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Age-Associated Chronic Diseases Require Age-Old Medicine: Role of Chronic Inflammation

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Abstract

Most chronic diseases - such as cancer, cardiovascular disease (CVD), Alzheimer disease, Parkinson disease, arthritis, diabetes and obesity - are becoming leading causes of disability and death all over the world. Some of the most common causes of these age-associated chronic diseases are lack of physical activity, poor nutrition, tobacco use, and excessive alcohol consumption. All the risk factors linked to these chronic diseases have been shown to up-regulate inflammation. Therefore, downregulation of inflammation-associated risk factors could prevent or delay these age-associated diseases. Although modern science has developed several drugs for treating chronic diseases, most of these drugs are enormously expensive and are associated with serious side effects and morbidity. In this review, we present evidence on how chronic inflammation leads to age-associated chronic disease. Furthermore, we discuss diet and lifestyle as solutions for age-associated chronic disease.

Keywords

chronic disease; aging; inflammation; diet; life style

1. Introduction

Aging is an inevitable truth for every living organism, yet it represents a mystery in the evolution of higher organisms. Aging leads to accumulated knowledge, wisdom and experience, but it also leads to declining health and mortality. How aging proceeds is not well understood. It has been postulated that in the process of aging multiple cellular and molecular events malfunction, ultimately leading to various chronic ailments and diseases, including Alzheimer disease, Parkinson disease, other neurodegenerative disorders, rheumatoid arthritis, atherosclerosis and other cardiovascular disease (CVD), macular degeneration, and diabetes.

Chronic disease often referred to as noncommunicable diseases. These diseases usually emerge in middle age after long exposure to an unhealthy lifestyle involving tobacco use, alcohol use, stress, lack of regular physical activity, and consumption of a high-fat diet or red meat. It has been well established that the incidence of chronic disease rises sharply with age and that the majority of patients with a chronic ailment are over the age of 65 years. In

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the United States, about 80% of these older adults have one chronic condition, and about 50% have at least two.

Aging is a diverse and complex process and many theories have been advanced to explain the molecular regulation of aging and chronic diseases, but much remains unclear. Therefore, analysis of the molecular mechanisms of aging and its associated chronic diseases represents a fundamental keystone in improving longevity. In particular, researchers have been exploring the complex relationship between inflammation and aging and its associated chronic diseases. Chronic inflammation results in the generation of free radicals that activate the process of damage and deterioration in target cells and organs, which further leads to chronic disease. Mechanistically, these free radicals are known to induce the activation of signaling molecules and transcription factors associated with several chronic diseases (Lavrovsky et al., 2000; Rahman, 2003; Shi et al., 2006). Thus, evidence indicates that chronic inflammation with advancing age can precede several chronic diseases.

According to the American College of Preventative Medicine and several other organizations, most chronic diseases can be prevented by changing lifestyle (such as dietary habits, smoking, alcohol consumption, and exercise). A recent study in more than 23,000 adults found that a healthy lifestyle lowered the risk of developing chronic diseases such as CVD, type 2 diabetes, cancer, and stroke by 78% (Ford et al., 2009). Modern science has developed several drugs for treating chronic diseases, but these drugs are usually enormously expensive and are associated with serious side effects and morbidity. Thus, constructive efforts and strategies are needed to prevent, ameliorate, or treat these diseases with minimal adverse effects. Plant products and plant-derived nutraceuticals are known to be the best agents for reducing the risk of chronic diseases or treating them effectively. Plant products have traditionally been used against several chronic ailments, but in modern Western medicine only a limited number of plant products are being used to treat diseases.

2. Inflammatory Pathways

Inflammation, regarded as a response of a tissue to injury, pathogen invasion, or irritants, is characterized by increased blood flow to the tissue causing increased temperature, redness, swelling, and pain. Short-term or acute inflammation is a protective attempt by the organism to remove injurious stimuli and to initiate the healing process. Long-term or chronic inflammation, however, leads to several inflammatory disorders and chronic diseases.

The process of inflammation is complex and is usually tightly regulated: one mediator initiates and maintains inflammation, and another shuts down the process. In states of chronic inflammation, an imbalance between the two mediators occurs, resulting in cellular damage. A number of mediators are known to activate inflammatory pathways, if it persists leads to chronic diseases. Here we discuss some of the important inflammatory pathways (Figure 1) involved in aging and chronic disease.

2.1. Nuclear factor κB (NF-κB) pathway

Among the approximately 2000 transcription factors, NF-κB is one of the major transcription factors in humans. It was discovered only 25 years ago by Sen and Baltimore (Sen and Baltimore, 1986). NF-κB is constitutively active in most cancers, and many of the signaling pathways that are involved in cancer are likely to be networked through the activation of this protein complex (Grivennikov et al.; Karin, 2009; Prasad et al., 2010). NF-κB is activated by cigarette smoke, bacteria, viruses, stress, and other factors. In unstimulated cells, NF-κB remains in an inactive p50–p65 (RelA)–IκBα trimer form in the cytoplasm. NF-κB is activated by one of two pathways, classical (or canonical) and

nonclassical (or noncanonical). IκBα kinase (IKK) is the regulatory kinase that is involved in both pathways during NF-κB activation. A complex of three proteins, IKK consists of two catalytic proteins (IKKα and IKKβ) and one regulatory protein (IKKγ, also known as the NF-κB essential modulator (NEMO)). In the classical pathway NF-κB responds to stimulation factors, such as IκBα, which is phosphorylated at Ser 32 and Ser 36 by IKK. During this process the NF-κB dimer (p50–p65) is also phosphorylated by IKK and then is translocated to the nucleus, where it binds to its cognate response elements in promoters, leading to activation of the transcription of responsive genes (Vallabhapurapu and Karin, 2009). In the nonclassical pathway, the processing of the p100–RelB complex to the p52–RelB dimer is activated in response to specific extracellular signals (Senftleben et al., 2001).

2.2. Signal transducer and activator of transcription 3 (STAT3) pathway

STAT3 is also one of the most recognized signal molecules. It is one of the central regulators of inflammation, which helps in tumor growth and metastasis. STAT3 activation can be inductive as well as constitutive. This transcription factor is activated by various cytokines, growth factors, and oncogenic molecules (Groner et al., 2008), but constitutive activation of STAT3 is often found at the invasive front of tumors adjacent to infiltrated immune cells. There are number of mechanisms by which STAT3 is activated, but mainly it is activated by autocrine and paracrine production of interleukin (IL)-6 from a tumor-inflammatory environment that leads to STAT3 phosphorylation. STAT3 is also kept in an inactive form in the cytoplasm of nonstimulated cells (Spiotto and Chung, 2000). However, like other members of its family, its activation does not require inducible degradation of an inhibitor but instead is mediated by phosphorylation of a critical tyrosine residue (Tyr 705) that initiates STAT3 dimerization through phosphotyrosine–SH2 domain interaction (Yoshimura et al., 2006). The dimerized transcription factors enter the nucleus and activate a broad range of genes. However, unphosphorylated STAT3 is also capable of dimerization and induction of transcription (Braunstein et al., 2003; Yang et al., 2007). Activation of STAT depends mainly on the JAK family of tyrosine kinases; in the case of STAT3 the major activator is JAK1 (Zhang et al., 2000). STAT3 transcriptional activity and DNA binding are further enhanced through Ser 727 phosphorylation (Wen et al., 1995).

2.3. Activator protein 1 (AP-1) pathway

The AP-1 complex is composed of Jun-Jun homodimers (Abate and Curran, 1990; Curran and Franza, 1988; Hartl and Vogt, 1992) or heterodimers of members of the Jun (c-Jun, JunB and JunD) and Fos (c-Fos, FosB, Fra-1 and Fra-2) families. AP-1 activity is induced by growth factors, cytokines, and oncoproteins. The activation of AP-1 is mediated by at least two regulatory events (Brenner et al., 1989; Westwick et al., 1994). First, some AP-1 proteins (such as c-Jun) are encoded by immediate early genes that are transcriptionally induced. Second, AP-1 activity can be regulated by posttranslational modification, including phosphorylation by mitogen-activated protein kinases (MAPKs), which comprises the extracellular signal-regulated kinase, p38 MAPK, and c-Jun NH2-terminal kinase. The exact mechanism of a specific condition or treatment on AP-1 activation and the relative role of different MAPKs in these processes are diverse. Upon activation, AP-1 binds to the 12-*O*-tetradecanoylphorbol-13-acetate response element and induces transcription of a variety of genes involved in multiple cellular functions, such as proliferation, survival, differentiation, and transformation.

2.4. Wnt/β-catenin pathway

Wnt ligands are secreted glycoproteins that activate β-catenin–dependent (or canonical) and β-catenin-independent (or noncanonical) signaling pathways. It interacts and binds to the transmembrane receptor Frizzled. Activation of Frizzled homologs by Wnt ligands leads to activation of the modular protein Dishevelled, which in turn reduces the phosphorylation

and degradation of β-catenin, generally leading to the latter's accumulation in the nucleus. The accumulation of β-catenin by Wnt signaling leads to binding of β-catenin to TCF/LEF, promoting changes in the transcriptional machinery that leads to activation of target genes (Akiyama, 2000). In the β-catenin–independent pathway, β-catenin - an integral cell-cell adhesion adaptor protein as well as a transcriptional co-regulator - is targeted for degradation by the APC/Axin/GSK-3 β-complex, becoming phosphorylated by coordinated action of CK1 and GSK-3β, which leads to the ubiquitination and proteasomal degradation of the β-catenin through the β-TrCP/SKP complex. Noncanonical Wnts cause intracellular calcium flux, leading to the activation of $^{Ca2+-}$dependent effector molecules such as calcium/calmodulin-dependent kinase II, nuclear factor associated with T cells (NFAT), and protein kinase C in a pertussis toxin-sensitive manner (Kuhl et al., 2000). Because NFAT is associated with the regulation of various genes, including cytokines, cell cycle, differentiation, and apoptosis, the noncanonical pathway can modulate cell behavior via gene transcription.

2.5. Hypoxia inducible factor 1 (HIF-1) pathway

HIFs are transcription factors that function in response to the available oxygen in the cellular environment — specifically, in low-oxygen conditions (hypoxia). On activation, this complex affects the transcription of numerous hypoxia-inducible genes. In normoxic conditions, the α subunits of HIF are hydroxylated by HIF prolyl-hydroxylases and then ubiquitinated by the VHL E3 ubiquitin ligase (Maxwell et al., 1999). However, in hypoxic conditions HIF prolyl-hydroxylase is inhibited because it utilizes oxygen as a cosubstrate (Semenza, 2004). In stabilized hypoxic conditions, HIF-1 upregulates several genes such as glycolysis enzyme, vascular endothelial growth factor, plasminogen activator inhibitor 1, angiopoietins 1 and 2, platelet-derived growth factor B, the TIE-2 receptor, and matrix metalloproteinases. It has also been shown that NF-κB modulates HIF-1 expression in the presence of normal oxygen pressure. HIF-1 is a potent inducer of metastatic genes (including chemokine receptor 4, its ligands [SDF-1], and lysyl oxidase) in a broad range of tumor cells (Arya et al., 2007) as well as of E-cadherin, a key factor governing metastatic potential in the majority of epithelial cancers (Hanahan and Weinberg, 2000).

2.6. Nuclear factor erythroid 2-related factor (NRF2) pathway

NRF2 is a transcription factor that binds to a DNA regulatory element called the antioxidant response element and activates the enzymes involved in the phase II detoxification of xenobiotics (glutathione transferases, quinone reductase, epoxide hydrolase, heme oxygenase 1, UDP-glucuronosyl transferases, γ-glutamylcysteine synthetase, and other enzymes). NRF2 is normally kept in the cytoplasm by its negative regulator Keap1 (Dinkova-Kostova et al., 2002). Once NRF2 is dissociated from Keap1, cytosolic NRF2 is phosphorylated and translocates into the nucleus in response to protein kinase C activation and MAPK pathways (Itoh et al., 1999). After translocation into the nucleus, NRF2 interacts with bZIP family transcription factors such as CREB, ATF4, and fos or jun and activates the genes through the antioxidant response element. NRF2 plays a major role as a central regulator of the adaptive response to oxidative stress. NRF2-induced activation of genes is inhibited by small Maf proteins, including MafG and MafK, to maintain the oxidation level of the intracellular environment.

2.7. Peroxisome proliferator-activated receptor γ (PPARγ) pathway

PPARs are nuclear receptor proteins, which function as transcription factors that regulate the expression of genes (Michalik et al., 2006). PPARs play essential roles in the regulation of cellular differentiation, development, metabolism, and tumorigenesis in higher organisms (Belfiore et al., 2009). There are three forms of PPAR:α, β/δ, and γ (Ricote and Glass, 2007). PPARγ (also known as the glitazone receptor) is involved in controlling the

expression of different genes, including the gene that stimulates lipid uptake and adipogenesis by fat cells. Normally it is present in adipocytes, skeletal muscle cells, osteoclasts, osteoblasts, and several immune-type cells, PPARγ regulates fatty acid storage and glucose metabolism. Because saturated fatty acids have been shown to induce the expression of inflammatory gene products in several cell types (Shi et al., 2006), PPAR agonists on circulating levels of these fatty acids may inhibit inflammation indirectly. In addition, PPARs act directly to negatively regulate the expression of proinflammatory gene products in a ligand-dependent manner by antagonizing the activities of other proinflammatory transcription factors, such as NF-κB and AP-1 (Jiang et al., 1998; Marx et al., 1998; Ricote et al., 1998).

3. Inflammation and Chronic Diseases

The Roman physician Cornelius Celsus was the first to characterize inflammation, and in the 19th century the German physician Rudolf Virchow suggested a link between inflammation and chronic disease. The major chronic diseases associated with inflammation and aging are cancer, CVD, diabetes, pulmonary disease, and neurological disease (Figure 2).

It is evident from extensive observations and experiments within the last few decades that most chronic diseases are preceded by a chronic low level of inflammation. Molecular studies on the causes of inflammation have shown that numerous biomarkers are involved in the process of inflammation. Among these biomarkers, transcription factors (such as NF-κB and STAT3), inflammatory cytokines and chemokines (tumor necrosis factor α (TNF-α), IL-1, IL-6, IL-8, and monocyte chemotactic protein 1), proinflammatory enzymes (such as COX-2, 5-LOX, 12-LOX, and matrix metalloproteinases), prostate-specific antigen [PSA], C-reactive protein [CRP], adhesion molecules, vascular endothelial growth factor [VEGF], TWIST, and other factors are common in most chronic diseases (Aggarwal, 2004). Aging results in an increase of inflammatory cytokines that contribute to the progression of many degenerative diseases (McGeer and McGeer, 2004; van't Veer et al., 2000).

As people grow and age, inflammation starts due to several environmental and physiological factors. Chronic inflammation damages cells of the brain, heart, arterial walls, and other body structures, leading to various inflammatory diseases such as heart disease, Alzheimer disease, Parkinson, disease rheumatoid arthritis, psoriasis, and prostatitis. As a person ages the levels of the inflammatory markers are often sharply elevated, indicating the presence of an underlying inflammatory chronic disorder (Bremmer et al., 2008; de Gonzalo-Calvo et al.; Kriete and Mayo, 2009). Chronic inflammation has also been linked to the biological aging process (Ferrucci et al., 2004). For instance, genetic blockade of NF-κB in the skin of chronologically aged mice reversed the global gene expression program and tissue characteristics to those of young mice, demonstrating that the disruption of a single gene is sufficient to reverse features of aging, at least in the short term (Adler et al., 2008). Sarcopenia, or muscle loss with aging, is driven by a smoldering inflammatory state induced by elevated IL-6 and CRP levels (Jensen, 2008).

Cancer is one of the major diseases caused by chronic inflammation. Various proinflammatory biomarkers have been found to be elevated in several cancer types. STAT3 was found to be activated in 82% of patients with late-stage prostate cancer, and a higher level of STAT3 activation correlated with more severe disease and shorter patient survival times (Horinaga et al., 2005; Mora et al., 2002; Tam et al., 2007). Persistently activated STAT3 maintains constitutive NF-κB activity in tumors (Lee et al., 2009). In another study NF-κB was expressed in 60% of colorectal cancer patients (Scartozzi et al., 2007). That the overproduction of cytokines in cancer patients is associated with cancer-related fatigue is well documented. For instance, the overproduction of IL-6 in patients with multiple

myeloma is associated with more severe disease (Klein et al., 1990). Among patients with benign prostate hyperplasia, the levels of the cytokines IL-1α, IL-6 and TNF-α were elevated with increased prostate-specific antigen serum levels (Bouraoui et al. 2008). Similarly, breast cancer patients had elevated cytokines level (Schmidt et al., 2007). The elevation of cytokines makes the diseases more severe.

Inflammation also mediates CVDs (Berg and Scherer, 2005; Thomas and Advani, 2006). The known biomarkers for systemic inflammation in CVD are cholesterol and CRP (Ridker et al., 2005). CVD is also associated with aging: CVD affects 15% of adults in their late 30s and early 40s, 50% of persons 55–64 years old, and 65% of persons 65 years and older. CRP is also a common marker for CVD and atherosclerotic disease (Tomiyama et al., 2005).

Rheumatoid arthritis is an autoimmune disorder in which excess levels of cytokines such as CRP, TNF-α, IL-6, IL-1β, and IL-8 cause or contribute to this inflammatory syndrome (Deon et al., 2001). Of these markers, only high-sensitivity CRP is well standardized and widely available.

The levels of CRP and IL-6 have been shown to be significantly higher among persons who subsequently developed diabetes than among those who did not (Pradhan et al., 2001). Abnormal expression of NF-κB has also shown to be involved in the development of diabetic microvascular and neuropathic complications (Jeffcoate, 2005). Other inflammatory cytokines, such as IL-1 and TNF-α, were found to be increased in diabetes and their level also increases with aging, indicating an association between inflammation and aging (Jeffcoate, 2005; Mendoza-Nunez et al., 2011).

Multiple sclerosis is an age-related autoimmune disease that affects the brain and spinal cord. This disease is characterized by damage to the myelin sheath, the protective covering that surrounds nerve cells, causing the nerve impulses to slow down or not function at all. For most patients the neurologic deterioration progresses over time. It usually affects people beginning in their 20s or 30s and is one of the most common causes of nontraumatic disability among young and middle-aged people. This disease can be triggered by chronic inflammation of the central nervous system. In patients with multiple sclerosis, the levels of COX-2–derived prostaglandins are elevated in the cerebrospinal fluid (Palumbo et al., 2011), as is the level of activated NF-κB. The constitutively activated RelA subunit of NF-κB in the nuclei of resting microglia facilitates a rapid response to pathological stimuli in the central nervous system (Gveric et al., 1998). The levels of other cytokines, such as IL-1α, IL-2, IL-4, IL-6, IL-10, IFN-γ, TGF-β1 and 2, and TNF-α, have been found to elevated in the frozen sections of central nervous system tissue from multiple sclerosis patients (Woodroofe and Cuzner, 1993).

Crohn’s disease occurs due to chronic inflammation in the intestines (also called inflammatory bowel disease). This disease can begin at the ages of 15–30 years, and by the time a person reaches 60–80 years of age it becomes severe. Symptoms manifest not only in the intestine but also in other organs such as eyes and joints. Crohn's disease appears to involve primarily an overactive response of Th1 cells that leads to overproduction of various cytokines, such as IL-2, IL-12, IL-18, interferon-γ and TNF-α (Desreumaux et al., 1997; Rutgeerts and Geboes, 2001).

4. Dietary Agents, Inflammation, and Chronic Diseases

Chronic diseases are the leading causes of death and disability in the United States: about 70% of all deaths in the United States are caused by these conditions. However, most of these diseases are preventable by adopting lifestyle changes such as eating nutritious foods, being physically active, and avoiding tobacco. Because most chronic diseases have been

linked to diet, modifying a diet could prevent or delay them. Relatively low intake of fruit and vegetables is a risk factor for many of the most important chronic diseases (Block et al., 1992), whereas greater consumption of natural products - including, spices, nuts, whole-grain cereals, legumes, fruits and vegetables (Figure 3B) - is associated with a lower risk of many diseases (Ames and Wakimoto, 2002).

4.1. Fruits and vegetables

A growing body of research is showing that fruits and vegetables are critical to good health. Fruits and vegetables contain essential vitamins, minerals, fiber, and phytochemicals that protect from chronic disease. More than 25,000 phytochemicals have been identified that may have potential against various cancers. These phytochemicals are safe and usually target multiple cell signaling pathways (Aggarwal and Shishodia, 2006). Major chemopreventive compounds identified from fruits and vegetables include carotenoids, vitamins, resveratrol, quercetin, silymarin, sulphoraphane, and indole-3-carbinol (Figure 3A).

Fruits and vegetables in whole or their active components have been shown to act against several chronic diseases. For instance, in a study of 310 primary breast cancer cases with 353 control cases in Germany, intake of vegetables and whole-grain products was inversely associated with the risk of breast cancer (Adzersen et al., 2003). In another study, lycopene, which is present in fruits such as watermelon, apricots, pink guava, grapefruit, rose hip, and tomatoes, demonstrated anticancer activity in both in vitro and in vivo tumor models as well as in humans (Nishino et al., 2002).

Ursolic acid is found in several fruits, including rosemary, apple, beefsteak, pear, plum, bearberry, loquat, and jamun (Liu, 1995). It exhibits anticancer potential against breast cancer (Es-saady et al., 1996), colon cancer (Andersson et al., 2003), non-small cell lung cancer (Hsu et al., 2004), cervical cancer (Yim et al., 2006), multiple myeloma (Pathak et al., 2007), pancreatic cancer (Chadalapaka et al., 2008), melanoma (Harmand et al., 2005), and prostate cancer (Zhang et al., 2010). Ursolic acid targets a wide spectrum of signaling pathways, such as cell cycle progression, cell proliferation, and cell survival. It has also been shown to inhibit spontaneous or chemical-induced tumorigenesis in mammary glands, liver, lung, cervix, and gastrointestinal tract in different animal model studies (Aggarwal and Ichikawa, 2005). Other than these several other fruits and vegetable act as anticancer agents.

Fruits and vegetables also have shown to reduce mortality by CVD. Evidence indicates that persons who consume more fruits and vegetables often have a lower prevalence of important risk factors for CVD, including hypertension, obesity, and type 2 diabetic mellitus. In a study of 1299 elderly Massachusetts residents, the risk of death was lower among those who consumed large amounts of carotene-containing fruits and vegetables than among the residents who ate small amounts (Gaziano et al., 1995). Fruits and vegetables have been shown to suppress CVD biomarkers, including CRP, in in vitro models (Hermsdorff et al., 2010), animals (Rein et al., 2006), and humans (Franzini et al., 2010).

Greater intake of fruit and cruciferous vegetables may be inversely associated with the risk of rheumatoid arthritis. Rheumatoid arthritis appears to be less severe in southern Mediterranean countries, such as Italy and Greece, where fruit, vegetables, and olive oil are consumed in greater amounts than in many other countries (Pattison et al., 2004). Further, a recent experimental study demonstrated that fruits and vegetables suppress the production of the inflammatory agents involved in arthritis (Siddique and Saleem, 2011).

Fruit and vegetable intake has also been associated with the decrease of multiple sclerosis (Ghadirian et al., 1998), Crohn’s disease (Hou et al., 2011), diabetes (Esposito et al., 2010),

and other chronic diseases (Harikumar and Aggarwal, 2008). In addition, experimental studies have shown that fruits and vegetables also suppress the inflammatory risk factors involved in chronic diseases other than arthritis. Without a doubt, the consumption of fruits and vegetables reduces the age-associated progression of chronic diseases.

4.2. Spices

Spices are used all over the world to add flavor, taste, and nutritional value to food. It has been demonstrated that phytochemicals (Figure 3B) such as curcumin (which is found in turmeric), diallyldisulfide (garlic), thymoquinone (black cumin), capsaicin (red chili), gingerol (ginger), anethole (licorice), diosgenin (fenugreek), and eugenol (clove, cinnamon) possess therapeutic and preventive potential against several chronic diseases. Besides these phytochemicals, ellagic acid (clove), ferulic acid (fennel, mustard, sesame), apigenin (coriander, parsley), betulinic acid (rosemary), kaempferol (clove, fenugreek), sesamin (sesame), piperine (pepper), limonene (rosemary), and gambogic acid (kokum) have potential to act against chronic diseases.

Extensive research over the past several years has indicated that spices and their bioactive components might be used for preventive care and in treating different types of cancer by modulating the different stages of tumorigenesis, including tumor cell survival, proliferation, invasion, and angiogenesis. The anticancer activities of spices are mediated through the suppression of inflammation. As examples, curcumin suppresses the inflammatory markers NF-κB and COX-2 (Shishodia et al., 2003), cinnamaldehyde inhibits age-related NF-κB activation and targets inflammatory COX-2 and induced nitric oxide synthase (Kim et al., 2007), and anethole inhibits NF-κB activation and cytokine production (Chainy et al., 2000). Eugenol blocks the release of the cytokines TNF-α and IL-1β (Kim et al., 2003), and [6]-gingerol inhibits the production of TNF-α and IL-1β in lipopolysaccharide-stimulated murine peritoneal macrophages in vitro (Tripathi et al., 2007). Several other spices and spice-derived nutraceuticals have shown anti-inflammatory and antitumor activities.

Animal studies have also shown the benefits of spices. In one study, oral administration of extracts of spices such as black pepper, asafoetida, pippali, and garlic increased the life span of mice transplanted with Ehrlich ascites tumor by 64.7%, 52.9%, 47.0% and 41.1%, respectively (Unnikrishnan and Kuttan, 1990). In another study, the addition of Garam masala (a mixture of food-seasoning spices) suppressed dimethylbenz[a]anthracene (DMBA)-induced translactational and transplacental carcinogenesis in mice. When Garama masala were given to pregnant mice per day from days 13–19 of gestation in addition to DMBA (5 mg/day), the multiple-site tumor incidence declined significantly, from 62% to 19%, indicating its antitumor properties (Rao and Hashim, 1995).

Garlic, ginger, cloves, mustard, bay leaf, caper, oregano, thyme, and other spices are protective against CVD. Spices are effective and powerful preventative agents because they modify risk factors associated with CVD, including raised cholesterol and triglyceride levels, high blood pressure, sticky platelets, and chronic systemic inflammation. Caraway, chili pepper, nutmeg, licorice, black pepper, white pepper, paprika, coriander, and saffron all exhibit low to moderate PPARα transactivation, which helps to improve the lipid profile and reduce the risk of CVD (Mueller et al., 2011). In addition, curcumin was shown to inhibit CRP-induced PAI-1 mRNA expression in human endothelial cells, thereby indicating its cardioprotective properties (Chen et al., 2008).

The compounds found in spices also help to control many of the pathological conditions that underlie diabetes and metabolic syndrome. Spices have been shown to block the inflammation believed to drive diabetes (Aggarwal, 2010), and they lower blood sugar level, improve cholesterol and lipid status, and reduce blood pressure. In both animal experiments

and clinical trials, spices such as fenugreek seed, garlic, onion, and turmeric have been documented to possess antidiabetic potential (Srinivasan, 2005). In an experimental study spices such as sumac and black cumin extracts inhibited α-amylase (a glycoside hydrolase), indicating that spices may be of interest in the treatment and prevention of hyperglycemia and diabetes (Giancarlo et al., 2006).

Spices can also be used in the prevention and treatment of multiple sclerosis (Kannappan et al., 2011), arthritis (Ramadan et al., 2011), Crohn's disease (Aggarwal, 2004), and other chronic diseases (Aggarwal and Sung, 2009). The effects of spices against chronic diseases are mediated through the suppression of age-associated inflammatory markers (Surh, 1999).

4.3. Cereals and legumes

Consumption of whole-grain cereal and legumes forms the basis of a healthy diet. Growing evidence suggests that cereals and legumes play important roles in the etiology of chronic diseases. The major cereals or whole-grain foods are wheat, rice, and maize; others include barley, sorghum, millet, rye, and oats. The most commonly consumed legumes are beans, lentils, lupins, peas, and peanuts. These cereals and legumes contain chemopreventive antioxidants and anti-inflammatory phytochemicals such as vitamins and polyphenols (Figure 3B).

Cereals and legumes have been found to reduce the risk of several chronic diseases, including cancer. The consumption of whole-grain cereals and legumes lowers the risk of cancers of the oral cavity, pharynx, esophagus, gallbladder, larynx, bowel, colorectum, prostate, breasts, liver, ovaries, bladder, renal, and thyroid gland as well as lymphomas, leukemias, and myeloma (Chatenoud et al., 1998; Jacobs et al., 1998). In a multicenter case-control study of African-American, white, Japanese, and Chinese men with prostate cancer, intake of legumes was inversely related to prostate cancer (Kolonel et al., 2000). Mechanistic studies have shown that fibers and phytochemicals present in whole-grain cereals and legumes have chemopreventive action against a wide variety of cancers. For example, isoflavones (including daidzein, genistein, and equol) are nonsteroidal diphenolic compounds that are found in leguminous plants and have antiproliferative activities. Tocotrienol and inositol hexaphosphate, which are abundantly present in various high-fiber foods such as cereals and legumes, have exhibited anticancer activity in both in vitro and animal models. These compounds interfere with key pathways in malignancy by inhibiting cell proliferation, cell cycle progression, metastasis, invasion, and angiogenesis and by inducing apoptosis (Kolappaswamy et al., 2009).

Consumption of wholegrain cereal and legumes can protect against CVD. A hypocaloric diet that included oats improved systolic blood pressure and the lipid profile compared with a hypocaloric diet without oats (Saltzman et al., 2001). A prospective cohort study with postmenopausal women (n = 229) participating in the Estrogen Replacement and Atherosclerosis trial found that higher weekly intake of cereal fiber or whole grains was associated with a smaller decline in minimum coronary artery diameter as well as with less progression in percent stenosis, indicating that higher intake of cereal fiber and whole-grain products is associated with less progression of coronary atherosclerosis (Erkkila et al., 2005). The isoflavones present in legumes, such as in soy protein, have also been shown to reduce CVD risk factors. In an experimental study with monkeys, isoflavones or phytoestrogen-intact soy protein had favorable effects on plasma lipid and lipoprotein concentrations, specifically by significantly reducing low-density and very-low-density cholesterol concentrations, in both males and females (Anthony et al., 1996). The isoflavone genistein has been shown to act against the risk of CVD. It also inhibits ultraviolet light-induced cutaneous aging in mice and photodamage in humans (Wei et al., 2003). Thus, legumes and cereals are protective against CVD risk and aging.

Legumes and cereals are also associated with a reduced risk of several other chronic diseases. Black soy peptide supplementation controlled the glucose level of newly diagnosed type 2 diabetes mellitus patients (Kwak et al., 2010), and intake of breakfast cereals and whole-grain products may lower the risk of diabetes mellitus (Kochar et al., 2007). The Japanese rice *Oryza sativa* Japonica was found to ameliorate neurological symptoms in an autoimmune encephalitis model and prevent reduce the prevalence of multiple sclerosis (Shapira et al., 2010). Rice bran improves joint health, pain, and arthritis by suppressing the inflammatory markers COX1, COX2, and 5-LOX (Roschek et al., 2009). In a case-control study, soy proteins increased body weight, fat-free mass, and fat mass in patients with Crohn's disease, who are often malnourished (Capristo et al., 2000). Thus, legumes and cereals help with the prevention and treatment of various chronic diseases.

5. Conclusion

The accumulated results from in vitro, animal, and clinical studies of the last few decades have provided evidence that fruits, vegetables, cereals, legumes and spices are linked to age-associated chronic diseases. Consumption of diets rich in natural foods increases the amount of plant-based nutraceuticals, such as antioxidants and anti-inflammatory agents, in the body. These nutraceuticals fight against free radicals and modulate the inflammatory signaling pathway in cells, thereby suppressing the onset of osteoporosis, cancer, CVD, diabetes, multiple sclerosis, Crohn’s disease, and other chronic conditions. Because of their effects, foods provided by Mother Nature could be called “anti-aging” foods. However, more clinical studies on dietary factors and the risk of chronic disease are needed, as is further work to determine the amount of dietary agents needed to delay aging and chronic disease. In addition, the relationship between dietary consumption by of different age groups and chronic disease needs to be elucidated. Widely corroborated observations from such studies could provide a strong rationale and justification for dietary intervention studies aimed at reducing or preventing age-associated chronic diseases.

Highlights

- Most chronic diseases caused by chronic inflammation require chronic treatment.
- NF-κB and STAT3, play a major role in activating inflammation.
- Most life style risk factors activate NF-κB and STAT3.
- Suppression of NF-κB and STAT3 has the potential preventing chronic diseases.

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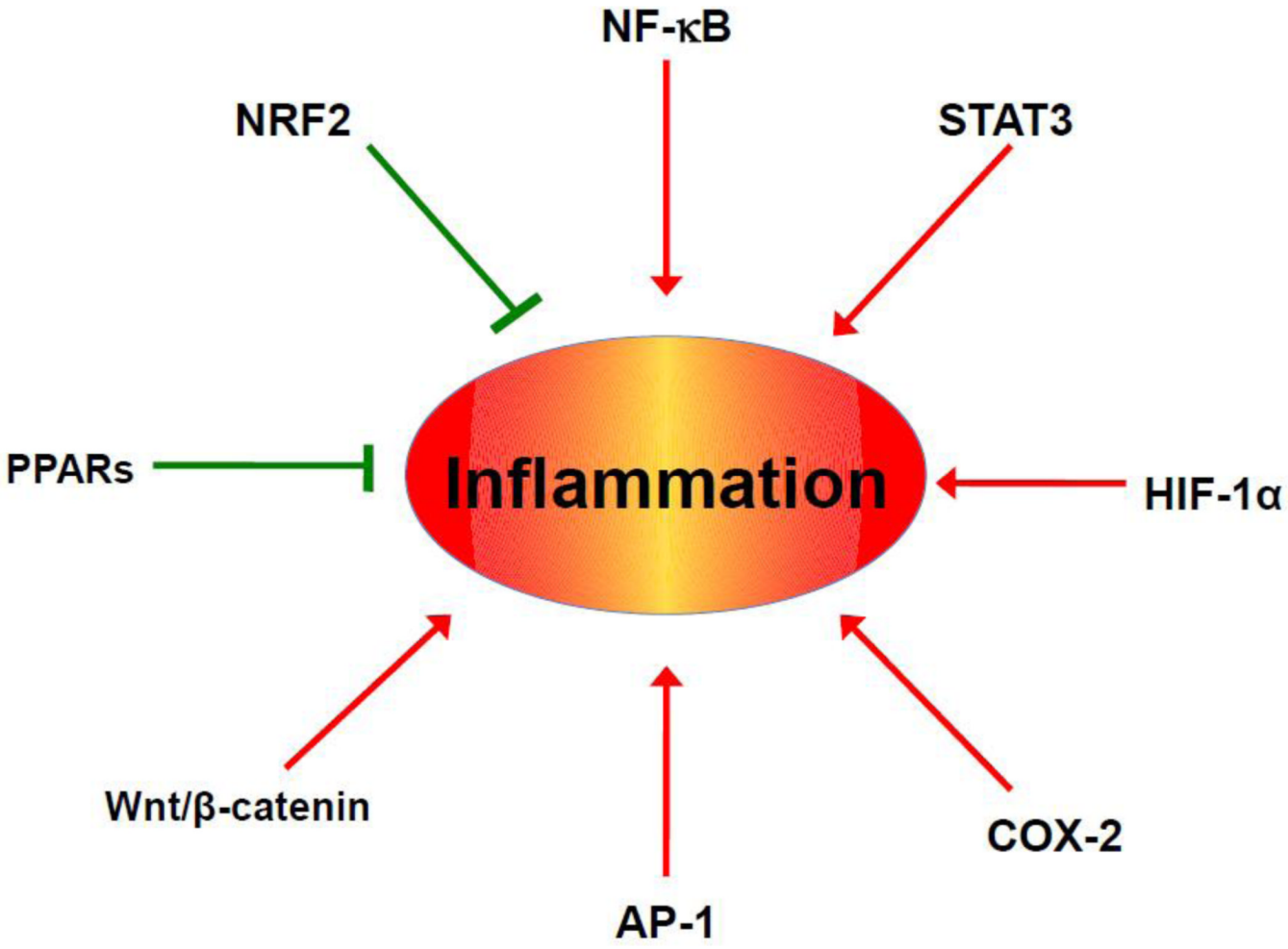

Fig. 1.
Inflammation regulatory cell signaling transcription factors.

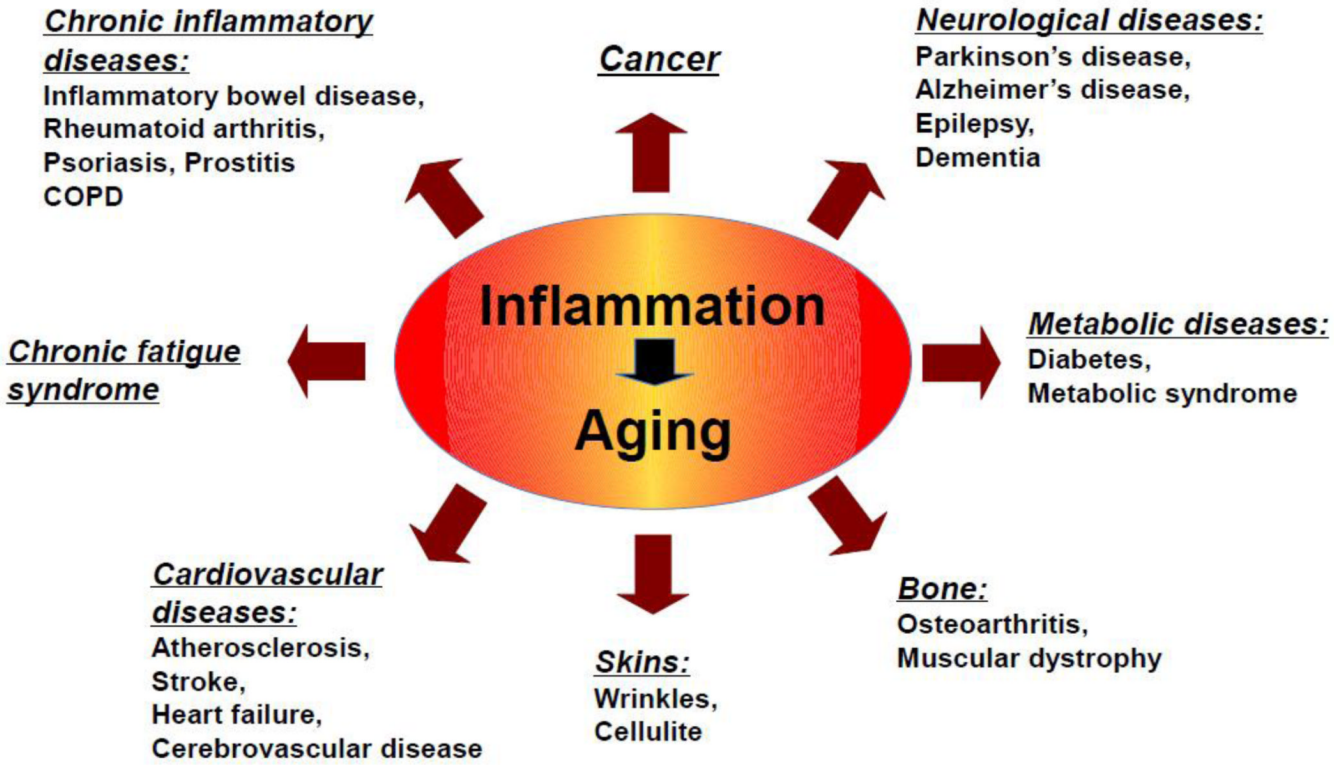

Fig. 2.
Aging associated chronic diseases regulated by inflammation.

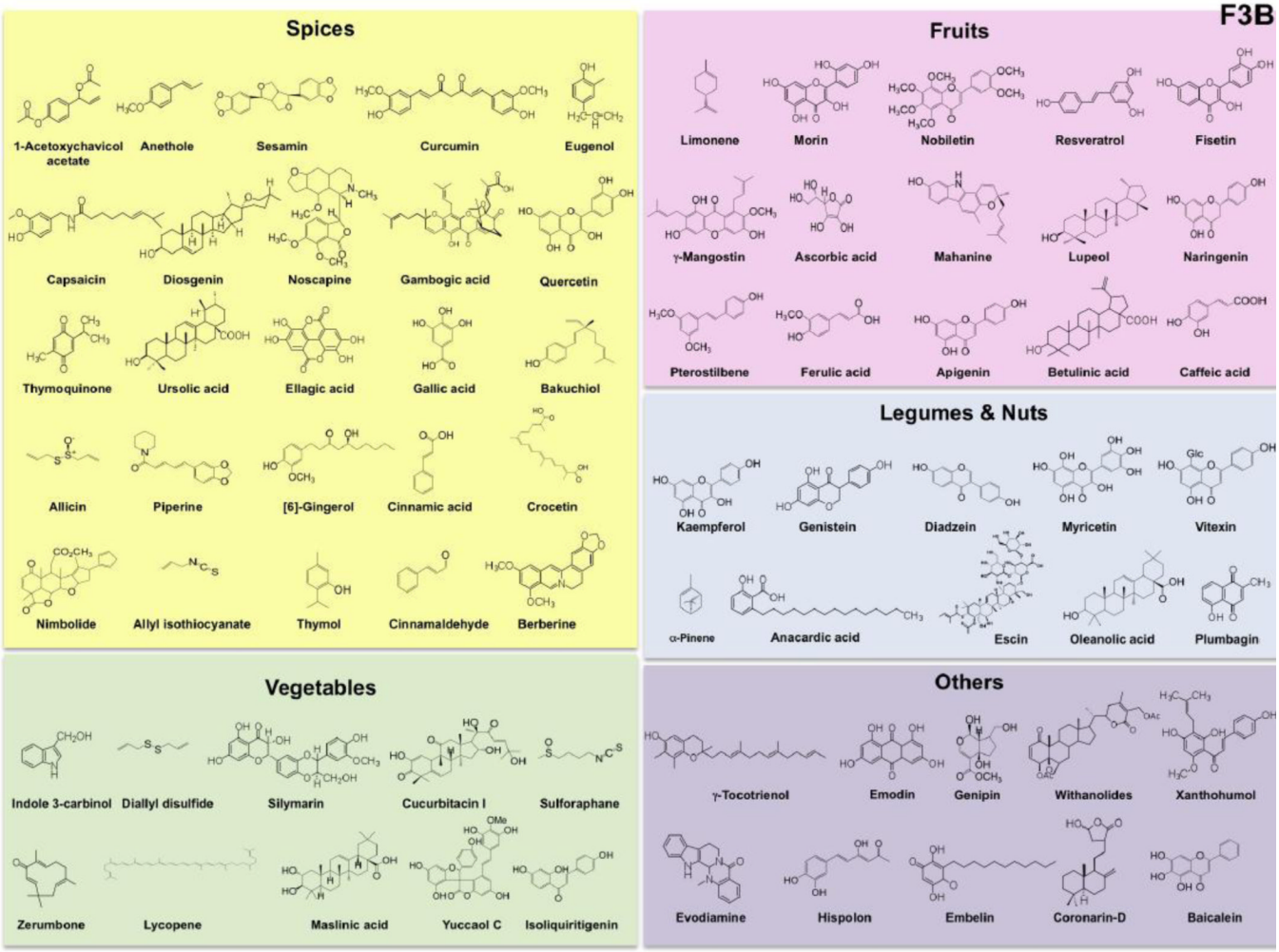

Fig. 3.

Natural products such as fruits, vegetables, spices, legumes and cereals (A) and their bioactive components (B) linked to beneficial health effects against age associated chronic diseases.