Phytochemicals on Chronic Diseases

Subjects: Food Science & Technology

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Redox balance is essential to maintain the body's normal metabolism. Once disrupted, it may lead to various chronic diseases, such as diabetes, neurodegenerative diseases, cardiovascular diseases, inflammatory diseases, cancer, aging, etc. Oxidative stress can cause or aggravate a series of pathological processes. Inhibition of oxidative stress and related pathological processes can help to ameliorate these chronic diseases, which have been found to be associated with Nrf2 activation. Nrf2 activation can not only regulate the expression of a series of antioxidant genes that reduce oxidative stress and its damage, but also directly regulate genes related to the above-mentioned pathological processes to counter the corresponding changes.

phytochemicals chronic disease Nrf2-ARE pathway redox balance

1. Phytochemicals Target Nrf2 for Diabetes Intervention

Diabetes is one of metabolic diseases in which a person has high blood sugar, either because the body does not produce enough insulin, or because cells do not respond to the insulin. This high blood sugar produces the classical symptoms of polyuria (frequent urination), polydipsia (increased thirst) and polyphagia (increased hunger) [1]. Diabetic patients have an increased risk to develop many complications such as diabetic retinopathy with progression of the disease leading to blindness and end-stage renal failure [2], cardiovascular disease (CVD) with leading atherosclerosis [3], diabetic nephropathy with leading scarring changes in the kidney tissure, loss of small or progressively larger amounts of protein in the urine, and eventually chronic kidney disease requiring dialysis [4]. During hyperglycaemia, reactive oxygen species and mitochondrial dysfunction caused excess oxidative stress that plays a causal role in the development and progression of the above diabetic complications [5]. In brief, as shown in **Figure 1**, ROS provoked by hyperglycemia and free fatty acids leads to activation of several signaling pathways, including NF-κB, p38 MAPK, and JNK, which cause chronic inflammation and production of a series of cytokines through suppressing secretion of insulin and promoting cell dysfunction [6].

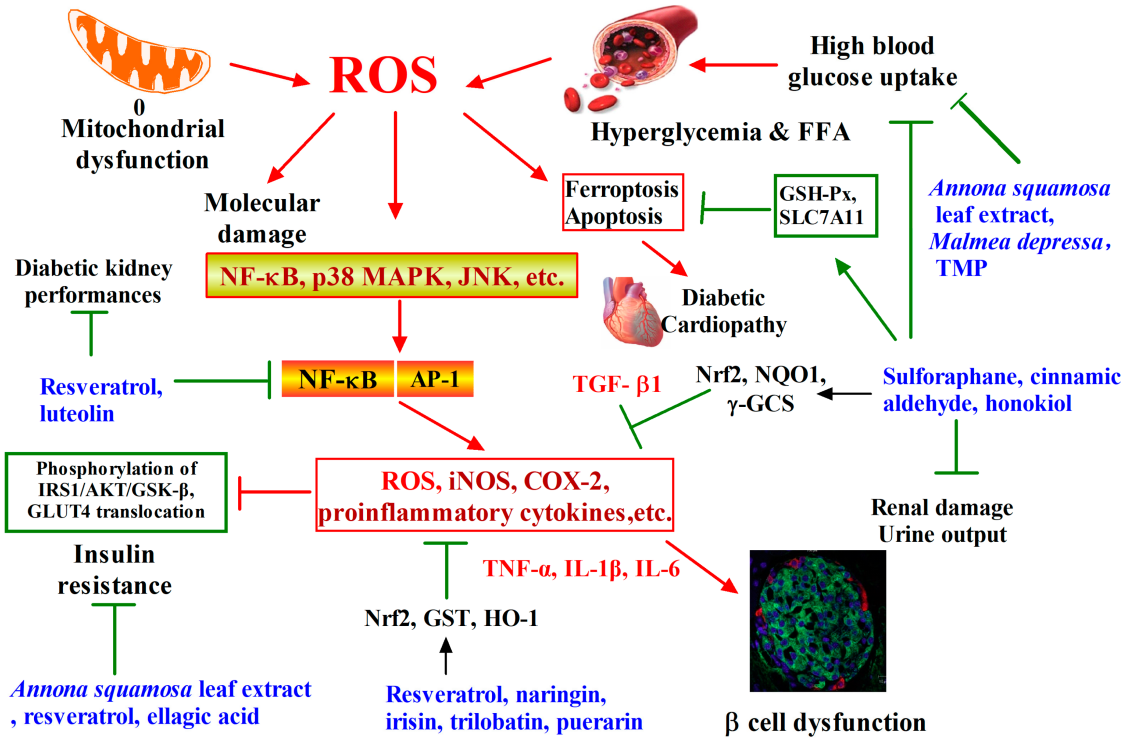

Figure 1. Phytochemicals target Nrf2 for diabetes intervention. Mitochondrial dysfunction and hyperglycemia lead to the massive production of ROS, which triggers molecular damage, inflammation, ferroptosis, insulin resistance, and β-cell dysfunction. A variety of phytochemicals activate Nrf2 signaling pathway, inhibit ROS levels, ferroptosis and inflammation, restore insulin signaling pathway transduction and protect β cells from injury.

2. Phytochemicals Target Nrf2 for Neurodegenerative Diseases Intervention

Neurodegenerative diseases are causes of the progressive loss of structure or function of neurons, including death of neurons due to the expression of certain gene alleles, toxicant administration and ageing [7]. Many neurodegenerative diseases, including Parkinson's Disease (PD), Alzheimer's Disease (AD), Huntington's Disease (HD) and Amyotrophic Lateral Sclerosis (ALS), occur as a result of neurodegenerative processes. The commonalities among neurodegenerative diseases include protein aggregation, proteasomal or autophagic dysfunction, inflammation, neuronal apoptosis, oxidative stress, mitochondrial dysfunction and interactions between neurons and glia [8]. Among these pathologies, the causal nature of mitochondrial dysfunction and oxidative stress in neurodegeneration is widely considered, and accumulated evidence suggests that free radicals are extremely important in causing neuronal death [9].

Consecutive and long stimulation from excess oxidative stress caused by ROS or RNS could induce damage in neurons. The central nervous system (CNS) is particularly sensitive to oxidative stress, owing to a high oxygen consumption and exposure under excess polyunsaturated fatty acids, making it particularly vulnerable to lipid peroxidation. Oxidative damage to key intracellular targets such as DNA or proteins by free radicals has been shown to be a major cause of the neuronal cell damage related to degenerative diseases [10]. In brief, as shown in

Figure 2, excess oxidative stress ROS and RNS lead to aggregation and accumulation of bad proteins like α-synuclein protein of Lewy bodies, amyloid precursor protein (APP) and amyloid β peptides, which are major neuropathological alterations in neurodegenerative diseases. These proteins released from neurons lead to the activation of transcription factor NF-κB and AP-1 in microgials and astrocytes, and sequentially induce ROS, iNOS, COX-2, NAPDH oxidase, proinflammatory cytokines and inflammatory mediators, which in turn damage neurons and finally cause neurodegenerative diseases [11].

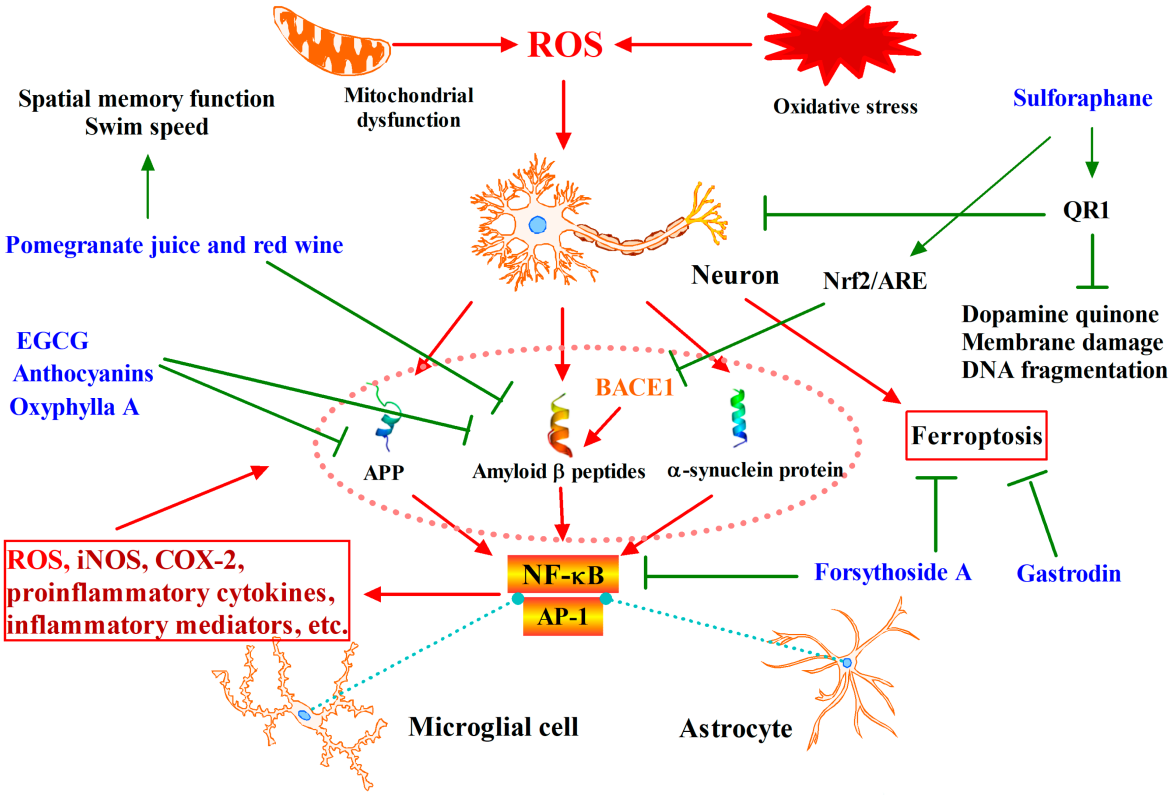

Figure 2. Phytochemicals target Nrf2 for neurodegenerative disease intervention. ROS and inflammatory factors promote the accumulation of harmful proteins such as APP, Amyloid β peptides, α-synuclein protein, and induce ferroptosis of cells, leading to nerve cell damage. A series of phytochemicals are reported to prevent neuron cell damage by blocking harmful protein production and ferroptosis, thereby preventing neurodegenerative diseases.

3. Phytochemicals Target Nrf2 for Cardiovascular Diseases Intervention

Cardiovascular diseases (CVD) are a class of diseases that involve the heart or blood vessels (arteries and veins) including atherosclerosis, coronary heart disease, cardiomyopathy, ischaemic heart disease, heart failure, hypertensive heart disease, inflammatory heart disease, valvular heart disease and myocardial infarction [12]. Cardiovascular diseases remain the biggest cause of deaths worldwide, according to the Global Burden of Disease (GBD) 2016 Study, noncommunicable diseases (NCDs) accounted for about 40% of total, age-standardized global burden of disease in women, and about 50% of total age-standardized global burden of disease in men; CVDs alone accounted for 20% of total burden in women and 24% of total burden in men [13].

The main cause of the majority of cardiovascular diseases comes from complications of atherosclerosis, and oxidized low-density lipoprotein (Ox-LDL) formation under the stimulation of reactive oxygen species which come from several different sources contributes the pathology of atherosclerosis [14]. This is likely to occur at the sites of endothelial damage which are caused by Ox-LDL itself as well as physical or chemical forces and infection. Endothelial cells, smooth muscle cells (SMCs), and macrophages are the sources of oxidants for the oxidative modification of phospholipids [15]. As shown in **Figure 3**, Ox-LDL can damage endothelial cells and induce the expression of adhesion molecules such as P-selectin, intracellular/vascular cell adhesion molecule-1 (I/VCAM-1) and proinflammatory cytokines such as monocyte chemoattractant protein-1 (MCP-1) and macrophage colony stimulating factor (mCSF). These processes lead to the tethering, activation, and attachment of monocytes and T-lymphocytes to the endothelial cells. Endothelial cells, leukocytes, and SMCs then secrete growth factors, chemoattractants and other proinflammatory cytokines that act on the migration of monocytes and leukocytes into the subendothelial space [16]. Monocytes ingest lipoproteins and morph into macrophages. Macrophages generate reactive oxygen species (ROS), which convert Ox-LDL into highly oxidized LDL, which is, in turn, taken up by macrophages themselves to form foam cells. Foam cells combine with leukocytes to become the fatty streak, and as the process continues foam cells secrete growth factors that induce SMC migration into the intima. SMC proliferation, coupled with the continuous influx and propagation of monocytes and macrophages, converts fatty streaks to more advanced lesions and ultimately to a fibrous plaque that will protrude into the arterial lumen. Later, calcification can occur and fibrosis continues, yielding a fibrous cap that surrounds a lipid-rich core. This formation may also contain dead or dying SMCs. In acute coronary syndromes (e.g., myocardial infarction), when fibrous plaques rupture, the formation and release of thrombi may ultimately occlude vessels [17]. The pathology that oxidative stress causes cardiovascular injury is further confirmed by animal and human studies [18].

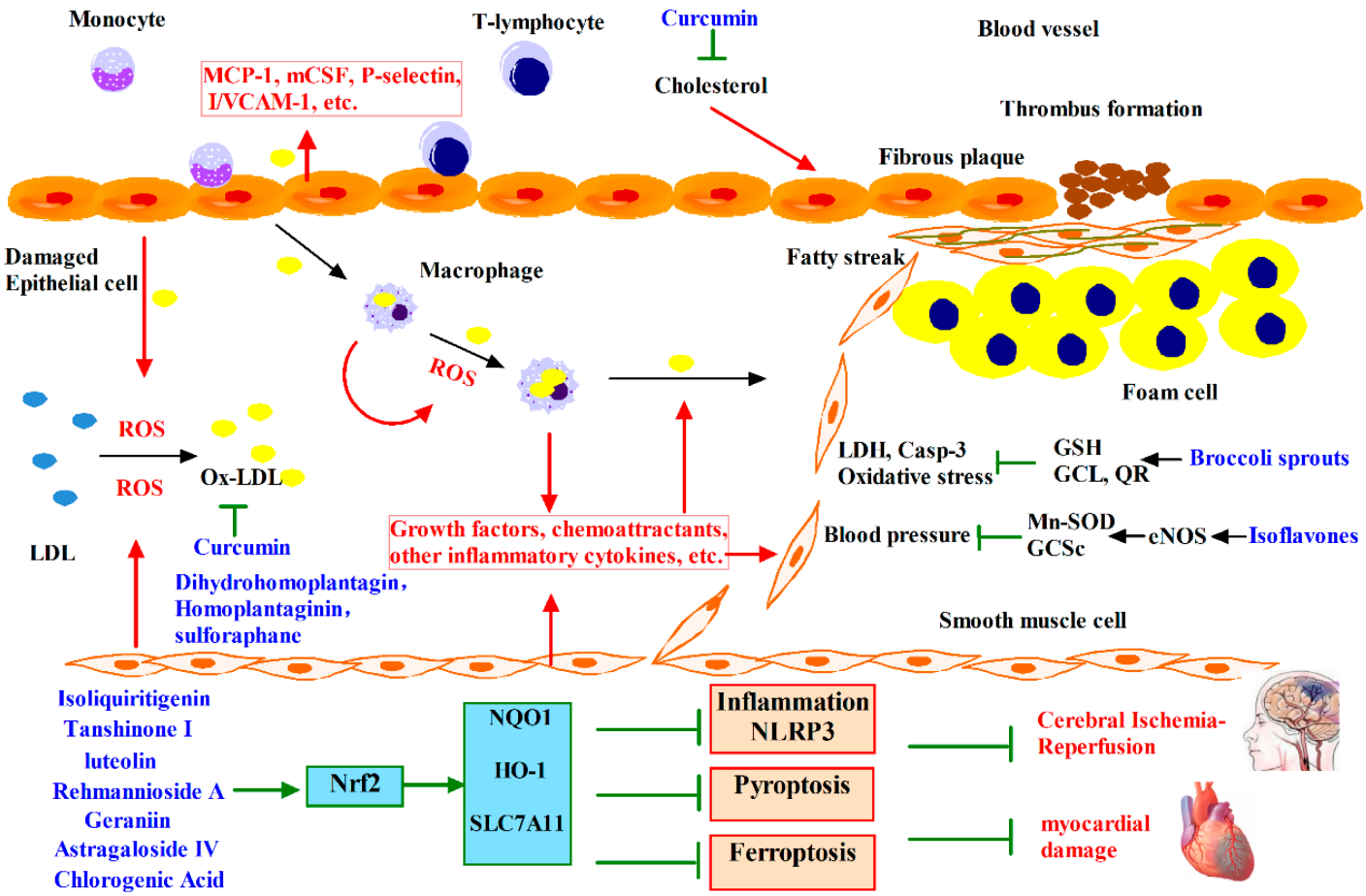

Figure 3. Phytochemicals target Nrf2 for cardiovascular diseases intervention. Ox-LDL can damage endothelial cells and induce the expression of proinflammatory cytokines. Monocytes take up lipoproteins and metamorphoze into macrophages, which can produce reactive ROS, and subsequently convert Ox-LDL to highly oxidized LDL and form foam cells, combine with leukocytes to form fatty streaks and eventually form fibrous plaques that protrude into the arterial lumen, leading to vascular obstruction. A variety of phytochemicals are found to activate the Nrf2 signaling pathway to ameliorate oxidative stress and prevent fibrous plaque formation. Phytochemicals attenuate heart and brain damage after ischemia-reperfusion injury by inhibiting inflammation, apoptosis and ferroptosis.

4. Phytochemicals Target Nrf2 for Cancer Intervention

Cancer is the second leading cause of death, after cardiovascular diseases, in occidental countries. Every year, around 10 million people worldwide are diagnosed with cancer, and approximately 6.2 million die of this disease. Only 5–10% of all cancer cases can be attributed to genetic defects, whereas the remaining 90–95% cancers have their roots in the environmental factors, among which almost 30–35% are linked to diet [19]. It is nearly impossible to prove what caused a cancer in any individual, because most cancers have multiple possible causes, but it is clear that the ratio in a number of cancers is low in the population having diets rich in vegetables, fruits and whole grains while it is high in the population having diets rich in processed or red meats [20].

Cancer development in humans is a multistep, long-term process, in which cancer cells acquired several biological capabilities such as sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, activating invasion and metastasis, reprogramming of energy metabolism, evading immune destruction, genome instability and mutation and tumor-promoting inflammation [21]. Due to cancer pathogenesis being traceable back to that impact cell growth and metastasis, oxidative stress is one of the main causes for carcinogenesis.

5. Phytochemicals Target Nrf2 for Inflammatory Diseases Intervention

Inflammation is a complex set of interactions among soluble factors and cells, and can arise in any tissue in response to traumatic, infectious, post-ischaemic, toxic or autoimmune injury [22]. Thus, inflammation is at the root of several degenerative disorders, such as autoimmune diseases, rheumatoid arthritis, asthma, emphysema, gastritis, colitis, osteoarthritis, chronic obstructive pulmonary disease, ageing, atherosclerosis, cancer [23]. As shown in **Figure 4**, inflammation occurs as part of the immune reaction and produces ROS to inactivate the foreign molecules and fight against the invading pathogens. A cascade of cytokine- and chemokine-mediated inflammatory reactions initiate and maintain a host response, involving activation and attraction of immune and non-immune cells. Leukocytes (neutrophils, monocytes and eosinophils), macrophages, lymphocytes, and plasma cells in venous system infiltrate into the disrupted and damaged tissue to recover from infection and to heal [22]. However, cytokines and chemokines persisting at inflammatory sites cause chronic oxidative stress that can mediate subsequent tissue injuries. Oxidative stress activates the redox-sensitive transcription factors such as NF-κB and AP-1, resulting in the production of pro-inflammatory cytokines and chemokines. Excess oxidative stress is also involved in the pathophysiologies of many inflammation-associated disorders. Therefore, the induction of antioxidant proteins and detoxifying enzymes through activation of Nrf2-ARE pathway is essential for the body's protection against inflammatory tissue injuries [24].

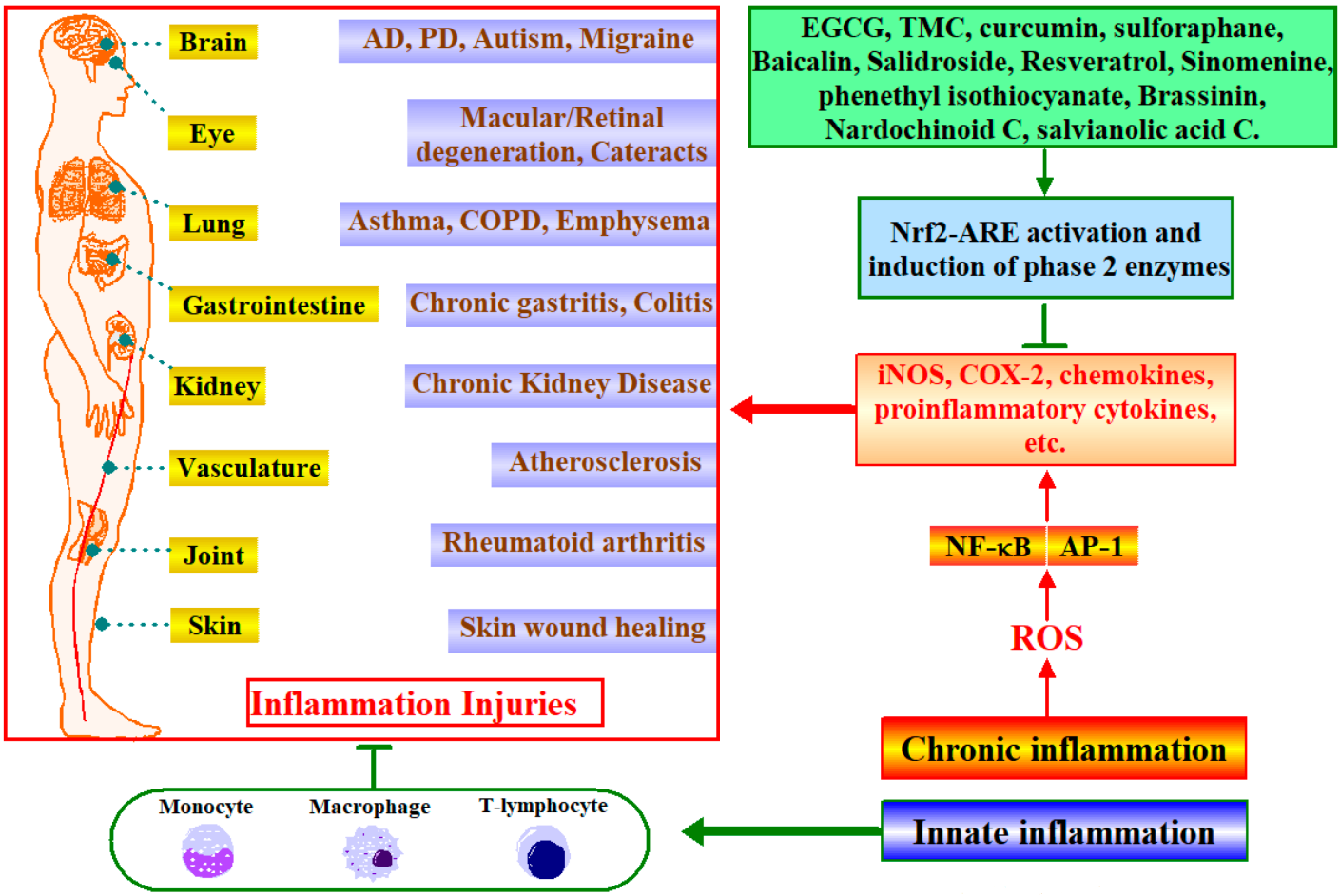

Figure 4. Phytochemicals target Nrf2 for inflammatory diseases intervention. Chronic inflammation produces ROS, which leads to the release of more inflammatory cytokines and inflammatory damage in various tissues and organs. A large number of studies have shown that phytochemicals can activate Nrf2-ARE signaling pathway and induce phase II enzymes, thereby inhibiting the expression of pro-inflammatory factors and preventing inflammatory damage.

6. Phytochemicals Target Nrf2-ARE Pathway for Other Chronic Diseases Intervention (Obesity, Ageing and Longevity)

Phytochemicals showed their potency in prevention on many other chronic diseases through activation of Nrf2-ARE pathway. Oxidative stress in accumulated fat appears as an earlier instigator of obesity-associated metabolic syndrome; thus, it is an important target for therapies.

Obesity is a medical condition in which excess body fat has accumulated to an extent and is reaching worldwide unprecedented prevalence in persons of all ages [25]. Obesity causes a series of health problems like metabolic syndrome [26] and likelihood of various diseases, especially including heart disease, type 2 diabetes, obstructive sleep apnea, certain types of cancer, and osteoarthritis [27]. Oxidative stress shows a strong relation to obesity. In

brief, as shown in **Figure 5**, hyperglycemia and excess oxidative stress stimulate adipocyte generation. Mature adipocyte could induce more oxidative stress and secret a series of proinflammatory cytokines such as IL6, PAI-1, MCP-1, and TNF-α, companying inhibition of adiponectin and leptin production to damage tissues and cause chronic inflammation. All of these events finally lead to metabolic syndromes, including diabetes, insulin resistance, atherosclerosis and hypertension. Besides, obesity per se may induce systemic oxidative stress in accumulated fat that, in turn, causes dysregulation of adipocytokines and further develops metabolic syndrome [25][28].

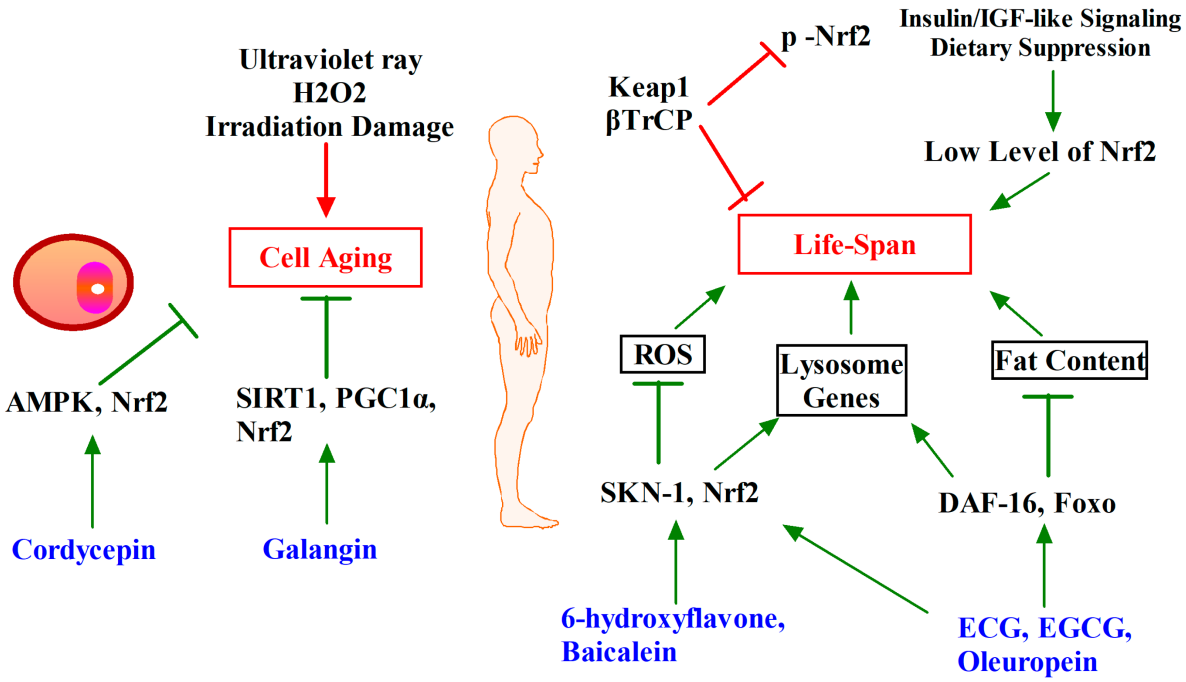

Figure 5. Phytochemicals target Nrf2 for ageing and longevity intervention. Phytochemicals inhibit cell senescence caused by external factors by activating Nrf2. In the in vivo setting, inhibition of Keap1 expression, with appropriate activation of Nrf2, can prolong lifespan. Phytochemicals can activate Nrf2 and other life-related signaling pathways, reduce ROS production, up-regulate lysosomal gene expression, reduce fat content, and ultimately extend the life span of animals.

The obesogenic environment of highly palatable foods with hidden fats and sugars can promote metabolic syndrome and obesity, whereas fruit and vegetables with phytochemicals can counteract metabolic syndrome and obesity [29]. For example, isoflavones and lignans have been proved to exert anti-obesity activity in nutritional intervention studies in both animals and humans [30]. Genistein, conjugated linoleic acid (CLA), docosahexaenoic acid, epigallocatechin gallate, quercetin, resveratrol and ajoene affect adipocytes during various stages of the adipocyte life cycle, resulting in either inhibition of adipogenesis or induction of adipocyte apoptosis which decreases lipid accumulation and induces lipolysis [31]. Moreover, polyphenol-rich grapes can target obesity-induced oxidative stress through activation of Nrf2-ARE pathway [32].

The role of Nrf2 in longevity has received much attention. For example, Nrf2 is identified as a mediator of caloric restriction [33], and as an effector of longevity signals, providing new therapeutic perspectives [34][35]. However, several blockbuster animal studies have shown that Keap1 is the key factor affecting lifespan. One study found that

p62(-/-) mice had accelerated aging and impaired mitochondrial function, and further studies found that the role of p62 in this process was to promote the autophagic degradation of Keap1 and indirectly promote the expression of Nrf2 [36]. In addition, studies on nude mice and nine other rodent species found that maximum life potential was not related to the protein level of Nrf2 itself, but was negatively correlated with Keap1 [37]. The molecule mechanism may be that Nrf2, when functioning normally, promotes NQO1 expression and limits peroxide production to maintain mitochondrial integrity and energy metabolism homeostasis to ensure that the life span is not shortened [38]. In addition, transcription factors such as SKN-1/Nrf2 and DAF-16/FOXO can up-regulate lysosomal gene expression, which plays important roles in prolonging life span by maintaining the normal function of lysosomes [39]. Another study showed that Nrf2, although not directly involved in longevity signaling, is essential for the maintenance of metabolic and protein homeostasis, and Nrf2 knockdown leads to a shortened lifespan in mice [40]. This suggests an indirect role for Nrf2. While Nrf2 activation is strongly associated with longevity extension, it also cannot be overexpressed. High Nrf2 expression levels also lead to death or other pathologies, but inhibition of insulin/IGF-like signaling and diet suppression mildly activate Nrf2 and prolong the lifespan of flies [41].

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