Natural Approaches to Controlling Inflammatory Disease

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Inflammation is simply a physiologic response process generated by the body in response to injury, infection, or irritation. In acute stages, the inflammatory process is vital to the healing process; however, chronic inflammation can increase disease-associated morbidity. New insights into the chronic inflammatory process now provide evidence that this mechanism is a negative contributor to an ever-expanding list of chronic conditions, including Alzheimer's disease, cardiovascular diseases, diabetes, asthma, cancer, and even depression.

As inflammation is increasingly acknowledged as a main precursor to morbidity in the pathology of chronic disease, medicine is elucidating both the effects of inflammation prior to clinical disease manifestation and preventative treatments geared toward reversal and attenuation of symptoms. Natural medical therapies directed toward anti-inflammatory effects have become more intensely researched in the last several years, providing significant insight into the role of inflammation in disease and offering options for effective preventative and symptomatic treatment.

Inflammation and the Disease Process

The inflammatory process is now being associated with several diseases in which an inflammatory component was previously unknown. Coronary artery disease, major depression, and cancer are associated with an increased level of interleukin-1 (IL-1), a proinflammatory cytokine, while elevated IL-1 levels and proinflammatory leukotriene (LT) B-4, most notably produced by omega-6 fatty acids, similarly characterize diseases such as arthritis, Crohn's disease, ulcerative colitis, and systemic lupus erythematosis.[1] Recent evidence indicates that inflammation plays a pivotal role in the origins and complications of atherosclerotic and type 2 diabetic disease, linked by C-reactive protein (CRP), plasminogen activator inhibitor-1, and homocysteine. These nonconventional risk factors are now known as markers indicative of general low-grade inflammation, vascular injury, and thrombotic processes.[2]

Chronic inflammation is believed to be an associated risk factor for cancer in the human body in the bowel and rectum. Localized inflammatory processes incite numerous pro-oxidative enzymes (e.g., the reduced form of nicotinamide adenine dinucleotide phosphate [NADPH] oxidase, nitric oxide synthase) that react among themselves and with other reactive oxygen species to create an environment that is rich in highly reactive, pro-oxidative species. These oxidants damage DNA, leading to mutations, and may activate oncogenes and/or inactivate tumor-suppressor proteins, allowing carcinogenic processes to occur.

Other causes of localized chronic inflammatory-induced tumor growth that have been proposed include an oxidative process that inhibits cellular apoptosis, cellular switching to a glycolytic metabolism, and neovascular genesis and vasorelaxation that can inhibit recruitment of immune cells, all of which act collectively as an opposing force to the normally rapid cytotoxic response.[3] Studies on these topics these lend credence to the concept of preventative cancer treatment via modulating chronic inflammatory conditions. Much of the literature on using fish oil as an anti-inflammatory approach to treating chronic inflammatory diseases shows significant benefits that include lowered disease activity and decreased use of anti-inflammatory medications.

Anti-Inflammatory Diets

The anti-inflammatory diet, although it is not a recent development in preventing and treating inflammatory diseases, serves as the cornerstone for mitigating the generalized, chronic inflammatory response. This treatment is applied in many forms, differing from practitioner to practitioner. What is consistent in the various forms of the anti-inflammatory diet is strict avoidance of foods that contain high amounts of arachidonic acid (AA), the main precursor of the negatively associated inflammatory cascade process. Metabolites of AA include platelet activating factor, prostaglandins (PGs), LTs, and thromboxanes, which are closely involved in both acute and chronic inflammatory responses.

The rate-limiting step in the creation of these inflammatory metabolites is the release of AA from membrane phospholipids, which are catalyzed by the enzyme phospholipase A2. The clinical implications associated with imbalanced intake and metabolism of the two essential fatty acids (EFAs), linoleic and alpha-linolenic acids, are directly related to their byproduct concentrations in the membrane phospholipid layer. Levels of these long-chain polyunsaturated fatty acids (arachidonic, eicosapentaenoic, and docosahexaenoic acids) may be affected by diet and disease and can alter the severity, character, and intensity of systemic inflammatory processes.[4]

An alteration or loss of regulation of the AA cascade leads to a chronic inflammatory state, which characterizes numerous physical disorders. A frequently indicated offender to be removed

from the diet is red meat, a significant source of linoleic acid (LA), and its product AA. Another source of dietary inflammation is hydrogenated foods, which often have an increased amount of LA and a decreased amount of the beneficial alpha-linolenic acid (ALA). Numerous studies highlight a link between foods that are high in omega-6 fatty acid and decreased intake of omega-3 fatty-acid–rich foods.[5] Dietary gluten and lectins are also recognized as common triggers of inflammation.

It is theorized that humans evolved on a diet consisting of a 1:1 ratio of omega-6 to omega-3 fatty acids. Today, the typical Western diet consists of a ratio between 10:1 and 25:1 and, in some cases, this ratio may be as high as 40:1. It is this imbalanced fatty-acid ratio that is linked to chronic inflammatory health problems.

A common misconception is that all commonly consumed omega-6 fatty acids (LA, AA, and gamma linolenic acid [GLA]) are unhealthy, when the reality is that only excessive intake of LA and AA (combined with a decreased intake of omega-3 fatty acids) contribute to chronic inflammation because these fatty acids are necessary for essential functions in the body.

High LA levels inhibit the delta-6-desaturase (D6D) enzyme, which is both the initial and rate-limiting enzyme in both the omega-6 and omega-3 fatty-acid pathways. This reduces further LA breakdown. In addition, because LA is not metabolized further, dihommo-gamma linolenic acid (DGLA), which is the precursor to GLA, is not formed. DGLA, in turn, is the precursor of a number of beneficial eicosanoids that are important for optimal cell functioning. GLA has considerable health benefits and is not linked to the problems associated with an unbalanced fatty-acid profile.

Polyunsaturated Fatty Acids and Lymphocyte Functions

The inflammatory mediators (PGs and LTs) that are produced via polyunsaturated fatty acid (PUFA) metabolism can directly influence the behavior of inflammatory immunologic cells and their production and balance of cytokines. Increased consumption of omega-3 PUFAs displaces the amount of AA in cellular membranes and thereby limits the production of proinflammatory eicosanoids. It is believed that acquired immunologic factors are affected by omega-3 PUFA intake and incorporation into cellular membranes and that fatty acids may stimulate some immune activity by way of noneicosanoid-dependent mechanisms.[6]

Fish oil (a rich source of omega-3 PUFA) supplementation in animals results in positively associated altered lymphocyte function, decreased macrophage-borne proinflammatory cytokines, and pacification of autoimmune disease symptomatology. In human subjects, dietary additions of omega-3 PUFAs have led to decreased monocyte and neutrophil chemotaxis and production of proinflammatory cytokines.[7]

Inflammatory-type diseases are amenable to fatty-acid replacement therapies because the composition of fatty acids in lymphocytes and other immune cells are modified by both bodily-fat amounts and types of fatty acids available for eicosanoid production. Fatty acids such as arachidonic, alpha-linolenic, eicosapentaenoic, oleic, linoleic, conjugated linoleic, gamma-linolenic, dihomo-gamma-linolenic, and docosahexaenoic, all have the ability to influence inflammatory responses that are associated with lymphocyte proliferation and cytokine production, as well as natural killer (NK)–cell activity.[8]

Anti-Inflammatory Supplements At-a-Glance

Supplements	Doses and notes
Vitamin B_6	50 mg per day
Magnesium	600–800 mg per day, in divided doses (an adjustment for bowel tolerance may be required)
Vitamin E	400–800 international units per day (in mixed or D-alpha-tocopherol form)
Fish oils	4 g per day, in a 1.5 EPA:DHA ratio (low peroxide levels are critical)
Devil's claw (*Uncaria tomentosa*)	75 mg of a standardized preparation, 3 times per day
Propolis	500 mg, encapsulated, three times per day
Boswellia (*Boswellia serrata*) also known as frankincense	300–500 mg, standardized for boswellic acids, 3 times per day, not with food

EPA = eicosapentaenoic acid; DHA = docosahexaenoic acid.

Cytokine production is reduced by omega-3 PUFAs, decreasing the severity of the cytokine-related disease processes. Because cytokine production and function are part of a normal host defense, they are necessary. Consumption of PUFAs in excess of 3–4 g per day may lead to impairment of the immune response, however. Increased consumption of PUFAs may also lead to increased lipid peroxidation and resultant oxidative species causing a reduction in T-cell directed function, NK cell function, and macrophage activity.[9] Consuming other sources of antioxidants, such as vitamin E, may mitigate increased oxidation due to consumption of PUFAs.

Vitamin B_6 and Inflammation

Vitamin B_6 (pyridoxine) plays several roles in the etiology and pathogenesis of chronic inflammation and inflammatory diseases. Pyridoxine is water-soluble and is preferentially absorbed in an acidic milieu in the proximal small intestine via simple diffusion. This vitamin's role in inflammation can be observed on a number of metabolic levels and in various pathologies.

In one study, pyridoxine-deficient rats developed increased concentrations of thiobarbituric acid reactive substances (indicators of lipid peroxidation) up to 30–43 percent, suggesting an enhanced inflammation response caused by pyridoxine deficiency.[10] In another study, median pyridoxine levels were significantly lower in human patients with inflammatory bowel disease (IBD) compared to controls and were even lower in patients with active IBD compared to those whose disease was quiescent. In addition, lower pyridoxine levels were positively correlated with CRP serum levels, and hyperhomocysteinemia occurred more frequently in patients with lower pyridoxine levels.[11]

Suboptimal levels of vitamin B_6 are associated with increased risk for cardiovascular disease and rheumatoid arthritis. The reasons for this are not evident and a clear pathophysiologic picture has not emerged for these two conditions, other than the inflammatory reaction shared by both diseases. In one study, decreased levels of plasma pyridoxal 5′-phosphate, the active form of vitamin B_6, were associated with higher levels of CRP independent of total plasma homocysteine. The researchers hypothesized that such evidence may indicate that vitamin B_6 deficiency contributes to chronic inflammatory processes.[12]

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Another aspect of inflammation in which vitamin B_6 is involved is fatty-acid metabolism. Inhibition of D6D, which is both the initial and rate-limiting enzyme in both the omega-6 and omega-3 fatty-acid pathways, can result from vitamin B_6 deficiency.[13] In addition, because LA is not metabolized further, GLA, which is the precursor to DGLA, is not formed. DGLA, in turn, is the precursor for a number of beneficial eicosanoids that are important for optimal cell functioning and production of PGE1, an anti-inflammatory PG.

Vitamin E, Zinc, and Magnesium

Other nutritional factors that are involved in positive upregulation of D6D include zinc, magnesium, and vitamin E. In one study, the enzymatic activity of D6D was increased at twice that of baseline level in subjects when their vitamin E microsomal membrane concentrations were increased, reflecting the vitamin's role in controlling the membranous metabolism of PUFAs.[14]

In addition, zinc has been shown to assist in converting LA to GLA via D6D, and a deficiency of zinc produced an EFA deficiency and downregulation of D6D.[15] Magnesium deficiency contributed to decreased formation of D6D molecules, resulting in a less-rapid conversion of LA to GLA in liver microsomes.[16]

By supplying patients with proper nutritional doses of these enzymatic cofactors, efficient activation of this D6D can induce complete fatty-acid metabolism and production of noninflammatory fatty-acid products, helping to reducing chronic inflammatory patterns further.

Cat's Claw

Cat's claw (*Uncaria tomentosa*) is a medicinal plant that is native to the Amazon River basin, with a history of traditional use for inflammatory conditions. Two active compound groups, alkaloids and flavanols, are presumed to be the major effector compounds.[17]

Studies of cat's claw have utilized two species, *Uncaria guianensis* and *Uncaria tomentosa* and both are considered to be equiactive but, currently, *U. tomentosa* has been more well-researched. A pulverized bark fraction of *Uncaria tomentosa* inhibited tumor necrosis factor–alpha (TNF-α) production by approximately 65–85 percent and has acted as a potent antioxidant.[18] These effects, immunomodulation of TNF-α and antioxidative abilities, are widely documented in the literature. What is more, the anti-inflammatory effects of this plant have been demonstrated recently.

In test subjects with osteoarthritis of the knee, a comprehensive study was undertaken to determine the adverse-effect, pain, medical, and subject-assessment scores of patients who took a purified extract of the herb. The researchers noted an absence of negative effects on red blood–cell indices and liver function or other side-effects compared to placebo.

In the *Uncaria*-treated group, activity-associated pain, medical and subjective assessment scores were "significantly" reduced within 1 week of therapy at doses that achieved a level of 13.6–21.7 µg per mL of each subject's blood and lipopolysaccharide-induced PGE2 synthesis was inhibited at a concentration higher than necessary to mitigate TNF-α production as had been explained in previous studies.[19]

In another study, an extract of *Uncaria tomentosa* was given to patients with active rheumatoid arthritis and who were undergoing sulfasalazine or hydroxychloroquine treatment in a 52-week, two-phase study. Twenty-four (24) weeks of treatment with the cat's claw extract resulted in a decreased amount of painful joints in treated subjects compared to those who were on a placebo (53.2 percent versus 24.1 percent) with minor side-effects, none of which were listed.[20]

Cat's claw is emerging as an effective botanical medicine that can be used for treating various inflammatory states and conditions, producing positive effects and few side-effects. The anti-inflammatory properties of this herb are undergoing further investigation and continued research promises to provide even more specific explanations of the herb's actions in inflammatory diseases.

Propolis

Propolis is a resinous substance derived from poplar and conifer buds and used by *Apis mellifera* bees for maintaining their hives. The pharmacologically active molecules in propolis are flavonoids and phenolic acids and their esters. These components have proven antibiotic effects on bacteria, fungi, and viruses.[21]

New evidence suggests that propolis may suppress the lipoxygenase pathway thereby decreasing PG and LT synthesis.[22] In studies using the rat paw edema model, it has been theorized that caffeic acid phenethyl ester (CAPE) is the constituent that is most responsible for the anti-inflammatory effects of propolis for reducing acute and chronic inflammation.[23]

One study investigated the effects of both CAPE and galangin (an ethanolic extract of propolis) on cyclo-oxygenase (COX) activity. Propolis inhibited COX activity significantly in a dose-dependent manner. Similar results were obtained independently with CAPE and galangin; however, the COX inhibitory effect of propolis containing galangin but not CAPE, was determined

to be approximately 10 times less potent than the extract containing CAPE. Both CAPE and galangin contribute to the activity of propolis, although CAPE is the stronger-acting constituent.[24]

The anti-inflammatory effects of this plant medicine have also been studied in other models of inflammation such as corneal injury and skin burns. It was shown to produce anti-inflammatory effects comparable to dexamethasone in treating experimentally induced chemical corneal injury.[25] Propolis was compared to silver sulfadiazine (SSD) for treating superficial second-degree burns. Burns treated with propolis had less inflammation and increased cicatrization compared to those treated with SSD, and no significant differences in microbial-wound colonization were noted between the two treatment groups in one study.[26] The researchers hypothesized that, had the dressing been changed more frequently (fewer than every 3 days), the antimicrobial and healing effects may have been enhanced.

Burns treated with propolis had less inflammation compared to those treated with silver sulfadiazine.

The two previous studies exemplify the broad use of propolis as an anti-inflammatory agent that can be useful for treating a number of conditions with various medical therapies, many of which may yet be discovered.

Boswellia

Boswellia *(Boswellia serrata)*, also known as frankincense, is native to the Indian continent, North Africa, and the Middle East, and is used widely as a traditional herb in Ayurvedic medicine for treating inflammatory disease.

The resin, or gum, from the plant contains pentacyclic triterpenes (boswellic acids) of which produce much of this plant's anti-inflammatory activity. Nearly 16 percent of the resin is comprised of essential oil. The acids contained in boswellia inhibit the enzyme 5-lipoxygenase by binding to the enzyme, resulting in decreased LT production in neutrophilic granulocytes.

Several clinical trials have attributed beneficial effects of this herb in treating chronic inflammatory diseases, such as rheumatoid arthritis, chronic colitis, ulcerative colitis, Crohn's disease, asthma, and tumor-associated brain edema.[27]

In a study of patients with colitis, a gum resin extract of *Boswellia serrata* was supplied at a dose of 900 mg, three times per day, for 6 weeks while a control group was maintained on 3 g per day of sulfasalazine for 6 weeks. Ninety (90) percent of the boswellia-treated patients experienced improvements in stool properties; histopathology; and levels of hemoglobin, iron, calcium, phosphorus, proteins, and total leukocytes and eosinophils, with few side-effects, while 60 percent of the sulfasalazine-treated patients experienced similar results. However, fourteen (14) of the 20 boswellia-treated patients experienced remissions, while only 4 of the 10 sulfasalazine-treated patients reached remission.[28]

Boswellia has been proven to be effective for treating asthma also and the beneficial effects are attributed to LT inhibition. Seventy (70) percent of subjects who were treated with 300 mg of the herb, three times per day, for 6 weeks, experienced improvements in forced expiratory volume 1 (FEV_1), forced vital capacity (FVC), and peak expiratory flow rate (PEFR). What is more, these same subjects had decreased eosinophilic counts and erythrocyte sedimentation rates, plus subjective improvements. The placebo group experienced a 27-percent improvement overall.[29]

Boswellia serrata can serve as a potent anti-inflammatory medicine and as a non-redox, noncompetitive specific inhibitor of the 5-lipoxygenase enzyme.

Conclusions

Science is continually discovering an inflammatory link in many chronic diseases, revealing this process as both a precipitive and propagative factor in these conditions. Because of this new understanding, physicians must now, more than ever, use preventative medicine to treat their patients.

Preventative anti-inflammatory treatments are numerous and may be applied at various levels of care. The most motivated patients can alter the course of their health positively and prevent chronic conditions, such as cardiovascular disease, cancer, Alzheimer's disease, et cetera, simply by manipulating the fatty-acid ratios of their dietary intake.

In addition, patients with preexisting "chronic" disease conditions may also affect the outcomes of these disease processes by adhering to similar protocols. Natural medicines and nutritional cofactors also collectively play an important role in preventing and treating diseases in which inflammation is active.

Greater understanding of these medicines and the benefits that they exert on various parts of the inflammatory process will allow practitioners use such natural anti-inflammatories safely to treat chronic inflammation as well as for general preventative health care. □

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