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A CONCISE UPDATE OF IMPORTANT ISSUES CONCERNING NATURAL HEALTH INGREDIENTS

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# Managing Chronic Inflammation: Natural Solutions

**The human immune system is a complex and multi-layered array designed to limit tissue damage from harmful agents and cells. The inflammatory process is a vital and necessary component of our immune defense system, and when these immune responses are temporary and local, the inflammatory process is beneficial. However, a breakdown in the regulation of the inflammatory response can result in processes that, instead, lead to the damage of tissues and organs; and are a hallmark of most chronic diseases. Therefore, understanding the various aspects of the inflammatory process allows for a more comprehensive approach to treating patients with most chronic conditions. Likewise, an immense amount of research is now being directed at finding agents that affect the inflammatory process at various levels. This review will focus primarily on the role of inflammation in chronic disease conditions and the role of diet, lifestyle and nutraceutical agents in the management of both acute and chronic inflammation.**

## Introduction

Formal descriptions of inflammation are very ancient, being described by the four hallmarks of redness, swelling, pain and heat as early as the first century A.D. These hallmark signs were long associated with acute injury or infections and are considered vital to the repair of damaged tissues. Over the past decades, we have linked inflammatory processes to many more diseases without these overt outward signs. They include inflammatory disease of the skin (psoriasis, eczema), bowels (Crohn's disease, colitis), central nervous system (Alzheimer's, multiple sclerosis), rheumatoid arthritis, allergies, asthma, atherosclerosis, cancer and diabetes to name just a few. While the tissues affected by these conditions may be different; the cells, cytokines and pathways of inflammation are very similar in each. Likewise, some of the lifestyle, diet and treatment protocols for these conditions may have a common thread- the overall reduction of the inflammatory burden.[1]

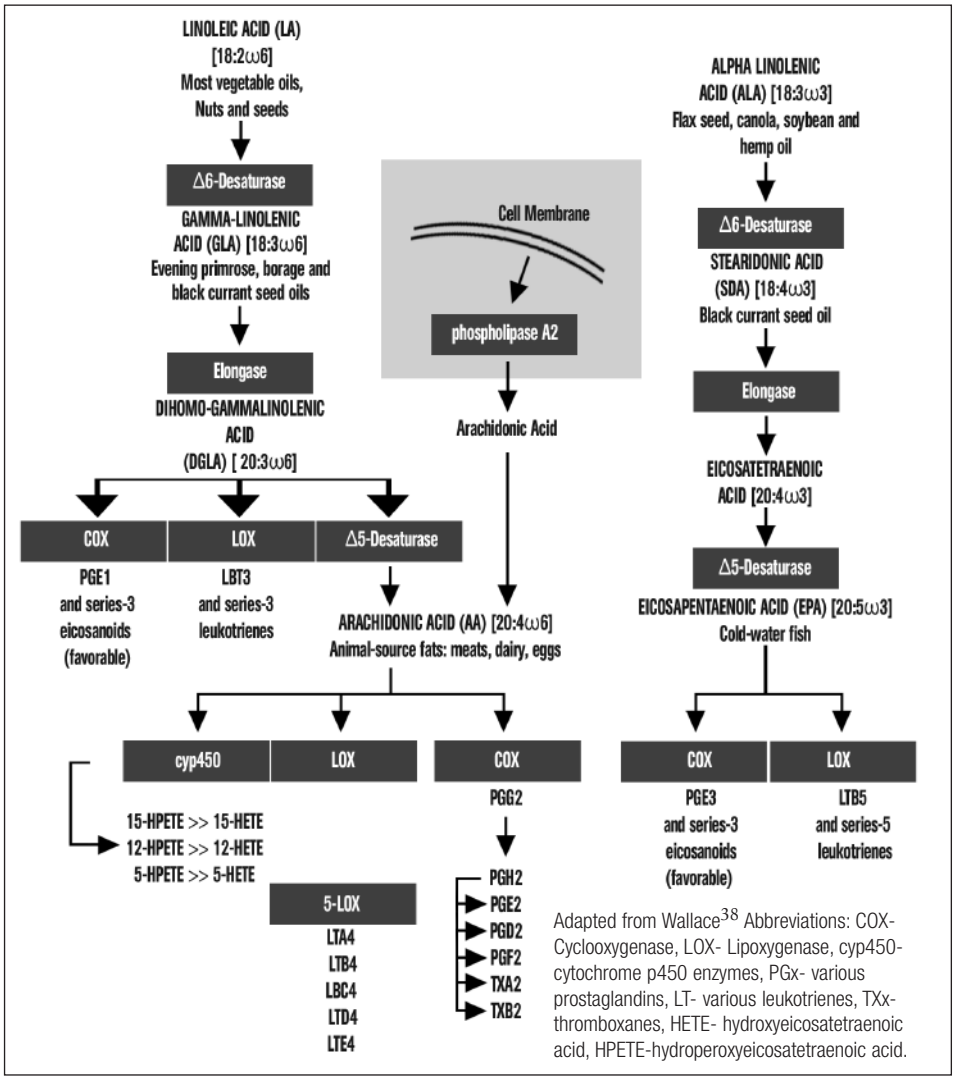
The basic process of inflammation begins with some sort of tissue injury- whether physical, chemical or biological. This injury results in the release of cytokines and chemoattractants from the damaged tissue that function to recruit immune cells (lymphocytes) from the bloodstream into the damaged tissue. These recruitment signals may come from the distressed cells directly or from mast cells and macrophages, immune cells embedded within the tissues. Next, up-regulation of adhesion molecules (e.g. selectins, ICAM, VCAM) on the damaged tissues allows for the docking of the recruited lymphocytes, permitting these immune cells to begin the process of diapedesis, where they alter their cellular structure and move from the arterial lumen to the tissue space through the endothelial junctions. Once these immune cells are in the extravascular space, they begin the process of "fighting" the cause of the tissue damage, sending more signals to recruit more cells and secreting compounds that alter vasodilation, platelet activity and fibrinolytic activity- resulting in the hallmark signs of inflammation. These processes are designed to eliminate the cause of injury and help repair the damaged tissue. Unfortunately, many of the signals which drive the inflammatory process are not transient and, instead of resolving the underlying damage, the inflammatory process results in a chronic cycle of tissue damage.[2]

## Mediators of Inflammation

In the past several decades, many of the cells, cytokines and genes that regulate the inflammatory process have been described. While only a few of these have resulted in measurable clinical markers, many of the mediator pathways have become the target of anti-inflammatory therapies. Perhaps the most

commonly targeted enzyme pathway for drug therapy, cyclooxygenase (COX), is responsible for the conversion of arachodonic acid into pro-inflammatory mediators such as prostaglandins (e.g. PGE2) and thromboxanes. (See Figure) Compounds such as the non-steroidal anti-inflammatory drugs (NSAIDs- aspirin, ibuprofen, naproxen) are non-specific inhibitors of both the constitutive COX-1 enzyme as well as the inducible COX-2 enzyme. Recently, COX-2 specific inhibitors (e.g. celecoxib), have been marketed in the attempt to eliminate the most common side effect (gastric ulcer) associated with non-specific NSAIDs, although several drugs in this class have been removed from the market due to increased cardiovascular risk. Other enzymes, in the lipoxygenase (LOX) family, are responsible for the conversion of arachidonic acid into other pro-inflammatory mediators (leukotrienes) and are often the target of specific anti-inflammatory therapy.[3] The enzyme responsible for liberating arachidonic acid from the phospholipids of the cell membranes, phospholipase A ($PLA_2$), is also an important target for anti-inflammatory therapies.[4] (See Figure Inset)






Adapted from Wallace[38] Abbreviations: COX- Cyclooxygenase, LOX- Lipoxygenase, cyp450- cytochrome p450 enzymes, PGx- various prostaglandins, LT- various leukotrienes, TXx- thromboxanes, HETE- hydroxyeicosatetraenoic acid, HPETE-hydroperoxyeicosatetraenoic acid.

Pro-inflammatory signals between cells are achieved through a network of cytokines and chemokines. A majority of these molecules are produced by immune cells, though many of these can be produced by certain cells under stress (such as pro-inflammatory adipokines from insulin-resistant adipose cells). Some of the more important pro-inflammatory biomarkers include monocyte chemotactic protein-1 (MCP-1), interleukins 1β (IL-1β), IL-6, tumor necrosis factor-α (TNF-α), intracellular adhesion molecule (ICAM), vascular cell adhesion molecule (VCAM), bradykinin, histamine, C-reactive protein (CRP), fibrinogen, serum ameloid A (SAA) and plasminogen activator inhibitor-1 (PAI-1). As many of these compounds are coordinately regulated or have direct influence on the expression or secretion of others, they are often up-regulated together in various disease states. Conversely, many anti-inflammatory agents result in the coordinate down-regulation of several of these biomarkers.[5]

Expression of many of these biomarkers is inter-regulated through a series of cell surface and nuclear receptors. Key among these is the nuclear transcription factor, nuclear factor-κB (NF-κB), responsible for the regulation of many pro-inflammatory cytokines, adhesion molecules, growth factors and inducible enzymes such as COX-2. Numerous compounds have been discovered to have an influence on NF- κB activity and regulation, helping to explain their anti-inflammatory and anti-cancer activities.[6,7] Other nuclear receptors of interest include the related peroxisome-proliferator-activated receptors (PPARs), liver X receptors (LXR) and the retinoic-acid receptors (RARs); responsible for the transcriptional regulation of numerous genes whose products are involved in the regulation of inflammatory processes, insulin sensitivity and other vital cell functions.[8,9] A growing area of research is also focused on a family of cell-surface receptors, called toll-like receptors (TLRs), which recognize various components of microbes or stressed host cells to trigger immune/inflammatory responses. These receptors, as well as the classic receptors for cytokines and growth factors also play a role in understanding the inflammatory process, but have yet to become clinical targets for risk management.[10]

## Clinical Markers of Chronic Inflammation

C-reactive protein (CRP), a liver protein which is produced in response to inflammation, is one of the most common indicators used to detect inflammation in the body. CRP is

usually used to predict an individuals risk for cardiovascular disease, but can be used more generally to indicate inflammation and disease risk. Type 2 diabetes and other negative health conditions are associated with elevated CRP levels.[11-13] CRP is primarily secreted by the liver and is triggered by interleukin 6 (IL-6) as well as other inflammatory cytokines generated by monocytes, macrophages, and adipose tissue.[11,14] CRP is measured by a high sensitivity assay (hs-CRP). Currently, hs-CRP levels <1.0 mg/L indicates a low cardiovascular risk, 1.0-3.0 mg/L indicates an average risk, and levels greater than 3.0 mg/L indicate a high cardiovascular risk. Some suggest there may be added value in expanding the range to consider values less than 0.5 mg/L (very low risk) and greater than 10 mg/L (very high risk).[11] CRP values have not been established for other disease-specific conditions, but since CRP is triggered by inflammatory cytokines from sources through out the body, it may be useful as an indicator of chronic inflammation for a wide range of diseases.

Another marker of inflammation specific to cardiovascular disease that has emerged in recent years is lipoprotein-associated phospholipase A2 (Lp-PLA2). After adjusting for CRP and LDL cholesterol, Lp-PLA2 is an independent predictor of cardiovascular risk in some groups.[15-17] As more becomes unveiled about the intricacies of the inflammatory process, disease specific markers, such as Lp-PLA2 , may replace or become more widely used alongside other general markers of inflammation like CRP.

## Lifestyle Factors Contributing to Chronic Inflammation

### Diet

There are a number of different dietary factors that can cause or contribute to inflammation. Polyunsaturated fatty acids (PUFAs), namely the omega-6 PUFAs arachindonic and linoleic acids, hold the strongest evidence for pro-inflammatory effects. Linoleic acid, one of the main PUFAs in the Western diet, can be converted to arachindonic acid, a precursor to components in the inflammatory process. Because linoleic acid competes with omega-3 fatty acids for metabolism, the conversion of linoleic acid to arachidonic acid depends largely on the ratio of omega-3 to omega-6 fatty acids consumed. Plant seed oils such as corn, sunflower, and safflower make up a large percentage of dietary sources of linoleic acid. Foods derived from these oils, including margarine, also contribute to the high ratio of omega-6 to omega-3 fatty acids typically seen in the Western diet. Arachidonic acid is also consumed directly in meat, eggs, and other common foods in the Western diet.[18,19]

Omega-3 fatty acids, including those found in fatty fish like EPA and DHA, have anti-inflammatory effects. Omega-3 fatty acids are usually consumed in lower quantities than omega-6 fatty acids in the Western diet, which contributes to inflammation.[18] The typical American diet may have omega-6/omega-3 fatty acid ratios in the 15-20:1 range. As stated previously, these high ratios can contribute to chronic inflammation.[20,21] Some studies suggest trans and saturated fats may also lead to increased levels of inflammation.[22,23] The Nurses' Health Study reported women with the highest intakes of trans-fat had CRP and IL-6 levels that were higher (73% and 17%, respectively) than those who consumed the least amount of trans-fats.[22] In a study of patients with heart failure, higher intakes of saturated and trans-fats were independently associated with higher amounts of TNF-α.[24] It is conceivable that high intakes of saturated and trans-fats can promote inflammation, however most of this data is observational and the mechanisms are unclear.

Glycemic index (GI) and glycemic load (GL) may contribute to inflammation as well. The Nurses' Health Study reported that of the 902 diabetic women, CRP levels were 32% higher in those with the highest GI diets compared to the lowest.[25] In another study involving 244 generally healthy middle-aged women, glycemic load was positively related to CRP levels.[26] The mechanism for this potential relationship is not clear but could be related to elevated glucose and/or insulin levels, both known to contribute to inflammation.[19] This preliminary evidence implies that diets with a high GI/GL (diets high in refined carbohydrates) may contribute to chronic inflammation. This relationship needs further investigating and more clinical trials.

### Obesity

Studies suggest excess adipose tissue is associated with higher amounts of CRP and other inflammation markers in children, the elderly, and those with metabolic syndrome, diabetes, and heart disease. Where fat is stored may be more critical than the amount, as visceral abdominal fat is a better predictor of inflammation levels than other obesity measures.[27] Adipose tissue is more than a passive storage of fatty acids, we now know it is responsible for secreting over 50 proteins, or adipokines, with a variety of roles. Adipose tissue functions differently in obese individuals compared to those who are lean. Dysregulation of adipose tissue can lead to an increase in macrophages and the amount of pro-inflammatory cytokines produced is directly related to weight gain. Visceral abdominal obesity appears to play a role in chronic inflammation. Studies show that weight loss leads to reductions in inflammatory markers, strengthening the connection between obesity and inflammation.[27,28]

### Sedentary Lifestyle

A sedentary lifestyle may indirectly contribute to inflammation as it promotes weight gain and obesity. An inactive lifestyle may also contribute to the inflammatory burden in more direct ways. Cytokines, or myokines, are released by active skeletal muscle into the circulation system where they reduce inflammation in muscle cells and at distant sites.[29] A sedentary lifestyle, therefore, may contribute to inflammation by reducing the amount of circulating anti-inflammatory cytokines and by increasing pro-inflammatory myokine production from inactive muscle beds.

### Smoking

Studies show that those who smoke have higher CRP levels than non-smokers. A prospective study following smokers and

non-smokers for 18 years, showed smokers had elevated inflammatory markers compared to non-smokers. Smoking causes increased oxidative stress, which may be one way smoking could drive inflammation and promote development of CVD, COPD, and other disorders.[30]

## Lifestyle Interventions to Prevent and Reduce Inflammation

### The Mediterranean Diet and Beyond

The Mediterranean diet has many different variations, but in general includes generous amounts of fruits and vegetables, whole grains, beans, nuts and seeds, deep-sea fish, and fermented dairy. Olive oil and wine are also consumed in moderately high amounts. The Mediterranean diet has become one of the most studied diets for its ability to reduce all-cause and cardiovascular mortality and may also be an effective way to reduce inflammation. An epidemiological study revealed that those who consumed a diet most closely resembling the traditional Mediterranean diet had CRP levels 20% lower than those who did not closely follow the diet.[31] A study involving a group of healthy elderly individuals also showed similar results.[32] Another small trial showed that after consumption of a single Mediterranean style meal, postprandial CRP levels were decreased while consumption of a Western style meal did not decrease CRP levels.[33] After two years on the Mediterranean diet, patients with metabolic syndrome had significant decreases in levels of CRP and other inflammation markers compared to those on a control diet (prudent diet).[34] The results from these trials are not surprising as many components of the Mediterranean diet, such as marine omega-3 fatty acids, red wine, and olive oil, are all known to have positive effects on inflammation.

Eicosapentanoic acid (EPA) and docosahexanoic acid (DHA), found in coldwater fatty fish (tuna, salmon, sardines, etc), are the two most studied omega-3 fatty acids. Diets rich in EPA and DHA can reduce or prevent inflammation and reduce the risk of cardiovascular events. Studies have shown reductions in inflammation and positive effects on cardiovascular disease, rheumatoid arthritis, inflammatory bowel disease, and other conditions with the use of fish or fish oil supplements.[35] Some clinical trials have shown omega-6/omega-3 ratios from 2:1 – 6:1 have reduced inflammation and improved cardiovascular disease risk.[20,21] While diets high in omega-3 fatty acids have beneficial effects on inflammation and other conditions, the optimal amounts needed varies for different diseases and populations. With the typical Western diet consisting mostly of omega-6 fatty acids, a small increase in omega-3 fatty acids may be beneficial for inflammation.

Anti-inflammatory effects have been reported with various alcoholic beverages, mainly red wine which may provide additional benefits because of its antioxidant properties. Research suggests those with moderate alcohol consumption have lower CRP levels and other markers of inflammation than either those who do not drink or are heavy drinkers.[36]

### Weight Loss

In addition to diet, weight loss has also been shown to reduce CRP and other inflammatory markers. In a 12-week dietary intervention study, 83 obese women had a 26% reduction in CRP with an average weight loss of 7.9 kg. Weight loss interventions from 6 months to 2 years have reported that weight loss due to exercise, dietary restriction, medication or gastric bypass surgery can reduce CRP levels by 3-70% along with other inflammatory markers.[27] The improvement in inflammatory markers may depend on the amount of weight loss and/or the individual's starting BMI.[27,37] In those who are overweight or obese, weight loss can be an effective way to reduce inflammation, regardless of the weight loss method.

### Physical Activity

Research also suggests that physical activity, such as traditional exercise or sports, can reduce inflammation.[29] An inverse association between markers of systemic inflammation, fitness status, and physical activity has been observed in cross-sectional studies. An inverse, independent dose-response relationship between plasma CRP and physical activity has also been observed in other large population studies in both men and women. Aerobic exercise and resistance training, or a combination of the two, have been shown to have positive effects on inflammation. Anti-inflammatory effects may extend beyond physical activity resulting in weight and fat loss. The potential decrease in CRP levels may also depend on health status, fitness level, and baseline CRP levels. Anti-inflammatory effects may also be related to the skeletal muscles' ability to produce cytokines (myokines). Myokines are released into circulation by active skeletal muscle which reduces inflammation in muscle cells. While research shows physical activity has beneficial effects on inflammation, it is still unclear which type, intensity, and frequency of physical activity is the best to reduce inflammation in different populations.

## Nutraceutical Intervention of Acute and Chronic Inflammation

Many of the foods, spices and traditional healing substances associated with reducing inflammation have been analyzed to find specific anti-inflammatory mechanisms associated with specific dietary components. Many of these have been extensively studied in enzyme inhibitory assays, cell-culture and animal studies to further elucidate their anti-inflammatory effects.[38] A wide-variety of clinical trials have been performed on many of these agents. While these studies confirm their clinical use, the diverse study designs and doses have made it difficult to compare these agents to one another. We will review the most commonly used agents, describing their known mechanisms and current clinical application.

### Fatty Acids

As discussed above, diets high in omega-3 fatty acids and low in omega-6 and trans-fatty acids generally reduce the overall inflammatory burden. This would seem logical due to a decrease

in arachidonic acid intake (or its precursors) while at the same time increasing fatty acids that directly compete for enzymes within the arachidonic acid cascade (COX, LOX etc.). Intervention trials have been performed in order to see whether fatty acids in the form of dietary supplements are able to change the inflammatory burden and modify disease outcomes. The most common of these fatty acids are EPA and DHA from fish oil, and gamma-linolenic acid (GLA) from Evening Primrose oil, Borage oil and Black current seed oil.

Omega-3 fatty acids from fish oil have been studied extensively in patients with rheumatoid arthritis.[39] Meta-analysis data suggest a modest improvement in tender joints and morning stiffness with the addition of fish oil supplementation.[40] Dosing and fish oil content vary widely in different clinical trials. The most significant benefits seem to require at least 3 grams/day, although benefits were seen in some trials with 2.6 grams/day,[41] 30mg/kg/day,[42] and 40 mg/kg/day.[43] Significantly more benefit is seen when patients who use fish oil supplements are also consuming a low arachidonic acid, anti-inflammatory diet.[42] A recent review of the literature for beneficial dietary and nutraceutical agents in rheumatoid arthritis shows that omega-3 therapy is one of the most consistent and promising.[44]

The role of fish oils has also been explored in patients with inflammatory bowel diseases such as ulcerative colitis and Crohn's disease. Reviews of the various clinical trials have shown that doses as high as 4.5 and 5.4 grams per day have limited benefit on preventing relapses, but often reduce the dependence on steroid therapy and dramatically reduce inflammatory markers.[45] A specially prepared enteric-coated, free fatty acid preparation (1.8 g/day EPA, 0.9 g/day DHA) was able to significantly reduce the level of relapse, compared to placebo, in a group of Crohn's disease patients (n=78).[46] Another group recently reported that stimulated T-cells and monocytes taken from Crohn's disease patients supplemented with fish oil (1.6 g/day EPA, 1.08 g/day DHA- non-enteric coated) and an antioxidant blend (vitamins A, C, E, selenium, and manganese) produced lower interferon-gamma and PGE2, compared to placebo.[47] In general, these data suggest that individuals with inflammatory bowel conditions may benefit from increasing fish oil intake equivalent to 2.5-5 grams per day.

The role of GLA from Evening Primrose oil and Borage oil for rheumatic diseases has been reviewed.[48] In these diseases (rheumatoid arthritis, Raynaud phenomenon and Sjögren syndrome), high doses of GLA (450 mg to 2.8 grams) delivered via Evening Primrose oil or Borage seemed helpful in many patients. Unfortunately, few well-designed clinical trials have been performed to make clear recommendations. Additionally, mixed results have been reported for the use of Borage oil for atopic eczema.[49,50]

## Botanical Components

A wide variety of plant compounds have been used in traditional medicine throughout the world to treat inflammatory conditions (acute and chronic). The anti-inflammatory agents in many of these have been purified and studied in a variety of experimental models (especially as anticancer agents).[51] Clinical use of the whole herb, herbal extracts, or isolated compounds as anti-inflammatory agents is widespread throughout the U.S.

### Turmeric /Curcumin

Turmeric (*Curcuma longa*) roots have long been used as both a food ingredient (spice, coloring agent) and medicinal agent in East Asia. This plant, related to ginger, contains the potent anti-inflammatory agent, curcumin. Curcumin is known to be a potent inhibitor of NF- κB, COX-2, LOX as well as many other enzymes within the inflammatory pathway (many regulated through NF- κB).[52] Curcumin also reduces other inflammatory mediators such as IL-6, IL-1β, MCP-1 and metalloproteanases in animal models.[53,54] Animal and cell culture studies have shown positive benefits for curcumin in diverse conditions such as ulcer prevention and healing, treating and preventing hepatotoxicity, direct anti-inflammatory studies (induced edema studies), reduction in advanced glycation end products (AGEs), anti-bacterial, anti-viral and anti-tumor to name a few.[55,56]

While curcumin is likely one of the most diverse and powerful natural anti-inflammatory agents known, and both its mechanisms and applications are fairly clear; few clinical trials have been published to confirm its wide use in humans. Reports have confirmed that oral doses of curcumin inhibit the production of COX-2, limiting the formation of $PGE_2$, as well as reducing pro-inflammatory mediators from LOX in animals and humans.[57,58] A small pilot study in patients with inflammatory bowel diseases (5 Crohn's, 5 proctosigmoiditis) showed improvements in inflammatory markers and disease measurements as well as a reduction or elimination of previous medications. The dose in this study was either 550 mg curcumin twice daily or 360 mg three times per day (1st month) followed by 360 mg four times per day.[59] A similar study also showed improvement in patients with irritable bowel syndrome taking curcumin/turmeric.[60] A study in Thailand showed that 3 grams of curcumin/day in divided doses significantly reduced both duodenal and gastric ulcers (76% patients had complete healing) in 12 weeks.[61] Curcumin is considered to be extremely safe and no toxicity is noted even at very high doses.[62]

### Quercetin and related flavonoids

Plant flavonoids are widely distributed in nature and are frequently consumed in most diets. Numerous biological activities have been attributed to the consumption of flavonoids, including strong anti-inflammatory activity. For instance, quercetin impedes several steps in the conversion of arachidonic acid to inflammatory eicosanoids by inhibiting phospholipase A2, COX-2 and 5-LOX.[38] In addition, quercetin is also one of the few known agents to inhibit mast cell degranulation, an important first step in allergic reactions; as well as diminish mast cell production of pro-inflammatory cytokines.[63,64] Due to its combined affects on mast cells, quercetin has become a key agent for treating and preventing allergic reactions, especially allergic rhinitis.

Quercetin and other related bioflavonoids are used regularly in acute and chronic inflammatory conditions, and may be especially helpful in injury related conditions due to their beneficial affects on extra-cellular tissue repair and capillary permeability.[65,66] In the classic animal model, rat paw edema,

quercetin is one of the more potent anti-inflammatory flavonoids tested.[67]

Unfortunately, there have been few published clinical trials using quercetin and related flavonoids as dietary supplements, perhaps because these agents are not generally patentable. One study showed a statistical improvement in symptoms of interstitial cystitis in 20 patients given 1000 mg of quercetin/day for 4 weeks.[68] The same dose was previously used in a placebo-controlled trial showing improved pain scores in men with chronic prostatitis.[69] In both of these studies, bromelain and papain were added to the quercetin formula as it is commonly believed that these plant-derived enzymes increase the bioavailability of quercetin and other bioflavonoids.

### Enzymes (Plant and Animal)

Clinical use of enzymes (primarily proteases) to reduce both acute and chronic inflammatory conditions is widespread. Most popular is the use of the pineapple enzyme complex bromelain, the papaya enzyme papain, and various combinations of animal proteases such as trypsin and chymotrypsin. Historically, these enzymes have been used for sports injuries, arthritis, and post-surgical inflammation, and now are commonly used for chronic inflammatory conditions and even for cancer treatment.



The therapeutic mechanisms for bromelain have been well-studied.[38,70] Relevant to this review are bromelain's anti-edema, fibrinolytic, and anti-inflammatory activities. Bromelain has been shown to inhibit the production of the pro-inflammatory $PGE_2$ while promoting the formation of the anti-inflammatory $PGE_1$, perhaps by affecting COX-2 enzyme activity and/or the activity of NF- κB, and inhibiting the pro-inflammatory bradykinin pathway.[71,72,73] Animal models of inflammatory diseases have shown bromelain to consistently and safely reduce inflammation; and are often more potent than currently available drugs.[74,75,76]

Clinical trials in humans using single enzyme or mixed enzyme preparations have been very promising. A commercial preparation of bromelain, trypsin and rutinose has been shown to be well-tolerated and as effective as diclofenac in both knee and hip osteoarthritis.[77,78] Bromelain alone may also be effective for similar conditions.[79] Commercial preparations of bromelain, papain, trypsin and rutin have been used in Germany and Eastern European countries for post-operative surgery, sports injuries, prostatitis, arthritis and cancer-related therapies for decades. While few of the clinical trials have been published in English, many commercially available mixed enzyme products are now available in the U.S. It should be noted that these preparations should be taken on an empty stomach to promote as much intact absorption of enzymes without loss of activity due to food digestion. Enteric-coated products are also thought to be preferable, except in the case of bromelain and papain, plant enzymes that can tolerate the low pH of the stomach. Enzyme activity is measured in units (different units are used for each enzyme) although no uniform labeling requirements of enzymatic activity units are yet required in the U.S.

### Boswellia

The resin of *Boswellia serrata* has been used for inflammatory conditions in Ayurvedic medicine for many years. The triterpene compounds, known as boswellic acids, are considered to be the main active compounds. Boswellic acids are strong inhibitors of 5-LOX and TNF-α induced metalloproteinase expression.[80,81]

A placebo-controlled trial in patients with osteoarthritis of the knee given 1000 mg/day of boswellia extract (40% boswellic acid) showed statistical improvements in pain scores, swelling and movement in 8 weeks.[82] Other clinical trials have shown similar benefits in patients with chronic colitis[83] and bronchial asthma.[84]

### Caffeic Acid phenethyl ester (CAPE)

CAPE is a phenolic compound derived from propolis, a natural substance produced by honey bees from tree resin.[85] CAPE is thought to be one of the major anti-inflammatory agents of propolis, although other compounds may also play a role.[86,93] CAPE appears to be a strong inhibitor of the IL-1β induction of NF-κB, which would have wide-ranging anti-inflammatory effects. CAPE has also been shown to directly inhibit COX enzymes while also being immunostimulating. Propolis has been used medicinally for thousands of years and propolis extracts are now commercially available as dietary supplement.[85]

In a rat model of colitis, propolis was able to attenuate colitis symptoms and reduced colonic levels of NF-κB, IL-1β and TNF-α.[87] IL-1β induced damage to human cartilage and chrondrocytes is inhibited by propolis extracts.[94] CAPE was also able to inhibit the inflammatory cascade following chest irradiation in mice.[88] While more studies are needed to confirm the wider role for propolis extracts and CAPE in clinical practice, the long historical use of propolis, as well as its safe record of use, suggests that this compound may play a profound role in various anti-inflammatory therapies.

### Other botanicals

Many other botanicals have been used historically to treat inflammatory conditions, some of which have confirmed anti-inflammatory mechanisms.

**Chinese skullcap** (*Scutellaria baicalensis*), a member of the mint family, has been used traditionally in China for a number of conditions, especially those involving inflammation. Several compounds, namely baicalein, baicalin, and wogonin (all flavones) have been shown to inhibit inflammation by various mechanisms (inhibition of COX-2, TNF-α, and various adhesion molecules). [89,90,91]

**Ginger** (*Zingiber officinale* L.), being in the same family as turmeric, has a similar history of medicinal use. The various gingeroles are considered to be the most active component of the root, although other compounds likely have some influence on the anti-inflammatory action as well.[95] Inhibition of TNF-α, NF-κB and COX-2 have all been associated with ginger extracts.[96] While most clinical trials using ginger focus on its anti-nausea affects, especially in pregnant women and motion sickness, various extracts are currently being used for rheumatic and other inflammatory conditions.[97,98]

**Devil's claw** (*Harpagophytum procumbens*) root is a traditional medicine of southern and eastern Africa, where it is used for various rheumatic conditions. Like many of the other herbs, components of Devil's claw have been shown to block TNF-α induced NF-κB production resulting in reduced COX-2 activity and lower amounts of the pro-inflammatory $PGE_2$.[99,100] Promising, but preliminary, clinical trials for back and arthritis pain (daily dose of extracts containing 50-60 mg harpagosides) have been published.[101]

**Cat's claw** (*Uncaria tomentosa*) has also become a popular herbal supplement. Ethanol extracts of Cat's claw are strong inhibitors of NF-κB and TNF-α, resulting in lower activities of both cytokines and pro-inflammatory enzymes and mediators.[102] A small preliminary clinical trial in patients with rheumatoid arthritis suggests that Uncaria extracts may have modest benefits in reducing pain and tender joints.[103]

Numerous other botanical extracts have been shown to inhibit various components within the inflammatory system. Likewise, several have been used in promising clinical trials, some with described potential mechanisms. They include herbs like nettles (*Urtica dioica.*), basil (*Ocimum* spp), willow (*Salix* spp), feverfew (*Tanacetum parthenium*), Thunder God vine (*Tripterygium wilfordii* Hook F), green tea (*Camellia sinensis*) and gotu kola (*Centella asiatica*).[104,105]

## Conclusion

Understanding that inflammatory processes are integrally related to most chronic disease processes is a vital key to formulating a treatment strategy. Selecting dietary patterns that greatly reduce the inflammatory burden, while increasing anti-inflammatory foods and nutraceuticals, will often create a large window of opportunity for other more specific treatment strategies. Like foods, nutraceuticals should be combined to take advantage of multiple mechanisms and potentiate synergy. More and more data is being generated on the anti-inflammatory properties of phytochemicals, primarily as potential anti-cancer agents. This data is confirming the traditional use of many of the plants and plant extracts that have been clinically effective for rheumatic and chronic disease throughout the world.

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