



# FIGHTING INFLAMMATION WITH FORTIFICATION

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## Introduction

There are two types of inflammation; acute and chronic. Acute inflammation is part of a healthy immune system response. However, chronic, low-grade, tissue inflammation may lead to the pathogenesis of a variety of chronic diseases. Chronic inflammation plays an important role in diseases as apparently diverse as cardiovascular disease, diabetes, osteoporosis, arthritis, Alzheimer's disease, and auto-immune diseases. Moreover, the less dramatic daily discomforts of life, such as chronic pain, depression, memory loss, general cognitive decline, and general muscle fatigue, all seem to be connected in some way to an underlying inflammatory condition.

## Market Size

Important market drivers for anti-inflammatory products include a general increasing consumer awareness of the connection between good nutrition and health, and particularly the notion that there are specific nutrients and food ingredients that have special functional properties needed to improve health. For example, chronic pain and discomfort is an important public health problem affecting 116 million Americans. To put this problem in some perspective, this is more people than are affected by heart disease, diabetes and cancer combined. Chronic inflammation is often an important component of the pathology of these pain-producing conditions. Common chronic conditions associated with the use of anti-inflammatory medications include people with asthma and chronic obstructive pulmonary disease, rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease and psoriasis.

The opportunity to use nutrients to address inflammation could complement the growing market for anti-inflammatory drugs, which is substantial and is likely to grow in the future. Moreover, with the predicted large increases of the elderly in many countries, and the growing obesity epidemic in both developed and developing countries, there is a huge potential market for products that can deliver efficacious doses of specific anti-inflammatory nutrients and bioactive compounds.

## In Demand Nutrients

The information summarized below highlights some of the newer clinical trial evidence to support the role of various potential nutrients that may improve inflammatory status (**Table 1**).

**Table 1. Anti-inflammatory Foods, Nutrients and Bioactive Factors Used in Clinical Trials**

<p><b>Omega-3 Fatty acids</b></p> <ul style="list-style-type: none"> <li>• Fish Oil</li> <li>• DHA</li> <li>• EPA</li> </ul>	<p><b>Vitamins</b></p> <ul style="list-style-type: none"> <li>• Vitamin E</li> <li>• Vitamin C</li> <li>• Riboflavin</li> <li>• Niacin</li> </ul>	<p><b>Botanicals</b></p> <ul style="list-style-type: none"> <li>• Lemon Verbena</li> <li>• Curcumin</li> <li>• Grape seed extract</li> </ul>
<p><b>Minerals</b></p> <ul style="list-style-type: none"> <li>• Zinc</li> <li>• Selenium</li> <li>• Manganese</li> </ul>	<p><b>Bioactives &amp; Antioxidants</b></p> <ul style="list-style-type: none"> <li>• Coenzyme Q10</li> <li>• Quercetin</li> <li>• EGCG</li> <li>• Soy isoflavones</li> <li>• Beta-carotene</li> <li>• L-carnitine</li> <li>• Polyphenols</li> </ul>	<p><b>Fruit Extracts/Powders</b></p> <ul style="list-style-type: none"> <li>• Bilberry</li> <li>• Orange</li> <li>• Tomato</li> <li>• Blackcurrant</li> <li>• Bing cherry</li> </ul>

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Fish oil is a natural product with high concentrations of long chain omega-3 polyunsaturated fatty acids (PUFAs), which have therapeutic anti-inflammatory benefits and protective actions in various inflammatory diseases, including periodontitis.<sup>1</sup> The general public has a growing awareness of the importance of chronic inflammation in disease development, including the potential anti-inflammatory actions of omega-3 fatty acids in fish oil. Growing concern about environmental contaminants in some fish products, however, has helped spur the market for clean, sustainably sourced omega-3 fatty acids and omega-3 fortified food products.

Long-chain omega-3 fatty acids, such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) have significant anti-inflammatory effects in pre-clinical studies in cell culture and animal models, as well as complementary observational studies of the beneficial anti-inflammatory effects of high fish intakes in human populations. Evidence from clinical trials to support a beneficial role of fish oil fatty acids as anti-inflammatory agents in various conditions and populations are highlighted below.

Arthritis is associated with significant joint pain and often reflects an underlying inflammatory process associated with tissue destruction. In a double-blind, placebo-controlled study, 45 subjects with joint pain discomfort received a nutritional supplement or placebo for nine weeks. The nutrient supplement included lemon verbena extract (containing 14% verbascoside) and fish oil omega-3 fatty acids. Joint dysfunction and pain were evaluated once per week in both groups. This study found a significant reduction in symptoms of pain and stiffness<sup>2</sup> that



could be due to the beneficial anti-inflammatory effects of fish oil.

A study<sup>3</sup> of fortified milk consumption in 107 children, who were assigned to either a supplemented milk group, who consumed 0.6 L per day of a fish oil-enriched dairy product, or a control group, who consumed 0.6 L per day of standard whole milk, found anti-inflammatory effects of fish oil-fortified milk. The enriched milk contained long-chain polyunsaturated fatty acids, oleic acid, as well as carbohydrates, vitamins and minerals and was relatively low in saturated fat. Both of the study groups consumed the dairy drink for five months. Serum levels of adhesion molecules were used as indices of vascular endothelial cell activation in both groups at baseline and five months, in addition to other blood measures. In the enriched dairy drink-supplemented group, adhesion molecules E-selectin and ICAM-1 and lymphocyte levels were decreased, suggesting an anti-inflammatory effect of fortified milk. In another study of 103 children with attention-deficit/hyperactivity disorders, eight weeks of daily supplementation with 635 mg EPA and 195 mg DHA decreased serum inflammatory cytokines.<sup>4</sup>



Multiple sclerosis is another disease with a significant pro-inflammatory profile. A study of patients with multiple sclerosis evaluated the efficacy of fish oil supplementation (4 g/d for 12 months) on serum pro-inflammatory cytokine levels, oxidative stress markers, and disease progression. In this study, fish oil treatment decreased the serum levels of TNF-alpha, IL-1 beta, IL-6, and nitric oxide metabolites compared with the placebo group.<sup>5</sup>

The consumption of a high-fat meal (HFM) produces an acute inflammatory response and has been used as an experimental inflammatory model to test the effects of various treatment interventions in humans. HFM promotes postprandial increases in nitric oxide in exhaled breath, a marker of airway inflammation. In a study of 17 non-asthmatic young men, a single HFM increased airway inflammation (exhaled nitric oxide) and omega-3 fatty acid supplementation from fish oil (3 g/d for 3 weeks) protected against HFM-associated changes in airway health.<sup>6</sup>

Fish oil may also help balance the inflammatory response triggered by exercise. A study of elite athletes reported that compared to placebo, fish oil supplementation (2.5 g/d for 6 weeks) helped optimize cytokine levels (markers of inflammation) that are elevated during exercise (<http://www.ncbi.nlm.nih.gov/pubmed/17923401>). A second study in untrained males also reported lower levels of exercise-induced inflammation following supplementation with docosahexaenoate; an omega-3 fatty acid in combination with mixed tocopherols and flavonoids for a 14 day period (<http://www.ncbi.nlm.nih.gov/pubmed/14652498>).

Free radical stress can cause tissue damage and result in an inflammatory response. Adequate intakes of **vitamin A**, **vitamin C** and **vitamin E**, important antioxidant vitamins, and other



*During World War II, when British air pilots ate bilberries, they reported an improved ability to adjust to glare and an increase in their visual acuity and nighttime vision. Learn more about this botanical at [Fortitechpremixes.com](http://Fortitechpremixes.com)*

carotenoids may help prevent free radical damage and to help maintain healthy inflammation. Fruit and berry juices are good sources of dietary polyphenols. Various dietary polyphenol compounds have important antioxidant properties.

Nonalcoholic fatty liver inflammation (nonalcoholic steatohepatitis) is often associated with obesity. In an important study published in the *New England Journal of Medicine*, investigators studied the effects of vitamin E (800 IU per day x 96 weeks) on nonalcoholic fatty liver inflammation in adults without diabetes. They found that vitamin E treatment was associated with a significantly higher rate of improvement in nonalcoholic steatohepatitis compared to placebo and a reduction in markers of liver inflammation.<sup>7</sup> In a small study of 13 older Italian men with impaired fasting glucose, investigators found that treatment with 1000 IU vitamin E and 1000 mg vitamin C for four weeks reduced blood levels of TNF- $\alpha$ , an indicator of inflammation.<sup>8</sup> In another study, subjects with metabolic syndrome, which is associated with an increased risk of diabetes and cardiovascular disease, were randomized to 800 IU per day of alpha-tocopherol or 800 IU gamma-tocopherol or a combined vitamin E treatment or placebo for six weeks. C-reactive protein concentration and serum TNF- $\alpha$  were reduced by the combined treatment and TNF- $\alpha$  was also reduced by alpha-tocopherol treatment alone.<sup>9</sup>

**N-acetylcysteine (NAC)** is a thiol-containing antioxidant with anti-inflammatory properties and has been shown to reduce the number of cardiovascular events in hemodialysis patients. Treatment with NAC (2 x 600 mg/daily) for eight weeks significantly diminished IL-6 levels, whereas no such changes were observed in the placebo group.<sup>10</sup>

**Coenzyme Q10** is an endogenous lipid-soluble antioxidant. Statin therapy, a popular medication used to lower blood cholesterol, can reduce the biosynthesis of coenzyme Q10. An investigation of the effects of a coenzyme Q10 supplementation (300 mg/d; 150 mg/b.i.d) on oxidation and inflammation in patients who have CAD and use statin therapy found that coenzyme Q10 supplementation decreased the inflammatory marker IL-6 in these patients.<sup>11</sup>

The effect of **bilberry juice** on serum biomarkers of inflammation and antioxidant status has been studied in subjects with elevated levels of at least one risk factor for cardiovascular disease (CVD). In this study, 62 subjects were randomized to receive either placebo or bilberry juice for four weeks. Supplementation with bilberry juice resulted in significant decreases in plasma inflammatory biomarker concentrations of C-reactive protein (CRP), IL-6, IL-15, and monokine induced by INF-gamma (MIG).<sup>12</sup>

**Concord grape juice** contains polyphenol compounds, which have antioxidant and anti-inflammatory properties and influence neuronal signaling. Concord grape juice supplementation has been shown to reduce inflammation, blood pressure and vascular

pathology in individuals with CVD, and consumption of such flavonoid-containing foods is associated with a reduced risk for dementia.<sup>13</sup> In a small study, Concord grape juice supplementation was given for 12 weeks to 12 older adults with memory decline, but not dementia. Consumption of Concord grape juice caused a significant improvement in a measure of verbal learning and non-significant enhancement of verbal and spatial recall in these older subjects.<sup>13</sup>



The effects of **strawberry fruit antioxidants** in beverage form on meal-induced postprandial inflammatory has been studied in 24 overweight adults who consumed a high-carbohydrate, moderate-fat meal (HCFM) accompanied by either a strawberry or a placebo beverage in a cross-over design.<sup>14</sup> Postprandial changes in plasma anthocyanins, their metabolites, insulin, glucose and inflammatory markers were assessed for 6 h. The strawberry beverage significantly attenuated the postprandial inflammatory response induced by the HCFM as measured by high-sensitivity C-reactive protein and IL-6.

A Danish study<sup>15</sup> investigating the effects of orange (250 mL per day) and blackcurrant juice (250 mL per day) compared to a sugar drink (placebo) on inflammatory markers in 48 patients with peripheral arterial disease observed that, following a 28-day treatment period, there was a significant decrease in inflammatory markers due to the juice treatment.

Spanish investigators found that consumption of tomato juice containing 21 mg lycopene for two weeks resulted in a significant reduction in C-reactive protein, a marker of inflammation.<sup>16</sup> In a clinical trial of 117 healthy adults conducted in the United States, researchers found that consumption of encapsulated fruit and vegetable juice powder concentrate for 60 days had a positive effect on various inflammatory biomarkers.<sup>17</sup>



A proteomic approach to investigate the metabolic response to cherry fruit consumption was conducted in 18 men and women, who consumed Bing sweet cherries (280 g/d for 28 days). Cherry consumption selectively reduced several biomarkers associated with inflammatory diseases.<sup>18</sup>

In another study, researchers in the United Kingdom investigated the effects of **grape seed extract (GSE)**, a flavonoid-rich product, as a potential mediator of inflammation in 32 patients with type 2 diabetes.<sup>19</sup> Patients received either GSE (600 mg per day) or placebo for four weeks in a double-blind crossover study. GSE treatment caused a significant reduction in inflammation measured by serum C-reactive protein biomarker. A similar study in healthy pre- and postmenopausal women conducted in the United States found that consumption of 36g of lyophilized grape powder for four weeks caused a significant reduction in serum tumor necrosis factor-alpha (TNF- $\alpha$ ), an important cytokine that can trigger the inflammatory response.<sup>20</sup>



In addition to trials of juices and extracts on inflammation, studies have also investigated the effect mixtures of purified bioactive compounds on inflammation. For example, Neiman and colleagues.<sup>21</sup> studied the effect of a bioactive mixture in trained cyclists on exercise-induced inflammation. Strenuous exercise can lead to acute inflammation to repair exercise-induced damage. Forty cyclists were randomized to placebo, quercetin (1000 mg), or a mixture of quercetin plus 120 mg epigallocatechin 3-gallate (EGCG), 400 mg isoquercetin, and 400 mg EPA and DHA for two weeks before, during, and one week after three days of heavy exercise exertion. The bioactive mixture caused a significant reduction in biomarkers of inflammation immediately after the exercise bout.

**Curcumin** is a traditional Indian spice that has gained much interest as a potential anti-inflammatory compound. A clinical study from Japan has investigated whether a combination of soy isoflavones and curcumin could influence the blood levels of prostate specific antigen (PSA) in men who had elevated PSA, but who did not have evidence of prostate cancer based on a negative prostate biopsy.<sup>22</sup> Eighty-five men were randomized to receive either placebo or soy isoflavone-curcumin for six months. Changes in PSA, a marker of prostate inflammation, were evaluated before and after supplementation. The investigators found that the mixture significantly reduced serum PSA concentrations. A study conducted in India with 72 patients with type 2 diabetes found that 300 mg curcumin for eight weeks caused a significant reduction in biomarkers of inflammation in the blood.<sup>23</sup>



Mixtures of antioxidant nutrients have also been investigated for their effects on inflammation in various disease conditions. For example, investigators in the United States found that a combination of alpha-tocopherol (800 mg), beta-carotene (24 mg), vitamin C (1000 mg), selenium from selenomethionine (0.2 mg), riboflavin (7.2 mg), niacin (80 mg), zinc (60 mg), and manganese (5 mg) consumed daily for four months in patients with a history of sporadic colorectal adenoma had a beneficial effect on markers of inflammation and oxidative stress.<sup>24</sup>

Asthma is another inflammatory disease where nutrients may help support more healthy function. A study from Egypt randomly assigned 60 children with asthma to either placebo or a nutrient supplement containing omega-3 fatty acids, vitamin C and zinc and found that there was significant improvement in pulmonary function.<sup>25</sup>

In a study from Iran, 36 CKD patients on hemodialysis were randomized to receive either placebo or 1000 mg per day L-carnitine for 12 weeks.<sup>26</sup> The investigators found that carnitine supplementation was associated with a significant reduction in C-reactive protein and the pro-inflammatory cytokine IL-6.

A study of zinc supplementation in 40 healthy elderly subjects in Detroit found that 45 mg zinc per day for six months decreased

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the concentration of serum C-reactive protein and various other inflammatory biomarkers.<sup>27</sup>

Overall, the studies highlighted above represent clinical intervention trials which demonstrate the promising efficacy of various nutrients and bioactive food factors or botanical sources as anti-inflammatory ingredients.

### Product Applications

Beverage Serving Size: 8oz			
Nutrient	Label Claim/ serving size	UoM	%DV
Vitamin C	120	mg	200%
Zinc	3.75	mg	25%
Selenium (from selenomethione)	17.5	mcg	25%
Manganese	1	mg	50%
Niacin	10	mg	50%
Vitamin B2	0.17	mg	10%
N-Acetyl-L-Cysteine	300	mg	n/a

Cookie Serving Size: one cookie			
Nutrient	Label Claim/ serving size	UoM	%DV
Vitamin C (Sodium Ascorbate)	60	mg	100%
Vitamin E	15	IU	50%
CoQ10	100	mg	n/a
Quercetin	50	mg	n/a
EGCG (Green Tea)	50	mg	n/a
Curcumin	100	mg	n/a
Zinc	7.5	mg	50%

Capsule Serving Size: one capsule			
Nutrient	Label Claim/ serving size	UoM	%DV
Curcumin	300	mg	n/a
Piperine (Black Pepper Extract)	10	mg	n/a
Soy Isoflavones	40	mg	n/a
Hesperidine (citrus extract)	170	mg	n/a
Zinc	15	mg	100%
Vitamin E	15	IU	50%
EGCG	120	mg	n/a
Lycopene	10	mg	n/a

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## Future Trends

Chronic Inflammation can occur anywhere throughout our bodies - and for many reasons, ranging from trauma or an injury, to an infection, to autoimmune response that may be associated with issues such as asthma, heart disease, colitis and diabetes, just to name a few. With much of the general public embracing the concept of healthy aging, and their desire to incorporate products into a daily regime to address chronic inflammation, opportunities will exist for products that can complement the arsenal of pharmaceuticals on the market today.

Hippocrates has been credited with the quote, "let food be thy medicine," and from the many trends we have seen within the functional food, and beverage, categories, consumers have, and will increasingly supplement their diets with products that can positively impact their overall health and wellness. The key, however, will be to create products that not only live up to their intended claims, but as importantly, taste good. No one is going to purchase a product if it does not taste good and utilizing a custom nutrient premix in its development can help to mitigate this issue.

A premix is a single blend of multiple nutrients that not only preserves or enhances the taste of a product, but can also ensure its stability, texture and shelf life. There are basic steps to follow when dry-blending a multiple-ingredient formula to make a homogeneous premix:

- Test all active ingredients, identify and potency limits. If raw materials are not tested prior to use, it may be difficult to determine whether a problem with the final product is related to blending or to the ingredients.
- If possible, render all ingredients free-flowing. This can be done with milling, particle coating, granulation, making pre-blends, titration, spray drying and other techniques.
- Purchase ingredients that have consistent particle size distribution or that have a narrow range of variation.
- Screen lumpy or cohesive ingredients as you add them to the blender. It will reduce agglomeration during mixing.
- Always add a portion of the largest quantity ingredient to the blender first. It will coat the blender and prevent lesser ingredients from sticking to the walls.
- Before adding small-quantity active nutrients to the blend, be sure that each one is geometrically diluted to assist with adequate blending. That helps prevent loss from ingredients adhering to the blender wall or because the material had not been dispersed enough for uniform blending. Never add ingredients that account for less

*It's important to check with the regulatory entities in your region to determine product claims*

than one percent of the total blend into an empty blender.

- Finally, take adequate samples from the top, bottom, and center of the blender. List at least three of the lower potency ingredients to determine the adequacy of the blend. Take samples again after discharge to identify any segregation that may have occurred during material transfer.

Most experts on formulation agree that there is a science to blending powders that are part of the finished product and that will work for every product. However, blending powders is very different from blending liquids. Where over-blending is almost impossible, powder-to-powder blends can be “un-mixed” when particles segregate. There are two common blending processes employed in the nutraceutical/dietary-supplement industry to achieve a homogeneous product: dry-blending and wet-granulation. Dry blending is the most common method used to manufacture premixes. A physical property of powders is a critical aspect of dry blending. Before blending starts, first consider the properties of the ingredient powders including flowability, particle size, shape and density.

### Regulatory Considerations

Regulatory bodies around the world may have differing parameters regarding claims surrounding inflammation. In developing label claims for a food, beverage or pharmaceutical product, manufacturers should seek legal guidance to affirm compliance with the appropriate regulatory body in their state and or country. The intent of the information provided within this paper is to help manufacturers facilitate thoughts and ideas surrounding product development.

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