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Mini Review

Nanotechnology-Based Polyphenol Delivery: A Novel Therapeutic Strategy for the Treatment of Age-Related Neurodegenerative Disorder

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Received: March 27, 2017; **Accepted:** April 20, 2017; **Published:** April 28, 2017

Abstract

Age is the major risk factor for the development and progression of Neurodegenerative Diseases (ND). The extension of lifespan is considered a leading cause of the increase in ND prevalence, especially in developing countries. Currently, there is no cure for any of them; thus, the challenge for physicians and researchers is to discover therapeutic strategies able to slow down neurodegeneration and/or improve the patient's quality of life. In addition to genetics and environmental stressors, the increase in cellular oxidative stress as one of the potential risk factors in ND has been demonstrated. Over the past years the scientific community has focused on the antioxidant properties of a heterogeneous class of natural compounds, known as nutraceuticals, such as vitamins, carotenoids and polyphenols. Among polyphenols, curcumin, resveratrol and tea polyphenols are the most extensively investigated given their therapeutic potential for ND treatment. Despite the strong antioxidant activity of polyphenols, their low bioavailability and rapid metabolism are the major issues that affect their neuroprotective potentiality. A promising solution lies in polymeric nanoparticle-based polyphenol delivery systems that prevent the degradation of bioactive compounds and enhance their absorption and bioavailability. Currently, food-grade lipid-based nanoparticles, polysaccharide nanoparticles, nanoemulsions, biopolymeric nanoparticles, nanocomplexes (proteins, carbohydrates) and copolymers (protein-carbohydrate conjugates) are highly investigated nanoparticle systems to enhance the bioavailability of polyphenols. The high potential of nanoparticle-basedsystems in nutraceutical delivery might make them a good therapeutic strategy for the treatment of ND.

Keywords: Aging; Neurodegenerative disease; Polyphenols; Bioavailability; Solubility; Nanoparticle-based delivery systems

Abbreviations

ND: Neurodegenerative Disease; AD: Alzheimer's Disease; PD: Parkinson's Disease; HD: Huntington's Disease; ALS: Amyotrophic Lateral Sclerosis; ROS: Reactive Oxygen Species; ECGC: (-)-epigallocatechin-3-gallate; Aβ: amyloid-beta; BBB: Blood-Brain Barrier

Introduction

Aging is a primary risk factor of Neurodegenerative Disorders (ND). Neurodegeneration is a pathological condition characterized by dysfunction and/or slowly progressive loss of selective neuronal cells in the brain and spinal cord [1,2]. ND, such as Alzheimer's Disease (AD), Parkinson's Disease (PD), Huntington's Disease (HD) and Amyotrophic Lateral Sclerosis (ALS) share common cellular and molecular mechanisms including protein misfolding and aggregation, mitochondrial dysfunction, defective cellular transport and inflammation [3]. They are severely disabling, progressive and incurable disorders, thus a pressing problem in terms of human suffering and economic cost [4,5]. It is widely reported that the incidence of age-related neurodegenerative disorders can be expected to increase, given that the number of people aged 65 or older is foreseen to grow to 20% of the population by the year 2050, especially in developing countries [6,7]. At present, the challenge for physicians and researchers is to discover new therapeutic strategies to slow down neurodegeneration and thus improvethe patient's quality of life.

Although the etiology of ND has not yet been fully elucidated, risk factors such as genetics and environmental stressors may play key roles. In addition, the increase in cellular oxidative stress as one of the potential common etiologies in ND has been also reported [2,8]. Increased oxidative stress determines cell damage, impairment of the DNA repair mechanisms and mitochondrial dysfunction, which in turn have been recognized as crucial factors in accelerating the aging process and in the development and progression of ND [9,10].

Recently, a considerable number of natural compounds present in the diet and able to prevent the occurrence of ND have been described. Several studies have focused on the antioxidant activity of a heterogeneous class of molecules, known as nutraceuticals, such as vitamins, carotenoids and polyphenols; these compounds are widely present in fruit, vegetables, cereals, olives, dry legumes, beverages (such as tea, wine, beer and chocolate) and in other natural products [11,12]. Among nutraceutical compounds, polyphenols are considered to be one of the most bioactive agents. Despite the

Citation: Squillaro T, Peluso G and Melone MAB. Nanotechnology-Based Polyphenol Delivery: A Novel Therapeutic Strategy for the Treatment of Age-Related Neurodegenerative Disorder. Austin Aging Res. 2017; 1(1): 1004.

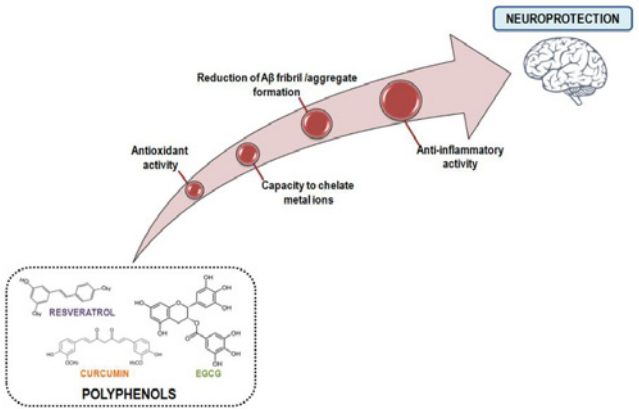

Figure 1: Proposed biological processes involved in neuroprotection by natural polyphenols.

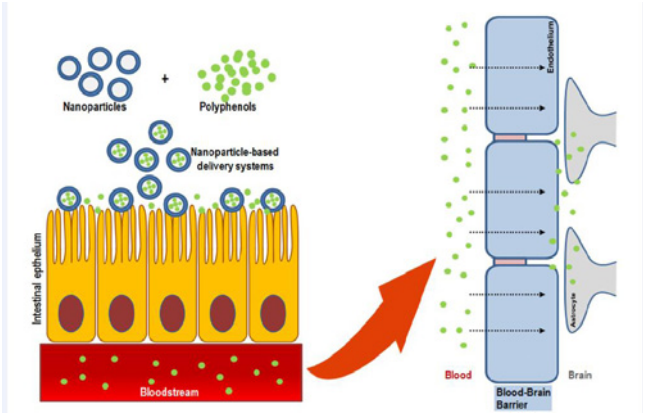

Figure 2: Schematic representation showing the capacity of nanoparticle-based delivery systems to enhance the bioavailability of polyphenols by extending the residence time in the intestinal tract, increasing their concentration in the bloodstream and improving their ability to cross the blood-brain barrier.

strong antioxidant and other biological activities of polyphenols, their inefficient delivery system and low oral bioavailability are the major issues that affect their neuroprotective potentiality and limit their applications in functional food or medicine [13].

Recently, polymeric nanoparticle-based delivery systems that encapsulate bioactive compounds have been developed for both biomedical and functional food sectors in order to preserve them from the adverse environment of the gastrointestinal tract and transport them to target sites [14-16]. These systems offer a relevant strategy to improve the delivery of bioactive compounds with low oral bioavailability.

In the present mini-review, we discuss the polyphenol antioxidant and neuroprotective properties, the main factors influencing their bioavailability and the highly investigated nanoparticle-based polyphenol delivery systems.

Oxidative Stress and Neurodegeneration

Cellular Reactive Oxygen Species (ROS) generation derives from both exogenous (ultra violet rays, ionizing radiations, drugs, environmental toxins and chemicals) and endogenous sources (mitochondrial and non-mitochondrial ROS-generating enzymes). In healthy conditions, the production of ROS is balanced by defense mechanisms of antioxidant enzymes (e.g. superoxide dismutase, catalase, glutathione peroxidase) and small-molecule antioxidants (e.g. vitamin E and vitamin C). On the other hand, in some pathological conditions, such as ND, an imbalance between the ROS production and the antioxidant defense system resulting in excessive accumulation of ROS has been reported [8,10]. Prolonged oxidative stress has been recognized as a crucial factor in accelerating the aging process and in the development and progression of ND. Furthermore, alterations in the activity of antioxidant enzymes, mitochondrial perturbation and mutations in specific genes are widely described in ND [2,9]. As the brain is one of the most metabolically active organs, it is extremely vulnerable to ROS-mediated injury for many reasons, e.g. excessive ROS production due to high oxygen consumption to sustain high energy needs; a high level of polyunsaturated fatty acids in neuronal membranes makes them particularly vulnerable to free radical attack,insufficient antioxidant defense mechanisms and, in particular, low levels of catalase, glutathione peroxidase, and vitamin E [17,18].

According to these findings, the challenge for the scientific community is to find agents able to protect the brain against oxidative damage and thereby potentially treat neurodegeneration.

Polyphenols and Neurodegeneration

Polyphenols are secondary metabolites of plants commonly involved in the defense against ultraviolet radiation or pathogens [19]. They have at least one aromatic ring with one or more hydroxyl groups attached and are classified into diferuloylmethanes, stilbenes, flavonoids, phenolic acids and tannins [20,21]. Polyphenols display a high antioxidant activity since they can decrease oxidative damage directly by neutralizing free radicals or indirectly by modulating the expression of free radical-generating enzymes or the expression of intracellular antioxidant defense enzymes [2]. Curcumin (diferuloylmethane), resveratrol (stilbene) and the green tea polyphenol, Epigallocatechin-3-gallate (ECGC) (flavonoid), are the most extensively investigated polyphenols given their therapeutic potential in ND [20,21]. Many epidemiological studies have documented that moderate intake of wine, the most well-known source of resveratrol, can reduce the incidence of age-related ND. Moreover, regular flavonoid-rich food consumption has been correlated with a reduction in dementia risk and a delay in the symptoms of AD [22]. A growing body of evidence suggests the role played by curcumin and resveratrol in enhancing the activity of specific antioxidant enzymes such as superoxide dismutase, catalase and glutathione peroxidase [2,11,23]. In addition to their antioxidant activity, the neuroprotective role of polyphenols can be ascribed to other mechanisms of action such as the reduction in amyloid-beta (Aβ) fibril/aggregate formation (a hallmark of AD) [2,24], the capacity to chelate metal ions accumulating in specific brain regions of AD, PD, HD and ALS patients [2,25] and the anti-inflammatory activity exerted by inhibiting the expression of pro-inflammatory genes (e.g. cyclo-oxygenase, nitric oxide synthesis and several cytokines) (Figure 1) [2,26].

Despite the strong antioxidant and other biological activities of polyphenols, their inefficient delivery system and low oral

bioavailability are the major issues limiting their application in the medical field. The term bioavailability commonly refers to "the fraction of an ingested compound that reaches the systemic circulation and the specific sites where it can exert its biological action" [13,27]. Polyphenol bioavailability relies upon modifications arising at the levels of the first-pass metabolism, permeation in the intestinal tract and/or their low solubility. As polyphenols interact with salivary proteins rich in proline, they are exposed to the stomach acid condition which influences their stability; they are subject to a rapid metabolism and are conjugated to methyl and sulfate groups and glucuronic acid in the intestinal tract and in the liver. These metabolic transformations determine remarkable changes in the polyphenol structure and biological activities [2,28].

Another important issue is the capacity of polyphenols and their metabolites to cross the Blood-Brain Barrier (BBB), a selective diffusion barrierthat limits the passage of most compounds from the bloodstream to the brain tissue [29,30]. The polyphenol permeation rate through the BBB is greatly correlated with their lipophilicity; less polar molecules show a greater brain uptake than the more polar molecules. In accordance with these findings, the polyphenol fraction reaching the bloodstream and thus target tissues, such as the brain, is different from that present in the ingested food.Therefore, the capacity to design a polyphenol delivery system able tocross the BBB and perform its biological activity is the challenge for the scientific community.

Nanoparticle-Based Polyphenol Delivery Systems

At present the use of polyphenols in functional foods or medicine is limited because of their inefficient systemic delivery and low oral bioavailability [14]; thus, new strategies able to modulate polyphenol bioavailability are strongly needed. Recently, polymeric nanoparticle-based delivery systems that encapsulate bioactive compounds have been developed for both biomedical and functional food sectors in order to preserve and transport them to target functions [14-16]. The nanoparticle systems are able to enhance the absorption and bioavailability of bio-functional molecules mainly by protecting them from the adverse environment of the gastrointestinal tract, extending the residence time in the intestinal tract, increasing their permeation in the small intestine and their solubility rate and concentration in the bloodstream, and promoting their conveyance to the target organ (Figure 2) [14,31]. A growing body of studies show that food-grade macromolecules are the best polyphenol delivery systems for oral consumption because of their safety. Macromolecules of food origin are biodegradable, biocompatible and also bio-functional [14,32]. Currently, lipid-based nanoparticles, polysaccharide nanoparticles, nanoemulsions, biopolymeric nanoparticles, nanocomplexes (proteins, carbohydrates), and copolymers (protein-carbohydrate conjugates) are highly investigated food-grade nanoparticle systems to enhance the bioavailability of polyphenols (such as curcumin, resveratrol and ECGC, characterized by poor bioavailability) [14,33,34]. The choice of the most suitable nanoparticle-based delivery system relies upon the polyphenol properties, i.e. their solubility and cell-membrane permeability. Commonly, polyphenols are classified in three groups: i) Low solubility and low cell-membrane permeability (such as curcumin); ii) Low solubility and high cell-membrane permeability (such as resveratrol); iii) High solubility and poor cell-membrane permeability (such as ECGC) [14,35]. Several studies showed the capacity of the solid lipid nanoparticle-based system to improve the solubility and bioavailability of lipid-soluble polyphenols [14,36,37]. Chen et al. demonstrated that solid lipid nanoparticles are able to control curcumin release and improve their bioavailability [38]. The use of food polysaccharides in the nanoparticle preparation is highly investigated given their adhesion capacity to mucosal surfaces, a crucial characteristic for prolonging the polyphenol residence time in the intestine [14]. The literature data report that the protein-polysaccharide complex nanoparticles are a biocompatible strategy to increase polyphenol bioavailability. Hu et al. showed that the encapsulation of ECGC in chitosane-caseinophosphopeptide nanoparticles (a delivery system deriving from the controlled self-assembly of a polysaccharide and a bioactive peptide deriving from the digestion of milk casein) enhances its permeation rate through cell membranes and its antioxidant activity [14,39].

In the last year an increasing body of studies have demonstrated the efficiency of food-grade nanoparticle-based delivery systems in enhancing polyphenol solubility and bioavailability. Despite the promising results, more efforts should be made to improve nanoparticle design, to enhance the stability of nanoparticles in the gastrointestinal environment and to better illuminate the effects of encapsulation on the metabolism of polyphenols [14]. The answer to these issues may provide significant advances in the field of scientific and technological innovation.

Another challenge to be addressed is the presence of possible side effects due to nanoparticle administration. A body of evidence showed that characteristics such as size, surface chemistry, chemical composition, surface activity and solubility may determine the toxic potential of nanoparticles, thus contributing to the increase in studies focusing on the evaluation of the side effects deriving from their exposure. However, the growing use of food-grade materials and biodegradable compounds for nanoparticle manufacture contributes to minimizing the occurrence of adverse health effects. In addition, in vitro assays are widely used to assess the toxicity of nanoparticles by using cell lines chosen according to the exposure route and target organ, and to provide precious findings destined for the setup of preclinical and clinical studies [40]. An interesting in vitro study suggested that Poly(Lactic-co-Glycolic Acid) (PLGA) curcumin nanoparticles were safe and effective [41]. Yallapu and collaborators reported that curcumin nanoformulations appear to be very compatible with erythrocytes and did not show any occurrence of thrombus [42]. A recent study demonstrated that food-grade β-lactoglobulin nanoparticles with various particle size and surface charge were non-cytotoxic to Caco-2 cells [43]. Semete et al. performed a histopathological evaluation to demonstrate the safety of PLGA nanoparticles for Balb/C mouse tissues [44].

Conclusions

Despite the growing evidence of therapeutic effects of polyphenols in the treatment of ND, their low bioavailability still represents a critical concern. Currently, polymeric nanoparticle-based polyphenol delivery systems are considered a promising solution. Although nanoparticles have been shown to improve the bioactive compound

concentration in the bloodstream, more efforts are needed to translate these findings "from bench to bedside". The optimization of nanoparticle based-systems might prove to be an effectivestrategy to improve the delivery of bioactive compounds with low bioavailability, such as curcumin and resveratrol, for the treatment of ND.

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Citation: Squillaro T, Peluso G and Melone MAB. Nanotechnology-Based Polyphenol Delivery: A Novel Therapeutic Strategy for the Treatment of Age-Related Neurodegenerative Disorder. Austin Aging Res. 2017; 1(1): 1004.