Therapeutic Nutrition and Botanical Medicines for the Promotion of Wellness and Alleviation of Pain and Inflammation: A Detailed Review for Integrative Clinicians

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Introduction

At any given time, nearly thirty percent of the American population suffers from musculoskeletal pain, joint swelling, or limitation of movement[1], and approximately 1 of every 7 (14% of total) visits to a primary healthcare provider is for the treatment of musculoskeletal pain or dysfunction.[2] Resulting in more than $100 billion in US healthcare costs each year, back pain is the most prevalent medical problem in the US, is the leading cause of long-term disability, and is the second leading cause of restricted activity and the use of prescription and non-prescription drugs.[3] Additionally, the health of the American population is consistently and progressively declining: obesity and diabetes are "ever-growing" epidemics among children and adults[4,5], infant mortality has recently increased for the first time in 40 years[6], and self-reported health status and health-related quality of life among adults are declining.[7] In the 25 years between 1975 and 2000, the incidence of cancer increased significantly, and the number of people diagnosed with cancer is expected to double in the next several decades.[8] Despite these negative health trends, America spends more on healthcare than does any other nation—an unprecedented $1.55 trillion, which is roughly 15% of the U.S. gross domestic product.[9]

Numerous adverse effects are produced as a direct result of pharmaceutical management of benign musculoskeletal pain. According to a 1998 review by Singh[10], "Conservative calculations estimate that approximately 107,000 patients are hospitalized annually for nonsteroidal anti-inflammatory drug (NSAID)-related gastrointestinal (GI) complications and at least 16,500 NSAID-related deaths occur each year among arthritis patients alone. The figures for all NSAID users would be overwhelming, yet the scope of this problem is generally under-appreciated." More recently following the withdrawal of the arthritis drug rofecoxib (Vioxx) in late September 2004, Topol[11] extrapolated that as many as 160,000 adverse cardiovascular events (including stroke, myocardial infarction, and death) may have resulted from the collusion of Merck's intentional failure to withdraw what was known for years to be a dangerous drug, the FDA's failure to enforce regulatory standards to protect the public, and the overutilization of Vioxx. Soon after the removal of Vioxx from the healthcare market, several other so-called "anti-inflammatory drugs" such as valdecoxib (Bextra)[12], celecoxib (Celebrex)[13], and naproxen (Aleve)[14] were likewise associated with excess cardiovascular injury and death. Although the advertising-induced feeding frenzy on Celebrex made it the most successful drug launch in US history with more than 7.4 million prescriptions written within its first 6 months[15], within 2 years of its release evidence linking the drug to increased cardiovascular events (including death) was accumulating[16], and the drug has since been linked to a wide range of adverse effects such as membranous glomerulopathy and acute interstitial nephritis[17], acute cholestatic hepatitis[18], and toxic epidermal necrolysis.[19,20] When compared with placebo in cardiac surgery patients, Bextra/valdecoxib is associated with a 3-fold to 4-fold increased risk of heart attack, stroke, and death[21], and currently 7 million arthritis patients, many of whom are already at high risk for cardiovascular disease, are being treated with this drug.[22]

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Increasingly aware of the negative effects of pharmaceutical management of musculoskeletal pain, patients and healthcare providers alike are looking to natural treatments and chiropractic healthcare[23,24] with the hopes of avoiding the risks of iatrogenic disease, such as drug-induced renal failure[25,26], hepatotoxicity[27,28], gastrointestinal ulceration and hemorrhage[29,30.31.32], osteonecrosis[33,34], joint degeneration35, hypertension[36], myocardial infarction[37], and premature death[38,39] that are associated with the non-steroidal anti-inflammatory drugs ("NSAIDs"), non-NSAID analgesics such as acetaminophen, and the relatively new selective cyclooxygenase-2 inhibitors (cox-2 inhibitors, or "coxibs"). It is tragically paradoxical that many of the pharmaceutical drugs used for the suppression of arthritis symptoms and advertised as "arthritis relief" actually exacerbate joint destruction and chronic inflammation by interfering with the biosynthesis of the glycosaminoglycans that are essential components of joint cartilage while also promoting destruction of subchondral bone.[40,41,42,43]

In addition to reviewing the biochemistry of inflammation and eicosanoid metabolism, this article reviews the most commonly used and well-researched nutritional and botanical interventions for the treatment of pain and inflammation, namely "essential fatty acids", glucosamine and chondroitin sulfate, vitamin D, proteolytic enzymes, Devil's Claw (*Harpagophytum procumbens*), Cat's Claw (*Uncaria tomentosa*), Willow bark (*Salix alba*), and Boswellia (*Boswellia serrata*). This review will provide physicians of all disciplines with clinically useful information to help their patients attain improved health and well-being. Osteoarthritis and chronic low-back pain, the two most prevalent musculoskeletal afflictions, will serve as prototypes for this discussion.

The Biochemistry of Inflammation: From NF-kappaB to Eicosanoids

Numerous influences and pathways are involved in the processes of inflammation. Clinicians are tasked with appreciating these contributions while maintaining a conceptual overview that facilitates effective clinical intervention.[44] As the processes of inflammation have been elucidated with increasing clarity and precision in the past several years, most clinicians will benefit from a brief review of the current understanding of inflammation. Simplistic, linear models of inflammatory processes must be discarded in favor of conceptualizations that incorporate the biochemical, nutritional/botanical, neurogenic inflammation, and psychogenic contributions to inflammation modulation.

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The process of inflammation may be said to begin with the translation of an environmental trigger into a biochemical signal that initiates the inflammatory pathway. As discussed in more detail in the paragraphs that follow, environmental triggers can include injury, radiation, infection, oxidative stress, and certain foods, particularly those high in fat and those with a high glycemic index (ie, "simple sugars"). Regardless of the original locus or etiology, each of these stimuli may lead to activation of the NF-kappaB cascade, which is a major pathway for the amplification of inflammatory processes.[45,46] A ubiquitous nuclear transcription factor that promotes the activation of genes that encode for inflammatory mediators and enzymes, NF-kappaB can be thought of as the major intracellular "amplifier" which ultimately increases the production of the direct mediators of inflammation such as cytokines, prostaglandins, leukotrienes, nitric oxide and other reactive oxygen species ("free radicals"). Preparation for the process of inflammation begins when two subunit proteins—p50 and p65—merge in the cytoplasm to form NF-kappaB, which is kept in an inactive state by inhibitor kappaB (IkB). When triggered by any of the common stimuli listed above, IkB is phosphorylated and destroyed by inhibitor kappaB kinase (IKK). The destruction of IkB allows NF-kappaB to move into the nucleus of the cell where it activates genes encoding for inflammatory responses. These genes then elaborate their inflammatory products such as interleukin-1 (IL-1), IL-6, tumor necrosis factor, and the proinflammatory destructive enzymes including nitric oxide synthase, lipoxygenase, cyclooxygenase, and matrix metalloproteinases including collagenase and gelatinase, which destroy connective tissue. Nitric oxide synthase catalyses the formation of nitric oxide (NO-), which plays an important role in the development of peripheral osteoarthritis[47] and spinal disc degeneration[48] via oxidative destruction of articular tissues. Cyclooxygenase transforms arachidonic acid into prostaglandins and thromboxanes, which recruit leukocytes to the area of inflammation, exacerbate edema, sensitize peripheral neurons to increased pain perception, and ultimately facilitate the liberation of proteinases, such as matrix metaloproteinases, (MMP) which destroy joint structures. Present in several isoforms, the lipoxygenase enzyme acts on arachidonic acid to produce leukotrienes that also increase inflammation, joint destruction, and production of MMP. Overall, this same inflammatory response plays a part in the genesis and perpetuation of numerous inflammatory disorders, such as osteoarthritis, cancer, rheumatoid arthritis and other autoimmune diseases, and numerous conditions associated with pain and inflammation. This process of NF-kappaB activation and modulation of genetic expression is illustrated in Figures 1 and 2.

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Figure 1. The creation and activation of NF-kappaB—a crucial step in the amplification of proinflammatory gene expression. *Adapted from Vasquez A. Integrative Orthopedics. Natural Health Consulting Corp. (OptimalHealthResearch.com): 2004*

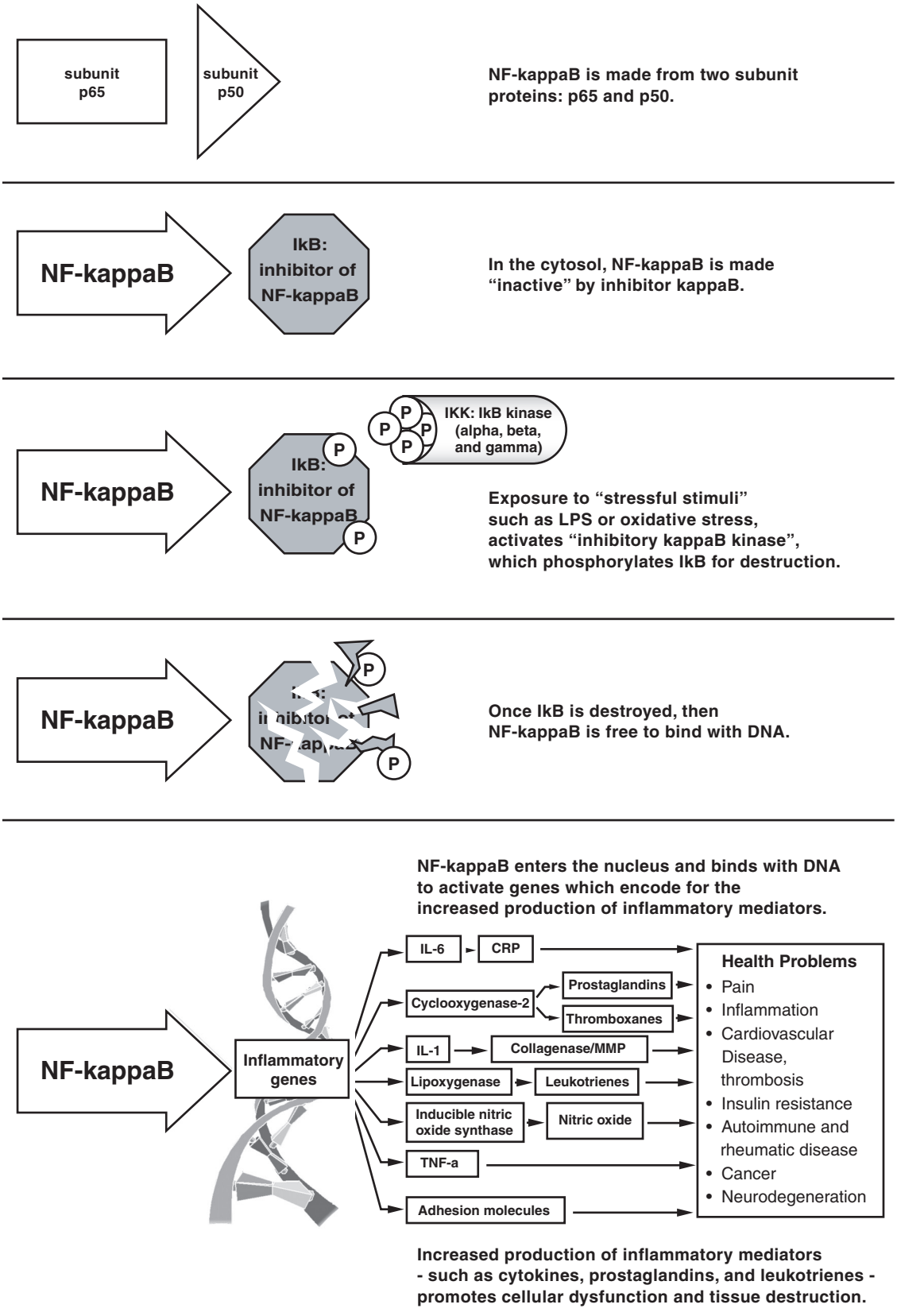
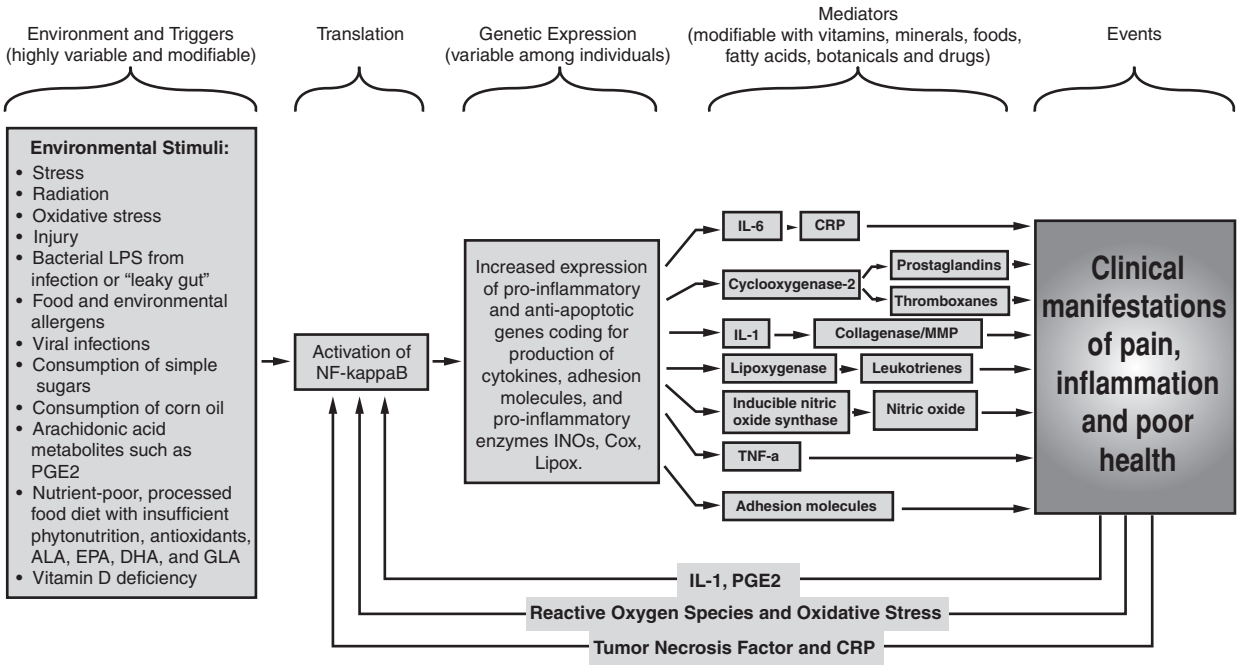
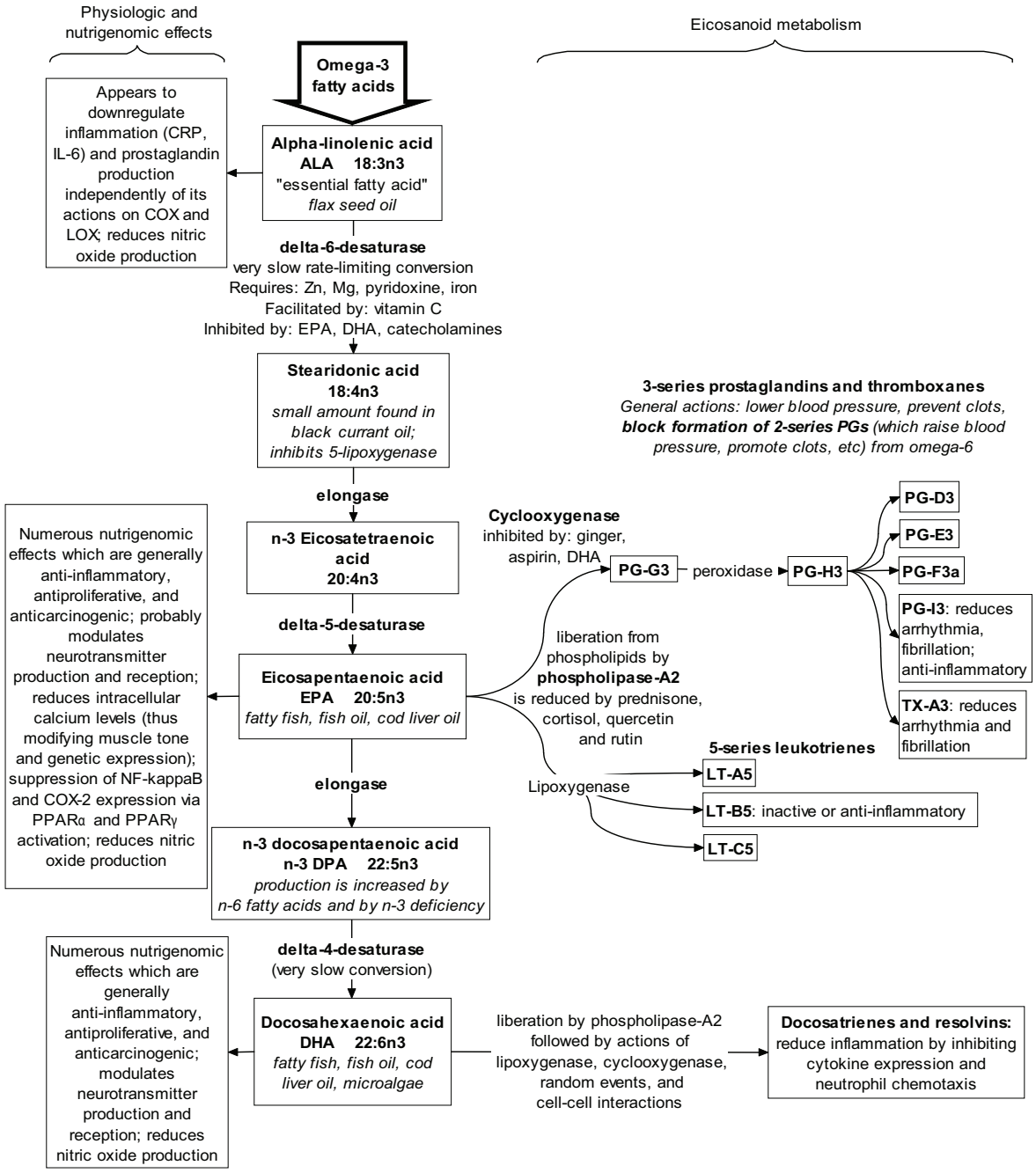


Figure 2. Translation of environmental traumas into biochemical inflammation. Note the self-perpetuating "vicious cycle" where inflammatory mediators promote additional inflammation via activation of NF-kappaB.



Activation of NF-kappaB results in the upregulation of genes which encode for the production of inflammatory cytokines such as tumor necrosis factor alpha (TNF-·), interleukin-1 (IL-1), and IL-6 as well as enzymes with generally proinflammatory effects such as inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2) and the lipoxygenases (LIPOX). IL-6 stimulates production of C-reactive protein (CRP), which is a sensitive serum marker of inflammation (such as in osteoarthritis and rheumatoid arthritis) and which is associated with an increased risk of cardiovascular disease, progressively deteriorating health and "rapid biological aging" in men and women.49,50 INOS increases production of the free radical nitric oxide which is elevated in degenerating spinal discs51 and peripheral joints52 and which contributes directly to joint destruction via destructive oxidation of articular tissues.53 COX-2 is responsible for the conversion of arachidonic acid to prostaglandins, several of which increase the perception of pain by sensitizing peripheral nociceptors54 in addition to having a central hyperalgesic effect55 and promoting the destruction of articular structures by increasing production of proteolytic enzymes, variously named collagenases, gelatinases, and matrix metalloproteinases.56 Similarly, LIPOX catalyzes the conversion of arachidonate to the lipoxygenases, which, among their many properties, promote swelling, inflammation, chemotaxis, and tissue destruction via release of increased quantities of proteolytic enzymes. In their anti-inflammatory roles, LIPOX and COX also act on gamma-linolenic acid for the production of the anti-inflammatory 15-HETrE and prostaglandin E-1, respectively, as well as on the omega-3 fatty acids EPA and DHA for the production of anti-inflammatory prostaglandins, leukotrienes, docosatrienes, and resolvins as discussed in the sections that follow. Our discussion of the mechanisms of anti-inflammatory nutritional interventions must also include mention of the phytonutraceutical activation of peroxisome proliferator-activated receptors (PPARs), since fatty acids and selected botanical medicines exert their actions at least in part by activation of PPAR-alpha and PPAR-gamma, which then mediate health-promoting and anti-inflammatory effects that are clinically significant.

Figure 3: Metabolism of omega-3 fatty acids and related eicosanoids. *From Vasquez A. Integrative Orthopedics. Natural Health Consulting Corp. (OptimalHealthResearch.com): 2004*



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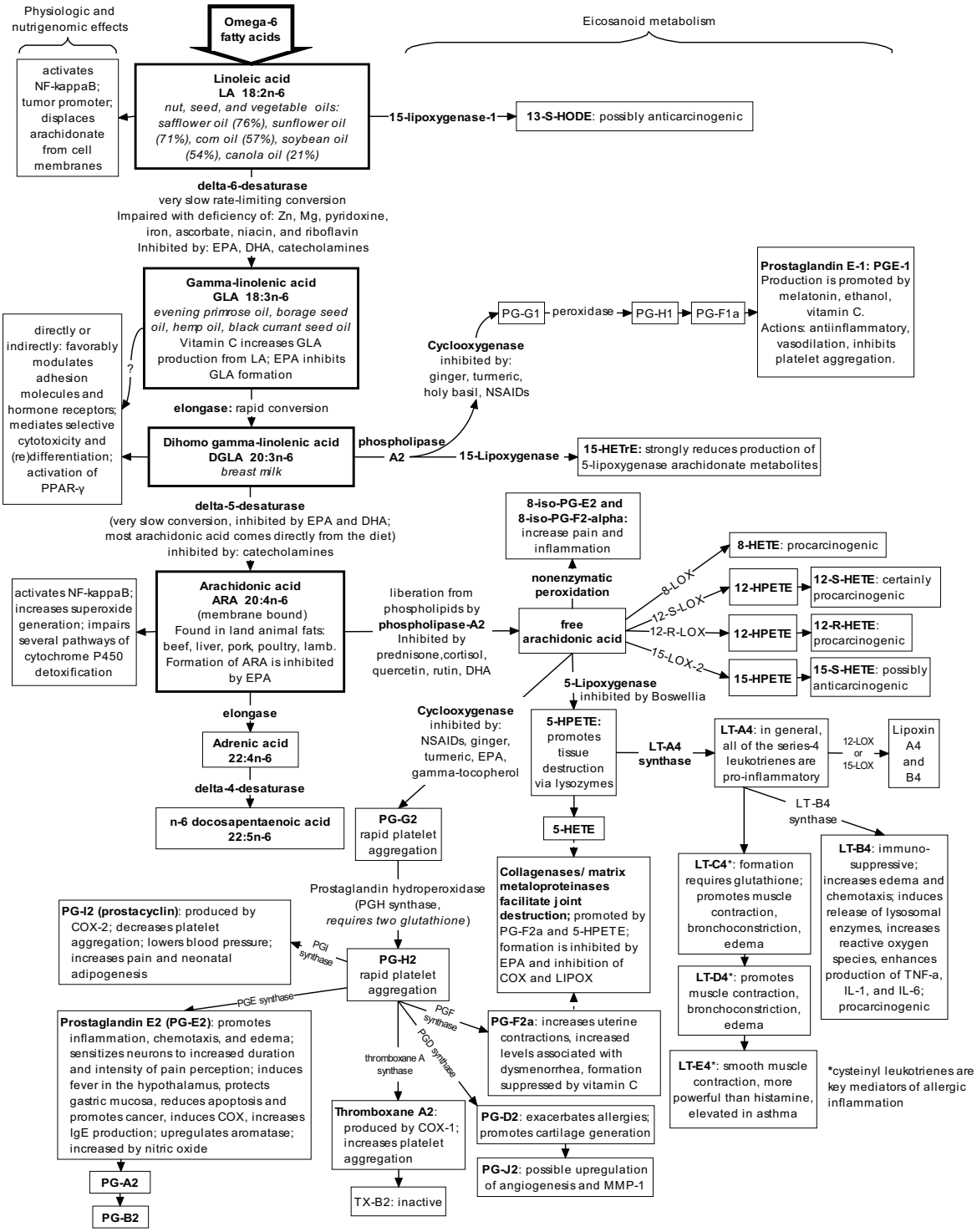
As fatty acid receptors that influence genetic expression via suppression of NF-kappaB activation as well as via NF-kappaB-independent pathways, PPARs when activated in moderation induce numerous beneficial physiologic responses, including direct and indirect anti-inflammatory , anti-cancer, and cardioprotective effects.[57,58,59] The biochemical flowchart beginning with the dietary intake of fatty acids and ending in the catalyzed production of lipoxygenases and prostaglandins is provided in Figure 3 for omega-3 fatty acids and in Figure 4 for omega-6 fatty acids.

Figure 4. Metabolism of omega-6 fatty acids and related eicosanoids. *From Vasquez A. Integrative Orthopedics. Natural Health Consulting Corp. (OptimalHealthResearch.com): 2004*



The process of inflammation is not unalterable, nor must pharmaceutical drugs always be employed to modify its course. Numerous dietary, nutritional, and botanical medicines can favorably influence this pathway and the resultant clinical sequelae. Unlike pharmaceutical drugs which are generally designed to target a specific, isolated event along the cascade (as seen with selective cox-2 inhibitors), natural therapeutics generally intervene at numerous junctures, thus allowing for safe yet powerful clinical benefit, generally with nonexistent or negligible adverse effects. Now that readers have a conceptual overview of the inflammatory process, understanding the mechanisms of action for each of the clinical therapeutics listed below will be greatly facilitated.

Nutrition Against Disease: Interventional Nutrition for the Natural Alleviation of Inflammation and Promotion of Optimal Health

An altruistic interest in our patients' care and adherence to scientific principles converge to direct us against the use of popular symptom-suppressing and anti-inflammatory chemical drugs which all-too-often accelerate joint destruction[60] and premature mortality[61,62] and to instead choose a more rational and holistic approach that improves long-term health outcomes.[63,64,65] It is important to note that inflammation is a systemic, body-wide phenomenon which is more appropriately and effectively ameliorated by whole-body improvements than it is to single-intervention therapies that target isolated enzymes and biochemical processes.

The pro-inflammatory nature of the standard American diet: The typical American/Western diet is proinflammatory in nature and contributes directly to the initiation and exacerbation of chronic inflammation and disorders such as joint destruction, diabetes mellitus, cardiovascular disease, and cancer.[66,67,68,69] The chiropractic physician Dr. David Seaman[70] deserves recognition and accolades for his 2002 review of the literature published wherein he proposed the proinflammatory nature of the standard Western diet—typified by the common American diet with an abundance of omega-6 and trans fatty acids, simple sugars and starches, and nutritionally-depleted convenience foods and a serious deficiency of vitamins, minerals, omega-3 fatty acids, and phytonutrients. The concepts that Dr. Seaman promoted as a hypothesis a mere 3 years ago have by this time been scientifically validated in clinical trials in humans. While it has long-been documented that increased consumption of refined grains and carbohydrates correlated with the rapid and population-wide onset of "diseases of Western civilization" such as diabetes, arthritis, cardiovascular disease, cancer, and neuropsychiatric illness[71], we are only now beginning to understand the biochemical and physiologic mechanisms by which dietary components influence physiologic function and, ultimately, health and disease.

Consumption of refined "simple" carbohydrates such as sugar, white bread, pastry, candy, and fruit juice generally leads to a rapid increase in blood glucose followed by an accompanying increase in insulin. While it is well known that elevation in blood glucose following consumption of sugar or fruit juice results in oxidative stress[72] and to suppression of immune function (inhibition of neutrophil-mediated bacterial phagocytosis[73]) for several hours, only recently has glucose consumption (75 grams; 300 calories) been shown to directly promote inflammation and to increase expression of chondrolytic enzymes such as MMP-2 and MMP-9[74], higher levels of which correlate with and appear to contribute to the progression of joint destruction.[75] Wheat consumption has been shown to trigger migraine headaches[76] in certain patients, and in recent experimental studies the wheat protein gliadin was shown to induce a pro-inflammatory effect via activation of NF-kappaB.[77,78] Cow's milk can contribute to adverse effects that can include migraine headache[79], otitis media[80], and joint inflammation[81,82], and it is a rich source of emulsified arachidonic acid which is the precursor to prostaglandins and leukotrienes and their pain-enhancing and joint-destroying properties via prostaglandin-E2 (PG-E2), PG-I2 and PG-F2·, leukotriene-B4, and 5-HETE as illustrated in Figure 4. Rich sources of arachidonic acid such as cow's milk, beef, liver, pork, and other grain-fed land animal meats add fuel to the inflammatory fire by providing the biochemical precursor (arachidonic acid) which is necessary for the production of prostaglandins, thromboxanes, and leukotrienes that promote and perpetuate processes such as atherosclerosis[83], cancer[84], arthritis and joint destruction.[85] To demonstrate the pro-inflammatory effect of a typical Western meal, Aljada et al[86] administered a single meal of egg and sausage muffin sandwiches with 2 hash browns and documented a postprandial increase of 150% for NF-kappaB (from ~190 to ~510 AUC) which lasted for approximately 2 hours and was associated with increases in oxidative stress and the inflammatory marker CRP. Thus, data are consistent with the general conclusion that typical Western dietary components including refined carbohydrates, cow's milk, wheat, and arachidonate-rich animal products will promote pain, free-radical damage, immunosuppression, inflammation, and numerous diseases via molecular, immunologic, and biochemical mechanisms. By extension, treatment of "inflammatory diseases" without addressing the proinflammatory nature of the patient's diet becomes questionable; anti-inflammatory efficacy almost always improved following dietary improvements as described here.

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The Supplemented Paleo-Mediterranean Diet: The health-promoting diet of choice for the majority of people is a diet based on abundant consumption of fruits, vegetables, seeds, nuts, omega-3 and monounsaturated fatty acids, lean meats and fish. This diet prohibits and obviates overconsumption of chemical preservatives, artificial sweeteners, and carbohydrate-dominant foods such as candies, pastries, breads, potatoes, grains, and other foods with a high glycemic load and high glycemic index. This "Paleo-Mediterranean Diet" is a combination of the "Paleolithic" or "Paleo diet" and the well-known "Mediterranean diet", both of which are well described in peer-reviewed journals and the lay press. The Mediterranean diet is characterized by increased proportions of legumes, nuts, seeds, whole grain products, fruits, vegetables (including potatoes), fish and lean meats, and monounsaturated and n-3 fatty acids.[87] Consumption of this diet is consistently associated with improvements in insulin sensitivity and reductions in cardiovascular disease, diabetes, cancer, and all-cause mortality.[88] The Paleolithic diet detailed by collaborators Eaton[89], O'Keefe[90], and Cordain[91] is similar to the Mediterranean diet except for stronger emphasis on fruits and vegetables (preferably raw or minimally cooked), omega-3-rich lean meats, and reduced consumption of starchy foods such as potatoes and grains, the latter of which were not staples in the human diet until the last few thousand years. Emphasizing the olive oil and red wine of the Mediterranean diet and the absence of grains and potatoes per the Paleo diet appears to be the way to get the best of both dietary worlds; the remaining diet is characterized by fresh whole fruits, vegetables, nuts (especially almonds), seeds, olive oil, lean meats rich in n-3 fatty acids, and red wine in moderation. In sum, this dietary plan along with the inclusion of garlic and dark chocolate (a rich source of cardioprotective, antioxidative, and anti-inflammatory polyphenolic flavonoids[92,93]) is expected to reduce adverse cardiovascular events by more than 76%.[94]

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Biochemical justification for this type of diet is ample and is well supported by numerous long-term studies in humans wherein both Mediterranean and Paleolithic diets result in dramatic reductions in disease-specific and all-cause mortality.[95,96,97,98] Diets rich in fruits and vegetables are sources of more than 5,000 phytochemicals, many of which have antioxidant, anti-inflammatory, and anti-cancer properties.[99] Oleic acid, squalene, and phenolics in olive oil and phenolics and resveratrol in red wine have antioxidant, anti-inflammatory, and anti-cancer properties and also protect against cardiovascular disease.[100] N-3 fatty acids have numerous health benefits via multiple mechanisms as described in the sections that follow. Increased intake of dietary fiber from fruits and vegetable favorably modifies gut flora, promotes xenobiotic elimination (via flora modification, laxation, and overall reductions in enterohepatic recirculation), and is associated with reductions in morbidity and mortality. Such a "Paleolithic diet" can also lead to urinary alkalinization (average urine pH of ? 7.5 according to Sebastian et al[101]) which increases renal retention of minerals for improved musculoskeletal health[102,103,104] and which increases urinary elimination of many toxicants and xenobiotics for a tremendous reduction in serum levels of thus the adverse effects from chemical exposure or drug overdose.[105] Ample intake of amino acids via dietary proteins supports phase-2 detoxification (amino acid and sulfate conjugation) for proper xenobiotic elimination[106,107], provides amino acid precursors for neurotransmitter synthesis and maintenance of mood, memory, and cognitive performance[108,109,110,111], and prevents the immunosuppression and decrements in musculoskeletal status caused by low-protein diets.[112]

Described here for the first time, the "supplemented Paleo-Mediterranean diet" provides patients the best of current knowledge in nutrition by relying on a foundational diet plan of fresh nuts, seeds, fruits, vegetables, fish, and lean meats which is adorned with olive oil for its squalene, phenolic antioxidant/anti-inflammatory and monounsaturated fatty acid content. Inclusive of medical foods such as red wine, garlic, and dark chocolate which may synergize to effect at least a 76% reduction in cardiovascular disease[113], this diet is supplemented with rational doses of additional vitamins, minerals, and fatty acids for reasons described in the sections that follow.

Multivitamin/multimineral supplementation (excluding iron and excess vitamin A and including additional vitamin D): Leading pioneers in the science of nutritional medicine include the late Roger Williams, whose classic texts Biochemical Individuality[114] in 1956 and Nutrition Against Disease[115] in 1971 established the scientific and conceptual rationale for the use of interventional nutrition for the preservation of health and in the treatment of human disease, and Linus Pauling, whose concept of using the "right molecules" such as vitamins, minerals, and other dietary factors opened the field of "orthomolecular medicine."[116,117] More recently, Robert Heaney[118] advanced our understanding of the adverse effects of chronic subclinical nutritional deficiencies with the phrase "long-latency deficiency diseases", and Bruce Ames has helped us appreciate the importance and biochemical/physiologic mechanisms of optimal nutrition[119] and high-dose vitamin supplementation[120], respectively.

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Although practitioners of natural healthcare have long advocated the use of supplemental vitamins and minerals, the value of this health-promoting practice has only recently been conceded by allopathic groups such as Harvard Medical School and the American Medical Association[121] who stated in 2002 that, "Most people do not consume an optimal amount of all vitamins by diet alone" and "…it appears prudent for all adults to take vitamin supplements." Vitamin and mineral supplementation helps compensate for inadequacies of foods grown in depleted soils or by non-organic techniques[122,123], and to ensure adequate nutritional intake during times of dietary indiscretion (reduced intake) or illness (increased utilization or excretion). Since vitamins commonly function as enzyme cofactors, their daily consumption is required to maintain enzymatic activities, and their provision in supraphysiologic quantities can be used to overcome genotrophic defects and facilitate activity in variant (ie, "slow" or "defective") enzymes.[124] Vitamin E supplementation must be in the form of mixed tocopherols and include a high (~40%) percentage of gamma-tocopherol[125] to avoid the purported adverse effects of alpha-tocopherol when used alone[126], and vitamin E appears to improve the action of insulin[127] and to ameliorate neurodegenerative disorders[128], arthritic pain[129], inflammation in diabetics[130], and may provide protection against the effects of urban pollution.[131] Excess vitamin A clearly carries a risk of hepatotoxicity[132] and is controversially associated with an increased risk for birth defects when consumed in doses greater than 10,000 IU per day by pregnant women. The most notable exception to the generally health-promoting benefits of mineral supplementation is iron, which should not be administered to those who are not iron deficient due to its oxidative and oncogenic properties.[133] Indeed, iron overload is quite common in the general population[134] and particularly among patients with musculoskeletal pain[135,136,137] and is causatively associated with numerous maladies including cardiovascular disease[138,139], cancer[140,141], diabetes mellitus[142], hypogonadism and infertility[143], thyroid disorders[144], infectious disease[145], and spinal and peripheral arthropathy.[146,147,148,149]

Vitamin D deserves special attention in the discussion of vitamins, particularly in light of the recent upsurge in research documenting its manifold health benefits[150,151] and the importance of obtaining and maintaining optimal serum levels.[152] Although cholecalciferol is a prehormone naturally produced in the skin by chemical reactions induced by exposure to sunlight (UVB radiation), it is also found in small amounts in a few foods and is therefore also referred to as "vitamin D." Insufficient dietary sources of vitamin D along with insufficient sun exposure have created an epidemic of vitamin D deficiency in America[153] and other industrialized nations[154] which contributes to the development of mental depression[155,156,157], diabetes mellitus[158,159], cancer[160,161], hypertension[162,163], cardiovascular disease[164,] polycystic ovary syndrome165, and autoimmune/inflammatory disorders[166] such as type-1 diabetes[167], and multiple sclerosis.[168] The research

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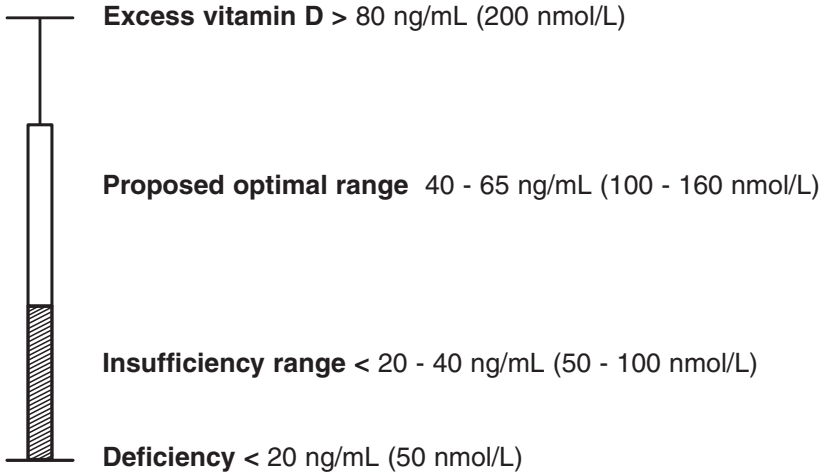
indicates that risk for and severity of many of these and other illnesses can be safely reduced with the use of vitamin D in daily doses of 1,000 IU for infants, 2,000 IU for children, and up to 4,000 IU for adults as we have recently justified elsewhere[169] provided that serum calcium is periodically assessed monitor for hypercalcemia, the most reliable sign of vitamin D excess. Doctors can easily assess vitamin D status with measurement of serum 25-OH-vitamin D, and we recently proposed that serum levels of 40 - 65 ng/mL (100 - 160 nmol/L) as shown in Figure 5 from Vasquez[170] and Vasquez et al[171] will provide optimal protection from the many diseases associated with vitamin D deficiency while minimizing risk for adverse effects. Doctors should remember that vitamin D deficiency is common in patients with generalized musculoskeletal pain[172] and low-back pain[173], that vitamin D has anti-inflammatory benefits[174,175,176], and that treatment with vitamin D can safely lead to dramatic reductions in musculoskeletal pain in a large percentage of patients.[177,178]

Figure 5. Proposed normal and optimal ranges for serum 25(OH)D levels based on current research. *From Vasquez A. Integrative Orthopedics. Natural Health Consulting Corp. (OptimalHealthResearch.com): 2004*



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Generally speaking, vitamin/mineral supplementation has been shown in clinical trials to improve nutritional status and reduce the risk for chronic diseases[179,180], improve mood[181], enhance wellbeing[182], potentiate antidepressant drug treatment[183], alleviate migraine headaches (when used with diet improvement and essential fatty acids[184]), improve immune function and infectious disease outcomes in the elderly[185] (especially diabetics[186]), reduce morbidity and mortality in patients with HIV infection[187,188], alleviate premenstrual syndrome[189,190], ameliorate bipolar disorder[191], reduce violence and antisocial behavior in children[192] and incarcerated young adults (when used with essential fatty acids[193]), improve scores of intelligence in children[194], and to benefit children with attention deficit and hyperactivity disorder.195 Vitamin supplementation has anti-inflammatory benefits as evidenced by significant reduction in CRP in a double-blind placebo-controlled trial.[196] In an increasingly toxic world[197,198,199] wherein the average American shows a body burden of more than a dozen different pesticides[200,201] and where toxic metal accumulation is commonplace[202,203.204], vitamin and mineral supplementation becomes even more necessary to help protect against oxidative damage caused by pollution and heavy metals[205,206,207,208,209] and to support the nutrient-dependent detoxification reactions that are required for the proper elimination of xenobiotics.[210,211,212,213,214] Of course, dietary modification and nutritional supplementation needs to be tailored to the needs, goals, health status, and pharmacotherapy (if any) of each individual patient; however, the recommendations included in this article will be safe and beneficial for the vast majority of patients.

"Essential fatty acids": To the extent that most fatty acids are neither produced de novo or not produced in sufficient amounts for the attainment of optimal health, nearly all of the dietary fatty acids discussed here can be considered "essential" insofar as they must be supplied from diet or supplementation. Strictly speaking, the term "essential fatty acids" (EFA) refers only to n-3 alpha-linolenic acid and n-6 linoleic acid, both of which are the "first in line" in their respective n-3 and n-6 categories.

Fatty acids obtained from diet, supplements, and endogenous production effect powerful biological actions via numerous mechanisms such as 1) altering cell membrane/receptor function, 2) modulating gene transcription, 3) modulating hormone production and reception, and 4) shifting eicosanoid metabolism from proinflammatory to relatively less inflammatory and perhaps "anti-inflammatory." Three major groups of unsaturated fatty acids are present in the human diet—n-3 (ALA, EPA, DHA), n-6 (linoleic acid, GLA, arachidonic acid), and n-9 (oleic acid).

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Based on a survey of the literature including recent reviews by Vasquez[215,216,217] and Larsson et al[218], we may reasonably conclude that the fatty acids with the most clinically significant health-promoting benefits are the n-3 fatty acids ALA, EPA, and DHA, the n-6 fatty acid GLA, and the n-9 fatty acid oleic acid, as summarized in the sections that follow. The n-6 fatty acids linoleic acid and arachidonic acid show proinflammatory, hyperalgesic, atherosclerotic, and oncogenic properties via numerous mechanisms and should be minimized in the diet of most patients.[219,220,221,222]

alpha-linolenic acid (ALA): ALA is an essential fatty acid as it is the "first in line" in the family of omega-3 polyunsaturated fatty acids (PUFA). Sources include flax seed oil (57% ALA), canola oil (9% ALA), soy oil, breast milk, English/black walnuts, soybeans, pine nuts, green vegetables, and beans. Conversion of ALA to the more biologically active EPA and DHA does not reliably or efficiently occur in humans.[223] No increase in DHA has been consistently observed in humans after supplementation of ALA[224]; in fact, supplementation with flax seed oil has actually been shown to reduce DHA levels in humans.[225] Although ALA can reduce blood pressure and cardiovascular mortality[226], it does not reduce serum lipids as do EPA and DHA. In a study of men with metabolic syndrome, ALA was shown to have anti-inflammatory benefits independent of its conversion to EPA or DHA.[227] The mechanism of action appears to be downregulation of NF-KappaB (the main "amplifier" for the expression of proinflammatory gene products[228]) rather than the direct modulation of eicosanoid biosynthesis. One study using flaxseed oil as a source of ALA to treat rheumatoid arthritis found no clinical or biochemical benefit (i.e., no change in Hgb, CRP, ESR)[229]; however, the poor results of this study may have been due to the inferior quality of the flaxseed oil product that was used which only supplied 32% ALA compared with the much higher concentration of 57% found in most products. Moderate intakes of ALA from flaxseed oil profoundly reduce production of proinflammatory prostaglandins (e.g., PG-E2, measured by urinary excretion) by 52% to 85% in humans[230] which is superior to the 42% reduction induced by rofecoxib (the drug "Vioxx").231 In summary, increased intake of ALA appears to provide cardioprotective[232] and anti-inflammatory benefits2[33,234], and ALA can help reduce the frequency and severity of migraine headaches when used as part of a comprehensive natural treatment plan that includes diet change and nutritional supplementation.[235]

Eicosapentaenoic acid: EPA, 20:5n3: EPA is essentially absent in vegan diets since the major dietary source is fish oil. Dietary EPA is incorporated into cell membranes where it modulates neurotransmitter and hormone receptor function and where it is stored before liberation by phospholipase for eicosanoid production. EPA-derived eicosanoids have anti-inflammatory properties, including a reduction in the production of pro-inflammatory eicosanoids such as LT-B4, PAFs, and cytokines such as TNF-alpha and IL-1, and a large reduction in PG-E2 and TX-B2.[236] Unfortunately, EPA can decrease production of DGLA, the metabolite of GLA that has health-promoting properties.[237] EPA doses of at least 4 grams per day are needed to increase bleeding time.[238] EPA supplementation reduces urinary excretion of calcium in patients with hypercalciuria and Docosahexaenoic acid: DHA, 20:6n-3: DHA is found only in plants of the sea, phytoplankton/microalgae, and consumers of microalgae (such as fish). Like EPA, DHA is an important component of cell membranes and generally appears to improve cell membrane function via improving receptor function and signal transduction. In late 2003, bioactive metabolites of DHA—the docosatrienes and resolvins—were discovered to mediate potent anti-inflammatory benefits.[248] Animal studies have shown that induction of DHA deficiency causes memory deficits and a reduction in hippocampal cell size[249], and DHA deficiency in humans is consistently associated with mental depression, learning disorders (e.g., ADD/ADHD), and other neuropsychiatric disorders such as schizophrenia—these findings are consistent with the view that the nervous system has an absolute requirement for DHA for proper function.[250] DHA appears essential for optimal cognitive function in infants and adults, and DHA in fish oil provides some protection against thrombosis, arrhythmia, cardiovascular death, Alzheimer's disease[251], otitis media (when used with nutritional supplementation[252]), and coronary restenosis following angioplasty.[253] Supplementation with DHA (often in the form of fish oil, which includes EPA) has been shown to benefit patients with bipolar disorder[254], Crohn's disease[255], rheumatoid arthritis[256,257,258], lupu[s259], cardiovascular disease[260], psoriasis[261], and cancer.[262] DHA appears to have an "anti-stress" benefit manifested by 30% reductions in norepinephrine and improved resilience to psychoemotional stress.[263,264] Supplementation with EPA+DHA in fish oil is extremely safe and reduces all-cause mortality.[265]

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227) "CONCLUSIONS: Dietary supplementation with ALA for 3 months decreases significantly CRP, SAA and IL-6 levels in dyslipidaemic patients. This anti-inflammatory effect may provide a possible additional mechanism for the beneficial effect of plant n-3 polyunsaturated fatty acids in primary and secondary prevention of coronary artery disease." Rallidis LS, Paschos G, Liakos GK, Velissaridou AH, Anastasiadis G, Zampelas A. Dietary alpha-linolenic acid decreases C-reactive protein, serum amyloid A and interleukin-6 in dyslipidaemic patients. Atherosclerosis. 2003 Apr;167(2):237-42

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Docosahexaenoic acid: DHA, 20:6n-3: DHA is found only in plants of the sea, phytoplankton/microalgae, and consumers of microalgae (such as fish). Like EPA, DHA is an important component of cell membranes and generally appears to improve cell membrane function via improving receptor function and signal transduction. In late 2003, bioactive metabolites of DHA—the docosatrienes and resolvins—were discovered to mediate potent anti-inflammatory benefits.[248] Animal studies have shown that induction of DHA deficiency causes memory deficits and a reduction in hippocampal cell size[249], and DHA deficiency in humans is consistently associated with mental depression, learning disorders (e.g., ADD/ADHD), and other neuropsychiatric disorders such as schizophrenia—these findings are consistent with the view that the nervous system has an absolute requirement for DHA for proper function.[250] DHA appears essential for optimal cognitive function in infants and adults, and DHA in fish oil provides some protection against thrombosis, arrhythmia, cardiovascular death, Alzheimer's disease[251], otitis media (when used with nutritional supplementation[252]), and coronary restenosis following angioplasty.[253] Supplementation with DHA (often in the form of fish oil, which includes EPA) has been shown to benefit patients with bipolar disorder[254], Crohn's disease[255], rheumatoid arthritis[256,257,258], lupus[259], cardiovascular disease[260], psoriasis[261], and cancer.[262] DHA appears to have an "anti-stress" benefit manifested by 30% reductions in norepinephrine and improved resilience to psychoemotional stress.[263,264] Supplementation with EPA+DHA in fish oil is extremely safe and reduces all-cause mortality.[265]

Gamma (ɣ)-linolenic acid: GLA, 18:3n6: The most powerful health-promoting n-6 fatty acid, GLA is found in varying concentrations in evening primrose oil, borage seed oil, hemp seed oil, and black currant seed oil. Most if not all of the actions of GLA are mediated following its elongation to the biologically active DGLA, from which eicosanoids that have cardioprotective and anti-inflammatory benefits are derived. Low levels of DGLA are associated with increased risk for stroke and myocardial infarction.[266] DGLA metabolites reduce the formation of the arachidonate-derived 2-series prostaglandins, 4-series leukotrienes and platelet-activating factor.[267] GLA supplementation results in the formation of two biologically active metabolites from DGLA formed by cyclooxygenase and lipoxygenase. Prostaglandin E-1 (PG-E1) is the main metabolite formed from DGLA by cyclooxygenase and its production is increased by vitamin C.[268] PG-E1 decreases platelet aggregation,[269] inhibits vascular smooth muscle cell proliferation in vitro[270], causes vasodilation[271], and thus helps lower blood pressure.[272]

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PG-E1 has anti-inflammatory benefits and is probably the most potent prostaglandin with respect to bronchodilation.[273] Production of PG-E1 is increased by n-3 fatty acids.[274] 15-HETrE is the second main metabolite from GLA/DGLA and is formed from DGLA via 15-lipoxygenase. 15-HETrE has potent anti-inflammatory action by inhibiting the conversion of arachidonic acid to leukotrienes via inhibition of 5-lipoxygenase and 12-lipoxygenase.[275,276] Clinically, this is very important because several common and serious health problems including allergy, asthma, cardiovascular disease, and cancer are at least partially dependent upon the function of lipoxygenase for the production of leukotrienes. Notably, prostate cancer cells can be rapidly killed in vitro by lipoxygenase inhibition.[277] Clinical benefit associated with GLA supplementation is seen in patients with, eczema[278], breast cancer (when used with tamoxifen[279]), premenstrual syndrome[280], rheumatoid arthritis[281,282], diabetic neuropathy[283], migraine headaches (when used with ALA[284]), and respiratory distress syndrome (when used with EPA).[285]

Oleic acid: N-9 oleic acid appears to have health-promoting benefits, namely cardioprotection and anti-inflammation which are both partially mediated via suppression of NF-kappaB.[286] Most clinical trials in humans have used olive oil as a source of oleic acid, and since olive oil is a complex mixture of oleic acid, squalene, and phenolic antioxidants/anti-inflammatories, therefore, determination of the benefits of oleic acid alone (i.e., without squalene and phenolics) is difficult. Other sources of oleic acid include flax seed oil and borage oil. Olive oil should be consumed in the diet to attain sufficient quantity of oleic acid along with the health-promoting, anti-inflammatory, anti-cancer, and cardioprotective squalene and phenolic antioxidants. Dietary consumption of olive oil is consistently associated with reductions in cancer and cardiovascular disease, particularly when used as a component of a health-promoting diet.[287,288]

Nutrigenomics: Modulation of Genetic Expression via Interventional Nutrition

The study of how dietary components and nutritional supplements influence genetic expression is referred to as "nutrigenomics" or "nutritional genomics" and has been described as "the next frontier in the postgenomic era."[289] Various nutrients have been shown to modulate genetic expression and thus alter phenotypic manifestations of disease by upregulating or downregulating specific genes, interacting with nuclear receptors, altering hormone receptors, and modifying the influence of transcription factors, such as proinflammatory NF-kappaB and the anti-inflammatory peroxisome-proliferator activated receptors (PPARs).[290,291,292,293] Indeed, the previous view that nutrients only interact with human physiology at the metabolic/post-transcriptional level must be updated in light of current research showing that nutrients can, in fact, modify human physiology and phenotype at the genetic/pre-transcriptional level.

Fatty acids and their end-products modulate genetic expression in several ways, as these examples will illustrate. In general, n-3 fatty acids decrease inflammation and promote health while n-6 fatty acids (except for GLA, which is generally health-promoting) increase inflammation, oxidative stress, and the manifestation of disease.

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Corn oil, probably as a result of its high n-6 LA (linoleic acid) content, rapidly activates NF-kappaB and thus promotes tumor development, atherosclerosis, and elaboration of pro-inflammatory mediators such as TNFa.[294,295,296] Similarly n-6 arachidonic acid increased production of the free radical superoxide approximately 4-fold when added to isolated Kupffer cells in vitro. Prostaglandin-E2 is produced from arachidonic acid by cyclooxygenase and increases genetic expression of cyclooxygenase and IL-6; thus, inflammation manifested by an increase in PG-E2 leads to additive expression of cyclooxygenase, which further increases inflammation and elevates C-reactive protein.[297] Some of the unique health-promoting effects of GLA are nutrigenomically mediated via activation of PPAR-gamma, resultant inhibition of NF-kappaB, and impairment of estrogen receptor function.[298, 299] Supplementation with ALA leads to a dramatic reduction of prostaglandin formation in humans[300], and this effect is probably mediated by downregulation of proinflammatory transcription, as evidenced by reductions in CRP, IL-6, and serum amyloid A.[301] EPA appears to exert much of its anti-inflammatory benefit by suppressing NF-kappaB activation and thus reducing elaboration of proinflammatory mediators.[302, 303] EPA also indirectly modifies gene expression and cell growth by reducing intracellular calcium levels and thus activating protein kinase R which impairs eukaryotic initiation factor-2alpha and inhibits protein synthesis at the level of translation initiation, thereby mediating an anti-cancer benefit.[304] DHA is the precursor to docosatrienes and resolvins which downregulate gene expression for proinflammatory IL-1, inhibit of TNFa, and reduce neutrophil entry to sites of inflammation.[305] Oxidized EPA activates PPAR-alpha and thereby suppresses NF-kappaB and the activation of pro-inflammatory genes.[306,307] Other nutrients that inhibit the activation of NF-kappaB include vitamin D[308 309], lipoic acid[310], green tea[311], rosemary[312], grape seed extract[313], resveratrol[314,315], caffeic acid phenethyl ester (CAPE) from bee propolis[316], N-acetyl-L-cysteine[317], selenium[318], and zinc.[319] Therefore, we see that fatty acids and nutrients directly affect gene expression by complex and multiple mechanisms, as graphically demonstrated in Figure 6, and the synergism and potency of these numerous anti-inflammatory nutraceuticals supports the rationale for the use of nutrition and select botanicals for the safe and effective treatment of inflammatory disorders.

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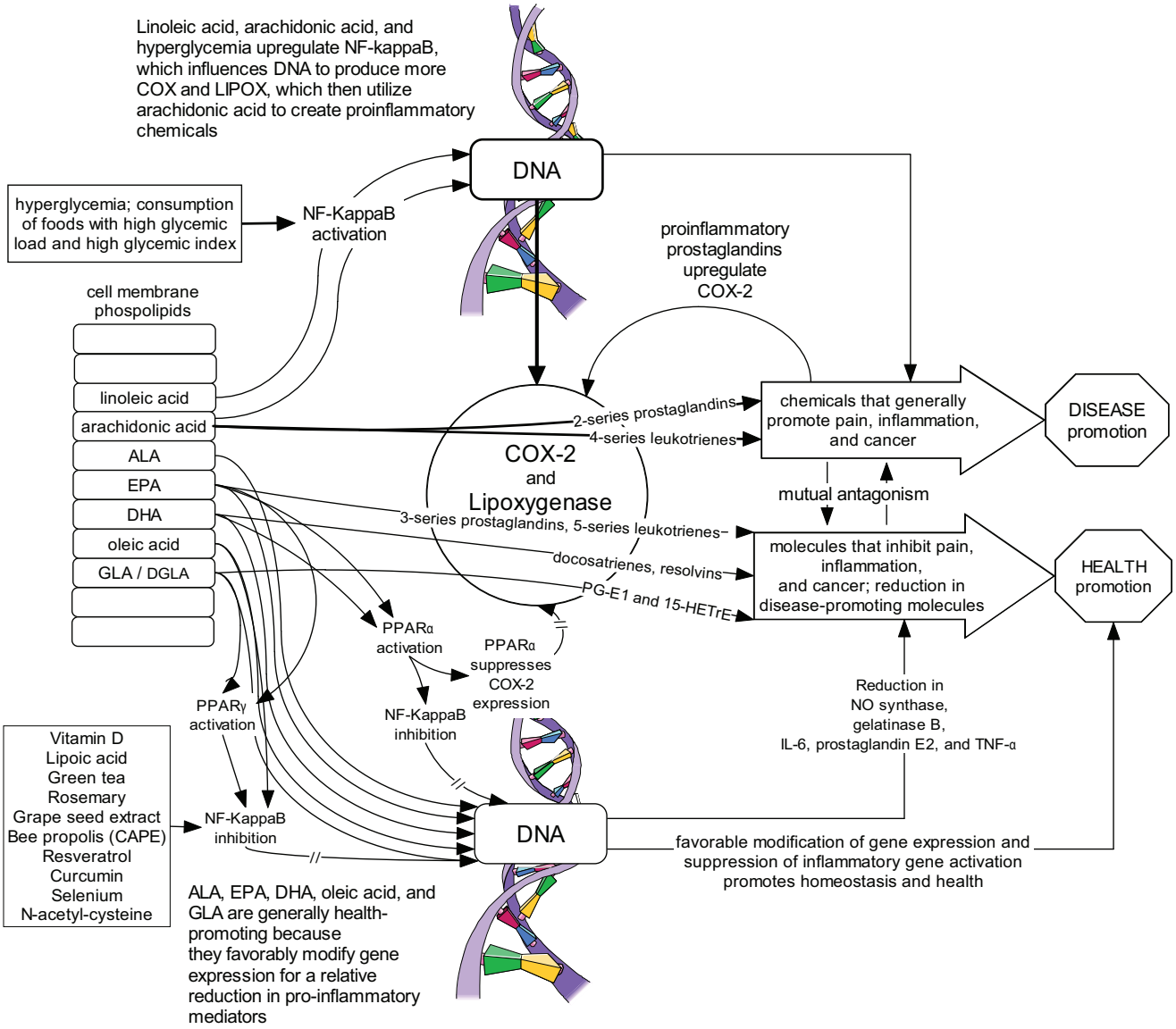
Figure 6. An integrated model of fatty acid effects on eicosanoid production and nutrigenomics. *Used here with permission.. (Vasquez A. Reducing Pain and Inflammation Naturally. Part 2: New Insights into Fatty Acid Supplementation and Its Effect on Eicosanoid Production and Genetic Expression. Nutr Perspect 2005; January: 5-16)*



Selected Nutritional and Botanical Therapeutics for the Alleviation of Joint Pain and Inflammation

Subsequent to the overall health improvement and anti-inflammatory benefits provided by the supplemented Paleo-Mediterranean diet described above, many patients who require additional anti-inflammatory interventions can be safely and effectively treated with the following phytonutraceuticals, each of which is supported by experimental and clinical data in humans. Mechanism(s) of action, indications, contraindications, dosage, and common drug interactions (if any) are listed for each.

Glucosamine and chondroitin sulfate: Glucosamine and chondroitin are the "building blocks" from which cartilage is built and oral supplementation is intended to enhance cartilage anabolism and to thus counteract the enhanced cartilage catabolism seen in destructive arthritic processes.320 Clinical trials with glucosamine and chondroitin sulfates have shown consistently positive results in clinical trials involving patients with osteoarthritis of the hands, hips, knees, temporomandibular joint, and low-back.[321,322,323,324,325,326,327] For example, glucosamine sulfate was superior to placebo for pain reduction and preservation of joint space in a 3-year clinical trial in patients with knee osteoarthritis.[328] Arguments against the use of glucosamine due to inflated concern about inefficacy or exacerbation of diabete[s329] are without scientific merit[330,331] as evidenced by a 90-day trial of diabetic patients consuming 1500 mg of glucosamine hydrochloride with 1200 mg of chondroitin sulfate which showed no significant alterations in serum glucose or hemoglobin A1c[332] and by the previously cited 3-year study which found significant clinical benefit and no adverse effects on glucose homeostasis.[333] The adult dose of glucosamine sulfate is generally 1500-2000 mg per day in divided doses, and the dose of chondroitin sulfate is approximately 1000 mg daily. Both treatments are safe for multiyear use, and rare adverse effects include allergy and nonpathologic gastrointestinal upset. Clinical benefit is generally significant following 4-6 weeks of treatment and is maintained for the duration of treatment. In contrast to coxib and other mislabeled "anti-inflammatory " drugs that consistently elevate the incidence of cardiovascular disease, death, and other adverse effects,[334,335,336,337,338] supplementation with chondroitin sulfate appears to safely reduce the pain and disability associated with osteoarthritis while simultaneously reducing incidence of cardiovascular morbidity and mortality.[339,340] In a study with animals that spontaneously develop atherosclerosis[341], administration of chondroitin sulfate appears to have induced regression of existing atherosclerosis. In a six-year study with 120 patients with established cardiovascular disease, 60 chondroitin-treated patients suffered 6 coronary events and 4 deaths compared to 42 events and 14 deaths in a comparable group of 60 patients receiving "conventional" therapy; chondroitin-treated patients reported enhancement of well-being while no adverse clinical or laboratory effects were noted during the 6 years of treatment.[342]

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Vitamin D (cholecalciferol): Vitamin D insufficiency is epidemic in the United States[343,344,345] and is extremely prevalent (>90%) among patients with chronic musculoskeletal pain[346], limb pain[347], and low-back pain.[348] The mechanism by which this pain is produced has been clearly elucidated: 1) vitamin D deficiency causes a reduction in calcium absorption, 2) production of parathyroid hormone (PTH) is increased to maintain blood calcium levels, 3) PTH results in increased urinary excretion of phosphorus, which leads to hypophosphatemia, 4) insufficient calcium phosphate results in deposition of unmineralized collagen matrix on the endosteal (inside) and periosteal (outside) of bones, 5) when the collagen matrix hydrates and swells, it causes pressure on the sensory-innervated periosteum resulting in pain.[349] In patients with vitamin D deficiency, oral supplementation with vitamin D clearly produces anti-inflammatory benefits[350,351], and treatment with vitamin D can safely lead to dramatic reductions in musculoskeletal pain in a large percentage of patients.[352,353] Routine annual measurement of vitamin D status should be the standard of care[354] since failure to diagnose vitamin D deficiency and to provide adequate replacement doses are both ethically questionable[355,356] and scientifically unjustifiable in light of the low cost, manifold benefits, rare adverse effects, and high prevalence of vitamin D deficiency.[357] Physiologic requirements are approximately 4,000 IU per day in men[358] and can only be achieved with high-dose oral supplementation or full-body sun exposure on a frequent or preferably daily basis. As reviewed in the recent monograph by Vasquez et al[359], relative contraindications include the use of thiazide diuretics or presence of a vitamin D hypersensitivity syndrome such as primary hyperparathyroidism, adrenal insufficiency, hyperthyroidism, hypothyroidism, or granulomatous disease such as sarcoidosis, Crohn's disease, or tuberculosis). Serum calcium is periodically monitored in patients receiving moderate doses of vitamin D (adult range 4,000 – 10,000 IU per day), as hypercalcemia is the best laboratory indicator of vitamin D excess. High doses of vitamin D (up to 100,000 IU per day) have been safely used during pregnancy[360,361,362]; periodic testing of serum calcium is required to monitor for hypercalcemia.

Proteolytic enzymes: Oral administration of proteolytic enzymes (such as pancreatin, bromelain, papain, trypsin and alpha-chymotrypsin) for therapeutic purposes is well established on physiologic, biochemical, and clinical grounds, and a brief review of their historical use is warranted. One of the first experimental studies was published by Beard in 1906 in the British Medical Journal wherein he showed that proteolytic enzymes significantly inhibited tumor growth in mice with implanted tumors[363], and a year later in that same journal, Cutfield[364] reported tumor regression and other objective improvements in a patient treated with proteolytic enzymes. In the American research literature, anti-cancer effects of proteolytic enzymes were reported during this same time in the Journal of the American Medical Association in anecdotal case reports of patients with fibrosarcoma[365], breast cancer[366], and head and neck malignancy[367]—all of whom responded positively to the administration of proteolytic enzymes; no adverse effects were seen. Although nearly a century would pass before Beard's study and results were replicated with modern techniques[368,369], by now it is well established that orally administered proteolytic enzymes are well absorbed from the gastrointestinal tract into the systemic circulation[370,371] and that the anti-tumor, anti-metastatic, anti-infectious, anti-inflammatory , analgesic, and anti-edematous actions result from synergism between a of

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variety of mechanisms of action, including the dose-dependent stimulation of reactive oxygen species production and anti-cancer cytotoxicity in human neutrophils[372], a pro-differentiative effect[373], reduction in PG-E2 production[374], reduction in substance P production[375], modulation of adhesion molecules and cytokine levels[376], fibrinolytic effects and a anti-thrombotic effect mediated at least in part by a reduction in 2-series thromboxanes.[377] Unfortunately, enthusiasm for the enzyme treatment of cancer waned prematurely when trypsin was judged to not be a "miracle cure", when the mechanism of action could not be determined, and as enthusiasm surrounding drug and radiation treatments grabbed the attention of medical community.[378] However, modern controlled clinical trials in cancer patients have established the value of enzyme therapy, which produces important clinical benefit (e.g., symptom reduction and prolonged survival) for little cost and with negligible adverse effects.[379,380,381,382] Research in other clinical applications for proteolytic enzymes has consistently shown benefit when properly formulated and manufactured preparations are administered appropriately in the treatment of cellulitis, diabetic ulcers, sinusitis, and bronchitis.[383] For example, in a double-blind placebo-controlled trial with 59 patients, Taub[384] documented that oral administration of bromelain significantly promoted the resolution of congestion, inflammation, and edema in patients with acute and chronic refractory sinusitis; no adverse effects were seen in any patient.

When not treating patients with cancer or infectious disease, chiropractic and naturopathic physicians today use these enzymes mostly for the treatment of inflammatory and injury-related disorders. Reporting from the Tulane University Health Service Center, Trickett[385] reported that a papain-containing preparation benefited 40 patients with various injuries (e.g., contusions, sprains, lacerations, strains, fracture, surgical repair, and muscle tears); no adverse effects were seen. In a recent open trial of patients with knee pain, Walker et al[386] found a dose-dependent reduction in pain and disability as well as a significant improvement in psychological well-being in patients consuming bromelain orally. Most of the bromelain studies reviewed by Brien et al[387] were suggestive of a positive benefit in patients with knee osteoarthritis, but inadequate dosing clearly prohibited the attainment of optimal results. Bromelain also attenuates experimental contraction-induced skeletal muscle injury[388], reduces production of hyperalgesic PG-E2 and substance P[389], is generally effective in the amelioration of trauma-induced injury, edema, and inflammation, and is practically non-toxic. Although bromelain may be used in isolation, enzyme therapy is generally delivered in the form of polyenzyme preparations containing pancreatin, bromelain, papain, trypsin and alpha-chymotrypsin.

Devil's Claw (Harpagophytum procumbens): Harpagophytum has a long history of use in the treatment of musculoskeletal complaints, and recent clinical trials have substantiated its role as a moderately effective analgesic suitable for clinical utilization. At least 12 clinical trials have been published on the use of Harpagophytum in the treatment of musculoskeletal pain, and all trials have found the botanical to be clinically valuable and with adverse effects comparable to placebo.[390] Harpagophytum's clinical benefit appears to derive chiefly from its analgesic effect, since administration of the herb does not alter eicosanoid production in humans.[391,392] In patients with osteoarthritis of the hip and knee, Harpagophytum is just as effective yet safer and better tolerated than the drug diacerhein.[393,394]

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In a study involving 183 patients with low-back pain, Harpagophytum was found to be safe and moderately effective in patients with "severe and unbearable pain" and radiating pain with neurologic deficit.[395] Most recently, Harpagophytum was studied in a head-to-head clinical trial with the formerly popular but dangerous selective cox-2 inhibitor Vioxx (rofecoxib); the data indicate that Harpagophytum was safer and at least as effective.[396] About 8% of patients may experience diarrhea or other mild gastrointestinal effects, and fewer patients may experience dizziness; Harpagophytum may potentiate anticoagulants. Treatment should be continued for at least 4 weeks, and many patients will continue to improve after 8 weeks from the initiation of treatment.[397] Products are generally standardized for the content of harpagosides, with a target dose of at least 30 and preferably up to 60 mg harpagoside per day.[398,399] However, the whole plant is considered to contain effective constituents, not only the iridoid glycosides.[400] Chrubasik[401] noted that while Harpagophytum appears to be safe and moderately effective for the treatment musculoskeletal pain, different proprietary products show significant variances in potency and clinical effectiveness. Data suggest that Harpagophytum is better than placebo and at least as good as commonly used NSAIDs[402], suggesting that Harpagophytum should be clinically preferred over NSAIDs due to the lower cost and greater safety.[403]

Cat's Claw (Uncaria tomentosa): Thirty patients with osteoarthritis of the knees benefited from highly-concentrated freeze-dried aqueous extraction of U. guianensis dosed at 1 capsule of 100 mg daily.[404] Reduction in pain was approximately 36% at 4 weeks. A year-long study of patients with active rheumatoid arthritis (RA) treated with sulfasalazine or hydroxychloroquine showed "relative safety and modest benefit" of Uncaria tomentosa (UT).[405] Uncaria inhibits NF-ÎB, TNF·, COX-2, and thus PGE-2 production.[406] No major adverse effects have been noted; however, headache and dizziness are more common in patients receiving Uncaria than in patients in placebo groups. This herb should probably not be used during pregnancy based on its historical use as a contraceptive. Most products are between 250-500 mg and are standardized to 3.0% alkaloids and 15% total polyphenols dosed 1-3 times per day. Other studies with Uncaria tomentosa have shown enhancement of post-vaccination immunity[407] and enhancement of DNA repair in humans.[408]

Willow bark (Salix alba): In a double-blind placebo-controlled clinical trial in 210 patients with moderate/severe low-back pain (20% of patients had positive straight-leg raising test), extract of willow bark showed a dose-dependent analgesic effect with benefits beginning in the first week of treatment.[409] In a head-to-head study of 228 patients comparing willow bark (standardized for 240 mg salicin) with Vioxx (rofecoxib), treatments were equally effective yet willow bark was safer and 40% less expensive.[410] Actions of willow bark are manifold including anti-oxidative, anti-cytokine, along with cyclooxygenase- and lipoxygenase-inhibiting effects. A non-purified extract of the phytomedicinal is required for full clinical benefit. The daily dose should not exceed 240 mg of salicin, and products should include other components of the whole plant. Except for rare allergy, no adverse effects are known, yet use during pregnancy and with anti-coagulant medication is discouraged.

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407) "C-Med-100 is a novel nutraceutical extract from the South American plant Uncaria tomentosa or Cat's Claw which is known to possess immune enhancing and antiinflammatory properties in animals. However, statistically significant immune enhancement for the individuals on C-Med-100 supplement was observed..." Lamm S, Sheng Y, Pero RW. Persistent response to pneumococcal vaccine in individuals supplemented with a novel water soluble extract of Uncaria tomentosa, C-Med-100. Phytomedicine. 2001 Jul;8(4):267-74

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Boswellia (Boswellia serrata): Boswellia shows anti-inflammatory action via inhibition of 5-lipoxygenase[411] with no apparent effect on cyclooxygenase.[412] A recent clinical study showed that Boswellia was able to reduce pain and swelling while increasing joint flexion and walking distance in patients with osteoarthritis of the knees.[413] While reports from clinical trials published in English are relatively rare, a recent abstract from the German medical research[414] stated, "In clinical trials promising results were observed in patients with rheumatoid arthritis, chronic colitis, ulcerative colitis, Crohn's disease, bronchial asthma and peritumoral brains edemas." Additional recent studies have confirmed the effectiveness of Boswellia in the treatment of asthma[415] and ulcerative colitis.[416] Minor gastrointestinal upset has been reported. Products are generally standardized to contain 37.5–65% boswellic acids, which are currently considered the active constituents with clinical benefit. The target dose is approximately 150 mg of boswellic acids thrice daily; dose and number of capsules/tablets will vary depending upon the concentration found in differing products.

MSM (Methylsulfonylmethane): MSM is a fairly popular nutritional supplement for the amelioration of allergies, interstitial cystitis, and joint pain, although the research supporting its use is quite limited.[417] MSM is relatively inexpensive and appears safe, especially for short-term use; one clinical trial used 2,600 mg for 30 days with no major adverse effects.418 Doses of 1-3 grams per day appear safe and are reasonable for patients who may derive benefit.

Spinal Manipulation: Mechanisms of Action and Synergism with Nutritional/Botanical Interventions

The clinical benefits and cost-effectiveness of chiropractic management of musculoskeletal conditions is extensively documented, and that spinal manipulation generally shows superior safety to drug and surgical treatment of back and neck pain is also well established.[419,420,421,422,423,424,425] Adjunctive therapies such as post-isometric relaxation[426] and correction of myofascial dysfunction[427] can lead to tremendous and rapid reductions in musculoskeletal pain without the hazards and expense associated with pharmaceutical drugs.

Applied to either the spine or peripheral joints, high-velocity low-amplitude joint manipulation appears to have numerous physical and physiological effects, including but not limited to the following: 1) releasing entrapped intraarticular menisci and synovial folds, 2) acutely reducing intradiscal pressure, thus promoting replacement of decentralized disc material, 3) stretching of deep periarticular muscles to break the cycle of chronic autonomous muscle contraction by lengthening the muscles and thereby releasing excessive actin-myosin binding, 4) promoting restoration of proper kinesthesia and proprioception, 5) promoting relaxation of paraspinal muscles by stretching facet joint capsules, 6) promoting relaxation of paraspinal muscles via "postactivation depression", which is the temporary depletion of contractile neurotransmitters, 7) temporarily elevating plasma beta-endorphin, 8) temporarily enhancing phagocytic ability of neutrophils and monocytes, and 9) activation of the diffuse descending pain inhibitory system located in the periaqueductal gray matter—this is an important aspect of nociceptive inhibition by intense sensory/mechanoreceptor stimulation. While this list of mechanisms-of-action is certainly not complete, for purposes of this paper it is sufficient to have established that, indeed, joint manipulation in general and spinal manipulation in particular have objective mechanistic effects that correlate with their clinical benefits. Additional details are provided in numerous published reviews and primary research[428,429,430,431,432,433,434] and by Leach[435], whose extensive description of the mechanisms of action of spinal manipulative therapy is unsurpassed. Given such a wide base of experimental and clinical support published in peer-reviewed journals and widely-available textbooks, denigrations directed toward spinal manipulation on the grounds that it is "unscientific" or "unsupported by research" are clearly unfounded.

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Select nutritional interventions as surveyed in this paper may have enhanced effects and benefits when combined with spinal manipulative therapy. For example, enhanced respiratory burst clearly carries both antitumor and antimicrobial benefits, and this physiologic effect can be induced by oral consumption of proteolytic enzymes[436] as well as by chiropractic spinal manipulative therapy.[437,438] Likewise, we would expect synergism between spinal manipulative therapy[439,440,441] and nutritional[442] and botanical[443,444] interventions in the treatment of asthma, particularly since these treatments are mediated primarily via different mechanisms—namely the neurophysiologic inhibition of neurogenic inflammation (proposed) and the biochemical reduction in pro-inflammatory mediators such as leukotrienes, respectively. As a final example, synergism would be expected in the treatment of low-back pain when spinal manipulation, therapeutic exercise, proprioceptive retraining, oral vitamin D supplementation, and botanical medicines such as Harpagophytum and Willow Bark are used together in holistic, integrative, multicomponent treatment plans.[445]

Summary and Conclusions

There is a plethora—a superabundance—of peer-reviewed research documenting the effectiveness and safety of natural, nonpharmaceutical non surgical treatments for musculoskeletal pain and inflammation. Dietary improvement and supplementation, along with vitamin D, fatty acids, proteolytic enzymes, botanical medicines, and chondroprotective agents such as chondroitin sulfate produce excellent clinical benefits with negligible risk for the majority of patients with musculoskeletal pain.

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