Polyphenols as potential enhancers of stem cell therapy against neurodegeneration

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Introduction
Polyphenols comprise an enormous family of phytochemicals that are found in the plant kingdom; many of these are reported to be biologically active. Polyphenols are abundantly found in fruits, vegetables, nuts, cocoa, wine, tea, and coffee; thus, the ingestion of the food sources of polyphenols has been widely recommended to prevent cardiovascular diseases (CVD) (Crowe et al., 2011).

Polyphenols have been extensively studied as a possible natural option in the therapy of a wide range chronic diseases such as diabetes, but also for cardiovascular and neurodegenerative disorders and cancer. However, prior to reviewing such therapeutic effects, it is necessary to determine whether consumption from dietary sources has an association in the origin of the previously mentioned diseases. In this respect, the Mediterranean diet, which is rich in fruits, vegetables, polyunsaturated fats, and low-saturated fat, is considered as a protective diet related to a low risk of cardiovascular and cerebrovascular events, diabetes, neurodegenerative diseases and cancer (Bonaccio et al., 2017; Guasch-Ferré et al., 2017).

Polyphenols have been explored as potential drugs from ancient times, albeit they have not been defined and classified to date (Figure 1). Many natural compounds have been tested in vitro; in that they possess multiple beneficial effects. However, in fact, during only the last 40 years, natural polyphenols have been administered to humans to measure biological effects, and many of these are added to food as supplemental protective agents. Only in the last 15 years, some synthetic polyphenols have been approved for human diseases (Hu et al., 2017).

On the other hand, stem cells were described in 1961 and the advance in their applications are expanding (Pierce and Verney, 1961). The modulation of cellular development and differentiation (including the reversion of differentiated cells into pluripotent cells) through the addition of chemicals or compounds has opened new perspectives in cellular intervention. Some polyphenols are found among compounds exerting effects on stem cells; notwithstanding this, their mechanisms of action are unclear to date.

Regarding chronic degenerative diseases, protection, damage-limiting, and repairing are cornerstone processes; all of which are approached to understand their etiology or progress, but also to identify potential targets and generate new therapeutic strategies. Thus, the history of both polyphenols and stem cells has converged to understand and treat these disrupted processes (Figure 1), and the numbers of articles and projects considering them as a combination are increasing (Figure 2). Polyphenols have mainly demonstrated acting as preventive and protective agents, while therapy with SC to repair damage is increasing. Thus, unsurprisingly, their combinatory use is studied for application in some diseases entailing a high global burden, such as obesity, diabetes mellitus, Alzheimer’s disease (AD), and Parkinson’s disease (PD).

Abstract
The potential of polyphenols for treating chronic-degenerative diseases (particularly neurodegenerative diseases) is attractive. However, the selection of the best polyphenol for each treatment, the mechanisms by which they act, and their efficacy are frequently discussed. In this review, the basics and the advances in the field, as well as suggestions for using natural/synthetic polyphenols alone or in a combinatorial strategy with stem cells, are compiled and discussed. Thus, stem cells exhibit several responses when polyphenols are added to their environment, which could provide us with knowledge for advancing the elucidation of the origin of neurodegeneration. But also, polyphenols are being included in the innovative strategies of novel therapies for treating neurodegenerative diseases as well as metabolic diseases related to neurodegeneration. In this regard, flavonoid compounds are suggested as the best natural polyphenols due to their several mechanisms for acting in ameliorative effects; but increasing reports are involving other polyphenols. Even if some facts limiting bioactivity prevent them from conventional use, some natural polyphenols and derivatives hold the promise for being improved compounds, judged by their induced effects. The current results suggest polyphenols as enhancers of stem cell therapy against the targeted diseases.

Key Words: Alzheimer’s disease; chronic degenerative diseases; combinatorial therapy; metabolism; neurodegenerative diseases; neuronal damage; neuroprotection; Parkinson’s disease; polyphenols; stem cell assays

Search Strategy
In this manuscript, we review the effects of polyphenols on stem cell systems linked to the study of metabolic disorders related to neurodegeneration or neurodegenerative diseases (Information was collected and revised from National Center of Biotechnology Information, PubMed, Global health, Embase, Web of Science, Google scholar and clinical trials databases) but additionally, the potential for them to act as a potential combinatorial therapy on these diseases.

Polyphenols in Metabolic Disorders Related to Neurodegeneration
The reported effects of polyphenols are clearly linked to their potential for regulating metabolic disorders, and these disorders to neurodegenerative diseases (Del Bo et al., 2019). In a systematic review regarding polyphenol intake, it was found that Japan appears to be the major polyphenol consumer (1500 mg/d), followed by North America (900 mg/d). It was found that the greatest polyphenol consumption (1170 mg/d) was associated with less risk of CVD and mortality, and higher polyphenol intake (2632 mg/d) increased protection against metabolic disorders. Nevertheless, some studies referred the mentioned effect at doses of 1200 and above mg/d. Among polyphenols analyzed in diet, lowest risk for cardiovascular events were observed when flavonoids were consumed in a range of 115-944 mg/d. It is noteworthy that the high variability among the results is probably the result of intrinsic factors such as population characteristics, different habits among the countries, markers/endpoint measures for diabetes and CVD, and food sources.

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Another meta-analysis reported that 100 mg/d of flavonoids leads to a linear decrease of all-cause and CVD mortality (6% and 4%, respectively), highlighting the intake of different forms of flavonoids: flavonols, flavones, flavanones, anthocyanidins, and proanthocyanidins (Grosso et al., 2017). The ingestion of a variety of flavonoids (anthocyanidins, proanthocyanidins, flavonols, flavones, flavanones, and flavan-3-ols) of between 139 and 604 mg/d attenuates the risk of CVD (Wang et al., 2014). The mechanisms linked to the previously mentioned effects are mostly that polyphenols may exert antioxidant, anti-inflammatory, and vasodilatory activities (Figure 3). In this manner, a relationship has been found between a low grade of inflammation based on the use of plasmatic (C-reactive protein) and cellular (leukocyte and platelet counts and the granulocyte:lymphocyte ratio) biomarkers and the ability to reduce oxidative stress and inflammation, prevent glycation, and lipoprotein oxidation (Bohn et al., 2015). In fact, resveratrol is considered to modulate macrophage accumulation, inflammation, and the Notch signaling pathway (Huang et al., 2019). Numerous studies in vitro and in vivo were carried out, showing the positive effects of polyphenols from green tea in cancer prevention/treatment involving changes in metabolic rates. The modulation of some of these proteins (particularly enzymes and cytokines) have been linked to neurodegenerative diseases. Unfortunately, little evidence from human studies is available, thus rendering it necessary to run perform investigations to establish safety limits for doses employed within a clinical context, particularly for modulating those cell metabolic disorders linked to neurodegeneration (Zhang et al., 2014).

Grape and wine polyphenols comprise another vast group that has been studied in depth; available data support the benefits on CVD by regulating the inflammatory mediators, decreasing inflammation, protecting optimal blood lipids, and inhibiting platelet aggregation, oxidative stress and low density lipoprotein oxidation (Bohn et al., 2015). In fact, resveratrol is considered one of the most outstanding polyphenols, and the core of the recommended moderate consumption of wine is found in the so-called “French Paradox” (Pastor et al., 2019). This compound possesses many properties, including the ability to reduce oxidative stress and inflammation, prevent glycation, and diabetes, neurodegeneration, and to interfere in the progress of several cell cycle events (Gallniak et al., 2017). In H9c2 cardiac cells treated with high glucose and palmitate as a model of diabetic cardiomyopathy, resveratrol proved to restore autophagy, suppressing mTOR and its downstream effectors 4EBP1 and 4EBP1 through the activation of AMPK and JNK1. A disruption was observed of the Beclin1–Bcl-2 complex, attenuating the blockade of PD-L1/PD-1 has succeeded as immunotherapy in the early stages of several types of cancer (Baumeister et al., 2016). Pre-treatment with EGCG inhibited PD-L1/PD-1 signaling, enhancing T-cell activity, and resulting in the inhibition of the growth of lung cancer (Rawangkan et al., 2018). The inhibition of the growth of lung cancer (Rawangkan et al., 2018). In models of metabolism disorders, EGCG treatment appears to enhance hepatic glucose homeostasis and inhibit glucogenesis by blocking PEPCK and G-6-Pase and lipogenesis through SREBP-1C, PPAR-γ, and ACC1 in the liver. Additionally, molecular simulations revealed that EGCG is capable of binding to the active side of α-glucosidase and α-amylase (Li et al., 2018). EGCG also improves insulin resistance by promoting glucose uptake and the antioxidant enzymes superoxide dismutase (SOD) and glutathione peroxidase, attenuating oxidative stress and the inflammatory markers malondialdehyde, tumor necrosis factor alpha (TNF-α), interleukin 6 (IL-6), and nuclear factor kappa B (NF-κB), in addition to the increase of the glucose transporter 2 protein and downstream proteins peroxisome proliferator-activated receptor and coactivator PGC-1β in human hepatoma HepG2 cells (Zhang et al., 2018). EGCG also modulates macrophage accumulation, inflammation, and the Notch signaling pathway (Huang et al., 2019). Numerous studies in vitro and in vivo were carried out, showing the positive effects of polyphenols from green tea in cancer prevention/treatment involving changes in metabolic rates. The modulation of some of these proteins (particularly enzymes and cytokines) have been linked to neurodegenerative diseases. Unfortunately, little evidence from human studies is available, thus rendering it necessary to run perform investigations to establish safety limits for doses employed within a clinical context, particularly for modulating those cell metabolic disorders linked to neurodegeneration (Zhang et al., 2014).
Moreover, it should be considered that the role of polyphenols in the gut, and probably key for regulating the absorption of nutrients and substances regulating metabolism, is due to their unique regulation of bacterial strains in the gut microbiota, in part through action on the barrier integrity involving cell-regulation effects, and for the prevention of the entry of bacterial fragments such as lipopolysaccharide into the blood (Cardona et al., 2013; Roopchand et al., 2015; Schneeberger et al., 2015; Zhu et al., 2015; Anhe et al., 2016). It should be emphasized that, regardless of the polyphenol type, adequate intake levels depend on the desired gene-to-modulate (Sears and Ricordi 2012; Sears, 2017).

### Polyphenols Regulating Processes Linked to the Origin of Neurodegeneration

Neurodegenerative disorders are diseases of the nervous system (brain, spinal cord, and peripheral nerves) whose origin can derive from metabolic, infectious, toxic, or even hereditary processes (Hou et al., 2019). In recent decades, these pathologies represent a significant public health, social, and financial problem, due to the increase in life expectancy, increasing their prevalence, morbidity, and mortality (Hou et al., 2019; Hung et al., 2019). Some factors such as environmental and genetic factors play a key role for suffering from and for the progression of neurodegenerative diseases (Migliore and Coppeede, 2009). In developed countries, pathologies such as Alzheimer disease, cerebrovascular accidents, and Parkinson disease comprise a great clinical problem (Migliore and Coppeede, 2009; Hung et al., 2019). Patients with neurodegenerative diseases generally experience a gradual loss of memory and reasoning capability, mood changes, and personality alterations (Losada-Barreiro and Bravo-Diaz, 2017).

Although most neurodegenerative diseases have different pathological characteristics and their origins are not totally clear, most of them entertain important points of convergence. Modifications in neuronal electrical activity (Duffy et al., 1984; Surmeier and Schumacker, 2013; Kumar et al., 2017), mitochondrial dysfunction (Wu et al., 2019), inflammation (Swardfager et al., 2010; Green et al., 2019), protein-handling abnormalities (Guerra-Araiza et al., 2013; Song and Zou, 2015), and oxidative stress (Song and Zou, 2015) are some of the changes observed in neurodegenerative diseases.

Dysfunctions in voltage-dependent ion channels are common in neurological pathologies (Duffy et al., 1984; Kumar et al., 2017). The primary function of voltage-gated ion channels is the generation and propagation of action potential in neurons. Reports indicate that changes in voltage-gated potassium (Kv) channels are important components in the physiological changes in AD (Surmeier and Schumacker, 2013). Also, electrical impairment in K-selective voltage-gated channels and voltage-gated sodium channels are critical in multiple sclerosis (Duffy et al., 1984). In PD, electrical disturbances are reported in L-type calcium channels (Surmeier and Schumacker, 2013). Likewise, K-selective voltage-gated channels and voltage-gated sodium channels have been proposed as key elements in the pathogenesis of (Duffy et al., 1984). In this sense, quercetin, catechin and resveratrol blocked sodium current; and quercetin also has effect on calcium channels; suggesting a key role for specific polyphenols in specific tissues or organs.
role as modulator in neurodegeneration through action on ion channels (Wallace et al., 2006).

On the other hand, mitochondrial dysfunction and inflammation are constant in neurodegenerative diseases. In neurodegenerative diseases, a reduction in mitochondrial function may be produced by the following: 1) maintenance of the loss of the chemical and/or electrical transmembrane potential of the inner membrane; 2) dysfunction of the electron transport chain; or 3) decrease in the carriage of vital metabolites into mitochondria (Kumar et al., 2017; Wu et al., 2019). Regarding inflammation, reports indicate an increase of IL-1, TNF-α, and transforming growth factor beta in AD, PD, multiple sclerosis, cataracts, and Huntington’s disease (Swaffager et al., 2010; Chen et al., 2018). In addition, dysregulation in the concentrations of IL-6 has been associated with neurodegenerative diseases (Green et al., 2019).

Protein aggregation and misfolding are common in neurodegenerative diseases. Misfolded proteins are generally inactive; however, the accumulation of these proteins can cause stress in cells and organelles such as the endoplasmic reticulum (Hetz and Saxena, 2017). Other important changes that might affect protein aggregation are their posttranslational modifications. These posttranslational modifications are both reversible and irreversible post-translational chemical changes that occur in the later stages of protein biosynthesis, which have been associated in many neurodegenerative diseases (Hetz and Saxena, 2017).

Even though the etiology of neurodegenerative diseases is not fully elucidated, oxidative stress is one of the most important mechanisms that has been associated with neurodegenerative diseases. Reports indicate that tissues possess distinct oxygen requirements that vary in their metabolic demands. The central nervous system is composed of a large number of fatty acids and with low levels of antioxidant defenses (Guerra-Araiza et al., 2013). The brain requires more than 20% of the total oxygen consumption, in that they require the use of glucose. Neurons and astrocytes are mostly responsible for the oxygen and glucose consumed. Thus, an increase in the production of free radicals or ROS may easily change the redox homeostasis (Gandhi and Abramov, 2012; Song and Zou, 2015). The oxidative stress is originated from the loss of balance in the cell. Redox homeostasis due to two causes 1) the overproduction of ROS or free radicals, and 2) by antioxidant-system dysfunction (Song and Zou, 2015).

Neurodegenerative diseases consistently involve free-radical reactions that are initiated by redox, thermal, or photochemical processes, increasing the oxidative stress (Guerra-Araiza et al., 2013). The accumulation of oxidative stress can produce cellular impairment and may affect the DNA repair system, accelerating aging and neurodegeneration (Gandhi and Abramov, 2012; Song and Zou, 2015). Therefore, oxidative stress can damage lipids, proteins, DNA, and other biomolecules, producing neural injury and death (Losada-Barreiro and Bravo-Dáiz, 2017).

Depending on the oxidation of the biomolecules mentioned previously, several products can be observed. Malondialdehyde and 4-hydroxyaldehyde are the most important subproducts of the oxidation of polyunsaturated fatty acids. Nitrotyrosine is the product of protein oxidation through the action of reactive nitrogen and/or peroxides (Filgueiras et al., 2020). With respect to DNA, oxidation can produce protein-DNA crosslinks, mutations, or the breaking of strands. The most common oxidative product of DNA is 8-oxo-2′-deoxyguanosine. 8-Oxo-2′-deoxyguanosine results because guanine has a lower one-electron reduction potential than the other nucleosides in DNA (Wang et al., 2020b).

At present, no cure exists for neurodegenerative diseases, and treatments only offer symptomatic relief. Thus, further understanding of the pathophysiology of these diseases is essential for controlling the menace caused by these. Polyphenols have been suggested as effective agents limiting some neurological processes linked to the origin of the neurodegenerative diseases. Thus, EGCG is attractive by the properties mentioned above. But also, in terms of antioxidant effects as a key potential mechanism of action, polyphenols can activate genes in stem cells, among these Nr2, as well as modulate its activity (Schottker et al., 2015; Kahroba et al., 2020; Qader et al., 2020). When activated, it generates and increases antioxidative enzymes such as glutathione peroxidase, SOD and catalase (CAT). In fact, curcumin and quercetin can increase the activity of antioxidant enzymes such as glutathione peroxidase, SOD, CAT, or glutathione reductase in vitro and in vivo in cells linked to metabolic processes (i.e., hepatocytes); and they can even activate endogenous defense systems as well. Then, the reduction of free radicals also limits the cell’s decreasing morbidity and mortality (Schottker et al., 2015; Sears, 2017). As anti-inflammatory actions, some polyphenols have exhibited their effects, binding the inflammatory gene transcription factor identified as NR2 to its binding sites directly in the nucleus (Sears, 2017; Ye et al., 2020). In addition, these actions are associated with a stimulation of peroxisome proliferator activated receptor gamma (PPAR-γ). CAT: Catalase; ROS: reactive oxygen species.

**Effects of Polyphenols on Neurons and Stem Cells Suggesting Their Potential Against Neurodegeneration**

At the beginning of this century, Choi et al. (2001) reported that epigallocatechin gallate attenuates β-amyloid-induced neurotoxicity in cultured hippocampal neurons. During the last 15 years, stem cells have been converted into neural or glial stem cells, and these have been investigated as models to study neural disorders (Joannides et al., 2007; Murty et al., 2008; Prajumwongs et al., 2016). In such systems, neurotoxic agents such as glutathione peroxidase, SOD and catalase (CAT). In fact, curcumin and quercetin can increase the activity of antioxidant enzymes such as glutathione peroxidase, SOD, CAT, or glutathione reductase in vitro and in vivo in cells linked to metabolic processes (i.e., hepatocytes); and they can even activate endogenous defense systems as well. Then, the reduction of free radicals also limits the cell’s decreasing morbidity and mortality (Schottker et al., 2015; Sears, 2017). As anti-inflammatory actions, some polyphenols have exhibited their effects, binding the inflammatory gene transcription factor identified as NR2 to its binding sites directly in the nucleus (Sears, 2017; Ye et al., 2020). In addition, these actions are associated with a stimulation of peroxisome proliferator activated receptor gamma (PPAR-γ). CAT: Catalase; ROS: reactive oxygen species.

The motivation to study risk and modulatory factors is due to the limited potential role of polyphenol in modulate metabolic disorders linked to cell dysfunction, including those occurring in neurodegenerative diseases.
on cognitive function, particularly with the intervention of hippocampal formation and on nuclei linked to memory storage and processing (affected in the majority of neuropathologies). Main mistakes for transplanted NSC are revealed to differentiate into wrong types of neurons, malignant transformation, and immune rejection (Inagura et al., 2021).

Thus, dietary phytochemicals exerting a neuromodulatory effect and neurogenic properties are attractive for exploration as promised therapy. Some compounds, such as curcumin, resveratrol, blueberry polyphenols, sulforaphanes, salivonic acids, and some polysaturated fatty acids have shown to induce neurogenesis in the adult brain (Renaud and Martinoli, 2019). The latter have demonstrated to reduce oxidative stress and neuroinflammation, hence cell signaling, the activation of autophagy, and the affection of grown factors (Ebrahimi and Schluesener, 2012). Dietary polyphenols promote cell repair and survival, enhancing the ability of the brain to resist severe stress; those induced effects are suggested by means of conducting and activating trophic factors, antioxidant and DNA-repair enzymes, and proteins involved in mitochondrial biogenesis (Bhular and Rugheje, 2013).

While the mechanisms of action of polyphenols are unclearly revealed, certain clues have been discovered in the understanding of neurogenesis hallmarks. Thus, a proinflammatory state (the activation of microglia and the release of proinflammatory cytokines such as TNF-α, IL-1β, and IL-6) induced in mice by the injection of lipopolysaccharide in the chronic nervous system induced decreased hippocampal neurogenesis with marked inhibition of NSC differentiation (Rawangkan et al., 2018). The inclusion of polyphenols in dietary habits appears to increase neurogenesis, limiting neuroinflammation and disturbing the survival of newly generated cells in the DG (González-Sepúlveda et al., 2017). As the brain has increasing or static neurogenesis, that could be via the activation of the Akt/GSK-3beta signaling pathway and increased the expression of brain-derived neurotrophic factor (BDNF). In rats, curcumin proved to improve performance on several memory tasks after administration for 12 weeks (Bhular and Rupasinghe, 2013); while resveratrol, a stilbene, acts as a sirtuin-activator and to induce neurogenesis (Teixeira et al., 2020).

Polyphenols in vegetable oils exert action on the oleic acid-producing enzyme, steaoryl-CoA desaturase, which rescued NSC proliferation impairments in the AD brain (Georges et al., 2019). Epigenetic factors also play a crucial role in regulating stem-cell proliferation and differentiation. Some studies suggest that NSC can be stimulated for proliferation and neural differentiation for the mitigation of cognitive dysfunctions. The use of cocoa polyphenols effects in mice (Elmann et al., 2018). This could imply a strategy to revert the evolution of neurons affected in neurodegenerative diseases, or at least for them to be a source of neural cells with the potential to play the key role of cells involved in disease manifestation. In this regard, Hou et al. (2015) reported the reprogramming of mouse cells into induced pluripotent stem cells (iPS) by means of a cocktail with seven small molecules (VPA, CHIR99021, E616452, Tranylcypromine, Forskolin, 3-deazaneplanocin A, and TNNP8). In addition, Zhao et al. (2015) promoted an improved method by adding four small molecules (AM580, EP2004777, SGCO946, and 5-aza-2-deoxycytidine). Other combinations of drugs have been reported in such cells (Inoue and Yamanaka, 2011; Biswas and Jiang, 2016; Farkhondeh et al., 2019). The resulting cell systems could be used to cell replacement, but they can also be employed as neuron-like systems to evaluate responses to polyphenol administration. In the best of our knowledge this has been poorly explored; but the effects of polyphenols during the transformation process, and on the transformed cells seem attractive as some of the used compounds have several rings and hydroxyl groups (like polyphenols).

Structure-(Protective) Activity Relationship of Polyphenols

The group of polyphenols represent a very complex group of phytochemical compounds (Figure 5).

They are also nutrients known to be powerful activators of the human genes involved in the synthesis of antioxidant enzymes, in the modulation of anti-inflammatory pathways, and in the activation of anti-aging genes, as well as critical factors for maintaining the efficiency of some organelles (Gonzalez-Sarrias et al., 2020). Their first two actions, as an antioxidant and as an anti-inflammatory, are noteworthy, due to neurodegenerative diseases such as PD, AD, amyotrophic lateral sclerosis, and multiple sclerosis. These diseases the concentrations of free radicals are cumulative. These compounds can act in a non-specific manner as free radical scavengers for human health (Maraldi et al., 2014). Additionally, some specific mechanisms have been described to a subgroup of polyphenols; some of them are commented below.

The anabolism of polyphenols is complex in both plants and animals. Their classification is dictated by the number of rings (C6) that they contain, as well as the structural elements binding these rings to each other. Essential classes include phenolic acids (C6-C3 and C6-C1), flavonoids (C6-C3-C6), stilbenes (C6-C2-C6), and lignans (C6-C3-C6-C6). They are the basis of this complex group and deriving from these there can be another modifications around their structure, which include hydroxylations, O-glycosylations and cis-trans isomerization. This yields another at least 8000 estimated compounds (Gorzyński-Bebicka et al., 2018). These polyphenolic have at least one galloly or catechol group (with hydroxyl groups in the ortho position), which confer on them the ability to react with ROS and metals, mainly by chelation processes (Ebrahimi and Schluesener, 2012). In addition, initially, antioxidant properties were linked to the pharmacological activities of polyphenols. Their chemical structures confer them several activities as metal-chelators, antioxidants, protein complexes-stabilizing, estrogen-like, enzyme-binding, which let us to infer their usefulness in some neurodegenerative diseases treatments (Gonzalez-Sarrias et al., 2020). Additional ways for there to be action in biological systems have been reported.

Thus, although structure-activity has been poorly explored among all polyphenols, there are some data for specific compounds. Among recently supported mechanisms, flavolignans have been shown to inhibit the binding of ligands to the inflammatory complex system; on yielding a result, the reduction of the transcription of NF-κB and the activation of antioxidant enzymes such as Nrf2 (Vargas-Mendoza et al., 2020). These actions are associated with the activation of the peroxisome proliferator-activated receptor gamma and,

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**Figure 5** | Natural and synthetic polyphenols: structure-efficacy to treat chronic-degenerative diseases.

### Rosmarinic acid reduced amyloid β aggregation by increased monoamine secretion, in turn disrupting AD development in a murine model. This also could have implications in PD, in that the therapeutic potential of polyphenols for neuroprotection was demonstrated in a mouse model of PD. The group of polyphenols represent a very complex group of phytochemical compounds (Figure 5). They are also nutrients known to be powerful activators of the human genes involved in the synthesis of antioxidant enzymes, in the modulation of anti-inflammatory pathways, and in the activation of anti-aging genes, as well as critical factors for maintaining the efficiency of some organelles (Gonzalez-Sarrias et al., 2020). Their first two actions, as an antioxidant and as an anti-inflammatory, are noteworthy, due to neurodegenerative diseases such as PD, AD, amyotrophic lateral sclerosis, and multiple sclerosis. These diseases the concentrations of free radicals are cumulative. These compounds can act in a non-specific manner as free radical scavengers for human health (Maraldi et al., 2014). Additionally, some specific mechanisms have been described to a subgroup of polyphenols; some of them are commented below.

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with a dietary intake of polyphenols, this attenuates oxidative stress, since these polyphenols generate an increased expression of antioxidative enzymes such as glutathione peroxidase, SOD, and CAT, an enzyme complex that is very effective in removing excessive free radicals and in reducing the risk for certain metabolic and neurodegenerative diseases (Ruhila and Rupasinge, 2013). Likewise, 7,8-dihydroxyflavones have been reported as modulators in PC12 neuronal-like cells, with a direct agonistic effect on Trk receptors, the main receptors of neurotrophic factors including nerve growth factor and BDNF. However, in the same evaluation, several other polyphenolic compounds act as extracellular signal-regulated kinase and phospholipase D3-kinase/Akt pathways (Moosavi et al., 2016).

It has been demonstrated that, in neural stem cells and in the studies of mouse models, polyphenols deriving from grapes have improved synaptic transmission through the CAMP response element-binding protein. In transgenic and knockout mice, these polyphenols have improved in reducing the oligomerization of Aβ peptides and have contributed to reduce in cognitive impairments. The main component of these grape-seed extracts has been denominated 3'-O-methyl-epicatechin-S-O-glucuronide; this component has shown improvements in reducing the abnormal folding of tau proteins (Elmann et al., 2018). Resveratrol, inhibits 842 fibril formation and protects from Aβ neurotoxicity by inhibiting inducible nitric oxide synthesis inhibition, the activation of AMPK-dependent pathways, and direct action on sonic hedgehog signaling for modulating cell differentiation (Konyalioglu et al., 2013; Cheng et al., 2015; Chiang et al., 2018). Probably, Piceatannol (with only one hydroxyl group different from resveratrol) induces greater effects in these processes that are linked to metabolic and neurodegenerative disorders (Arai et al., 2016; Kershaw and Kim, 2017).

On the other hand, quercetin, a naturally occurring flavonoid, is known as a powerful antioxidant, metabolic, and neuroprotective agent by mediating critical pathways in attenuating oxidative stress, inflammation, and metabolic dysregulation (Yang et al., 2017). Some flavonoids share structural features with CAMP or nucleoside triphosphates, providing them the ability to activate or inhibit proteins that share with metabolic pathways. As examples are the effects of resveratrol on CAMP phosphodiesterase, of the flavanins on ATP synthase and the respiratory chain, and of curcumin on glyoxalase 1 (Msuya and Mndolwa, 2005). With respect to the dose for the preclinical and clinical settings, some reports on stem cells and other cell systems also suggest that high circulating concentrations of polyphenols are not required to exert these effects. Their interaction with diverse enzymatic targets, in very small doses of polyphenols, may benefit from the different patterns found in the literature (Del Rio et al., 2016).

Although the structure–relationship according to kinetics has been less explored, it is known that polyphenol pharmacokinetics (particularly biotransformation and binding to plasma proteins and lipids) modulate bioefficacy (Jannin et al., 2004; Delmas et al., 2011). Differences in polyphenol uptake and bioavailability are in dependence of the route of administration and the analytical methods for measurement (Abd El-Mohsen et al., 2006). In addition, it has been proposed that polyphenols are retained at the cell membrane by albumin and lipoprotein receptors, offering a carrier-mediated diffusion to the extracellular space, in opposition to passive diffusion (Laçon et al., 2004). Moreover, polyphenols modify the pharmacokinetics of co-administered drugs; thus, this mechanism could be involved in the synergistic pharmacodynamic effects proposed for developing multi-drug therapies; indeed, different polyphenols and polyphenol-based drugs and hormones are administered in combination to treat a specific malady (Yang et al., 2014). Consequently, it is predicted that some physiological and pathological conditions impact polyphenol bioavailability and bifunctionality (Ulrich-Merzenich et al., 2010; Elmann et al., 2018). Recent works describe promising natural and synthetic polyphenol structures by designing those that enter into consideration both pharmacodynamic and pharmacokinetic properties (Martelli and Giacomini, 2018; Silva et al., 2019; Li et al., 2019; Farfán-García et al., 2020; Mizuno et al., 2020; Balaha et al., 2021; Gansuhk et al., 2021).

Combination of Polyphenols and Stem Cells As an Innovative Therapy

As is above sentenced, more than 8000 polyphenols have been identified in different food matrices such as chocolates, herbs and spices as free monomers or oligomers (Pandey and Rizvi, 2009), and their use is proposed in isolated or polyphenol combinations for degenerative disorders (Conte et al., 2003). Among their multiple modes of action, their antioxidant properties are repeatedly observed. In these experiments, mechanisms, such as the hypoxia inducible factor 1 alpha pathway. The decrease of oxidative stress/NS and many other mechanisms mentioned in the previous section, is a key in the therapeutics of neurodegenerative diseases (Ebrahimi and Schluesener et al., 2012), and it is clear that the increased consumption of polyphenols in diet is associated with decreases in metabolic disorders related to neurodegeneration (Renaud and Martinoi, 2019), neurodegenerative and psychiatric disorders (Gansuhk et al., 2021).

In addition to their attractive results, it has been noted that polyphenols might be used in an autologous and must be considered in humans in order to propose novel therapies with polyphenols at the core. Some studies have found that they are safe and tolerable in the medium, and long term of use. It has even been proposed that adverse effects are not common, but the reported cases do include minimal gastrointestinal problems and, more rarely, cephalgia, dizziness, and rashes (Galati and O’Brien, 2004, Koga et al., 2011). In contrast, their low bioavailability and modest effects in clinical trials as well as the thorny issue of protection conferred by natural molecules without effects from diet source, detracts from the appeal of polyphenols for pharmaceutical use. Therefore, several strategies have been proposed by pharmaceutical developers to solve these issues (Renaud and Martinoi, 2019). Here it has come to light that new medical-engineering progress in vehicle formulation has advanced to the extent that it allows polyphenols to be contained in liposomes, nanoparticles, nanocapsules, microcapsules, or in gel form, and also rectal suppositories. The aim of this was to effort an efficient systemic distribution, procure bone marrow for immunomodulatory effects, and possess controlled-release implant strategies (Augustin et al., 2013; Frozza et al., 2013; Neves et al., 2013; Souto et al., 2013).

Another controversial point comprises the balance between the focus on improving bioavailability and strategies to identify the appropriate dose-response of polyphenols under certain clinical conditions. It is suggested that higher doses are potentially harmful, in that they could be stress factors, toxins, or precursors, or that they may induce an unbalanced defense response or an extended life for cells favoring neoplasia (DiMeo et al., 2013).

Due to these, other complementary strategies for the administration of polyphenols have been studied. It is in this respect that treatment with stem cells has been proposed and explored. Stem cells are undifferentiated and specialized cells with a plastic potential to become diverse body cells. In this respect, human stem cells contain multilines of cells that maintain pluripotency and ability to self-renew and even help to reach a declination of nuclear ROS production and DNA damage (Renaud and Martinoi, 2019). This fact states that nuclear NFX4 regulation exerts an important pathophysiological effect on stem proliferation through the modulation of nuclear signaling and DNA damage (Sears et al., 2017). In relation to the amazing potential of stem cells, their capacity for self-renewal and their ability in terms of differentiation have contributed to consideration of their use in clinical applications such as cell-based or drug discovery, and tissue engineering. Because the objective of stem cell-based therapies is to treat, repair, and replace tissues in disease or in organs, with novel strategies that are healthy and functional. Therefore, polyphenol in combination as a therapy can be an option (Eckel et al., 2005).

Meanwhile, for neurodegenerative diseases linked to an extended state of metabolic disorders and chronic inflammation, stem cell therapies have emerged as promising methods for their cure by means of replacing damaged cells, tissues, or organs (Beshlawy et al., 2019). Since certain other tissue/organ transplantations entail many complications, such as those related to immunosuppression, surgical complications, organ unavailability, prolonged recovery, and high surgical costs (Quaglia et al., 2008; Houben et al., 2015; Bobbio et al., 2019), cell replacement (from stem cell therapy) appears to be effective solely with the appropriate number of cells that are transplanted and stable cell lines that allow to determine the efficacy of the enzyme, receptor, neurotransmitter, or hormone replacement after manipulating the cells in vitro, which is in an early stage of development, including many studies that considering that many of these assays have not been fully investigated in the clinic.

Based on that adult cells are differentiated and play a very specific role that consists of unique biological properties such as differentiation and indefinite self-renewal, they can give rise to a functionally mature progeny and help to maintain tissue homeostasis (Peirns-Pages et al., 2016). NSC, brain cells that become neurons, astrocytes, and oligodendrocytes by a process known as neurogenesis, are particularly attractive for cell replacement therapy in metabolic and NG diseases (Bond et al., 2015). As mentioned previously, a combination of some polyphenols and stem cells could have additional benefits (Figure 6).

In that polyphenols regulate some signal pathways, such as resveratrol and baiacalein can be reported to modulate Akt/P13K/mTOR signaling in which Cdk1 can inhibit neural inflammation via the downregulation of the NF-κB signaling pathway (Xue et al., 2010; Capiralla et al., 2012; Simao et al., 2012). Additionally, several flavonoids can inhibit Aβ and Aβ oligomerization, play an immunomodulatory role, and can reduce memory impairment through the downregulation of NF-κB (Paris et al., 2011; Ashafaq et al., 2012; Gelderblom et al., 2012) and could modulate differentiation in cells. This is supported in some studies on cancer stem cells and dietary polyphenols, suggesting the effect of quercetin. This latter has been elucidated, due to the inhibition of ALdeHyde dehydrogenase 1 activity and reverted apoptosis resistance as detected by substrate assay. Moreover, quercetin in combination with sulforaphane, an isocoumarin found to be endogenous in broccoli, possess anti-inflammatory effects (Dontu et al., 2003). Although it enhanced the binding of NF-κB, quercetin can also inhibit the growth of cancer stem cell-enriched xenografts associated with reduced proliferation, angiogenesis, and cancer stem-cell markers. Other levels of antioxidant and anti-inflammatory properties. Also, polyphenols have been reported to possess potent antioxidant activity through endogenous and exogenous mechanisms (Dontu et al., 2003).
Thus, due to several pitfalls in the polyphenols or in stem cell therapies alone, during the last few years, the evaluation of a combinatorial treatment for the treatment of metabolic and neurodegenerative diseases has been conducted. In this regard, Ge et al. (2017) reviewed the actions of iPS and polyphenols from spices. The authors suggested that iPS and spices could potentially serve as a combinatory therapy for diabetes mellitus, because stable polyphenol compounds in spices could enhance insulin secretion, confer strong resistance on β-cell destruction, and modulate the immune response.

Supporting this additive effect of polyphenols, Drapeau et al. (2019) reported that human consumption of a proanthocyanidin-rich extract resulted in a selective mobilization of stem cell types involved in regenerative and reparative functions, with applications for preventive health, regenerative health, and postponing the aging process. The pathways for effects on stem cells appear to lie beyond the described antioxidant effect (Wang et al., 2020a), Matsuno et al. (2020) suggested that polyphenols contribute to the stability of the genome.

Regarding applications in neurodegenerative diseases, Itoh et al. (2012) described that epigallocatechin induced an increase in the number of neural stem cells in brain regions damaged by traumatic events. In this line, Wang et al. (2020a) recently described the protective effects of polyphenols, including their maintaining of the number of cells in the hippocampus, a region with preserved neural stem cells. Tandon et al. (2018) compiled and presented detailed advances (involving all of the previously mentioned pathways) with respect to the studies of polyphenols in neural, embryonic, and mesenchymal stem cells, as well as in iPS, with potential applications for treating AD and multiple sclerosis; these authors suggest (based on more than 100 scientific works reported from 2006 to 2018), that polyphenols complement stem cell therapy and the reduction of neurodegeneration in AD and multiple sclerosis. In that AD and PD share neurodegeneration pathways, it is expected that this combinational therapy could be useful in applications in other neuron diseases (Moradi et al., 2021). In agreement with this, Zhuang et al. (2020) found that, in N2a cells, polyphenols induced a mode of cell death by oxiapoptophagy, associated with mitochondrial and peroxisomal dysfunction, thus supporting the potential additive effect of combined elements and in an age-related disease therapy.

Conclusions and Perspectives

Both polyphenols and stem cell therapies have exhibited improvement in in vitro and in vivo models of neurodegenerative diseases or those metabolic disorders linked to them. Moreover, in some cases, these innovative therapies explored in more than half of century ago have been suggested as better than those used conventionally (drugs with a high incidence of adverse effects or transplantation with a high rate of short-term problems). However, there are several limitations involved in these therapies; among these, for polyphenol administration, there are limitations in instability, bioavailability, and there are toxic effects at high doses, while for stem cells, there is a dependence of the environment for establishment and survival. The multiple suggested mechanisms for polyphenols remain unclear: the most supported action is through the limitation of cell damage by oxidative stress, while only some evidence deals with direct interaction on human proteins (as is notable by the limited number of polyphenol molecules crystallized on human proteins) (Berman et al., 2000).

Interestingly, the noted weakness of single (polyphenol or stem cells) therapy can be limited by the combinatorial approach (Figure 7).

![Figure 6](image6.png) Some polyphenols actions that could be involved in improvement of stem cell therapy.

Polyphenols exert important effects on stem cells through their actions in treatments for metabolic and neurodegenerative disorders. Resveratrol, the best studied polyphenol, has been found to enable stem cells to differentiate into cardiomyocytes, neurons, osteocytes, and B cells. They can also protect cells from toxicity. Quercetin is considered for diverse metabolic diseases due to its impact on enabled osteocytic and pancreatic B-cell differentiation, as well as it protects neuronal stem cells from injury. Catechin prevents osteocyte damage and advert differentiation into undesirable adipocytes. Genistein facilitates osteogenesis and prevent adipogenesis. Other polyphenols protect cells from reactive oxygen species and divert stem cell differentiation from adipocytic and toward osteocytic lineages.

![Figure 7](image7.png) The putative combinatorial strategy: polyphenols and stem cell therapy.

The properties of polyphenols can enhance stem cell therapy in that they modulate mechanisms related to the origin of the disease, but are also involved in the replacement efficacy of stem cells.

That is, polyphenols could aid in opportune differentiation, extending the life and function of the stem cells (by modulating oxidative, cell-cycle and inflammatory processes); they can facilitate osteogenesis and prevent adipogenesis. That is, polyphenols could aid in opportune differentiation, extending the life and function of the stem cells (by modulating oxidative, cell-cycle and inflammatory processes); they can facilitate osteogenesis and prevent adipogenesis. That is, polyphenols could aid in opportune differentiation, extending the life and function of the stem cells (by modulating oxidative, cell-cycle and inflammatory processes); they can facilitate osteogenesis and prevent adipogenesis.

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