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Antioxidants and human diseases

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ABSTRACT

Oxidative stress plays a pivotal role in the development of human diseases. Reactive oxygen species (ROS) that includes hydrogen peroxide, hyphochlorus acid, superoxide anion, singlet oxygen, lipid peroxides, hypochlorite and hydroxyl radical are involved in growth, differentiation, progression and death of the cell. They can react with membrane lipids, nucleic acids, proteins, enzymes and other small molecules. Low concentrations of ROS has an indispensable role in intracellular signalling and defence against pathogens, while, higher amounts of ROS play a role in number of human diseases, including arthritis, cancer, diabetes, atherosclerosis, ischemia, failures in immunity and endocrine functions. Antioxidants presumably act as safeguard against the accumulation of ROS and their elimination from the system. The aim of this review is to highlight advances in understanding of the ROS and also to summarize the detailed impact and involvement of antioxidants in selected human diseases.

Contents

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1. Introduction

The beneficial effect of antioxidants on the maintenance of health in human has become an important subject that has engaged many scientists across the world over the last decade. In the last few years, antioxidants have become the indispensable nutrients of the nutritional world. Antioxidants are important in terms of their ability to protect against oxidative cell damage that can lead to conditions, such as Alzheimer's disease, cancer, heart disease and also linked with chronic inflammation [1]. It is defined as the substances which at low concentration significantly inhibits or delay the oxidative process, while often being oxidized themselves. Recent reports suggest that several endogenous and exogenous antioxidants are used to neutralize free radicals and protect the body from free radicals by maintaining redox balance [2,3]. Singh et al. (2010) [4] quoted that antioxidants have gone from "Miracle Molecules" to "Marvellous Molecules" and finally to "Physiological Molecules" that they play a vital role in metabolic pathways and protect cells. However recent conflicting evidence has forced the scientists to dig deeper in order to explore the role of antioxidants and pro-oxidants, since free radical reactions have been implicated in every human pathological condition which includes neurodegenerative disorders like Alzheimer's disease, Parkinson's disease, multiple sclerosis, amyotrophic lateral sclerosis, memory loss, depression and cardiovascular diseases such as atherosclerosis, ischemic heart disease, cardiac hypertrophy, hypertension, shock and trauma. Further, it also implicated in pulmonary disorders which include inflammatory lung diseases such as asthma and chronic obstructive pulmonary disease and additionally diseases associated with premature infants such as bronchopulmonary dysplasia, periventricular leukomalacia, intraventricular hemorrhage, retinopathy of prematurity and necrotizing enterocolitis and in some autoimmune diseases like rheumatoid arthritis and also in several renal disorders such as glomerulonephritis, tubulointerstitial nephritis, chronic renal failure, proteinuria, uremia and finally gastrointestinal diseases like peptic ulcer, inflammatory bowel disease and colitis, diabetes, tumors and cancers [5].

2. Measuring oxidative stress

As oxidative stress is indicative of an inequity between oxidants and antioxidants, methods for quantifying oxidative stress mostly include straight or indirect measurement of oxidants and antioxidants [6,7]. In the following segment, some principles and commonly used methods for the measurement of oxidative stress and damage will be briefly outlined.

2.1. Pro-oxidants

The most abundant free radicals in biological systems are the oxygen-centered free radicals and their metabolites, usually referred to as ROS [7]. ROS are formed continuously as normal by-products of cellular metabolism; and, in low concentrations, they are essential for several physiological processes, including protein phosphorylation, transcription factor activation, cell differentiation, apoptosis, oocyte maturation, steroidogenesis, cell immunity, and cellular defense against microorganisms [7]. However, when produced in excess, ROS can damage cell functionality as they can harm cellular lipids, proteins, and DNA [7,8]. The plasma level of ROMs is considered an indicator of free-radical production [7]. ROMs is a collective term that includes not only oxygen-centered free radicals such as the superoxide anion and hydroxyl radical, but also some non-radical derivatives of oxygen, such as hydrogen peroxide (H_2O_2) and hypochlorous acid [9]. A ROMs kit has been developed to assess oxidant levels in plasma and other biological fluids; and the ROMs test has been validated by electron spin resonance [10], which is considered the "gold standard" for measuring total oxidative status. However, electron spin resonance is not suitable for routine analysis, as the method is complex and requires specific technical assistance not available in most laboratories. The utility of the ROMs assay in monitoring oxidative stress in goats [11], sheep [12], and dairy cows [13] has been reported.

The concentrations of individual oxidant components can be measured separately in the laboratory; but such measurements are time-consuming, labor intensive, and costly. Free-radical analytical system 4 technology has been shown to offer a quick, simple, precise, and reliable method for assessing the oxidative status in dairy cows [14] and in horses [15]. Such technology is particularly useful in the field, where it is not always practical or possible to get samples to a laboratory immediately. The possibility of assessing oxidative stress directly in blood samples provides veterinarians with a simple and reliable method for measuring oxidative stress in clinical situations such as the monitoring of therapy and in the antioxidant supplementation of domestic animals. However, given the lack of reference values for ROMs in ruminants, it is difficult to establish if and when these animals are actually experiencing oxidative stress. Therefore, it is important to calculate the specific referral ranges; because a correct biochemical evaluation of oxidative status is an essential premise to prevent and eventually to treat the effects of oxidative stress in ruminant medicine. Advanced oxidation protein products (AOPPs) are terminal products of proteins exposed to free radicals and arise from the reaction between plasma proteins and chlorinated oxidants mediated by myeloperoxidase, a neutrophil enzyme [16,17]. In humans, AOPPs have been linked to several diseases, such as chronic renal failure [18], diabetes mellitus [19], diabetic nephropathy [20], coronary artery diseases [21], and obesity [22]. Chronic accumulation of AOPPs has been demonstrated to promote inflammatory processes in the diabetic kidney [20] and in chronic renal failure [18], indicating that these products might be a by-product of neutrophil activation during infections. Studies in ruminants have shown higher levels of AOPPs than normal in lambs [23] and dairy cows [24] supplemented with Yerba Mate (*Ilex paraguanensis*). More information about the role of protein oxidation in ruminants' health and about oxidated proteins could be obtained by a comparison of AOPPs with other indicators of protein oxidation, such as advanced glycation end products (AGE). However, a correlation between AGE and inflammatory parameters is usually not found or is only weak, and the induction of proinflammatory activities caused by AOPPs seems to be more intense [25,26], suggesting that oxidative stress is more closely linked to inflammation and acute-phase reactions than to the advanced glycation process and its end products. AOPPs could thus better describe acute inflammation, whereas AGE might serve more as a marker of chronic long-lasting damage [25]. These observations are highly relevant, as increased levels of AOPPs could indicate the presence of inflammatory processes that can potentially compromise the correct embryonic development in dairy cows [14,27]. Lipids, in particular those that are polyunsaturated, are prone to oxidation. Lipids are one of the most susceptible substrates to damage by free radicals, and biomarkers of lipid peroxidation are considered the best indicators of oxidative stress [28]. Malondialdehyde (MDA) is one of several low-molecular-weight end products formed during radical-induced decomposition of polyunsaturated fatty acids [29]. MDA readily reacts with thiobarbituric acid, producing a red pigment that can be easily measured by spectrophotometry in the form of thiobarbituric acid-reactive substances (TBARS, [29]). It is worth noting that the MDA assay has been criticized for its low specificity and for artifact formation, since only a fraction of the MDA measured is actually generated in vivo. Furthermore, the TBARS assay, a common method used to measure MDA, is considered inaccurate, and returns results that differ according to the assay conditions used [30]. For example, studies on dairy cows have yielded contrasting results, with some reports failing to show any significant changes in plasma MDA concentrations during the peripartum period [31]; whereas in other studies MDA or TBARS concentrations were shown to increase around calving [8,16,32]. This apparent discrepancy could also have been mainly due to the great variation in individual MDA concentrations measured in the studies by Castillo et al. [31]. Similarly, studies on

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