Neurodegenerative diseases are becoming a big challenge for modern society. Neurodegenerative disorders strongly impact on patient and their caregivers. Moreover, since the population is becoming older, these pathologies will deeply influence medical and socio-economic conditions in the next years. Therefore, efforts are needed to find new strategies devoted to define new protocols and identify novel substances able to prevent neurodegeneration or to improve the quality of life of people affected by neurodegenerative diseases (Alzheimer’s Disease International, 2019).

Although neurodegeneration displays different clinical manifestations in different neurological disorders, similar mechanisms are involved in degeneration and in progressive loss of neuron subsets. The resulting neuronal dysfunction is critical since neurons, being post-mitotic cells do not proliferate and cannot be replaced. With age neuronal cells progressively lose their antioxidant defense mechanisms. As a consequence, oxidative stress causes molecular damage in cellular components such as protein, lipid and DNA. These injuries activate an immune response in the brain that promote molecular changes, including formation of aggregated misfolded proteins, resulting in neurodegenerative diseases. Indeed, the immune response triggered by oxidant environment generates a local inflammation that gives rise to cytokines and chemokines overexpression thus starting neurotoxicity.

Polyphenols, by counteracting the oxidative burst, actively protect neuronal cells and block the feed-forward loop of neurodegeneration. Polyphenols are natural antioxidants abundant in vegetables and fruits that are able to protect cells from oxidative injury, thus preventing neuronal death. Their bioavailability can be enhanced by transforming two different mechanisms, that they can directly scavenge endogenous and exogenous free radical species or they can activate indirectly anti-oxidant genes or enzymes that intervene in apoptotic pathways (Figure 1). This way they modulate the physiological and pathophysiological outcomes of oxidant exposure.

In the brain, polyphenols can prevent inflammation indirectly by enhancing cerebrovascular blood flow or directly by downregulating receptors and signaling pathways responsible for neuroinflammation such as nuclear factor-κb factors and Toll-like receptor 4, a crucial contributor of microglial activation. Activation of microglial cells corresponds to neuroinflammation, since these cells are the main reactive oxygen species producers in the brain and have a key role in neurodegeneration induction. Anti-oxidant compounds like polyphenols can be active in neuroprotection reducing reactive oxygen species levels and inducing anti-inflammatory cascade (Di Meo et al., 2020). In neurons, polyphenols such as resveratrol, curcumin, and epigallocatechin-3-gallate are able to directly activate specific intracellular signaling pathways that are crucial for neuronal survival and cell growth, such as PI3K/Akt, PKC-ERK1/2, Akt-ERK1/2 and MAPK pathways.

Polyphenols can also be effective in neuroprotection by acting on the synthesis of neurotrophic factors (brain-derived neurotrophic factor (BDNF), nerve growth factor, glial cell line-derivative neurotrophic factor). It is known that expression of BDNF and glial cell line-derived neurotrophic factor is enhanced by resveratrol, while quercetin and genistein are able to stimulate nerve growth factor-induced neurite outgrowth. In these cases, polyphenols directly bind the cognate neurotrophic receptor and activate the downstream neuroprotective pathways (Di Meo et al., 2020).

An example of indirect action of polyphenols is the activation of the transcription factor nuclear factor erythroid 2-related factor-2 which, translocates in the nucleus and orchestrates the expression of the antioxidant response element-dependent genes. Indeed, other polyphenols, show low bioavailability and absorption rate and they need to be transformed in their low-molecular weight metabolites to become effective. These polyphenols indirectly affect neuromodulation since they are converted in biologically active metabolites by the action of gut microbiota. Among polyphenols, flavonoids are well-known to exert direct health effects on brain functions determining positive effects on synaptic plasticity and neuronal activity. Ginkgo biloba leaves extract contains high levels of flavonoids and the standardized extract EGb761 has been shown to have neuroprotective effects in central nervous system and in neurodegenerative diseases (Ahlemeyer and Krieglstein, 2003).

Recently, we have demonstrated the efficacy of EGb761 in SK-N-Be, a human neuroblastoma cell line commonly used in studies related to oxidative stress and neurodegenerative diseases. Specifically, we found that EGb761 protected neuroblastoma cells against oxidative stress-induced apoptosis through regulation of p53 transactivation, a survival pathway never described before to be activated by EGb761.

p53 is a tumor suppressor protein with a key role in cell fate modulating cell homeostasis and apoptosis. Active p53 can be associated to neurodegenerative disorders onset by giving rise to neuronal death. Higher expression levels of p53 were detected specifically in the affected brain areas in several neurodegenerative disorders. In neuronal cells, p53 acts as an activator or repressor, modulates the expression of pro-apoptotic genes such Bcl2 family, caspases, or Fas. p53 also promotes apoptosis altering the expression of enzymes involved in the regulation of the neuronal redox state (Nakanishi et al., 2015). In addition, post-translational modifications of p53 can be induced by oxidative stress regulating the expression of genes involved in cell death or survival (Brochier et al., 2013). Our findings demonstrate that EGB 761 inhibits the acetylation increase of p53 induced by H2O2 insult and blocks mitochondrial membrane depolarization with a consequent decrease of BAX/Bcl-2 ratio. Remarkably, our observation agrees well with previous studies demonstrating that modification of the acetylation pattern of p53 decreases its transcriptional activity and suppresses the expression of PUMA, a member of Bcl-2 family that promote cell death (Brochier et al., 2013).

Interestingly, the imbalance between decreased acetylation of p53 and reduction of BAX/Bcl-2 ratio reflects a dual role for EGB 761 that depends on the cellular context. In fact, the effects on p53 acetylation in opposite way in cancer cells where apoptosis is specifically induced by p53 acetylation increase (Park and Kim, 2015).

From our perspective, the inhibition of p53 acetylation could be potentially viewed as a pathway to interfere with the prevention of neuronal death. It is known that in oxidizing environment p53 undergoes post-translational modifications, including acetylation, that determine conformational changes. These modifications alter its transcriptional activity and biological responses. Ant-oxidant polyphenols can act by restoring the cellular redox homeostasis. Moreover, this modification could be used to analyze if other polyphenols, alone or in synergy with EGB 761, could prevent neuronal apoptosis and neurodegeneration. Finally, flavonoids present in this extract might represent novel molecules displaying beneficial effects in neurodegeneration decreasing p53 acetylation and modulating its tumor suppressor activity in cancer cells (Park and Kim, 2015).

Polyphenols with low bioavailability, indirectly affect neuromodulation since they are converted in biologically active metabolites by the action of gut microbiota. Among these there is a growing interest for the neuroprotective effects of curcumin. This polyphenol is derived from turmeric of Curcuma longa, and it has been widely used in Asian traditional medicine and its therapeutic efficacy has been reported in different studies (Hatcher et al., 2008).

Our group recently observed that this molecule can be effective in Huntington’s disease (HD) an inherited progressive neurodegenerative (Elifani et al., 2019). Using a HD mouse experimental model, we have demonstrated that dietary administration of a standardized extract of curcumin, alleviated symptoms associated to HD. Curcumin was able to reduce the amount of misfolded huntingtin aggregates, a marker of HD, and to preserve animals from severe body weight loss and motor dysfunctions, that are associated with disease progression. In addition, in this pathology dietary administration of curcumin increased brain levels of BDNF, a growth factors that regulate neuronal survival whose downregulation is associated to brain pathology (Ju et al., 2013).

Our results point out that curcumin enriched diet activated also by improving gut microbiota, curcumin promotes the recovery of the intestinal epithelial barrier by restoring the villi length - the gut absorptive surface - and reducing intestinal muscular atrophy. Interestingly, both these traits have been previously described to be associated to the severe weight loss concomitant with typical of HD progression (Elifani et al., 2019).

Our data remark the paradox between curcumin neuroprotective efficacy and its poor bioavailability. This can be explained taking into account the interplay between curcumin and gut microbiota. Curcumin after ingestion undergoes subsequent modifications by enzymes produced by different bacterial strains of the gut that modify its bioavailability. This can be explained taking into account the interplay between curcumin and gut microbiota. Curcumin after ingestion undergoes subsequent modifications by enzymes produced by different bacterial strains of the gut that modify its bioavailability. This can be explained taking into account the interplay between curcumin and gut microbiota. Curcumin after ingestion undergoes subsequent modifications by enzymes produced by different bacterial strains of the gut that modify its bioavailability.

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These metabolites are known to be more active than native curcumin. Octahydrocurcumin and tetrahydrocurcumin are known to act as potent antioxidants and they represent the bioactive effectors of curcumin neuroprotection (Edwards et al., 2017).

Otherwise, it should be underlined that curcumin can regulate by itself the microbial composition of the gut thus affecting the ratio between beneficial and pathogenic bacteria and modulating the gut–brain axis homeostasis. The analysis of these modifications could help in shading light on the comprehension of curcumin neuroprotective effects (Di Meo et al., 2019).

According to previous studies performed on other neurodegenerative diseases, our data suggest that polyphenols like curcumin with low bioavailability in their native form can exert their positive neuronal effects following chemical modifications performed by enzymes of gut microbiota and that the resulting reactive metabolites are the mediators of biological effects (Blaut et al., 2003).

It is worthy to note that gut dysbiosis induces neuroinflammation leading to decrease of bacterial strains producing metabolites active in neuron survival such as butyrate. These events can trigger the onset of neurodegenerative diseases. Alteration of gut microbiota have been thought as co-factor favouring the onset of Alzheimer’s disease and Parkinson’s disease. In Alzheimer’s disease gut dysbiosis determines misfolding of neuronal amyloid-β and α-synuclein. In Parkinson’s disease the disruption of the epithelial barrier results in decrease of beneficial protective strains and in a decrease of butyrate, a short-chain fatty acid which protects dopaminergic neurons from degeneration by upregulating the neurotrophic factors, such as BDNF (Di Meo et al., 2019).

Our study in HD also suggests that curcumin acts positively on gut epithelial barrier allowing to increase of BDNF expression in the brain (Elifani et al., 2019). Thus, it is possible to hypothesize that curcumin supplementation could reduce malabsorption in neurodegenerative diseases and restore gut functions by interplaying with gut bacterial strains protecting neurons from death.

In our opinion, these results indicate that curcumin, despite its low bioavailability, can be considered as a novel therapeutic option against neurodegeneration thanks to the ability on acting on gut microbiota modulation. Further analysis on the modification induced by curcumin on gut microbiota are needed to better understand how this polyphenol acts in HD to keep a proper microbiota-gut-brain axis, to induce production of neuroactive metabolites and finally to identify novel targets active in neuroprotection.

Taking together, these results indicate that polyphenols can be effective in the prevention and in the treatment of neurodegenerative diseases as pharmaceutical or as dietary supplements through different mechanisms. Polyphenols that actively determine neuroprotection by affecting the expression of specific effectors with a key role in apoptosis, or polyphenols that modulate gut microbiota, provide new molecular perspectives to define their neuroprotective efficacy. Of course, other polyphenols besides Ginkgo or curcumin need to be further investigated to identify the molecular pathways or the gut microbiota effector responsible for the health effects in neurodegeneration.

In our perspective, it is important to consider that the increasing use of dietary bioactive polyphenols represents novel non-invasive strategy able to modulate different regulatory functions in human health. Their use is considered particularly powerful because of their low toxicity that make them safe to be tested in pre-clinical and clinical studies for the treatment of neurodegenerative diseases.

As scientific knowledge of polyphenols increases it is evident these molecules in their native form or their derivative metabolites represent attractive compounds with multiple biological activities. Their efficacy as antioxidants and their capacity to modulate pro-survival or anti-apoptotic signaling pathways are essential in preventing and slowing down neurodegenerative disorders. On the other hand, the interplay between the effectiveness of polyphenols and gut microbiota composition represents a promising field to develop new strategies to counteract neuronal pathologies.

Further researches are needed to fully elucidate polyphenols short and long term neuroprotective effects and to understand whether and how different molecules produce the same benefits. In practice, polyphenols, being a large class of natural compounds displaying different structures, can exert protective roles by regulating different pathways many of which are still not clear. Certainly, considering that different polyphenols and their synthetic derivatives have been commercialized as novel therapeutics against different diseases, additional human studies are needed to confirm biological mechanisms and public health implications.

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