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Commentary

# Nano-delivery systems for encapsulation of dietary polyphenols: An experimental approach for neurodegenerative diseases and brain tumors

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ABSTRACT

Neurodegenerative diseases (NDs) and brain tumors are severe, disabling, and incurable disorders that represent a critical problem regarding human suffering and the economic burden on the healthcare system. Because of the lack of effective therapies to treat NDs and brain tumors, the challenge for physicians is to discover new drugs to improve their patients' quality of life. In addition to risk factors such as genetics and environmental influences, increased cellular oxidative stress has been reported as one of the potential common etiologies in both disorders.

Given their antioxidant and anti-inflammatory potential, dietary polyphenols are considered to be one of the most bioactive natural agents in chronic disease prevention and treatment. Despite the protective activity of polyphenols, their inefficient delivery systems and poor bioavailability strongly limit their use in medicine and functional food. A potential solution lies in polymeric nanoparticle-based polyphenol delivery systems that are able to enhance their absorption across the gastrointestinal tract, improve their bioavailability, and transport them to target organs.

In the present manuscript, we provide an overview of the primary polyphenols used for ND and brain tumor prevention and treatment by focusing on recent findings, the principal factors limiting their application in clinical practice, and a promising delivery strategy to improve their bioavailability.

## 1. Introduction

Diet has a significant effect on human health. A growing body of literature now shows that diet in human health can no longer be considered simple nutrition because the quality and quantity of dietary intake greatly influence cell functions, epigenetic modifications, and gene expression [1].

Epidemiological studies show that an adherence to the traditional Mediterranean diet (MD)—a model of healthy eating based on consumption of a variety of vegetables, fruits, cereals, legumes, fish, seeds, nuts, olive oil, and moderate intake of red wine—is associated with a reduced incidence of several chronic diseases [2–4]. The MD provides a high absorption of vitamins, minerals, and variety of phytochemicals, such as carotenoids and polyphenols. Because of their anti-oxidant and anti-inflammatory activities, polyphenols are considered to be significant contributors to the overall health benefits of the MD [5]. Several studies demonstrate an inverse correlation between the consumption of polyphenols and the risk of developing numerous diseases, such as cardiovascular diseases, diabetes, NDs, and tumors, including brain tumors [6–8].

Neurodegeneration results in the slow and gradual dysfunction and loss of neurons in the brain and/or spinal cord. It is the primary pathological feature of acute and chronic NDs, such as Huntington's disease (HD), Alzheimer's disease (AD), and Parkinson's disease (PD) [9].

Brain tumors are the result of uncontrolled brain cell growth characterized by enhanced resistance to apoptosis [10]. Although NDs and brain tumors are two distinct pathological disorders, emerging evidence indicates that these diseases share common molecular and genetic mechanisms involved in dysregulated cancer cell growth and the progression of NDs [8,10].

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The causative etiology of these two conditions has not yet been fully explained, but risk factors, such as genetics and environmental stressors (diet, cigarette smoking, exposure to radiation or chemicals), seem to play critical roles [8,11]. In addition, an increase in cellular oxidative stress has been suggested as a contributing factor in both disorders [12].

Oxidative stress results from the imbalance between the production of reactive oxygen species (ROS) and antioxidant defenses. It leads to oxidative damage to DNA, proteins, and lipids; impairment of DNA repair mechanisms; mitochondrial dysfunction; and genome instability [13,14]. In particular, the brain is more susceptible to ROS injury than other organs because the high oxygen consumption required to meet its high energy needs results in excessive ROS production, the presence of high levels of polyunsaturated fatty acids in neuronal membranes that make them more prone to oxidation, and inadequate antioxidant defense mechanisms [15].

As potent antioxidant and anti-inflammatory molecules, dietary polyphenols may be promising candidates for the prevention and treatment of several chronic diseases [16]. Nevertheless, the efficacy of polyphenolic compounds strongly depends on their metabolism and bioavailability, defined as the amount of the ingested compound that can reach the systemic circulation. Polyphenols show a relatively low bioavailability due to both intrinsic factors (such as chemical structure, molecular weight, and low hydrosolubility), and extrinsic factors (such as low stability in the gastrointestinal tract, extensive phase I and phase II metabolism, and rapid elimination) [17,18]. Consequently, the clinical applications of polyphenols are still limited.

Recently, polymeric nanoparticle-based delivery systems able to encapsulate bioactive molecules have been developed in order to protect them from a stomach acid condition, ameliorate their absorption across the gastrointestinal tract, enhance their bioavailability, and transport them to target organs [8,19]. The most studied nanoparticle systems are based on biodegradable and biocompatible polymers that encapsulate polyphenolic molecules in nanostructures, such as nanospheres (NSs), nanocapsules (NCs), solid lipid nanoparticles (SLNs), cyclodextrins (CDs), liposomes (LSs), and micelles (MCs) [6,20].

Below we provide an overview of the primary polyphenols used for treatment of NDs and brain tumor prevention by focusing on recent findings, the principal factors limiting their application in the medical field, and a promising delivery strategy to improve their bioavailability.

## 2. Polyphenols

Polyphenols represent one of the most numerous and extensively distributed groups of natural compounds in the vegetable kingdom [21]. They are present as secondary metabolites of many plants and are involved in the defense against environmental stresses, such as ultraviolet radiation, pathogen infection, herbivores, and nutrient deficiency [6,8]. Furthermore, polyphenols contribute to the color and organoleptic proprieties of plants [6]. This class of molecules is widely present in fruits, vegetables, cereals, olives, dry legumes, beverages (such as tea, wine, beer, coffee, and chocolate), and in other natural products [22–24]. To date, more than 8000 different polyphenolic compounds have been identified [21].

Polyphenols have “at least one aromatic ring with one or more hydroxyl groups attached” and can be classified into flavonoids, phenolic acids, stilibenes, and lignans (Table 1) [17,25,26].

The basic structure of flavonoids contains the flavane nucleus (2-phenyl-benzo-γ pyran), which consists of 15 carbons with two aromatic rings connected by a three-carbon bridge ($C_6$-$C_3$-$C_6$). The basic flavonoid skeleton can present numerous substituents. Most flavonoids come about naturally as glycosides rather than aglycones. These polyphenolic compounds are sub-classified into flavones, flavonols, flavan-3-ols, isoflavones, flavanones, and anthocyanidins (Table 1). Other flavonoid groups, which are quantitatively more minor dietary components, are the chalcones, dihydrochalcones, dihydroflavonols, flavan-3,4-diols, coumarins, and aurones [19,21,26].

The phenolic acids can be further divided into benzoic acid (such as gallic acid) and cinnamic acid derivatives (including ferulic, caffeic, and coumaric acids) based on $C_1$–$C_6$ and $C_3$–$C_6$ backbones, respectively (Table 1) [21,26].

Stilibenes are characterized by a double bond (1,2-diarylethene) connecting the phenolic ring ($C_6$-$C_2$-$C_6$). The most representative stilibene is resveratrol and can occur in both *cis* and *trans* isomeric forms as well as conjugated derivatives (Table 1) [26].

Lignans are diphenolic compounds with a 2,3-dibenzylbutane structure formed by the dimerization of two cinnamic acid residues. Their basic chemical structure is referred to as $(C_6$-$C_3)_2$ (Table 1) [17].

Natural polyphenols have been shown to have potent antioxidant activity since they can inhibit the generation of free radicals by deactivating their active species and/or precursors. They also act as radical scavengers in the lipid peroxidation chain reactions, donating an electron to the free radical [21,27]. The role of polyphenolic compounds in promoting the activity of anti-oxidant enzymes, such as glutathione peroxidase, catalase, and superoxide dismutase, has been widely reported [21]. In addition to their antioxidant proprieties, most of the polyphenolic compounds show a modulatory activity in several cell signaling pathways associated with survival, cell growth, proliferation, differentiation, and apoptosis [21,28].

Dietary polyphenols play important roles in human health; it is widely shown that high intake of fruits, vegetables, and cereals, which are rich in polyphenolic molecules, has been related to lowered risks of chronic disorders [21,27].

In this review, we focus on the most extensively investigated polyphenols: curcumin (diferuloylmethane), the main bioactive component in turmeric; resveratrol (stilibene), abundant in grape skin and red wine; and the flavonoid epigallocatechin-3-gallate (EGCG), abundant in solid green tea extracts [8,25].

## 3. Polyphenols and neurodegeneration

### 3.1. Neuroprotective activity

NDs are a heterogeneous group of disorders characterized by the dysfunction and/or progressive loss of post-mitotic neuronal cells in the central or peripheral nervous system [17]. The major clinical manifestations of neurodegeneration are cognitive decline, dementia, motor abnormalities, sleep disturbances, behavioral, and psychological disorders [29]. Common NDs include AD, PD, and HD; these disorders share common cellular and molecular mechanisms, including accumulation of abnormal, misfolded, and aggregated proteins; mitochondrial dysfunction; inflammation; oxidative stress accumulation; defective neuronal transport; impairment of autophagic process; and alteration in proteasome activity [30–39].

NDs are progressive, severely disabling, and incurable diseases, and represent a serious problem regarding human suffering and health care system costs [40]. Because of the lack of effective therapies to treat them, the challenge for physicians and researchers is to discover new drugs to slow down neurodegeneration and improve their patients’ quality of life.

In addition to risk factors such as genetics and environmental influences, the increase in cellular oxidative stress also plays a key role in the common etiologies of NDs [12,17]. It is widely demonstrated that a dietary intake of polyphenols limits cellular oxidative stress and is a valid strategy for the prevention of NDs (Fig. 1) [41]. Polyphenols exert their anti-oxidant activity through different mechanisms, such as interaction with the hypoxia-inducible factor 1-alpha (HIF-1 alpha) pathway, modulating expression of protective genes against oxidative stress, regulation of ROS by interacting with oxidative pathways, and scavenging metal ions to prevent free radical damage [17,41,42].

A broad range of polyphenols has the ability to chelate metal ions ($Fe^{2+}$, $ZN^{2+}$, $Cu^{2+}$), which accumulate in specific brain regions of ND