Oxidative and Inflammatory Stressed Conditions: Beneficial Effects of Natural Antioxidants

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Abstract

Oxidative stress can be defined as a perturbation of the redox state of the cell due to excessive generation of ROS (reactive oxygen species) that endogenous antioxidants fail to neutralize. Oxidative stress leads to the damage of all the biomolecules of the body viz. nucleic acids, lipids and proteins by structural modifications and/or functional modulation. This disrupted balance between the oxidants and the antioxidants triggers oxidative insult mediated production of mutagens, varied regulation of different genes, and overexpression of molecules promoting inflammation. Inflammation is an immune response, leading to disrupted tissue homeostasis, and its chronic form leads to the development of several diseases like neurodegenerative diseases, cancers, heart diseases, diabetes, kidney diseases, etc. In this article, we outlined some major oxidative stress induced pathophysiological conditions associated with acute/ chronic inflammatory response. Many antioxidants are isolated from different natural sources. These compounds are found to ameliorate oxidative stress conditions and can modulate different inflammatory responses. Some of the antioxidant molecules like mangiferin, genistein, curcumin, arjunolic acid, resveratrol, etc. are discussed in this article with respect to their anti-oxidant and anti-inflammatory properties.

Keywords: Oxidative stress; Inflammation; Natural antioxidants; Anti-inflammatory properties; NFκB

Short Commentary

Adenosine tri-phosphate (ATP) is the chief source of energy for all types of eukaryotic cells. It provides the driving force to the total metabolic processes that take place inside the cell to perform its intracellular and extracellular functions at every single time point. Different organelles/compartments of a cell (Cytoplasm, Mitochondria, etc.) are constantly involved in several anabolic pathways namely glycolysis, Krebs cycle, β-oxidation, etc. for the breakdown of several macromolecules. Finally, ATP is generated in the electron transport chain (ETC) that take place in the inner mitochondrial membrane with the involvement of several mitochondrial enzymes [1]. As a consequence of the metabolic process several free radicals are generated in the cell [2]. These free radicals (Reactive oxygen and nitrogen species, ROS and RNS) are critical for the normal cellular homeostasis and to scavenge these free radicals there exists efficient antioxidant defence machinery comprising of several enzymes (SOD, CAT, etc.) or cellular metabolite (GSH) [3]. If the level of reactive intermediates increases inside the cell, it has many deleterious effects and gives rise to the pathophysiological condition commonly termed as oxidative stress condition [4]. Apart from these endogenous oxidative insults, a cell or a living system can face different exogenous oxidative insult by the use of different drugs, pollution, etc. The mitochondrial reactive intermediates can potentially up regulate a critical transcription factor, the nuclear factor kappa-B (NF-κB). This molecule can elicit uncontrolled intracellular inflammatory responses by up regulating the production of several inflammatory cytokines such as interleukin-1β (IL-1β), tumour necrosis factor-α (TNF-α), etc. [5] and other signalling intermediates like iNOS, cyclooxygenase-2 (COX-2), etc. [6]. Moreover, the reactive species can oxidize several intracellular macromolecules and can induce different inflammatory disorders mediating oxidative stress including several neurodegenerative and the autoimmune disorders. Oxidative stress condition can induce damage of the nuclear proteins leading to mutations and facilitate an environment for the development of carcinogenesis mediating inflammation [7,8].

So far, we have discussed the unavoidable consequences of ROS and RNS and researches around the world suggest that exogenous administration of antioxidants can inhibit the intracellular elevation of reactive intermediates and prevent the development of inflammation [9]. Scientists are working on several natural polyphenolic antioxidants namely arjunolic acid, mangiferin, genistein, resveratrol, etc. [10-12] which are pleiotropic in nature with minimum side-effects on the normal cellular homeostasis. These antioxidant molecules have been extensively studied by the chemists as well as the biologists. According to their inference, most of these natural antioxidants have drug-like physical and chemical properties. These molecules are classified as an efficient free radical scavenger with the potential to modulate the expression of different genes [4,11]. In this article, the role of different natural antioxidants, against different uncontrolled...
inflammatory response related to several pathophysiological conditions, are comprehensively discussed. An overall mechanism of action of different antioxidants against various pathophysiological conditions is represented in Figure 1.

Cancer, Neurodegenerative disorders, Cardiovascular disorders, Nephropathy, Diabetes

Figure 1: An overview of the mechanism of anti-inflammatory response of several antioxidants against different pathophysiological conditions.

Cancer, a complex disorder may occur due to the overload of intracellular reactive species, which can cause fatal changes in the nuclear material [4]. Different intermediates of the cellular inflammatory response are critical for the development and progression of cancer. NF-κB has a critical role in tumour formation as it can govern both the intracellular immunity and inflammatory responses. NF-κB can regulate the synthesis of different pro-inflammatory cytokines including TNF-α, IL-8, IL-1β, IL-6, IL-23, etc. [13]. More importantly, NF-κB can activate the STAT3 mediated signalling cascades. STAT3 can promote the development and progression of cancer by blocking the apoptotic pathway or by inducing metastasis, angiogenesis and invasion [14]. Different natural antioxidants like mangiferin or curcumin can suppress the activity of NF-κB and other pro-inflammatory cytokines. Genistein, a soy-derived antioxidant, which can modulate the activity of estrogenic receptors, can potentially inhibit the cellular processes activated via STAT3. Several other reports suggest that antioxidants like resveratrol, flavopiridol, and piceatannol can potentially inhibit the JAK-STAT pathway, thereby can prevent the development of cancer [11].

Apart from cancer, kidney and liver are the two vital organs, which are greatly affected by the exogenous ROS insult. Literature suggests that oxidative insult can activate immune responses which can directly induce the synthesis of different pro-inflammatory cytokines and lead to acute or chronic inflammation [13]. This type of inflammatory stress affects the normal function and alters the cellular physiology of the different cell types in the organs. It has been found that different antioxidants like mangiferin, genistein, curcumin or resveratrol have been found to suppress different inflammatory response induced by cellular regulators of inflammation including NF-κB and inflammatory caspases like caspase 1, caspase 5, caspase 11, etc. [15]. These antioxidants are also found to effective against the dysfunction of the organs associated with several metabolic disorders including diabetes.

Immunomodulatory role of these natural antioxidants is also well studied. Antioxidants are effective against T-cell and macrophage-dependent/independent delayed type hypersensitive reactions [16,17]. Antioxidants are found to suppress the activation of the macrophages and thereby inhibit the secretion of different granular enzymes [11]. Clinical and experimental data suggests that supplementation of antioxidants can ameliorate autoimmune disorder like rheumatoid arthritis (RA). Several antioxidants have been found to reduce some key inflammatory markers, critical for the pathogenesis of RA such as TLR3 and IL-1β in CD34+ cells, CRP, fibrinogen, etc. [18].

Overall it has been observed that natural antioxidants are efficient in maintaining the normal cellular homeostasis by lowering or preventing the excessive generation of reactive intermediates. These antioxidants also possess efficient gene regulation properties and have the ability to elicit different signalling response in normal and diseased cells. Finally, the beneficial bioactive nature of these small molecules with drug-
like properties will encourage the researchers to find out the detailed signalling mechanism in different pathophysiological disorders and to develop novel therapeutic options.

References


