflammatory processes (6).

Acute inflammation is a critical component of a functional immune response. Inflammation-related molecules, such as interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α), function as signaling molecules that eliminate injurious stimuli and stimulate tissue repair mechanisms (7). Many of these molecules serve as defense or protective mechanisms against further injury. However, dysregulation or chronic activation of the inflammatory response can have devastating consequences (1). Chronic inflammation is generally triggered by DAMPs in the absence of injury or infection, and ultimately causes tissue and organ damage through sustained activation of the immune system (1, 8). Chronic inflammation can induce many processes, such as oxidative stress, which may contribute to the development of inflammatory-associated diseases (1, 8). Research suggests that more than 50% of all deaths are attributable to inflammation-related diseases including ischemic heart disease, stroke, cancer, diabetes mellitus, chronic kidney disease, non-alcoholic fatty liver disease (NAFLD) and autoimmune and neurodegenerative conditions (9, 10). Chronic inflammation is associated with increased risk of many other conditions including chronic pain, mood and anxiety-related

disorders, acne, eczema, psoriasis, asthma, cancer, inflammatory bowel diseases, stroke, and chronic obstructive pulmonary disease (11-12, 19-28).

At present, many anti-inflammatory drugs or biologics have been designed to specifically target inflammatory signaling molecules in certain inflammatory diseases. At Hudson Medical, we strongly believe in addressing chronic inflammation prophylactically to reduce potential future risk of chronic inflammation-associated diseases. As such, we have developed a daily anti-inflammatory supplement to target chronic inflammation. Our anti-inflammatory supplement harnesses the power of three plant based and naturally occurring molecules, tetrohydrocurcumin, ergothioneine, and dihydroberberine. These molecules were carefully selected based on methodological review of current scientific evidence supporting their safety and efficacy in targeting inflammation.

Tetrohydrocurcumin

Tetrohydrocurcumin is a reduced form of curcumin, a plant-derived molecule shown to aid in the management of many chronic inflammatory conditions (29-31). Within the intestine, curcumin is enzymatically converted to tetrohydrocurcumin, which is readily absorbed to carry out its biological functions within the body (32). These biological functions include increasing the activity of antioxidant enzymes, preserving hepatocellular membrane integrity against toxins, enhancing insulin sensitivity, and reducing inflammatory cytokine production (33-36).

The safety and efficacy of tetrohydrocurcumin has been widely studied in the context of many chronic inflammatory conditions, such as ulcerative colitis and rheumatoid arthritis (37, 38). By eliminating harmful molecules called reactive oxygen species and suppressing pro-inflammatory transcription factors like nuclear factor kappa b (NF-κB), tetrohydrocurcumin has potent antioxidant and anti-inflammatory properties that have immense potential in modern medicine (39, 40). Research suggests tetrohydrocurcumin has protective effects against pro-inflammatory diseases including acne, diabetes mellitus, cardiovascular disease, neurological diseases, autoimmune diseases, depression, asthma, psoriasis and chronic obstructive pulmonary disease (41-45).

Ergothioneine

Ergothioneine is a naturally occurring substance with powerful antioxidant and anti-inflammatory properties. Although ergothioneine is present in all cell types, it is referred to as an adaptive cyto-protective agent because it accumulates in injured tissues in response to increased oxidative damage (46-47). As such, ergothioneine is highly concentrated in mitochondria, the epicenter of oxidative stress (46-49). Studies suggest that ergothioneine levels are significantly reduced in the tissues of subjects with neurodegenerative diseases, eye disorders, cardiovascular diseases, kidney diseases, diabetes and cancer (47-48). Further, cells with reduced ergothioneine levels have been shown to be more susceptible to oxidative stress, leading to deleterious cellular events like increased mitochondrial DNA damage (49). Studies

indicate ergothioneine blocks the production of pro-inflammatory cytokines known to be important biomarkers of various pathologies (49-51).

Ergothioneine reduces molecules responsible for oxidative damage and may reduce cellular inflammation by inhibiting processes that contribute to mitochondrial dysfunction (52). Recent research suggests ergothioneine may protect against metabolic syndrome, cardiovascular disease, development of lung injury following acute respiratory distress syndrome, chronic pain, diabetes mellitus and Alzheimer's disease (53-58).

Dihydroberberine

Research indicates that dihydroberberine, a naturally occurring molecule found in some plants, may serve a protective role in the development of many inflammatory-related conditions, such as ulcerative colitis and atherosclerosis (59-60). Dihydroberberine is a derivative of berberine, a molecule found in plants that has been shown to exhibit beneficial effects on metabolism (61). Research suggests that berberine activates AMP-activated protein kinase (AMPK), an enzyme known to improve insulin sensitivity, enhance lipid oxidation (the process in which fat is utilized for energy), inhibit adipocyte (fat cell) growth and improve cardiovascular health (60-61). Results from clinical studies have shown significant improvements in insulin sensitivity, reduction of body weight and decreased waist circumference following berberine supplementation for 3 months (61-62). When orally consumed, berberine can be simultaneously absorbed in the small intestine through two pathways: 1) berberine can be directly absorbed into the bloodstream at a very slow absorption rate 2) an enzyme called nitroreductase (NTR), localized to the intestinal wall tissue, accelerates absorption by transforming berberine into dihydroberberine, which can be rapidly absorbed (66). Dihydroberberine also has an approximately 5 times higher bioavailability than berberine (68).

Dihydroberberine has been shown to suppress activation of NF-κB, a pro-inflammatory molecule known to contribute to chronic inflammation (60, 65). Research also indicates dihydroberberine supplementation can significantly reduce atherosclerotic lesions, which are strongly associated with increased risk of emergency cardiothoracic events (60). The anti-inflammatory potential of dihydroberberine may be useful in preventing the development of chronic inflammatory disorders including atherosclerosis, ulcerative colitis, osteoarthritis, cancer, metabolic syndrome-related disorders like hyperuricemia, and diabetes mellitus (66-68). Further, as dihydroberberine has been shown to reduce adiposity (severe fat excess) and improve insulin sensitivity in mouse models, dihydroberberine supplementation may be an effective method for aiding glycemic control in humans (69).

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