Mitigation of Inflammation with Foods

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ABSTRACT: Constant overproduction of pro-inflammatory molecules leads to chronic inflammation. Unlike acute inflammation, which is essential for healing, chronic inflammation can delay healing and, if left unchecked, contribute to a host of diseases. There is growing evidence that some dietary factors can play important roles in maintaining health and even reversing the progression of chronic diseases, with anti-inflammatory effects as important underlying mechanism. Such findings add to the body of evidence that certain dietary components, including polyphenols and other types of compounds, found in various dietary factors including fruits, berries, vegetables, nuts, whole grains, and foods of marine origin, can play an important role in attenuating and mitigating chronic pro-inflammatory processes associated with chronic diseases.

KEYWORDS: dietary factors, dietary fiber, fish oil, fruits, inflammation, nuts, omega-3 fatty acids, açaí (Euterpe oleracea), cocoa, polyphenols, tea, vegetables

INTRODUCTION

Inflammation is an adaptive response that is triggered by noxious stimuli and conditions such as chemical or physical injury. Inflammation causes the activation of cellular and systemic components of the immune system. The initial response involves the innate immune system whereby cells—including macrophages, mast cells, and dendritic and natural killer cells—converge at the site of injury. Chemical mediators released by the innate immune cells, such as cytokines, chemokines, and reactive oxygen species, allow recruitment of leukocytes to the area of injury or infection and lead to the elimination of pathogens and/or tissue repair, with dendritic and natural killer cells initiating the adaptive immune response.[1] Generation of inflammatory mediators can then activate various downstream signaling pathways to modulate cell proliferation, cell death, and differentiation and amplify the response to the initial insult.

The response to tissue injury or infection requires a well-orchestrated interaction of immune and inflammatory cells and their products. Chronic inflammation (also called nonresolving inflammation), by contrast, is a prolonged, dysregulatory, and maladaptive response that involves persistent active inflammation, tissue destruction, and failed attempts at tissue repair. Such inexorable inflammation is associated with a host of chronic human conditions and diseases, including atherosclerosis, ischemic heart disease, cancer, obesity, inflammatory bowel disease, Crohn's disease, diabetes, and autoimmune diseases.[2−7]

The anti-inflammatory agents, including nonsteroidal anti-inflammatory drugs (NSAID) and disease-modifying antirheumatic drugs (DMARDS), are widely used in treating these disorders. However, many of them have dose-dependent side effects, and none of them are suitable for primary prevention, which significantly limit their use. On the other hand, it has been recognized that lifestyle and environment play an important role in inflammatory responses. As a major aspect of the environment, diet can be a key element in managing inflammatory process. In the past decade, understanding of the role of diet in promoting health by regulating inflammation, especially via certain nutrients or dietary components, has grown substantially. Dietary habits that encourage increased consumption of fruits, vegetables, whole grains, and nuts may lead to reduced inflammation.[8−10] From this perspective, we examine recent studies that have been conducted to demonstrate the potential of selective food choices in mitigating and attenuating inflammatory processes.

CHRONIC INFLAMMATION AND CHRONIC DISEASES

Inflammation and Atherosclerosis. Cardiovascular disease (CVD) continues to be the leading cause of death in developed countries. Atherosclerosis is one of the most common causes of CVD. Atherosclerosis is a chronic disease that begins in fetal life, slowly progresses during childhood and adolescence, and then accelerates in fits and spurts in adult life. Recent studies have indicated that atherosclerosis is an inflammatory disease,[5,11,12] and it has been widely accepted that inflammation plays a critical role in the pathogenesis of atherosclerosis. The recruitment and activation of macrophages is considered to be the most important early event in the development of atherosclerotic lesions. Activated macrophages release various pro-inflammatory cytokines that amplify the local inflammatory response in the lesion.[5]

The atherosclerotic process is initiated when cholesterol-containing low-density lipoproteins accumulate in the intima and activate the endothelium. Leukocyte adhesion molecules

Table 1. Commonly Measured Inflammatory Biomarkers

biomarker	inflammatory effect	major secretion cells	function
cytokines			
TNF-α	pro-inflammation	macrophages, endothelium	regulation of immune cells
IL-6	pro/anti-inflammation	macrophages, T cells	stimulation of immune response
IL-1	pro/anti-inflammation	macrophages, endothelium	regulation of immune responses
IL-4	anti-inflammation	Th2 cells, mast cells	inhibition of pro-inflammatory cytokine synthesis
IL-10	pro/anti-inflammation	macrophages, T cells	inhibition of pro-inflammatory cytokine synthesis
chemokines			
CCL2	pro-inflammation	macrophages	recruitment of leukocytes into inflammatory sites
CCL5	pro-inflammation	macrophages, T cells	recruitment of leukocytes into inflammatory sites
C-type lectin			
E-selectin	pro-inflammation	endothelium	adherence/migration
L-selectin	pro-inflammation	leukocytes	adherence/migration
P-selectin	pro-inflammation	endothelium, platelets	adherence/migration
acute-phase proteins			
CRP	pro-inflammation	hepatocytes	acute phase marker of inflammation
SAA	pro-inflammation	hepatocytes	acute phase marker of inflammation
cell adhesion molecules			
ICAM-1	pro-inflammation	endothelium and monocytes	adherence/migration
VCAM-1	pro-inflammation	endothelium	adherence/migration
adipokines			
adiponectin	anti-inflammation	adipocytes	modulation of metabolic processes
leptin	pro-inflammation	adipocytes	control of appetite

and chemokines promote recruitment of monocytes and T cells. Monocytes differentiate into macrophages and up-regulate pattern recognition receptors, including scavenger receptors and toll-like receptors. Scavenger receptors mediate lipoprotein internalization, which further leads to foam-cell formation. Toll-like receptors transmit activating signals that lead to the release of cytokines, proteases, and vasoactive molecules. T cells in lesions recognize local antigens and mount T helper-1 responses with secretion of pro-inflammatory cytokines that contribute to local inflammation and growth of plaque.[11]

Inflammation and Cancer. An association between cancer and inflammation was made more than a century ago from the identification of leukocytes in tumor tissue.[13] Since then, inflammation has been implicated in tumor development, invasion, and metastasis and in the development of clinical features such as fever and cachexia. More recently, inflammation has also been implicated as affecting the patient's ability to tolerate cytotoxic drugs.[1]

The presence of an inflammatory infiltrate in tumor tissue could represent its role as a contributor to either the development of cancer or the host response to the tumor. The link between chronic inflammatory diseases and cancer has been well documented. It is believed that 15−20% of deaths from cancers are attributable to underlying infection or inflammation.[1] The mechanism for cancer development in the presence of chronic inflammation involves the continuous presence of cytokines, chemokines, reactive oxygen and nitrogen species, and activation of key transcription factors such as nuclear factor-κB (NF-κB) and the signal transducer of transcription 3 (STAT3). It is believed that these factors result in genetic instability and subsequent mutations in oncogenic and tumor suppressor pathways.[1]

A few clinical studies investigated the consequences of tumor-associated inflammatory responses on the pharmacokinetics of cancer chemotherapy. The results suggest that a systemic inflammatory response may produce reduced

clearance of cytotoxic drugs, thereby resulting in increased toxicity.[1]

Chronic Inflammation in Linking Metabolic Syndrome, Obesity, and Diabetes. Obesity is now a leading public health concern in the United States. Approximately 68% of all adults in the United States are overweight, and 34% are obese.[14] Obesity is associated with a chronic, systemic low-grade state of inflammation. The link between inflammation and obesity was first observed in 1993, when the inflammatory cytokine TNF-α was shown to arise from adipose tissue in obese rodents and contribute to their insulin resistance.[15] It was later found that adipose tissue was infiltrated by macrophages in obese children and adults and mice, in proportion to how far they exceed normal body weight. These macrophages express TNF-α, inducible nitric oxide synthase (iNOS), and other inflammatory substances;[6] and the calcium-sensing receptor (CaSR) is expressed in human adipose cells and plays a role in obesity-associated pro-inflammatory cytokine expression while contributing to the abundance of differentiated adipocytes.[16]

Obesity results from chronic positive energy balance. However, adipose tissue is not merely a store of excess fatty acids or a heat insulator but also an endocrine organ. It secrets a variety of cytokines (e.g., TNF-α, IL-6), as well as adiponectin, intelectin, macrophage migration inhibitory factor (MIF), leptin, resistin, serpin, vascular endothelial growth factor (VEGF), and visfatin, all of which regulate immune function through endocrine, paracrine, and autocrine pathways. The medical complications of obesity, including diabetes, hypertension, and atherosclerosis, are characterized by increases in pro-inflammatory cytokines and markers of inflammation such as an elevated leukocyte count and increased circulating IL-6 and C-reactive protein (CRP) levels.[17]

Obesity-induced inflammation also plays an important role in the development of insulin resistance and type-2 diabetes. Insulin resistance is defined as an inadequate response by insulin target tissues, such as skeletal muscle, liver, and adipose tissue, to the physiological effects of circulating insulin.[18] Many

lines of evidence have shown that chronic activation of pro-inflammatory pathways within insulin target cells can lead to obesity-related insulin resistance. Adipocytes are the unique source of secreted adipokines such as leptin and adiponectin, which can promote insulin sensitivity, as well as resistin and retinol-binding protein 4 (RBP4), which can impair insulin sensitivity. Thus, the mixture of adipokines secreted by adipose tissue in a given pathophysiologic state can have important effects on systemic insulin sensitivity.[18]

ACCESSING CHRONIC AND SYSTEMIC INFLAMMATION

The increasing evidence for the role of systemic inflammatory response in the development of chronic diseases calls for the development of simple to use, easily accessible, and reliable assays to assess the status of inflammation. The potential targets for measurement of inflammation include pro- or anti-inflammatory cytokines, chemokines, cell adhesion molecules, acute-phase proteins, etc. Although numerous biomarkers have been proposed and used in basic research to assess inflammation and risk factors associated with inflammatory diseases and to monitor the effects of prevention and/or therapy, very few of them are considered to be applicable in clinical and public health practice.[19] It should be emphasized that for any given basic research studies, it is impossible and not necessary to measure all inflammatory biomarkers. It is important to select the biomarkers that are most relevant to the disease or the risk factors to be investigated.

Several groups of the most commonly used inflammatory biomarkers in the studies of dietary factors and inflammation are summarized in Table 1 and are briefly discussed as follows.

Cytokines. Cytokines are a diverse group of soluble short-acting proteins, glycoproteins, and peptides produced by various immune cells and vascular cells in response to inflammatory stimuli.[20] Cytokines may also be classified into pro-inflammatory and anti-inflammatory cytokines. Pro-inflammatory cytokines are produced predominantly by activated macrophages, involved in the up-regulation of inflammatory reactions. The most commonly assessed pro-inflammatory cytokines in clinical studies include TNF-α, IL-1, and IL-6.

TNF-α is a pro-inflammatory cytokine involved in systemic inflammation and a member of the group of cytokines that stimulate the acute phase reaction. Dysregulation of TNF-α is implicated in Alzheimer's disease, major depression, cancer, inflammatory bowel disease, and cancer. It is mainly produced by activated macrophages, mast cells, endothelial cells, adipose tissue, cardiac myocytes, neuronal cells, and fibroblasts. The primary role of TNF-α is to regulate immune cells. IL-1 and TNF-α work together in diverse ways, including containing bacterial infection;[21] inducing leucocytosis seen in inflammation of the central nervous system (CNS);[22] expressing osteoclastogenic molecules that contribute to focal osteolysis;[23] inhibiting hair follicular growth by condensation and distortion of the dermal papilla and vacuolation of the hair follicle matrix;[24] inducing of nitric oxide synthase (NOS) activity in brain cells;[25] bone marrow macrophage expression;[26] inducing human endothelial cell-derived neutrophil chemotactic factor expression;[27] and, inducing mannose receptor mRNA in mesangial cells, a carbohydrate-binding membrane protein that mediates endocytosis and phagocytosis.[28]

IL-6 is one of a number of interleukins that acts as both a pro-inflammatory and an anti-inflammatory cytokine and myokine (in muscle). It is secreted by T cells and macrophages

to stimulate immune response, for example, during infection and after trauma, especially burns or other tissue damage leading to inflammation.

Anti-inflammatory cytokines are involved in the down-regulation of inflammatory reactions, including IL-4, IL-10, IL-13, IFN-α, and TGF-β. However, a clear-cut classification of cytokines as pro- or anti-inflammatory may be difficult, as the net inflammatory response may be determined not only by the balance between pro- and anti-inflammatory cytokines but also by the timing of the release of cytokines, the local environment in which they are released, the presence of synergistic or competing factors, cytokine receptor density, and tissue responsiveness to each cytokine.[20]

Chemokines. The attraction of leukocytes to tissues is essential for inflammation and the host response to infection. The process is controlled by chemokines, the chemotactic cytokines. Chemokines belong to a large group of structurally related and secretable, largely basic, chemotactic cytokines, which can be divided into four families (CC, CXC, CX3C, XC) on the basis of the position of the first two cysteine residues. Chemokines can be expressed by different cell types including endothelial and other inflammatory modulating cells.[29,30]

Monocyte chemoattractant protein-1 (MCP-1/CCL2) is one of the key chemokines that regulate migration and infiltration of monocytes/macrophages. Both MCP-1 and its receptor CCR2 have been demonstrated to be induced and involved in various diseases. Migration of monocytes from the bloodstream across the vascular endothelium is required for routine immunological surveillance of tissues, as well as in response to inflammation.[31] CCL5 (RANTES) can be expressed by a number of different cell types, including monocytes/macrophages and T lymphocytes. It can mediate the arrest and transendothelial diapedesis of monoytes/macrophages and T lymphocytes. In addition, CCL5 can be stored and released from a-granules by platelets, and its deposition and immobilization on activated aortic endothelium or neointimal lesions constitute an important mechanism by which platelets contribute to exacerbation of lesion formation.[32]

C-Type Lectin. C-type lectins, also called C-type lectin receptors (CLRs), are defined as any protein containing one or more C-type lectin domain(s). They comprise a large family of proteins that share a common structural motif, and some act as receptors in pathogen recognition.[33] The large family of C-type lectins includes collectins, selectins, endocytic receptors, and proteoglycans. Some of these proteins are secreted, and others are transmembrane proteins. These proteins function as adhesion and signaling receptors in many inflammatory responses.[34] Among them, the selectins—a family of three members (E-, L-, and P-selectin)—are of major importance in mediating cell adhesion and migration, which play important roles in the early events of atherosclerosis.[5,35] Myeloid CLRs constitute an eclectic group of innate immune receptors with multiple functions in the initiation and regulation of immune responses. They can act as endocytic receptors that mediate the uptake of self-antigens and pathogens for either destruction or antigen retrieval and presentation to T cells. In addition, many CLRs signal to modulate myeloid cell activation and thereby affeact inflammation and the induction of adaptive immune responses.[36]

Acute-Phase Proteins (APPs). APPs are a class of proteins of which the plasma concentrations increase (positive APPs) or decrease (negative APPs) in response to inflammation. This response is called the acute-phase reaction. Positive APPs serve

important functions for the immune system such as destruction of pathogens or growth inhibition of microbials. The proteins that perform these functions include CRP, complement factors, mannose-binding protein, haptoglobin, ceruloplasmin, and serum amyloid A (SAA). Other proteins, such as coagulation factors and alpha 2-macroglobulin, affect coagulation to trap pathogens by forming localized blood clots. Negative APPs decrease inflammation and can be measured by a decrease in albumin, transferrin, retinol-binding protein, transcortin, antithrombin, and transthyretin.

Two APPs, the acute-phase reactants CRP and SAA proteins, are commonly measured in clinical studies. CRP rises in response to inflammation, whereas SAA proteins are involved in the recruitment of immune cells to inflammatory sites.[37] In acute inflammation, CRP, a member of the pentaxin protein family, can rise by up to 50000-fold of normal levels.[38] During the acute-phase response, regardless of cause, interleukin 6 and other cytokines are released by macrophages and adipocytes that trigger the synthesis of CRP (and fibrinogen) by the liver. For this reason, CRP is used as a screen to determine the degree of an infection or the progression of an inflammatory disease, but does not assist in the diagnosis of a specific disease. The role of CRP as both a marker of increased risk of developing cancer and a potential prognostic marker has been widely investigated.[1]

SAA proteins are a family of highly conserved acute-phase apolipoproteins synthesized primarily by the liver in response to stimulation by cytokines such as TNF-α, IL-1, and IL-6. Besides recruitment of immune cells to inflammatory sites, SAA proteins induce production of enzymes that degrade the extracellular matrix. Chronic degradation of the extracellular matrix inhibits repair of tissue, resulting in scar tissue. Elevations of SAA are commonly observed within the atherosclerotic milieu, diabetes, as well as in obesity, and metabolic syndrome, and other conditions associated with inflammation.[39]

Cell Adhesion Molecules (CAM). CAMs have a key role in the inflammatory response. The migration of leucocytes toward inflammatory foci and the interactions of inflammatory cells at these sites are mediated by CAMs. Adhesion molecules involved in inflammation mainly consist of the families of selectins and integrins and the immunoglobulin (Ig) gene superfamily.[40] In light of their central role in the recruitment of inflammatory cells to the site of atheroma development, CAMs are promising candidates to reflect underlying vascular inflammation and are regarded as future therapeutic targets.[41]

VCAM-1 and ICAM-1, the CAMs that belong to the Ig gene superfamily, are the most measured CAMs. ICAM-1 is expressed on the cell surface of cytokine-stimulated cells (e.g., endothelial cells and leukocytes) and certain types of carcinomas. It binds to LAF-1 and Mac-1 on neutrophils, T-cells, and macrophages and provides a mechanism for selective recruitment of leukocytes in different pathologic situations. VCAM-1 is expressed in activated endothelial cells and contains six or seven Ig domains of the H-type. It regulates adhesion of monocytes, lymphocytes, basophils, and eosinophils to activate endothelial cells.[42]

Adipocytokines. The term adipocytokine is used to describe certain cytokines that are mainly produced by adipose tissue, although it is important to note that they are not all exclusively derived from this tissue. Adiponectin, leptin, resistin, and visfatin are adipocytokines and are thought to provide an important link between obesity, insulin resistance, and related

inflammatory disorders. Adiponectin and leptin are the most abundant adipocytokines produced by adipocytes.[43]

Adiponectin is almost exclusively secreted by adipocytes. Serum levels of adiponectin are markedly decreased in individuals with visceral obesity and states of insulin resistance, such as nonalcoholic fatty liver disease, atherosclerosis, and type 2 diabetes mellitus. Studies indicate that adiponectin has an anti-inflammatory effect on endothelial cells through the inhibition of TNF-α-induced adhesion molecule expression. Adiponectin inhibits NF-κB activation in endothelial cells and interferes with the function of macrophages. Treatment of cultured macrophages with adiponectin markedly inhibited their phagocytic activity and production of TNF-α in response to stimulation with lipopolysaccharides (LPS)[44] Adiponectin also induces the production of important anti-inflammatory cytokines, such as IL-10 and IL-1 receptor antagonist (IL-1RA), and suppresses the production of interferon-γ (IFN-γ) by LPS-stimulated human macrophages. The presence of adiponectin in T-cell proliferation assays resulted in a decreased ability to evoke an allogeneic T-cell response, and adiponectin also markedly reduced the phagocytic capacity of macrophages.[43]

Similar to adiponectin, leptin is produced mainly by adipocytes. Circulating leptin levels are directly correlated with white adipose tissue mass. The main function of leptin is control of appetite. The effects of leptin on the immune system are its action as a pro-inflammatory cytokine. It is produced by inflammatory cells, and leptin mRNA and circulating leptin levels are increased by a number of inflammatory stimuli, including IL-1, IL-6, and LPS. Leptin-deficient mice are less prone than non-leptin-deficient mice to develop inflammatory diseases, regardless of whether these involve innate or adaptive immunity; reported conditions include experimentally induced colitis, experimental autoimmune encephalomyelitis, type I diabetes, and experimentally induced hepatitis.[45]

DIETARY FACTORS THAT MEDIATE INFLAMMATION

Dysfunction of the inflammatory responses is clearly implicated in the development of many chronic diseases. Hence, attempting to maintain an efficient equilibrated immune system is a valid approach to prevent chronic diseases.[46] Diet, as a major aspect of the environment, can play a major role in the modulation of inflammation. Different dietary patterns, based on mounting evidence from epidemiological and clinical studies, may either promote or retard inflammation[9,47−51] (Table 2).

Dietary Factors That Promote Inflammation. With the advent of agriculture and the development of food processing following the Industrial Revolution, both the nutrient quantities and types of foods have dramatically changed for Western populations. The so-called "Western diet" is characterized by high intakes of red meat, sugary desserts, high-fat foods, including partially hydrogenated fats, trans fats, refined grains, and carbonated beverages, and a low intake of fresh and dried fruits, nuts, vegetables, whole grains, insoluble fiber, and omega-3 fatty acid rich foods such as fish, flaxseed, fortified eggs, and walnuts.[52]

In the United States and most Western countries, diet-related chronic diseases represent the single largest cause of morbidity and mortality.[52] Researchers have identified Western diet and lifestyles as major culprits in the rise of chronic inflammation. The nutrition-poor and fat-, sugar-, and salt-rich Western diet coupled with dramatic falls in exercise levels in the Western

Table 2. Dietary Factors That Promote or Retard Inflammation

pro-inflammatory dietary factors

    high fat diet; including partially hydrogenated unsaturated plant fats ("artificial" trans fats)

    diets with a high glycemic index

    diets low in fruits, vegetables, raw nuts, and whole grains

    sugar-sweetened carbonated and noncarbonated beverages

    insufficient intake of fruits, vegetables, nuts, whole grains, and omega-3-rich food stuffs

    hidden or delayed food allergies promoting inflammation

anti-inflammatory dietary factors

    diets rich in monounsaturated and omega-3 fatty acids

    diets with a greater variety of fruits, vegetables, raw nuts, and whole grains

    diets high in soluble and insoluble fibers

    diets low in refined grains or minimally processed whole grains

    diets rich in polyphenols including tea, cocoa, red wine, berries, fruits, etc.

world with the advent of motorized vehicles has set the table on which chronic inflammation has been able to feast.

Activation of the innate immune system by the Western diet is likely caused by an excessive production of pro-inflammatory cytokines associated with a reduced production of anti-inflammatory cytokines.[50] It has been shown that macro-nutrient intake induces inflammatory stress, especially when it is rich in saturated fat and refined carbohydrates. Glucose and fat, or their products, might directly engage cell-surface receptors and trigger pro-inflammatory signals. Trans fat consumption has been shown to increase levels of CRP, a cell-signaling cytokine, as well as IL-6, soluble tumor necrosis factor receptor 2 (sTNFR-2), E-selectin, and soluble cell adhesion molecules (sICAM-1 and sVCAM-1),[53] which would explain why a higher intake of trans fatty acids adversely affects endothelial function and increases cardiovascular risk. E-selectin, sICAM-1, and sVCAM-1 are surface and soluble cell adhesion molecules that are overexpressed when endothelium tissues encounter inflammatory stimuli. Human endothelial cells treated with increasing concentrations of two trans fats (*trans*-C18:1 (9*trans*,*trans*-C18:2 (9*trans*,12*trans*)), have been found to increase NF-κB as measured by IL-6 and phosphorylation of IκBα, along with impairment of endothelial insulin signaling and NO production.[54] Trans fats also increase the level of low-density lipoprotein (LDL) cholesterol, but, unlike saturated fat, have the additional effect of lowering levels of high-density lipoprotein (HDL) cholesterol.[55]

Diets with a high glycemic index (GI) and glycemic load (GL) have also been associated with inflammation. Excess ingestion or production of glucose might increase the levels of advanced glycation end products (AGEs), which engage their receptor on macrophages and other cells that can induce oxidant stress and activate NF-κB, a pro-inflammatory transcription factor.[56]

Dietary Factors That Retard Inflammation. On the contrary, certain dietary factors, including adequate omega-3 fatty acids intake and increased consumption of fruits, vegetables, nuts, and whole grain, are associated with a lower incidence of chronic diseases. These dietary factors provide a variety of nutrients as well as non-nutritive bioactive constituents that could modulate immunomodulatory and inflammatory processes.[50,57] In several recently published human clinical trials, a certain so-called "healthy dietary

pattern", characterized by higher intake of low-fat dairy products, fruits, vegetables, whole grains, nuts, poultry, and fish, had been found to be associated with lower systemic inflammation in an ethnically and age diverse population.[58−61] Some anti-inflammatory dietary factors are summarized as follows.

Fruits and Vegetables. The attention to increasing fruit and vegetable consumption is a practical and important way to optimize nutritional benefits to reduce disease risk and maximize good health.[62] Numerous studies have shown an inverse correlation between fruit and vegetable consumption and inflammation status. The greater the variety of fruits and vegetables consumed in the diet, but not quantity, the greater the benefit in terms of risk for diseases associated with chronic inflammation such as cardiovascular disease, according to a cross-sectional 10-year risk assessment study of Puerto Rican adults aged 45−75 years.[63] Higher intakes of fruits and vegetables result in lower CRP concentrations and a lower risk of metabolic syndrome based on a cross-sectional study of female teachers, aged 40−60 years.[64]

Human clinical studies trials suggest that higher fruit and vegetable intake is associated with reduced levels of inflammatory markers, including CRP, IL-1, IL-6, or TNF-α, for different population and age groups.[65−68] For fruits and vegetables, bioactive compounds occurring in these plant foods, primarily carotenoids and polyphenols, play major roles in modulating inflammatory as well as immunological processes.[69−73] These foods are also rich in flavonoids, which inhibit eicosanoid biosynthesis.[74] Eicosanoids are involved in immunologic responses as they are the end products in the cyclooxygenase and lipoxygenase pathways, both of which are involved in the release of arachidonic acid, which is involved in the initial stages of inflammation. The release of arachidonic acid by neutrophils and other immune cells has been shown to be due to the ability of flavonoids to inhibit neutrophil degranulation.[75]

Despite the fact that fruits and vegetables as a whole tend to reduce chronic inflammation, the studies on individual fruit or vegetable remain limited. Fruits and vegetables represent a very diverse group of different foods. They differ from each other significantly in their nutrient and non-nutrient composition, which will further distinguish them for their bioactivities including anti-inflammatory effects.

Fish Oil. The action of polyunsaturated fatty acids (PUFAs) in antagonizing arachidonic acid (AA) metabolism is well recognized as playing a key anti-inflammatory effect of omega-3 PUFAs; the omega-3's have other anti-inflammatory effects resulting from altered eicosanoid production. Plant sources of omega-3 fatty acids contain α-linolenic acid (ALA, 18:3n-3) and are found in walnuts, flaxseed, pumpkin seed, oatmeal, canola, and certain fortified foods (e.g., fortified eggs; fortified yogurt) and in lesser amounts in Brussels sprouts, kale, mint, parsley, spinach, and watercress. Other sources of ALA include açai oil, cod liver oil, flaxseed oil, mustard oil, rapeseed oil, soybean oil, and walnut oil.

Omega-3-rich fish oil supplementation in animal and human studies has been shown to exert anti-inflammatory effects including decreased leukocyte chemotaxis, adhesion molecule expression, and inflammatory cytokine production, independent of changes in eicosanoid production.[76,77] A decrease of certain adhesion molecules involved in immune surveillance and homing was seen in critically ill patients consuming a nutritional formula containing fish oil and associated with
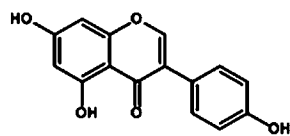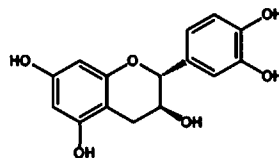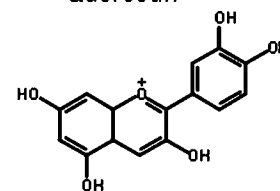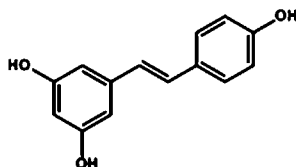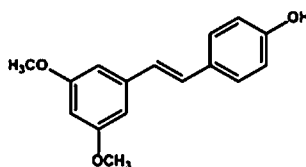
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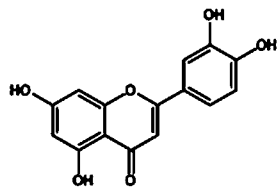
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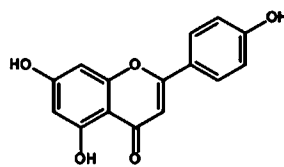
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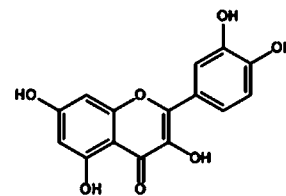
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Genistein

Catechin

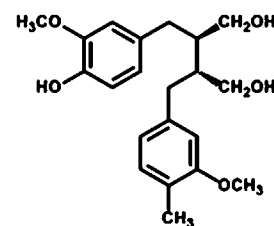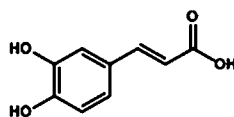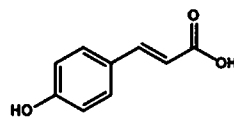Cyanidin
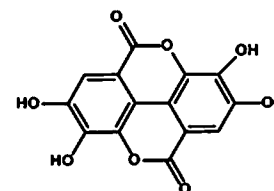
Stilbene

Resveratrol

Pterostilbene
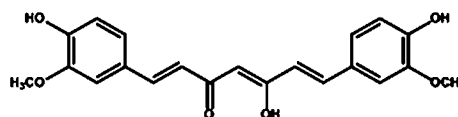
Lignan

Secoisolariciresinol

Phenolic acid

Caffeic acid

Coumaric acid

Ellagic acid

Curcuminoid

Curcumin

Figure 1. Structures of major groups of dietary polyphenols.

reduced progression of pressure wounds.[78] In a different experimental model, physiological doses of docosahexaenoic acid (DHA) reduced the adhesion and recruitment of neutrophils to endothelial cells. This may suggest one of several mechanisms whereby fish oil consumption helps reduce or prevent atherosclerosis, plaque formation, plaque rupture, and stroke.[79] de Caterina and colleagues have demonstrated that the down-regulation of VCAM-1 expression on endothelial cells is exerted by DHA at the level of VCAM-1 gene expression.[80]

The rich content of omega-3 may partly explain the beneficial effects of fish, fish oil, supplementation in inflammatory diseases such as rheumatoid arthritis,[81] cardiovascular disease,[82] and inflammatory bowl diseases.[77] Fish oil is rich in the omega-3 (n-3) polyunsaturated fatty acid, DHA, and eicosapentaenoic acid (EPA), both of which are considered to be major bioactive anti-inflammatory components in fish oil.[83] The mechanism underlying the protective effect of omega-3 involves inhibition in the expression of inflammatory factors such as VCAM-1 and ICAM-1 in endothelial cells.[84]
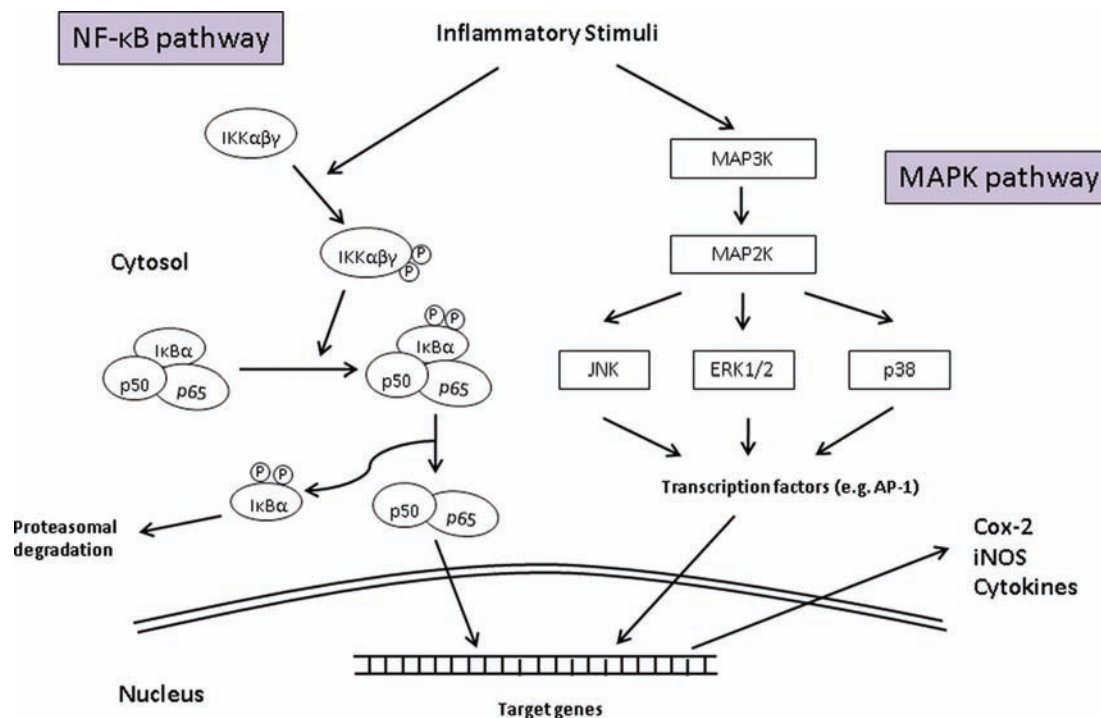
Figure 2. NF-κB and MAPK pathways in inflammation.

A novel group of trihydroxyeicosapentaenoic acid (THEA) mediators known as E-series resolvins have been identified as originating from the ingestion of EPA with potent anti-inflammatory bioactivity.[85] DHA-derived THEA mediators, termed D-series resolvins, have also been identified, which also exhibit potent anti-inflammatory properties. In addition, DHA metabolism results in the generation of dihydroxydocosatriene, a neuroprotectin D 1, also exhibiting potent anti-inflammatory activities.[85]

Nuts. Epidemiologic and clinical trial evidence has demonstrated consistent benefits of tree nut consumption on coronary heart disease (CHD) risk and associated risk factors.[86,87] Modulating inflammation has been recently recognized as one of the important mechanisms. Nut consumption is associated with lower concentrations of circulating inflammatory molecules such as IL-6, ICAM-1, and VCAM-1 and higher plasma adiponectin.[88] In recent clinical trials, nut consumption has also been shown to decrease the plasma concentration of CRP, IL-6, and some endothelial markers.[89] Nuts contain an array of bioactive compounds: polyphenols, polyunsaturated fatty acids, fiber, tocopherols, and tocotrienols, etc.[90] All of these compounds may contribute to the observed anti-inflammatory activities of nuts.[91]

Cocoa and Chocolate. The health benefits of cocoa and dark chocolate, especially their potential role in reducing the risk of cardiovascular diseases, have been widely recognized.[92−98] Antioxidant activity has long been considered as the major mechanism since a landmark in vitro study in 1996.[99] However, not until more recently have the anti-inflammatory effects of cocoa and chocolate been appreciated.[93] Regular consumption of dark chocolate was found to be associated with low serum CRP concentrations in two human clinical trials.[100,101] Cocoa flavanols may be largely responsible for the observed anti-inflammatory effects.[102,103] For instance, a recent study found that certain flavanols and procyanidins isolated from cocoa can moderate a subset of signaling pathways derived from LPS stimulation of polymorphonuclear cells.[104]

Tea. Teas are broadly classified into unfermented green teas, semifermented pauchong and oolong teas, and fully fermented pu'erh and black teas, depending on the the degree of fermentation.[105] Tea drinking, particularly of green tea, has been inversely related to the risk of cardiovascular disease, owing to its catechin content, a compound belonging to the flavonoid family.[106]

Catechins are the major component of green tea. The mechanisms of action are many. Catechins interfere with inflammatory processes that contribute to the progression of atherosclerosis.[107] Recent epidemiological studies, human clinical trials, and animal studies suggested that chronic tea drinking might lead to inhibition of low-grade inflammation as assessed by changes in various inflammatory markers.[108−110] Green tea contains high levels of flavonoids, mostly catechin and its derivatives such as epigallocatechin gallate (EGCG). These compounds display a wide array of bioactive effects including anti-inflammatory activities. They are potent agents for the treatment and prevention of inflammation-related cardiovascular diseases.[111,112] In vitro and in vivo evidence suggests that tea polyphenols exhibit the following effects: antioxidant; vasorelaxant; endothelial protective; and hypolipodemic, which contribute to antioxidative, antithrombogenic, anti-inflammatory, and hypotensive and hypocholesterolemic properties.[113]

Black teas, particularly those that are fermented, are virtually devoid of catechins yet have been shown in vivo to demonstrate cardiovascular benefits similar to those of green tea. During processing to produce black tea, the catechins are converted to theaflavins and thearubigins, both of which have been shown to exhibit higher potency than EGCG in NO production and vasorelaxation,[114] Green and black tea compounds also induce phosphorylation of eNOS and upstream signaling kinases.

■ ANTI-INFLAMMATORY DIETARY COMPONENTS AND THEIR MECHANISMS

Many plant-derived compounds (phytochemicals) have been found to possess anti-inflammatory effects. These compounds belong to chemically diverse groups and affect various inflammatory modulators through some common mechanisms.[115−117] In this review, we discuss three major groups of dietary anti-inflammatory compounds: polyphenols, n-3 PUFAs, and dietary fiber.

Polyphenols. Among all dietary phytochemicals, polyphenols are considered as the major anti-inflammatory constituents from dietary sources such as fruits, vegetables, tea, grains, and legumes.[70,118−120] Polyphenols are characterized by having one or more aromatic ring with one or more hydroxyl groups attached. They are important secondary metabolites of plants. Over 8000 polyphenol compounds have been reported in the plant kingdom—many occur in food. The structures of natural polyphenols range from simple phenolic acids to highly polymerized compounds, such as condensed tannins.[121,122] The structures of the most studied dietary anti-inflammatory polyphenols are summarized by groups in Figure 1.

The anti-inflammatory effects and underlying mechanisms of dietary polyphenols, especially the flavonoids, have been discussed in several excellent reviews.[69−72,122−124] Briefly, polyphenols have been found to possess anti-inflammatory activities through the following mechanisms:

Inhibition of Pro-inflammatory Enzyme Activates. Polyphenols have been shown to inhibit a series of enzymes that are activated in the course of the inflammatory process. These enzymes include nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), and lipooxygenase (LOX). The inhibition of these enzymes reduces the production of arachidonic acid, prostaglandins, leucotrienes, and NO, all of which are crucial mediators of inflammation.[71,125]

Modulation of the Production of Pro-inflammatory Molecules. As discussed earlier, pro-inflammation molecules, such as cytokines TNF-α, IL-6, and IL-1, are prominent contributors to chronic inflammatory responses. Polyphenols have been reported to inhibit the production of various pro-inflammatory cytokines induced by LPS or other stimuli. Several mechanisms underlying the inhibition of LPS-induced inflammatory cytokine production by flavonoids have been revealed, of which blocking of the NF-κB pathway and and blocking of the MAPK pathway have been proposed as the two major mechanisms[123,125,126] (Figure 2).

Inhibition of Pro-inflammatory Cell Adhesion Molecules. Recent studies also indicate that certain polyphenols suppress pro-inflammatory cell adhesion molecule production. For instance, the black tea polyphenol theaflavin suppresses LPS-induced ICAM-1 and VCAM-1 expressions in intestinal epithelial cells.[127] Resveratrol significantly attenuates LPS-induced monocyte adhesion to the endothelium.[128] These effects were found mediated at least in part by the modulation of NF-κB activation.

Scavenging Effects toward Reactive Oxygen Species (ROS). ROS are a double-edged sword as they are a byproduct of metabolism of oxygen and play a role in cell signaling and maintenance of cell homeostasis, but when elevated can result in oxidative stress, resulting in potentially significant damage to cell structures, including oxidation of polyunsaturated fatty acids (lipid peroxidation) and amino acids, inactivation of certain enzymes, and DNA damage. Cells defend themselves from oxidative stress via enzymes, including catalases, glutathione peroxidases, lactoperoxidases, peroxiredoxins, and superoxide dismutase. Other antioxidant compounds that protect cells from ROS include ascorbic acid, glutathione, tocopherols and tocotrienols (vitamin E), and uric acid. Under oxidative stress conditions, ROS play a key role in enhancing inflammation through the activation of NF-κB and AP-1 transcription factors.[122,129] As a group of important dietary antioxidants, polyphenols have been shown to regulate inflammatory genes by direct scavenging of ROS or via increasing the activity of antioxidant enzymes such as glutathione peroxidase.[122]

n-3 Polyunsaturated Fatty Acids (PUFA). n-3 polyunsaturated fatty acids (n-3 PUFA), also known as omega-3 fatty acids, have been recognized to have anti-inflammatory activity for many years.[130−132] The intake of n-3 PUFA, especially the two fish oil derived DHA and EPA, is inversely associated with lower concentrations of some inflammatory biomarkers, reflecting lower levels of inflammation, in some human clinical trials.[133−135] Western diets are low in n-3 fatty acids and rich in n-6 fatty acids, which are derived from animal products as well as from the consumption of commonly used vegetable oils (corn, canola, rapeseed, palm, soybean, and sunflower). Unlike n-3 fatty acids, n-6 fatty acids such as arachidonic acid produce more potent inflammatory eicosanoids. A diet disproportionately high in n-6 to n-3 fatty acids shifts tissue levels toward pro-inflammatory processes.[136,137] There is some evidence that the ratio of n-3 to n-6 fatty acids was nearly 1:1 prior to the advent of the agricultural revolution. Current estimates are that the ratio is now 1:15, which would facilitate driving inflammatory pathways while preventing inflammatory resolution, thereby contributing to disease pathogenesis.

The major mechanisms include (1) decreasing arachidonic acid content of cell membranes, (2) altering eicosanoid production, and (3) modulation of nuclear receptor activation.[51,138]

Dietary Fiber. Dietary fiber is primarily a storage and cell wall polysaccharide that cannot be digested and absorbed by the human body.[139] Foods such as whole grains, fruits, vegetables, legumes, and nuts are rich sources of dietary fiber, including soluble and insoluble fibers. A high level of dietary fiber intake has beneficial effects for developing a number of chronic diseases: heart diseases, diabetes, obesity, and gastrointestinal disorders.[140] Soluble fiber attracts water and slows digestion, which can have a beneficial effect on insulin sensitivity and in lowering absorption of dietary cholesterol. Insoluble fiber adds bulk to the diet, does not absorb water, and speeds passage of food and waste through the gastrointestinal tract.

The association of high dietary fiber intake and systemic inflammation has recently been investigated. In a review that included seven studies, significantly lower CRP concentrations (downward arrow 25−54%) are seen with increased fiber consumption ($\geq$3.3 g/MJ).[141] In another study, high dietary fiber diet is associated with lower plasma levels of IL-6 and TNF-α, but no association with CRP among postmenopausal women.[142] A clinical trial found that a high dietary total fiber intake is associated with lower CRP levels and mortality in kidney disease. This association was found to be stronger in magnitude in those with kidney disease.[143] In a study performed by investigators affiliated with the U.S. National Cancer Institute, drawing from data on 219 123 men and 168

999 women who participated in the National Institutes of Health-AARP Diet and Health Study, it was discovered that subjects who consumed between 25 and 30 g of fiber daily had a 22% lower risk of death from all causes. In commenting on the findings, the authors stated that "The anti-inflammatory properties of dietary fiber could explain, in part, significant inverse associations of dietary fiber intake with infectious and respiratory diseases as well as with CVD death".[144] The biological mechanism of anti-inflammatory effects of dietary fiber is largely unknown, although the impact of fiber may be related to its effect on glycemia.[9] How these indigestible components affect systemic inflammation needs further investigation.

■ RESEARCH STRATEGIES: AN EXAMPLE USING AÇAÍ FRUIT PULP

As we discussed earlier, even though many dietary factors are implicated for their anti-inflammatory effects, the biological mechanisms are still not fully understood and the bioactive compounds are yet to be identified. Moreover, studies on individual foods are still very limited. Thus, more investigations are needed. Here we propose a research strategy (Figure 3) in
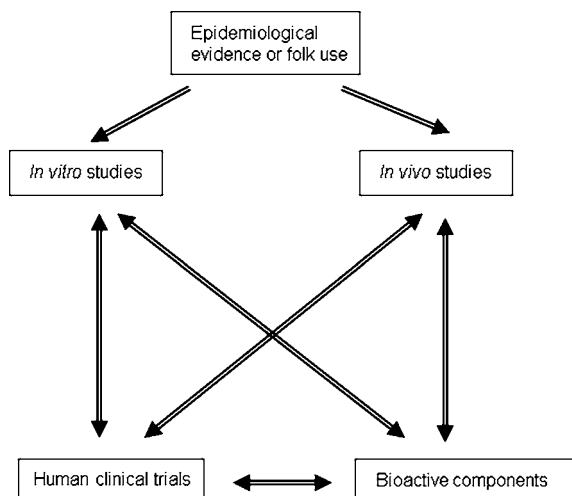
Figure 3. General research strategy in study anti-inflammatory dietary factors and bioactive components.

conducting such studies. Usually, the study of anti-inflammatory activities of a given food or dietary factor is initiated by epidemiological studies and/or folk/traditional medical usage. Investigations into the beneficial and therapeutic properties of foods entail a back-and-forth series of in vitro and in vivo studies. In regard to mechanisms, there are two aspects. The first aspect examines molecular mechanisms, which answers the question "how". The other aspect of mechanism is the search for bioactive compounds, which answers the question "what". To fully understand the anti-inflammatory effects of a food, both questions must be answered. These initial steps can be conducted in parallel. In the past 5 years, as part of a 17 year on-going investigation of this Amazonian palm fruit, we applied this strategy in the study of the anti-inflammatory properties of the Amazonian palm fruit commonly called "açaí" (*Euterpe oleracea* Mart.), pronounced ("ah-shy-ee").

In Vitro and in Vivo Anti-inflammatory Effects of Açaí. The pulp from açaí fruit (*Euterpe oleracea* Mart.) has received much attention in recent years as one of the new "super fruits"

due to its high antioxidant capacity and anti-inflammatory activities.[145] Our initial studies using freeze-dried açaí pulp discovered that it was a potential cyclooxygenase (COX)-1 and COX-2 inhibitor; it inhibited the COX-1 enzyme more efficiently than the COX-2 enzyme.[145] Its in vitro anti-inflammatory effects have also been demonstrated by other researchers. Pretreatment of IgE-sensitized mouse primary cultured mast cells with açaí pulp showed a dramatic dose-dependent suppression of antigen-induced degranulation, transcription of selective cytokine genes, and inhibition of FcεRI signaling pathways as well as the FcεRI-mediated complementary signaling pathway, suggesting the pulp is a potent inhibitor of IgE-mediated mast cell activation.[146] Açaí pulp anthocyanin-rich extracts have been shown to reduce inflammatory stress signaling in BV-2 (hippocampal) mouse microglia.[147] Results from this study showed that pretreatment of microglia with individual açaí pulp fractions was protective against LPS-induced NO release, COX-2 expression, nitrite production, inducible nitrous oxide synthase expression, p38 mitogen-activated protein kinases (p38-MAPK) expression, and TNF-α and NF-κB release. NF-κB is an important transcription factor, whereas the p38-MAPK pathway performs functions in regulating inflammatory gene expression in neurons, in synaptic plasticity, in extracellular release of NO in microglial cells, and in activation of cyclic-AMP response element-binding (CREB) protein critical to long-term memory formation.[148−150] These findings suggest that açaí may be able to combat some of the inflammatory and oxidative mediators of aging at the cellular level.

On the basis of the indications from in vitro experiments, an animal study was conducted by our group to investigate the atheroprotective effects of açaí juice in apolipoprotein E deficient (apoE$^{-/-}$) mice.[151] The levels of TNF-α and IL-6 were significantly lower in sera and in the residential macrophage with and without LPS stimulation from mice fed a diet containing 1% freeze-dried açaí juice powder. Anti-inflammatory effects in reducing pro-inflammatory cytokine production have been suggested as an important underlying mechanism of the atheroprotective effects of açaí juice.[151]

In addition, a randomized, double-blinded, placebo-controlled, crossover study with healthy subjects placed under oxidative stress found that oral consumption of a polyphenolic-rich açaí pulp juice blend resulted in increased antioxidant protection of erythrocytes, reduced formation of ROS in polymorphonuclear (PMN) cells, reduced migration toward different pro-inflammatory chemoattractants, and inhibition of lipid peroxidation.[152] A 12 week study of the effect of oral consumption of the same juice blend by healthy adults, 48−84 years of age, who had painful inflammation of joints that affected daily living, resulted in significant increased antioxidant protection of erythrocytes, improved range of motion (based on measurable dual digital inclinometric changes), a decrease in serum CRP, and reduction in perceived pain.[153]

Anti-inflammatory Flavonoids in Açaí Pulp. To systematically search and study the anti-inflammatory flavonoids in açaí pulp, 13 flavonoids were isolated.[154,155] Among them, velutin, a unique flavone found in açaí pulp, was found to exhibit superior inhibitory effect in NF-κB activation assessed by the SEAP reporter gene assay.[155] NF-κB plays an important role in the control of biological processes. In response to certain stimuli NF-κB is activated and translocated from the cytoplasm to the nucleus. It then binds to its response element on the promotor region leading to regulation of a wide

spectrum of gene expression. The anti-inflammatory effects and underlying mechanisms of velutin were further examined for its ability in reducing LPS-induced pro-inflammatory cytokine TNF-α and IL-6 production in RAW 264.7 peripheral macrophages and mice peritoneal macrophages.[156] Velutin exhibited the greatest potency among all flavones in reducing TNF-α and IL-6 production. Velutin also showed the strongest inhibitory effect in NF-κB activation (as assessed by SEAP assay) and exhibited the greatest effects in blocking the degradation of IκB, as well as inhibiting MAPK p38 and JNK phosphorylation; all important signaling pathways involved in the production of TNF-α and IL-6. These studies led to the discovery of the strong anti-inflammatory flavone velutin, which displays a level of anti-inflammatory activity not seen by any flavonoid to date.

Açaí polysaccharides (PS) have been shown to have potent immunomodulatory effects in the lung by stimulation of innate immunity following intranasal pulmonary infection. PS derived from açaí pulp when administered nasally have been demonstrated to augment intracellular expression of IFN-γ by NK cells in the lungs of *Francisella tularensis* SchuS4-infected mice and to confer protection against pulmonary type A infection by the *Burkolderia pseudomallei* strain 1026b.[157] Açaí PS significantly reduced the replication of *B. pseudomallei* in the lungs of infected mice and blocked bacterial dissemination to the spleen and liver, by enhancing IFN-γ responses by NK and T cells in the lungs. The investigators conducting this study commented that "Açaí PS was tested as a mucosal immunotherapeutic to treat pulmonary type A *F. tularensis* infections. It was found that i.n. pre-treatment of mice with açaí PS conferred up to 80% protection against *F. tularensis*-induced mortality, which to our knowledge, is the highest degree of protection demonstrated by an immunotherapeutic and also represents the first mucosal immunotherapeutic to confer significant survival against pulmonary type A *F. tularensis* infection".[157] This finding is significant because the protection observed occurred within 48 h after pulmonary infection. Similar responses were observed in human cells in vitro. Flow cytometry determined that açaí PS signals in part through TLR4, a toll-like receptor that recognizes highly conserved pathogenic patterns, stimulating a downstream signaling cascade that leads to the release of inflammatory cytokines and chemokines while up-regulating expression of immune cells. In the case of the açaí PS, it is likely signaled through TRL4/TRIF and carbohydrate receptors. These findings warrant further investigation to determine the range of beneficial effects of açaí PS, particularly in countering antibody-resistant bacterial infections, and/or to complement antibiotic immunotherapies.

CONCLUSIONS/REMARKS

A comprehensive food-based strategy for reducing inflammation and thus reducing the incidence and severity of a large array of chronic illnesses and declining health is supported by a large and growing volume of scientific investigations. The cost benefit of societal promotion of such strategies is enormous. Clearly, genes and cells are responding to certain foods containing nutrients and phytochemicals that induce cell communication and affect gene expression, with the potential for profound long-term health benefits. The untenable and expensive alternative is to continue to see individuals make poor food choices and experience the consequences. In the case of chronic inflammation, the avoidance of lifestyle choices that

promote it is obvious, but as important is incorporating foods in the diet that effectively prevent unnecessary and premature cell damage and death.

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Mention of trade names or commercial products in this publication is solely for the purpose of providing specific information and does not imply recommendation or endorsement by the U.S. Department of Agriculture.
The authors declare no competing financial interest.

ABBREVIATIONS USED

AGEs, advanced glycation end products
AM, macrophage
AP-1, activator protein 1
APPs, acute-phase proteins
CAMs, cell adhesion molecules
CAT, catalase
CCL5, chemokine (C−C motif) ligand 5 protein
CLRs, C-type lectin receptors
CNS, central nervous system
COX-2, cyclooxygenase-2
CREB, cyclic-AMP response element-binding
CRP, C-reactive protein
CVD, cardiovascular disease
ERKs, extracellular-signal-regulated kinases
HDL, high-density lipoprotein
GPx, glutathione peroxidase
ICAM-1, intercellular adhesion molecule-1
IFN-α, alpha interferon
IFN-γ, gamma interferon
IκB, inhibitory kappa B
IL-1, interleukin 1
IL-6, interleukin 6
iNOS, inducible nitric oxide synthase
JNK, c-Jun N-terminal kinases
LDL, low-density lipoprotein-cholesterol
LOX, lipooxygenase
IκBα, nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha
IRF-1, IFN regulatory factor
LDL, low-density lipoprotein
LPS, lipopolysaccharide
MAPK, mitogen-activated protein kinase
MCP-1, monocyte chemotactic peptide-1
M-CSF, colony-stimulating factor 1
MIF, macrophage migration inhibitory factor
MPO, myeloperoxidase
NADPH, nicotinamide adenine dinucleotide phosphate
NF-κB, nuclear factor-kappa B
Nrf-2, NF-E2-related factor-2
NO, nitric oxide

PBMC, peripheral blood mononuclear cell
PECAM-1, decreased platelet endothelial cell molecule
PMN, polymorphonuclear neutrophil cells
PPAR-γ, peroxisome proliferator-activated receptor gamma
PS, polysaccharides
RANTES, regulated on activation
SAA, serum amyloid A
SEAP, secreted alkaline phosphatase reporter gene assay
sICAM-1, soluble intercellular adhesion molecule-1
Sirt1, sirtuin1
SOD, superoxide dismutase
STAT3, signal transducer of transcription 3
sVCAM-1, soluble vascular cell adhesion molecule-1
TGF-β, transforming growth factor beta
TLR4, toll-like receptor 4
TNF-α, tumor necrotic factor alpha
TRIF, TIR-domain-containing adapter-inducing interferon-β
VCAM-1, vascular cell adhesion molecule-1
VEGF, vascular endothelial growth factor

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