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Nanotechnology, A Promising Tool to Combat the Pitfalls of The Phenolic Transport across Blood-Brain Barrier

Domínguez-Perles R[1], Queiroz M[2], Barros AIRNA[2], and García-Viguera C[1]*

[1]*Department of Food Science and Technology, Campus de Espinardo, Spain*

[2]*University of Trás-os- Montes and Alto Douro, Portugal*

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***Corresponding author:** Cristina García, Research Group on Quality, Safety and Bioactivity of Plant Foods. Department of Food Science and Technology, CEBAS-CSIC, Campus de Espinardo – 25, 30100 Espinardo, Spain; Tel: +34-00-968396200 Ext: 6304; Email: cgviguera@cebas.csic.es

Abstract

The growing interest in natural polyphenols during the last years is aimed to identify new applications to these natural compounds of biological interest, as well as to design new uses in the field of health care. In this regard, to date, it has been demonstrated a wide range of positive health effects for phenolic compounds, being most research studies focused on the anti-oxidant, anti- inflammatory, anti-microbial, and anti-aging effects, while the biological potential demonstrated for these compounds have led to search for specific applications in the field of neurodegenerative diseases. Indeed, brain related diseases factors like antioxidant and anti-inflammatory capacities, as well as proteins defibrillation and mitochondrial regulation have been pointed as the advantages of the use of all kind of phenolics. However, the transport of these molecules to can be prevented by specific biological barriers developed to protect these sensible structures. In this short review, the effects of phenolic compounds described in nervous tissues and cells, has been studied, as well as the downsides of their use, and how nanotechnology can help to provide new valuable alternatives to get enhanced biological impacts despite de constraint represented by the blood-brain barrier.

Keywords: Phenolic compounds; Nervous system; Blood-brain barriers; Bioavailability; Bassive transport; Bioactivity

Introduction

For several decades, it has been experienced a growing interest in natural phenolic compounds as bioactive molecules present in edible and non-edible plant material with potential effects on human health. The main goal of this trend is to find new applications to these natural compounds of biological interest and design new uses for them in the field of medical treatments [1-3]. Indeed, to date it has been demonstrated a wide range of positive health effects for phenolic compounds, being most research studies focused on the anti-oxidant, anti-inflammatory, anti-microbial, and anti-aging effects. In the last years, the biological potential demonstrated for phenolic compounds have led to the interest in assessing their effects in the treatment of neurodegenerative diseases [2-6].

Discussion

Proved facts on the neuroprotective effects of phenolic compounds

Several studies have contributed to establish a link between phenolic compounds and neuroprotection, revealing their potential against aging and neurodegenerative diseases [4,5]. In this regard, it is required to notice that there are innumerous possible patho physiological mechanisms related with neurodegeneration, even though the major pathways already identified are neuro- inflammation, oxidative stress, mitochondrial dysfunction, and protein misfolding, all of them susceptible to be affected by the presence of polyphenol [4,7,8]. However, despite the plethora of mechanisms responsible for neurodegeneration, oxidative damage to neuron molecules, and decreased cellular antioxidant species, such as glutathione in the brain, are major aspects of most common neurological diseases [4,8,9]. For instance, dopaminergic neurons of the central nervous system are susceptible to oxidative stress, turning oxidative stress into a risk factor for nigral substance degeneration. In this frame, polyphenols are recognized on their antioxidant particularities, while their presence in neurons has been related with lower levels of reactive oxygen species (ROS) [8]. However, radical scavenging is not the only biological activity of phenolics, which besides working as antioxidants, are also competent to increase the activity and expression of enzymes with antioxidant power. Hence, the endogenous glutathione system, one of the most important antioxidant defense of the organism, can also be boosted by

polyphenols, according to previous works *in vitro* and *in vivo* [8-10]. In addition, polyphenols also contribute to diminish the level of pro-inflammatory cytokines in brain therapeutic models, such as IL-1β, TNF-α, IL-4, IL-6, and IL-10 [10-12]. Resveratrol has been shown capable to decrease the level of nitrite and the expression of myeloperoxidase, an enzyme that, during microglial respiration, produces hypochlorous acid and tyrosyl radical that are cytotoxic to pathogens, but also to cells [13] Some polyphenols have shown the ability to prevent protein fibrillization, by promoting the clearance of aggregates and oligomers, thus stimulating the cell autophagic pathways [8] which proves once more their neuroprotective actions. Regarding this, for instance, phenolic compounds from green tea have been characterized on their fibril-destabilizing properties in neurological diseases. Hence, resorting to several *in vitro* studies, it has been demonstrated that epigallocatechin gallate and quercetin can prevent growth and aggregation of amyloidogenic α-synuclein and reduce their levels in the hippocampus and the striatum [14-16]. Mitochondrial disturbances can also be responsible for the damage observed in neurological diseases. Indeed, the loss of the mitochondrial transmembrane potential triggers mechanisms of apoptosis in dopaminergic neurons. In this sense, polyphenols have been noticed as competent to enhance mitochondrial function by increasing the ATP production, while lower ROS and lactate production [17,18].

Constraints to the biological action of polyphenols in the nervous tissues

Despite all the studies aimed at characterizing *in vitro* and *in vivo* the benefits of phenolic compounds, there are several biological limits that interfere with the beneficial properties of these compounds, preventing the direct extrapolation of the results retrieved, so far, on biological activity to the pathophysiology of the nervous system [19]. One of the main obstacle for the biological action of phenolics in cells is their bioavailability. In this regard, the amount of phenolic compounds that reaches the cells is conditioned by the physiochemical properties of the compounds, their interaction with food matrix, and the response to the gastrointestinal tract conditions, which means that in most cases, the concentration available is significantly lower to that administrated and, even, to that tested upon *in vitro* characterizations [8,12,20]. Moreover, a high proportion of phenolic compounds are esterified in glycoside or polymeric forms. This entails that they are poorly absorbed in the gastrointestinal tract, rapidly metabolized upon phase I and II metabolism, and excreted by both urine and bile [4,12,21,22]. This implies that, since the phenolic compounds bioactivity is mostly executed by their metabolites, as a result of the modifications triggered upon the gastrointestinal digestion, it could appear metabolites less effective as antioxidants than the original compounds [23,24]. Despite the evident effect of the factors discussed above, the main obstacle to take advantage of the biological potential of polyphenolic compounds in the nervous system is the final concentrations reached in the cells that for most compounds is not sufficient to trigger operative reactions capable to restore physiological condition of the nervous cells [4]. This is mainly due to the barriers existent between the central nervous system and the environments surrounding it [25]. In this concern, the most selective barrier is represented by the blood-brain barrier that constitutes a dynamic interface between the peripheral tissues and the central nervous system. Blood-brain barrier maintains normal brain function, preserving the homeostatic conditions for nervous cells, required to work appropriately and also shield them against invading organisms and damaging elements [26-28]. This barrier is primarily constituted of endothelial cells connected by adherent tight junctions and functions as a physical, metabolic/enzymatic, transport, and immunological barriers [25,27].

The main difficulties that the phenolic compounds find to cross to the blood-brain barrier are the endothelium of brain microvessles and multidrug resistance-associated proteins. Despite this, some phenolic compounds, such as anthocyanins and curcumin, are able to pass through in a lipophilicity-dependent way, while others cross the blood-brain barrier by a mechanism of phosphorylation/dephosphorylation that regulate their passage (quercetin), but the mechanisms of transport into the blood-brain barrier are still relatively unknown [4,29] and the administration of compounds of interest to develop their biological action in these cells deserve to be explored towards the description of new alternatives.

Nanotechnology contribution to bioavailability of phenolic compounds in brain cells

The drawbacks drawn related to polyphenols bioavailability in cells of the central nervous system led to an interesting field of studies to find new ways to overcome those pitfalls and thus, to take advantage of the biological properties of phenolic compounds. Nanotechnology seems to be a valuable contributor to give response to these constraints, and more specifically nanoparticles. These are promising and versatile delivery systems to transport compounds into remote areas of the body, like the brain [25-27]. Usually nanoparticles size range between 1 and 100nm and can have a natural or synthetic origin [25] Synthetic nanoparticles are manufactured using two basic methods: top-down and bottom-up. The first consists in size-reduction by mechanical processes to shrunk big materials to nano-scale, while the second one consists in the aggregation of diverse nanoparticles [18]. Among the different materials used to obtain nanoparticles it can be stressed poly (ethylenimine), poly (alkylcanonaacrylates) poly (amidoamine) dendrimers, poly (ε-caprolactone), poly (lactic-co- glycolic acid), polyesters (poly(lactic acid), and inorganic materials like gold and silica [18,25-29].

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The commodities and the nanoparticles obtained from them must be nontoxic, biodegradable, and biocompatible, be featured by a prolonged blood circulation time, and be stable, avoiding aggregation and dissociation [18]. These carriers can transport compounds by adsorbing, entrapping or bounding covalently to them [30,31]. The properties of nanoparticles make them a promising system to deliver biologically active compounds into brain, due to the possibility of modifying size, shape, hydrophobicity, surface charge, chemistry, and coating. In this connection, addressing appropriately these features, according to the characteristics of the bioactive molecule and the target tissue were their activity is desired can contribute to enhance the transport of phenolic compounds to the brain and thus, to improve their stability, while circulating, controlling the release of the compound through the blood-brain barrier [25,33].

Nanoparticles improve the solubility of phenolics by encapsulating them, and also protect the compounds from degradation in he gastrointestinal tract. Besides that, and maybe the most important feature of including polyphenols in nanoparticles is that they are able to enhance the absorption of the phenolic compound in brain cells either by disrupting the tight junction of the blood-brain barrier or promote the direct intake by endocytosis [18,25]. Regardless of all that some factors still need to be further studied to make nanoparticles even more helpful in the transport of bioactive compounds to brain cells. Factors like pH, ions, and enzymes, among others, can negatively modulate the properties of the nanoparticles and their delivery as well.

Conclusion

Phenolic compounds from all sorts of plants have been long studied regarding their potential use as bioactive agents. In brain related diseases there are a large amount of evidence that points towards the several potential uses of phenolic compounds as treatments for those diseases. Factors like antioxidant and anti-inflammatory capacities, as well as proteins defibrillation and mitochondrial regulation, have been pointed as the advantages of the use of all kind of phenolics. Otherwise, the transport of those molecules to cells and tissues, where they can be helpful, can be very complicated or even impossible and, in most cases, this situation is responsible for the loss of important properties of metabolites from phenolic compounds. Nano carriers present themselves as an innovating solution that can help to diminish in a great extent the pitfall of phenolic compounds bioavailability, specially concerning the central nervous system. Thus, although nanotechnology seems to contribute to promising solutions, additional studies should be made in order to make nano carriers even more resistant and suitable for the transport of a growing number of phenolic compounds, which might be helpful to combat neurodegenerative disabling illness.

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