Botanical Modulation of Inflammation and Allostasis

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Introduction and Overview

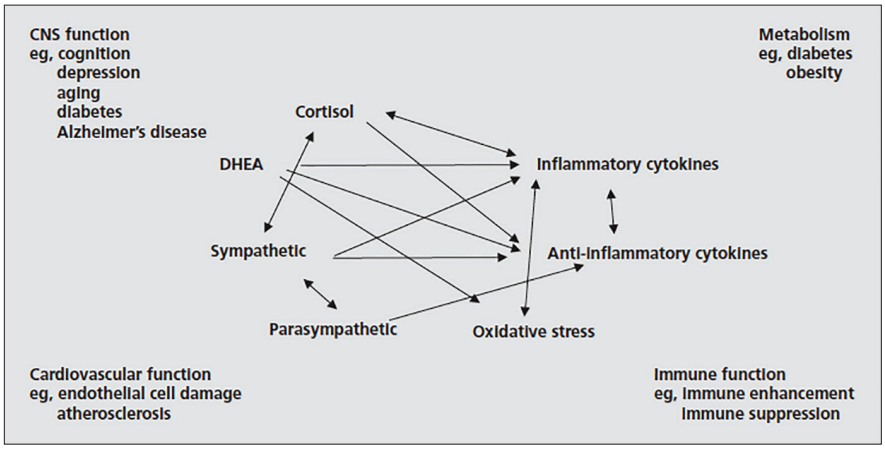
Allostasis and the Inflammatory Response

Inflammation is an intrinsically protective response of the immune system to injury, infection or invasion by microorganisms that usually leads to resolution and tissue healing within a short period of time. The immune response involves highly complex interactions between many signaling networks, molecules and systems that modulate cellular homeostasis and health while responding to systemic challenges.[1-4]

Our immune system is comprised of a vast network of cells and tissues connected through ongoing intercellular communication with intricate cascades of biochemical transformations mediated by enzymes and many other factors. The study of immune and inflammatory response spans multiple scientific disciplines including cell biology, biochemistry, biology and genetics. Current research explores the intricate interrelationship between inflammatory, epigenetic and allostatic processes. Continual communication and feedback loops facilitate the immune, cardiovascular, endocrine, epigenetic and neurological systems to work in an integrated manner to maintain stability. This process of "achieving stability through change" is the constant adaptive process of allostasis: the ongoing, active process by which the body maintains homeostasis while responding to ongoing events and challenges.[1] The epigenetic, immune and inflammatory responses are but a few aspects of this ongoing process of allostasis.

Complex inflammatory processes occur through multiple mechanisms and mediators leading to vasodilation, increased vascular permeability, migration of white blood cells to the affected area and many other events.[5] Acute inflammation is usually resolved within a short period of time - often around two weeks. When the inflammatory response becomes abnormally prolonged this creates wear and tear on the cells, tissues and organs of the body, which creates what is referred to as allostatic overload and eventually resulting in disease.[1] What kind of disease and where it occurs depends on which cellular systems are damaged due to the ongoing process of chronic inflammation.

An example of this complex interrelationship is seen with cytokines. There are both pro- and anti-inflammatory cytokines, which are produced by many cells throughout the body. Cytokines influence each other and are also regulated by glucocorticoids and catecholamines, both of which can increase production of pro-inflammatory cytokines. Glucocorticoids can also inhibit this production and their influence is found to depend on factors such as dosage along with cell or tissue type.



Nonlinear network of mediators of allostasis involved in the stress response. Arrows show the multiple pathways for regulation and indicate that each system regulates the others in a reciprocal manner, creating a non-linear network.

McEwen BS. *Protective and damaging effects of stress mediators: central role of the brain.* Dialogues in Clinical Neuroscience 2006. Vol 8(4):367-381.

The balance between parasympathetic and sympathetic nervous system engagement plays a role in the regulatory process of inflammation. Generally, the parasympathetic nervous system tends to engender

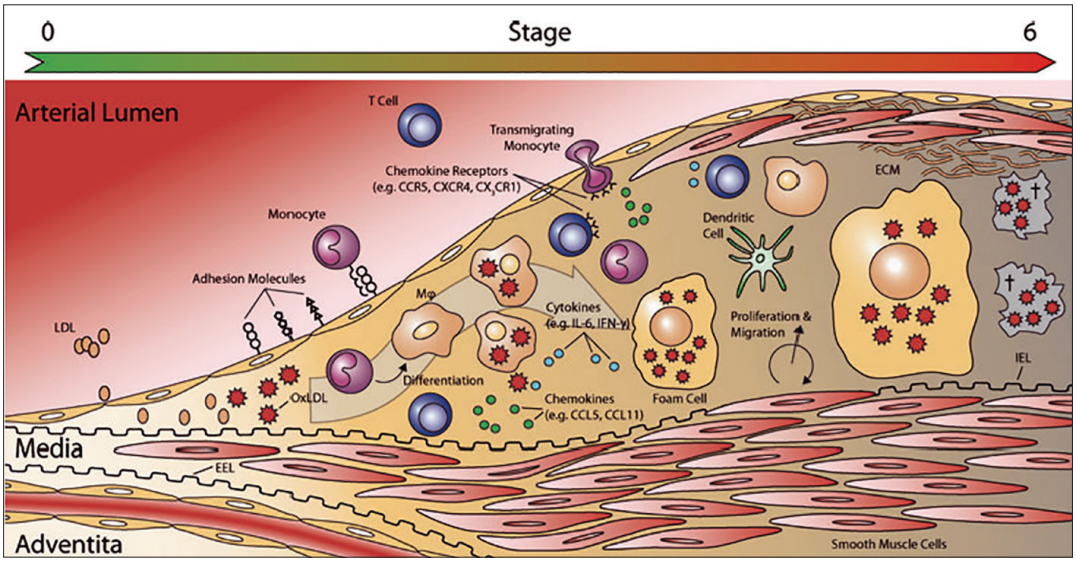
healing and repair and is found to exert an anti-inflammatory influence. Scientists find that the mediators of these systems function in a nonlinear manner. This means that when there is a change (increase or decrease) in one mediator, all the other mediators respond in a compensatory manner. These changes are dependent on multiple factors such as time and level of change of the mediators.[1]

Multiple stress factors, especially over time, can lead to allostatic overload. For example, loss of sleep causes multiple physiological changes including lessened parasympathetic tone, increased evening cortisol and insulin levels along with an increase in proinflammatory cytokine levels and oxidative stress markers.[1]

Due to the degree of complexity and continual interaction of intercellular communication throughout physiological systems, only a few of the multitudinous components and interactions involved with the inflammatory response will be discussed here.

Epigenetic Processes and Inflammation

Epigenetics explores the role of exogenous and endogenous factors on gene expression. Our health is not determined by our genes per se but rather by their response to stimuli. As one of the basic cellular regulation systems, epigenetic control plays key roles in regulating inflammatory and immune responses.[3] The combined influence of transcription factors (by regulatory gene proteins) and epigenetic mechanisms governs transcriptional control of gene expression. For example, in a study of the inflammatory processes of atherosclerosis, it is found that epigenetic modulators regulate vascular, immune and tissue-specific gene expression within the atherosclerotic lesion. They are also involved in transcriptional regulation of immune cells in the vascular wall, which modulates inflammation through expression of cytokines and chemokines.[3]



Schematic representation of plaque development.

Wierda RJ, Geutskens SB, et al. *Epigenetics in atherosclerosis and inflammation*. J Cell Mol Med. Epigenetics Review Series 2010. Vol 14(6A):1225-1240

Epigenetic processes are key factors in regulation of gene expression and cytokine expression.[3] Epigenetic modifications are mediated by various enzymes responsible for maintaining the epigenome (the overall epigenetic state of an organism), which is critical to normal development and health.[6] Multiple components influence epigenetic regulation of genes and cause modification of genes. Since epigenetic alterations accumulate over time, environmental, dietary and other factors exert a powerful influence on genetic

expression. Cell differentiation, such as monocyte differentiation into macrophages in the immune response and cell-specific gene expression, is determined in large part through epigenetic mechanisms.[3]

Scientists are interested in epigenetic processes because they are reversible and seen as a promising therapeutic target due to their inherent plasticity.[3, 6-8] Botanicals are of particular interest in this regard. There is a large body of research discussing the link between inflammation and reprogramming of the epigenome.[3,4; 6-8] For example, curcumin is found to act as an inhibitor of an epigenetic-mediating enzyme and through this mechanism to significantly influence the favorable LDL/HDL ratio.[3]

Chronic Inflammation and Disease

Decades of intensive research find a direct relationship between chronic inflammation, aging processes and disease. A persistent, dysfunctional inflammatory response that continues over time damages cells, disrupts cell-signaling networks, causes tissue damage and can predispose a person to autoimmune conditions or other diseases. Chronic inflammation is implicated in the pathogenesis of many conditions including atherosclerosis, arthritis, rheumatoid arthritis, chronic obstructive pulmonary disease (COPD), cancer, stroke, chronic pain, periodontal disease, neurodegenerative conditions and cardiovascular disease. Ongoing research identifies and maps the specific players, processes and targets in the inflammatory response and aims to discover compounds that can restore allostasis.[9-11]

Increased oxidative and genotoxic stress contribute to a vicious cycle of inflammation and oxidative stress that provokes cellular damage, epigenetic disturbances and a cellular environment where senescent cells create molecules that cause further disturbances for surrounding cells. Studies show that DNA damage in aging cells can activate the innate immune system release of inflammatory cytokines and induce activation of the NF-kB (nuclear factor-kappa beta) system. This chronic inflammatory response increases oxidative stress, lipid peroxidation and induces secretion of other deleterious products. This in turn causes degeneration of the cellular matrix and can trigger tissue-specific age-related degenerative conditions.[2] Inflammatory processes involving NF-kB, tumor necrosis factor (TNF) and cytokines are found to play critical roles in the development of inflammatory conditions including atherosclerosis, rheumatoid arthritis, irritable bowel disease, asthma and COPD.[12]

Immune and Inflammatory Responses

The two aspects of the immune system – innate and adaptive – function together in a highly integrated manner. Innate defenses respond directly to challenges while the adaptive defense system develops its response after initial encounter with a challenging molecule. The innate system, the body's first responder, instantly recognizes microbial, viral or other pathogens through mechanisms known as pattern recognition receptors. Toll proteins (toll-like receptors) are key in recognizing foreign microbes and activating innate cellular response.[13] The innate immune system calls the adaptive system into play. Adaptive system responses, highly specific to the pathogen that induced them, act through antibody and cell-mediated responses.[13,14]

The acute phase of inflammation is characterized by an influx of white blood cell components. These help neutralize and eliminate any invading microorganisms, help prevent infection and begin the process of healing and repair. The four cardinal signs of inflammation are redness, heat, swelling and pain. Loss of function can also occur. White blood cell components including macrophages, lymphocytes and leukocytes increase in numbers to play a primary role in the inflammatory process. During the resolution phase, these molecules return to normal numbers and function. Acute inflammation usually resolves within about two weeks.[13]

Some of the key compounds that promote the inflammatory process also play a role in the resolution of inflammation, helping restore healthy function and homeostasis.[5,9-11,15] These include enzymes (such as cyclocoxygenase), lipids (prostaglandins) and proteins (cytokines and others).

Inflammatory Response: Key Players

Natural Killer (NK) Cells

NK cells are a form of lymphocytes produced in and released from the bone marrow. They are a key player in the innate immune response and are mainly found in the blood circulation and in the spleen. In addition, they are cytotoxic and are able to directly kill problematic cells. NK cells modulate expression of cytokine and chemokine receptors.[16]

Macrophages

Innate defenses are mediated by NK cells and by phagocytic cells such as neutrophils and macrophages (MPs). MPs, which are found throughout the body and named according to their location. For example, Kuppfer cells are found in the liver and microglial cells are found in the brain. Microglial cells play a major role in modulating both pain and inflammation.[17-19]

MPs, often the first responders of the immune system, perform a variety of functions. They can act as phagocytes to eliminate apoptic cells, digest waste products from tissues, and help promote wound healing. MPs are essential for immunity, overall development and tissue homeostasis.[20]

Reactive oxidative species (ROS), produced by MPs, damage an invading microbe's cell wall, which makes it more permeable to attack and able to be neutralized and removed from the body. Hence, ROS formation and subsequent oxidative stress is linked with the inflammatory process.

During the inflammatory response, MPs secrete cytokines along with tumor necrosis factor. Cytokines activate white blood cells, including lymphocytes and neutrophils, and promote inflammation. The release and activity of cytokines is modulated by cell-signaling and through highly complex intercellular processes involving specialized membranes and molecules. When this inflammatory response becomes chronic or excessive due to dysregulation, it disrupts cellular function and contributes to disease formation.[13;20-22]

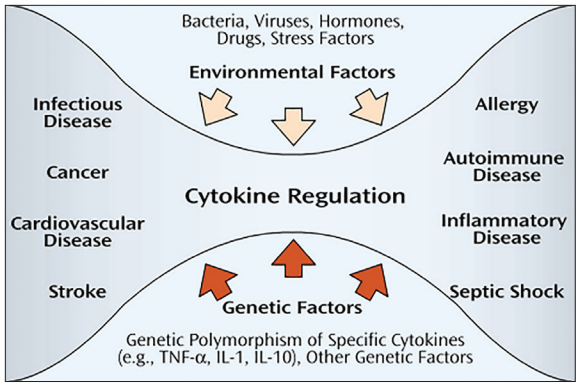
Cytokines

MPs communicate information to other immune cells through signaling molecules known as cytokines, which are secreted by MPs and by other immune system cells. Cytokines are important mediators of both the innate and specific defense systems. Often regarded as the hormones of the immune system, their role is considered as vital to life as that of hormones and neurotransmitters.[20,23]

Cytokines comprise a huge family of molecules that are classified according to their source and function. Cytokines provide molecular cues and messaging that help maintain physiological stability and communication between organ systems. Specific cytokines stimulate stem-cell growth, proliferation and cell differentiation. They can function as growth factors and growth inhibitors.[13,20,24] Some cytokines function as epigenetic regulators.[4,20] Binding to cell-surface receptors, they generate a cell-signaling cascade that

influences cell function, along with regulation of certain genes and their transcription factors.[20]

Cytokines are found to play a key role in signaling the brain; inducing it to produce neuro-chemical, neuro-endocrine, neuro-immune and behavioral changes as part of the immune response.[23] Many types of cytokines are synthesized and released within the central nervous system and in the brain where they are secreted by astrocytes and microglia. In some cases, neurons can also produce cytokines.



Cytokine regulation in health and disease.

Kronfol Z, Remick DG. *Cytokines and the brain: implications for clinical psychiatry*. Am J Psychiatry 2000. 157:683-694.

Cytokines modulate the HPAT (hypothalamic-pituitary-adrenal-thyroid) axis. Many symptoms that occur during inflammation and infection are attributed in part to the influence of cytokine activity including increased sleep and decreased appetite. Thus cytokines can act as immune-modulators and neuro-modulators, influencing metabolic and other pathways to maintain homeostasis and restore health.[23]

Chemokines and interleukins (ILs) are two interrelated members of the vast cytokine family. Chemokines are unique cytokines released by many different kinds of cells, most often induced by pro-inflammatory cytokines including TNF and IL-6.[20] ILs are a large, diverse group of compounds with implications too complex to discuss here. Generally, they are immune-modulators. IL-6 plays a role in both pro-and anti-inflammatory processes in functions including immunity, tissue repair and metabolism.[20]

Tumor Necrosis Factor (TNF)

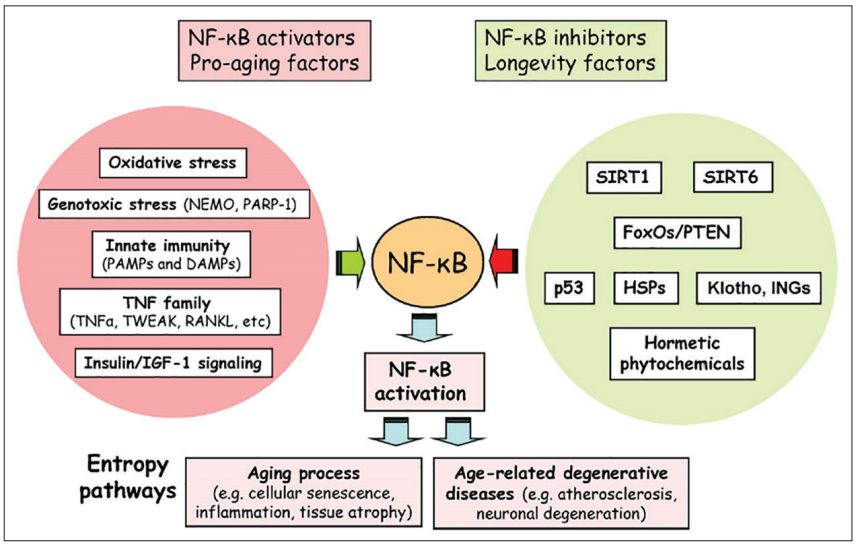
TNF (formerly known as TNF-a) is a glycoprotein that stimulates the acute phase of the immune response and regulates chemokine release. In the hypothalamus, TNF stimulates the release of corticotropic releasing hormone. A key factor in elevating synthesis of C-reactive protein and other mediators, it exerts many more effects as a major inducer of the inflammatory cascade. Excess TNF is found to play a role in conditions as diverse as irritable bowel syndrome, psoriasis, rheumatoid arthritis, asthma, infectious diseases, cancer and a number of autoimmune conditions.[20]

NF-kB (nuclear factor kappa-beta)

NF-kB, a major driver in the inflammatory process, is a transcription protein. Researchers consider it to be an ancient signaling pathway system that plays a key role the immune system with a vast influence on health and aging.[2] Activation mechanisms and responses are unique and specific for different cell types. The NF-kB system is a pleiotropic regulator that has both beneficial and detrimental responses. One of its beneficial functions lays in its key role in the innate immune response.

The NF-kB signaling system is considered a focal point linking the body's immune response and its transcriptionally-mediated adaptive response. NF-kB is a transcription factor and a mediator of gene expression. It is considered to be a cytoplasmic sensor that is activated by immune attacks and by many other signals including oxidative or genotoxic stress and tissue injury.[2] Through various mechanisms, NF-kB plays a role in controlling the magnitude and duration of the inflammatory response.[12] NF-kB regulates gene

expression and influences cell health.[10] Prolonged or excessive activation is linked with formation of disease processes.[2] NF-kB overexpression is linked to expression of multiple disorders including arthritis and cellular disturbances.[25,26] As a transcription factor, NF-kB can stimulate growth genes, promoting uncontrolled cellular growth.[27]



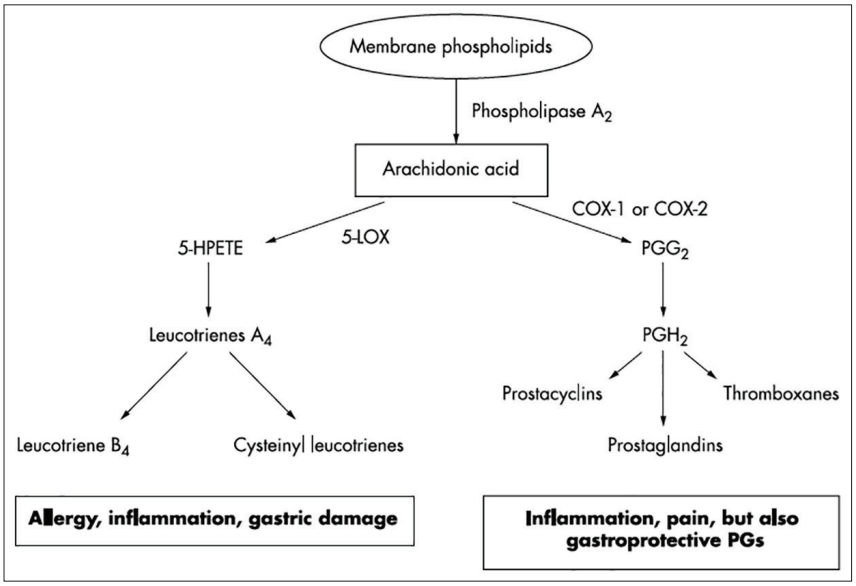
NF-kB system is at the hub of the aging network.

Salminen A, Kaarniranta K. *Genetics vs. entropy: Longevity factors suppress the NF-kB-driven entropic aging process*. Aging Research Reviews 2010. (9)298–314.

COX (cyclooxygenase) and the Arachidonic Acid (AA) Cascade

The COX-1 and COX-2 pathways are major players in the inflammatory cascade. COX is the key enzyme required to convert AA (arachidonic acid) to PGs (prostaglandins). While COX-1 is implicated in the inflammatory process it also plays a role in homeostasis and health, particularly in the kidneys and gastric mucosa. COX-2 induces the inflammatory cascade, but is sometimes involved in resolution of inflammation.[15,28] COX-2 is found to modulate brain health, neural response, development, imprinting and adaptation. However, chronic activation of COX-2 provokes numerous disease processes.[15]

AA is transformed by COX-2 enzymes to PGs and thromboxane. PGs along with the compounds thromboxanes, leukotrienes and lipoxins are collectively referred to as eiocosanoids. Eiocosanoids are significantly elevated during the inflammatory response.[29,30]



Products and enzymes of arachidonic acid metabolism involved in the inflammatory process.

Martel-Pelletier J, Lajeunesse D et al. *Therapeutic role of dual inhibitors of 5-LOX and COX, selective and non-selective non-steroidal anti-inflammatory drugs*. Ann Rheum Dis 2003. 762: 501-509.

PGs are phospholipid compounds that act as biological regulators; they respond contextually to either promote inflammation or enhance resolution of inflammation. They trigger signal transduction pathways, influence immune response and increase sensitivity of pain receptors.[13] PGs can support physiological homeostasis through modulating intracellular cell-signaling pathways.[8] PGs mediate inflammatory processes including cytokine production.[10,12,31]

Chronic Inflammation and Epigenetic Disruption

Factors that contribute to chronic inflammatory processes and cellular dysfunction include stress (chemical, physical and psychological), viral infection, bacterial imbalance (i.e. *Heliobactor pylori*), environmental pollutants (air pollution, smoke, etc.) and dietary contaminants (everything from fried foods to GMOs, xenobiotics and hormone/pesticide contamination). These incite the expression of inflammatory processes including reactive oxidative species, TNF, IL factors, NF-kB, COX-2 and 5-LOX, matrix metalloproteinases and chemokines. Chronic inflammatory conditions correlate with multiple adverse epigenetic changes including changes in genomic markers and cellular transcription dysfunctions.[4,6]

Epigenetic mechanisms modulate the expression of many pro-inflammatory factors including TNF-a, interleukins, tumor suppressor genes and oncogenes. They are found to modulate autocrine and paracrine activation of NF-kB. The inflammatory response is interwoven with the body's regulatory network involving signal- and gene-specific levels. Specific genes are activated for immune response, antimicrobial defense, and for tissue repair and remodeling.

Inflammatory genes are regulated by a number of transcription factors including NF-kB and by epigenetic activities such as DNA methylation.[6] Overexpression of transcription factors such as NF-kB is one of the key drivers responsible for expression of these genes. Over time, tissue changes and epigenetic disruption can occur at the sites of chronic inflammation.[4] For example, rheumatoid arthritis (RA) is an inflammatory condition with progressive degeneration of articular cartilage and bone. Epigenetic factors are found to contribute to RA.[6] Research findings estimate that up to 25% of all cancers are linked with chronic inflammation and its manifestations of cellular dysfunction including transcription errors, aberrant epigenetic processes (which influence normal gene expression), DNA methylation and other processes.[4]

Aging and Inflammation

The aging process has long been linked with inflammation and specifically with pro-inflammatory changes in cellular status. Multiple changes are noted in both the innate and adaptive immune response systems.[16] The combination of inflammation, decline in adaptive immunity, and changes in cell function and cell-signaling are thought to facilitate unhealthy aging and promote formation of degenerative diseases.[2]

Researchers report that with aging cytokines are often elevated and that IL-6 and TNF are upregulated. TNF regulates adaptive immunity and contributes to its decline with aging (immunosenescence). In addition, studies show that insulin and insulin-like growth factor signaling can stimulate the NF-kB system, which enhances the inflammatory response and exerts other negative influences on the aging process.[2] Research finds that the NF-kB system plays a key role in mediating aging and is overactive in many age-related, chronic inflammatory diseases.[2,12]

Members of the TNF family regulate many factors including age-related muscle atrophy (sarcopenia) and the cachexia that is seen in inflammatory conditions.[2] In both these conditions, the TNF signaling pathway is mediated through the activation of the NF-kB system. Multiple signaling pathways, endocrine regulation and metabolic factors are also implicated in muscle atrophy. Other members of the TNF family play a role in the catabolic aging process.[2] Inflammation is linked to frailty syndrome in the aging, which is characterized as dysregulation in multiple systems and low physiological reserves. Upregulated expression of stress-responsive genes in the inflammatory pathways is found to contribute to frailty syndrome.[16,32,33]

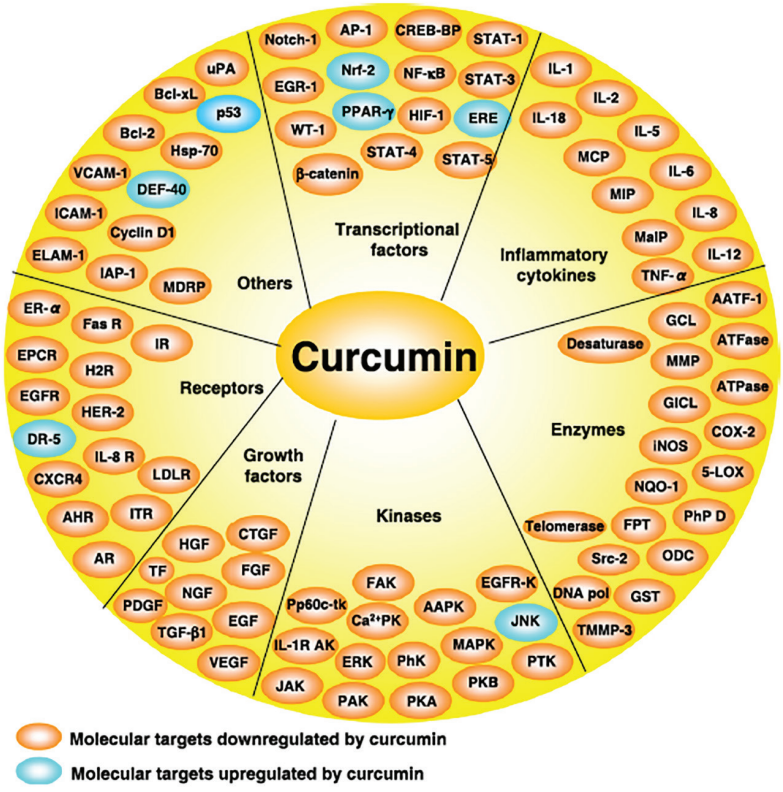
Integrative Approach to Inflammation

Multiple studies demonstrate the effectiveness of stress reduction, mindfulness, meditation practices and a healthy diet to mediate inflammation. Nutrigenomics integrates the science of genomics with that of nutrition to study the influence of dietary components on genes.[34]

Plant-based foods, herbs and spices contain multiple vitamins, minerals and phytonutrients essential to human health. Most of these plants have been used for thousands of years as part of the human diet and as medicines. Modern scientists are avidly studying these plants to discover their bioactive compounds in search for new answers to healing inflammation and helping to restore and maintain health.

Some of the compounds of greatest interest include the polyphenols, phytoestrogens, saponins, terpenoids, isothiocyanates, phytosterols, carotenoids and omega-3 fatty acids.[35] Phytonutrients such as these and others are found to modulate healthy inflammatory processes and to help restore normal cell function and cellular homeostasis. They are able to calm oxidative stress and inflammatory pathways including the NF-kB, LOX and COX pathways.[36]

Traditionally, researchers and clinicians have focused on targeting specific pathways, such as the well-known COX-2, in order to address inflammatory conditions. Currently, scientists are exploring targeting multiple pathways. Botanicals are of great interest due to their natural multi-target ability. For example, herbs such as Turmeric are found to exert far-reaching influence on multiple pathways. Curcumin can influence and modulate cytokines, enzymes, transcriptional factors, receptors and multiple other factors.[37]



This diagram, while it focuses on curcumin, illustrates the fact that plant polyphenolic compounds work through multiple pathways to modulate cellular health and function.

Anand P, Sundaram C, et al. *Curcumin and cancer: An "old-age" disease with an "age-old" solution.* Cancer Letters 267 (2008) 133–164.

Botanical medicines contain a wide array of natural compounds beneficial to mediate chronic inflammation and epigenetics to support the return of dysregulated biochemical pathways to homeostasis and health. Many botanicals are found to successfully calm NF-kB and to modulate cytokine expression.[2,10,12,24]

Polyphenols: Powerful Phytochemicals

Botanical polyphenols are found to alleviate inflammatory processes and to protect against age-related degeneration. Many polyphenols inhibit NF-kB activation and are potent antioxidants.[2,31] Polyphenols are a vast family of naturally-occurring phytochemicals produced by plants as part of their defense system. Almost half of the 10,000 known polyphenolic compounds are flavonoids. Flavonoids are classified into six major subgroups: flavones, flavonols, isoflavones, flavones, anthocyanidins and flavanols (catechins and proanthocyanadins).[38]

Polyphenols are abundant in vegetables, fruits, whole grains, herbs and spices. Epidemiological studies demonstrate an inverse relationship between a polyphenolic-rich diet and risk of chronic human diseases including cardiovascular, diabetes, osteoporosis, chronic inflammation, cancer and neurodegenerative conditions.[3,9,39] Plant phenolic compounds are widely studied for their role in preventing both occurrence and progression of tumor growth and are found to inhibit mutagenesis and carcinogenesis in humans.[40,41] They are also found to be cardio-protective, neuro-protective and cyto-protective.

Plant polyphenols protect cellular health through many actions such as scavenging free radicals, antioxidant and anti-inflammatory activity. They exert a powerful influence to normalize cell-signaling and to support healthy cellular function[40,41] including apoptosis (normal cell death), cellular metabolism and maintenance of healthy cellular structure.[39] Plant polyphenols modulate cell-signaling pathways and demonstrate the ability to modulate enzyme response to help decrease oxidative stress.[9,10,12,31,39,40]

Turmeric (*Curcuma longa*) and Wild Turmeric (*Curcuma aromatica*)

Turmeric rhizome, one of the most profoundly researched herbs, is found to work through multiple pathways. For centuries it has been world-renowned as a cooking spice, food, herbal medicine and dye. Traditional medicines prize these herbs for multiple benefits and they are noted for their anti-inflammatory influence, which is validated by modern research.[42]

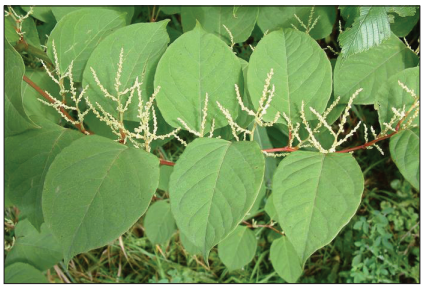
Turmeric's active constituents, curcuminoids, are yellowish-orange, lipid-soluble natural phenolic compounds. They demonstrate many protective health benefits, offering powerful anti-inflammatory, antioxidant, antineoplastic, antiviral and immune-modulating activity.[10] Curcumin works to calm inflammatory pathways including NF-kB, TNF and IL factors[43,44] and inhibits COX-2 and 5-LOX.[45-52] Curcumin shows hepato-protective, cyto-protective, neuro-protective and antioxidant properties.[44,49,50,53-56]

Turmeric *(Curcuma longa)*

Green Tea (*Camellia sinensis*)

With a 5,000-year history as valued beverage and medicine, tea prepared from *Camellia sinensis* is one of the most widely consumed beverages in the world. Polyphenols comprise 30% to 40% of green tea leaves. These are flavonols and flavanols (catechins) – including epigallocatechin-3-gallate (EGCG), which impart significant antioxidant and anti-inflammatory activity.[57-60] Tea polyphenols benefit cell cycle regulation and are found to be cell-protective.[61-63] EGCG, the main catechin in green tea extract, inhibits VEGF (vascular endothelial growth factor)[64,65] implicated in abnormal cell behavior, cell signaling and angiogenesis.[65-68]

Japanese Knotweed (*Polygonum cuspidatum*)
Polygonum has been used widely for centuries in Chinese medicine to prevent and treat disease. In modern research it is found to exert antimicrobial, anti-inflammatory, neuro-protective and cardio-protective functions. Knotweed contains quercetin, catechin and resveratrol, which all demonstrate powerful antioxidant and anti-inflammatory properties. Knotweed extract is found to inhibit inflammatory pathways including TNF-a, NF-kB and COX-2 expression.[69,70]


Knotweed *(Polygonum cuspidatum)*

Resveratrol
An active constituent of Knotweed, resveratrol, is extensively researched for its profound benefits. Numerous studies report its role in preventing age-related disorders including diabetes, cancer, cardiovascular and neuro-dengenerative conditions.[43,71] Research reports that resveratrol binds to numerous cell-signaling molecules, activates transcription factors, induces antioxidant enzymes, modulates cell-cycle regulation and inhibits expression of inflammatory processes.[72,73] Due to its inherent properties as a polyphenolic compound, resveratrol is neuro-protective and can help inhibit progression of age-related neurological decline and disease. A potent antioxidant, resveratrol works through multiple cellular pathways to support normal function.[74] Studies show that resveratrol indirectly inhibits NF-kB signaling.[2]

Amla (*Emblica officinalis*)
Amla fruit, also known as Indian Gooseberry, is a valued Ayurvedic restorative and rejuvenative tonic. Used for thousands of years as food and medicine, it supplies a rich source of vitamin C, flavonoids and carotenoids.[75] Amla fruit is traditionally given to relieve circulatory, digestive and respiratory conditions. Studies find it possesses potent antioxidant and anti-inflammatory activity.[76-79] Amla has an ORAC (oxygen radical absorbance capacity) value of 1770 – twice that of Acai berry and about 17 times that of pomegranate fruit.[79] Amla fruit contains gallic acid, ellagic acid and sesquiterpenoids, which are known to be free-radical scavenging, antioxidant, anti-inflammatory, antimutagenic and immunomodulatory.[80-82]

Fatty Acids: Dietary Foundation

Fatty acid intake (quality and quantity) is well-known to exert major influence on function and modulation of healthy inflammatory, immune and hormonal processes. Fatty acids can drive either pro- or anti-inflammatory processes and influence the AA cascade. EPA (eicosapentaenoic acid) and DHA (docosahexaenoic acid) – metabolites of omega-3 fatty acids – compete with the omega-6 arachidonic acid for conversion by COX enzymes into prostaglandins (PGs). Omega-3 oil metabolism results in higher production of anti-inflammatory PGs, while that of omega-6 results in formation of pro-inflammatory PGs.

An optimal dietary ratio of around 2:1 of omega-6 to -3 fatty acids is found to help suppress inflammation and provide a wide array of health benefits.[83] In the Western world, the dietary ratio is often about 15:1 – reflecting over-consumption of omega-6 oils along with pronounced deficiency of omega-3 oils.[83] This is widely recognized as a major contributory factor to diseases including cardiovascular, cellular dysfunction, autoimmune and inflammatory conditions.[83-85] Historically, fish constitutes the major dietary source of omega-3 oils. Important plant sources include flax, chia and hemp seeds and walnuts. Supplementing a healthy diet with fish and plant oils further enhances a balanced intake of the much-needed omega-3 oils.

Fish Oils
Fish oils from small fish, including krill, anchovy and sardines, provide essential fatty acids including EPA and DHA. Omega-3 fish oils inhibit COX-2 expression along with the oxidative metabolism of AA to the inflammatory PGs.[86,87] Omega-3 fatty acids can benefit serum lipid levels and help reduce C-reactive protein levels.[88] EPA is found to improve the prognosis of chronic inflammatory diseases including atherosclerosis.[89-91]

Studies find that EPA and DHA benefit bone mineral density in those with rheumatoid arthritis.[91] Fish oils benefit those with joint diseases such as arthritis[92,93] and can help reduce neck and back pain, likely through their influence in calming the inflammatory process.[94]

Sea Buckthorn Oil (*Hippophae rhamnoides*)
Sea Buckthorn oil (SBO)contains a unique fatty acid profile, offering a nutritious blend of omega-3, -6, -7 and -9 unsaturated fatty acids. It is one of only a few plants that is especially rich in the omega-7 fatty acid palmitoleic acid. The omega-7 group of fatty acids is of interest to researchers for its ability to calm inflammation and support multiple physiological functions. The potent antioxidant activity attributed to Sea Buckthorn derives partially from its highly concentrated content of flavonoids, vitamin C, tocopherols, tocotrienols and a rich array of carotenoids.[95-97]


Sea Buckthorn *(Hippophae rhamnoides)*

SBO enhances healthy glutathione levels at the cellular level along helps reduce production of reactive oxygen species.[98] In many studies, SBO was found to significantly influence the glutathione redox system, increasing available and circulating levels of glutathione.[99-100]

Herbs and Natural Compounds to Calm Inflammation and Pain

Natural foods, spices and herbs high in polyphenols provide the foundation of a healthy lifestyle and diet. A formulation of polyphenolic-rich botanicals provides a potent multi-targeted approach to calm inflammation and enhance restorative physiological functions. The addition of adaptogenic formulas enhances restoration of healthy allostasis and benefits any therapeutic approach. Focused botanical formulas chosen for their specific anti-inflammatory influence contributes a multi-faceted and synergistic approach to address chronic inflammation.

Pain, often a significant component of the chronic inflammatory process, is usually associated with injury or disease. Chronic pain affects around 100 million Americans – a greater number than those affected by diabetes, heart disease and cancer combined.[101] The most common chronic pain conditions include migraines and severe headaches, back pain, neck pain, facial pain, cancer pain, joint pain and neurogenic pain.[102]

Chronic pain involves non-resolving inflammation and continual firing of pain signals in the nervous system. Typically, the sensation of pain is transmitted by afferent neurons from the periphery of the body to the spinal cord and from there to the brain, eliciting various responses, including production of natural endorphins. Feedback loops modulate and modify this process. Inflammatory processes and

neurotransmitters are implicated in the complex pain response. Recent studies report that spinal glial-mediated neuro-inflammation is a key factor in the development of chronic pain. This involves production of chemokines via NF-kB which plays a major role in the inflammatory response.[18,19,103]

In current pain research, botanicals are being widely studied in the search for compounds that naturally exert a multi-targeted approach. Scientists often discover the advantage of using whole herbs, as each herb contains a complex array of biochemical compounds that naturally form a synergistic and multi-targeted effect. These herbs work on pathways other than the opioid receptors, for example through modulating dopamine and cannabinoid receptors[104,105] or by mediating neuroglial inflammation, particularly in the spine.[18,19]

This section discusses potent traditional herbs that are highly researched and recognized for their ability to work through multiple pathways to exert potent anti-inflammatory influence and help to alleviate pain.

Frankincense (*Boswellia serrata*)
Frankincense contains gum-like resinous constituents known as boswellic acids, which exhibit powerful anti-inflammatory, analgesic and health-promoting activity. Boswellic acids are the key compounds in Frankincense that are most studied, including one known as AKBA (acetyl-11-keto-beta-boswellic acid).

Boswellia extract is found to benefit those with inflammatory bowel conditions.[106] Boswellic acid extracts are found to down-regulate multiple inflammatory pathways including 5-LOX, COX-2 and NF-kB. LOX acts as a biological fuel for cellular dysfunction by stimulating EGF (epidermal growth factor), VEGF (vascular endothelial growth factor) and other growth factors.[36,107,108] These extracts are also found to induce apoptosis, modulate cell-signaling[36,109,110] and to exert immunomodulatory influence.[111-113]

Feverfew (*Tanacetum parthenium*)
This member of the Aster family is traditionally used to prevent migraine headaches.[114] Ancient Greeks and Europeans used it to reduce fever and to calm inflammation in disorders including psoriasis, rheumatism and colic. Feverfew is high in flavonoids and sesquiterpene lactones; both of which are known for their anti-inflammatory qualities. Parthenolide, one of the sesquiterpene lactones in Feverfew, is of great interest to researchers as it is found to interfere with the inflammatory actions of AA, histamine and NF-kB.[115,116] Parthenolide inhibits the 5-LOX and COX pathways and helps prevent conversion of AA to prostaglandins.[117] It inhibits pro-inflammatory, cytokine-mediated cell-signaling and inhibits PG synthesis through various pathways. It is thought to benefit migraines through multiple pathways including through inhibition of PG synthesis and by decreasing spasm of vascular smooth muscles.[118]


Feverfew *(Tanacetum parthenium)*

Magnolia (*Magnolia officinalis*)
Magnolia bark, widely used in Chinese medicine, is rich in biologically-active compounds including alkaloids, coumarins, flavonoids, lignans and terpenoids.[119] Its main active constituent is considered to be the polyphenol honokiol, which exhibits potent antioxidative and anti-inflammatory

activity. Research finds that Magnolia bark extract strongly inhibits COX-2 pathways, formation of prostaglandins, TNF, NF-kB and IL (interleukin) factors.[120-123] Honokiol is being studied for its neuro-protective influence as it is found to calm oxidative and inflammatory processes in neurons and microglial cells.[119]

Andrographis (*Andrographis paniculata*)

Andrographis *(Andrographis paniculata)*

Both Chinese and Ayurvedic medicines highly regard this herb for its ability to alleviate inflammatory and infectious diseases. Andrographis is high in flavonoids and diterpenoids. This herb acts as antipyretic and anti-inflammatory and is able to modulate both the humoral and cellular adaptive immune response. Andrographis is found to inhibit NO (nitric oxide) and PG production[124-128] along with expression of COX-2.[126,129] Andrographis extract is noted for its ability to reduce lipid peroxidation and inhibit formation of reactive oxygen species. It also enhances the antioxidant enzyme SOD (superoxide dismutase).[128,130]

Ginger (*Zingiber officinalis*)

Ginger is known and used worldwide as cooking spice, herbal home remedy and revered botanical medicine. It is a daily household remedy for digestive upset, sore throat, colds and flu. Ginger aids circulation and has a thermogenic and diaphoretic effect. It shows significant antioxidant[131-133] and anti-inflammatory activity. Ginger is found to inhibit COX-2 expression and NF-kB activation.[134-135] Ginger also influences PG metabolism, inhibits thromboxane synthesis and is found to significantly inhibit platelet aggregation and inflammation.[136-138]

Long Pepper (*Piper longum*) and Piperine from Black Pepper (*Piper nigrum*)

Long Pepper is one of the world's oldest culinary and medicinal spices. It was much more widely known, used and traded than Black Pepper until around the 14th century. Studies report that Long Pepper is antioxidant, anti-inflammatory and immunomodulatory.[40,139-143]

Black Pepper berries naturally contain the alkaloid piperine, a powerful and highly-researched compound. Piperine is known to be antioxidative, antimutagenic, antibacterial and hepato-protective.[144,145] Studies find piperine helps reduce levels of pro-inflammatory mediators including COX-2, IL factors and TNF-alpha. It also supports healthy glutathione and SOD levels.[146,147] It is found to inhibit VEGF and to modulate cytokine and growth factor responses.[143]

Corydalis Root (*Corydalis spp.*)

Corydalis is the premier herb in traditional Chinese medicine for pain of all kinds especially when combined with appropriate herbs. Modern studies report that Corydalis demonstrates potent analgesic and anti-inflammatory activity. Two alkaloids isolated from Corydalis, THP (tetrahydropalmatine) and DHCB (dehydrocorybulbine), demonstrate significant analgesic and sedative effects on the central nervous system.[102,148-150] In one study, 75mg THP showed nerve pain reduction in 78% of patients tested.[150]

THP and DHCB are found to exert a mild agonist effect on the m opioid receptor. The affinity of DHCB to dopamine receptors is found to be greater than 100 times its affinity for the m opioid receptor.[102] THP and DHCB, structurally similar, bind to dopamine receptors where they are potent

antagonists. Many studies show dopamine plays a role in modulating pain circuits in the brain. Studies with mice engineered to be deficient in dopamine were found to be more sensitive to pain suggesting that dopamine is involved with pain threshold.[104]

The alkaloid DHCB exerts analgesic effects independent of the opioid receptors and is found effective in both inflammatory and neuropathic pain models with repeated use. The Herbalome project is currently working on a DHCB-based drug for pain.[102,151] Researchers also find Corydalis root used as a whole herb extract is highly efficacious.[152] The analgesic effect of Corydalis involves participation of the cannabinoid receptors.[153]

White Willow Bark (*Salix alba*)

White Willow Bark *(Salix alba)*

White Willow bark, used for thousands of years by many cultures, is known to alleviate pain, calm inflammation and reduce fever. Hippocrates (400 BC) was said to advise his patients to chew on the bark to reduce fever and inflammation. In modern times, German chemist Felix Hoffman first isolated the compound salicin from the bark. This was later modified to the chemical acetylsalicylic acid, or aspirin. Salicin, a potent anti-inflammatory agent, inhibits over-expression of COX-2 and NF-kB factors which are implicated in inflammation and abnormal gene expression.[154,155] The advantage of White Willow bark extract is that it does not irritate the stomach lining. This is because the salicin naturally found in White Willow bark is only converted to the acid form after absorption by the stomach.

Native Americans used White Willow bark to calm joint pain. Modern studies confirm its effectiveness and safety as an analgesic giving relief in arthritic joint pain, low back pain, headaches and low back pain.[156-160]

Notoginseng (*Panax notoginseng*)

Chinese medicine highly reveres Notoginseng as the primary herb for all traumatic injuries including falls, fractures, contusions and pains. It is used both internally and externally as a hemostatic after traumatic injuries. Modern research find that Notoginseng is rich in saponins and immune-enhancing polysaccharides.[161] It is found to have the ability to address hypoxia and anoxia.[162] As a potent anti-inflammatory, Notoginseng modulates various inflammatory pathways and exerts pain-relieving effect in animal studies.[163-166]

White Peony Root (*Paeonia lactiflora*)

In Chinese medicine, Peony is a major tonic herb. Peony is found to contain flavonoids, proanthocyanidins, tannins, terpenoids, complex polysaccharides and glycosides, of which paeoniflorin is the most studied. Paeoniflorin, monoterponoids and other constituents of White Peony are known to be spasmolytic.[167-169] The compound paeoniflorin (PF) is found to calm pain and joint swelling and to lessen the decline of bone and cartilage in experimental arthritis. It suppresses multiple inflammatory processes including prostaglandin and leukotriene production, and production of reactive oxygen species, proinflammatory cytokines and chemokines. It inhibits formation of new blood vessels and production of matrix metalloproteinases. It is found beneficial to relieve both signs and symptoms of rheumatoid arthritis.[170]

PF is a monoterpene glycoside that is also neuro-protective. It is found to calm the microglial inflammatory response, to reduce production of pro-inflammatory factors from activated microglial cells and to calm inflammation-induced neurotoxicity.[171,172] Another constituent of White Peony, albiflorin, is found to exert anti-inflammatory benefits similar to paeoniflorin.[173]

Dong Quai Root (*Angelica sinensis*)
One of the most esteemed herbs in the Chinese materia medica, Dong Quai is especially revered as a nourishing tonic. Studies find that the analgesic and anti-inflammatory effects of Dong Quai are similar to those of acetylsalicylic acid. A preparation of Dong Quai showed 82.9% effective rate in 35 patients with migraine headache.[174]

High in coumarins and flavonoids, Dong Quai also contains volatile oils, vitamin A, carotenoids, vitamins B12, E and phytosterols (including beta-sitosterol) along with minerals. The root does not exert estrogenic activity.[175] Dong Quai is known for hematopoietic, antioxidant, immune regulatory properties and is neuro-protective.[176] A major component of Dong Quai, known as ligustilide (LIG), is shown to have neuro-protective and anti-inflammatory effects. Studies show that spinal astrocyte-mediated neuro-inflammation plays an important role in the pathogenesis of chronic pain. The spinal cord mediates the pain response and it is found that calming chemokine production in the spinal nerves helps decrease overall pain.[18,19,177] LIG exerts an anti-inflammatory influence, inhibiting NF-kB-mediated chemokine production in spinal astrocytes, and demonstrates effectiveness for inflammatory pain.[178]

Conclusion: Botanicals and Natural Compounds Modulate Inflammatory Response

Foods, spices and botanical medicines have been used safely and effectively for thousands of years to enhance health, calm inflammation and promote the healing response. Many botanicals are able to calm the inflammatory response through their dynamic interaction with the epigenetic and immune systems. Found to work through multiple pathways, they influence diverse cellular pathways to restore allostasis.

The epigenetic, immune and inflammatory responses are but a few aspects of this ongoing process of allostasis. Because of its inherent plasticity and far-reaching regulatory effects, epigenetic modulation is currently considered a highly-effective therapeutic target. It is theorized that botanicals offer a diverse complexity of molecular compounds that interface harmoniously with human physiology and molecular dynamics. There are no single or linear responses in human physiology; rather a continual, dynamic of cellular interactions, cascades and signaling. Botanical medicines demonstrate the ability to exert a modulatory effect and help promote resolution of chronic inflammation and restoration of allostasis.

Offering a broad spectrum of natural compounds with natural affinity for human physiology, botanical medicines are well-tolerated. Combination therapies are found to be beneficial either through adjunctive or synergistic enhancement. As researchers investigate the numerous compounds found in botanicals, they often discover that use of the actual plant material, and a combination of botanicals, offers comprehensive and synergistic therapeutic benefit.[2,9,10,12,24,31,37,39,40,152]

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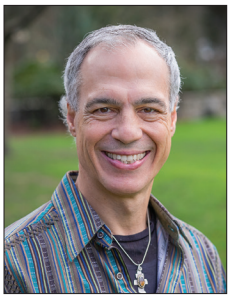

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