



Opinion

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The Importance of Antioxidants in the Enteric Nervous System

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Abstract

In recent years, natural antioxidants have been studied for their therapeutic potential because they are able to maintain the balance of oxidizing agents, thus mitigating oxidative stress. Oxidative stress is a key factor in various diseases related to the enteric nervous system, which is responsible for regulating activities in the digestive system influenced by the autonomic nervous system. The following review examines the importance of antioxidants in the enteric nervous system, boarding some examples of antioxidants with outstanding properties.

Keywords: Oxidative stress, Antioxidants, Enteric nervous system

Introduction

Antioxidants are defined as those substances that possess the ability to inhibit oxidation [1], can be classified into different categories, as natural antioxidants, or as synthetic antioxidants. In the first group we can subdivide exogenous antioxidants, which are mostly obtained from plant sources (carotenoids, vitamins, polyphenolic compounds), and endogenous antioxidants, where we can find enzymatic (glutathione peroxidase, glutathione reductase, catalase, among others) and non-enzymatic (ubiquinone, bilirubin, melatonin, among others). While in the synthesized ones their basis is to resemble a structure of polyphenolic compounds (Butylated Hydroxyanisole (BHA), Butylated Hydroxytoluene (BHT) [2-4]. However, in both groups, their main function is to maintain a balance of oxidative species, since an imbalance of these species can damage the cells of the organism, causing oxidative stress [5]. Oxidative stress is a key factor in several diseases such as cancer, Alzheimer's disease [6], gastric ulcer [7] and Parkinson's disease

[8], among others. However, the mechanism of antioxidants in reducing oxidative stress in the enteric nervous system has not been well clarified, so this review aims to resume the participation of some antioxidants.

Relationship of the Enteric System with Oxidative Stress-Antioxidants

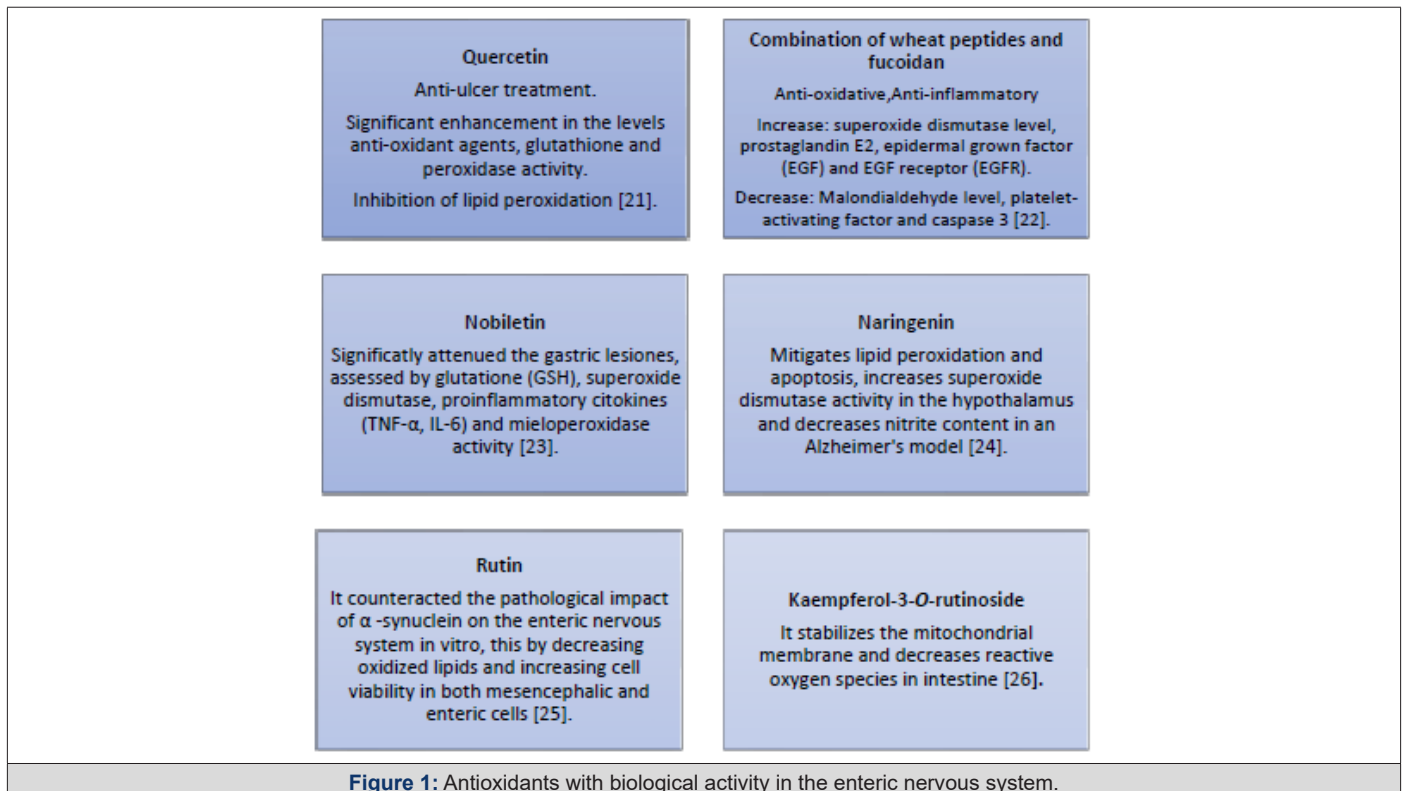
The enteric nervous system is a complex neuronal network present in the wall of the digestive system, organized in two ganglionic plexuses called the submucosal plexus and the myenteric plexus [9-11]. This system is responsible for regulating smooth muscle contractions, secretion, and blood flow in the digestive tract, influenced by the Autonomic Nervous System (ANS), as well as being responsible for the digestive secretions of electrolytes, enzymes, and mucus is involved in the immune and defensive functions of the digestive tract [11]. Given the complexity of its function, there

are multiple and complex causes that can trigger an affection of the enteric system, some of which are mainly genetic etiology where we find syndromes and congenital diseases such as Hirschsprung's disease [12], others can be of infectious origin such as Chagas disease or more recently evidence has been found of affections caused by SARS-CoV-2 [13]. By hormones such as oxytocin, adrenaline or corticotropin, which can alter the activity of the enteric system, as observed in conditions of psychological stress, anxiety, or extreme experiences [11].

Evidence has also been found that neurodegenerative diseases can affect both the Central Nervous System (CNS) and the ENS, such as Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis, spongiform encephalopathies, and even autism spectrum disorders [14,15]. However, one of the mechanisms that affects the ENS in most diseases is the dysregulation of the redox state caused by infections, poor nutrition or neurodegenerative diseases, which when there is oxidative stress can affect enteric neurons, glia, epithelium and mucosa, causing alterations in survival as well as in neurotransmission [11,16,17]. One of the inhibitory neurotransmitters on which most studies focus is Nitric Oxide (NO), which is one of the radicals present in the chain of formation of reactive nitrogen and oxygen species. This neurotransmitter is produced by enteric neurons and is responsible for the activation of NO-Guanylate Cyclase (NO-GC) enzymes present in both brain and intestinal tissues, specifically in the myenteric plexus, smooth muscle cells

and Interstitial Cells of Cajal (ICC) [11,18].

Recent publications have mentioned the close relationship between oxidative stress and gastrointestinal involvement in CHF, as it is proposed that the synthesis of NO is increased in the subtypes of ICC: Myenteric Plexus and Submucosa, may cause an increase in intracellular calcium, leading to an overproduction of free radicals in the cytoplasm, causing cellular damage [19] and consequently affecting, for example, the ENS. In Parkinson's disease, gastrointestinal motility is affected because there may be a pathogenic transmission through the vagus nerve from the ENS to the CNS; this correlation has been confirmed by the appearance of Lewy bodies and alpha-synuclein inclusions in neurons of the vagus and myenteric plexus. On the other hand, the overproduction of Reactive Oxygen Species (ROS) and mitochondrial dysfunction are closely related to calcium overload, which promotes the accumulation of proinflammatory cytokines, tau protein, and neurotoxins that cause reduced cerebral blood flow, angiopathy, and vascular dysfunction in AD [11,20]. The involvement of the antioxidant machinery is therefore fundamental, as it is responsible for promoting the balance of ROS and mitigating oxidative stress in the organism [5]. In recent years, there has been increasing interest in the function and action of antioxidants in various pathologies, and even the possible mechanisms of action are beginning to be elucidated. Figure 1 shows some antioxidants and their effects mainly in the ENS and CNS [21-26] (Figure 1).



Conclusions

The enteric nervous system is one of the most complex systems due to its relationship with the CNS and the digestive system; however, in recent years, studies have focused on oxidative stress as the main cause of the development of diseases, so different antioxidant compounds have been evaluated as an alternative for the preventive treatment of pathologies derived from damage caused by ROS. However, more research is needed to elucidate the mechanisms of action of antioxidants in counteracting neurodegenerative diseases such as those of the digestive system.

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Conflicts of Interest

None.

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