Can foods influence the onset and progress of neurodegenerative diseases?

Luca Piemontese*, Leonardo Brunetti, Rosalba Leuci

Over the course of the last few years, the advertisement and marketing of commercial food products in the European market has seen an increasing focus on the beneficial effects of such products for consumer health (Regulation, 2006). These so-called "health claims", which can be found on the label of some food products, have become a very important medium, aiming to reach the maximum amount of potential consumers possible, and the delivery of these promises has become a crucial objective for food companies or consortia. However, in most cases, the evidence backing up such claims (and their coveted acknowledgment on the product label) has often been cited as insufficient by institutions such as the European Food and Safety Authority (EFSA, Parma, Italy).

A direct consequence of this is that an increasing amount of research is now focused on studying potentially beneficial substances that are found in a large variety of foods. As such, the discovery of "nutraceuticals", bioactive small molecules found in foods and beverages, has led to the definition of "functional foods", intended as foods that have potentially positive effects on health beyond their basic function of nutrition. As an example, as detailed in Commission Regulation, 2012, extra virgin olive oil is potentially rich in polyphenols: thus, if its production involves extraction techniques that preserve their integrity (hydroxytyrosol and its derivatives oleuropein and tyrosol must be at least 5 mg per 20 g olive oil) and if proper storage conditions are maintained, the final product can bear a specific health claim on its label, certifying specific properties such as protection of circulating lipids from oxidative stress.

To date, the approved health indications are those regarding the capability of a food or beverage to prevent the development of chronic pathologies, based on the certified presence of bioactive and bioavailable compounds. However, European legislation is constantly evolving and the list of approved indications is often updated.

The emergency caused by the rising prevalence of neurodegenerative pathologies such as Alzheimer's disease (AD) (Schelten et al., 2021), exacerbated by the progressive aging of the world population and by the lack of disease-altering drugs, has led numerous research groups to focus their efforts on the discovery of novel therapeutic targets, whose pharmacologic alteration may halt or even reverse disease progression. Notably,

one such novel approach has highlighted the plausible correlation of AD with metabolic disorders such as diabetes (Brunetti et al., 2020).

Therefore, a fascinating challenge for future research will be to prevent and control the onset of the disease through a healthy diet. This would require foods and beverages rich in nutraceuticals with neuroprotective activity, targeting for example energetic metabolism and oxidative stress. Such an avenue of research would be of great interest for the whole food chain, from the production of raw materials to transformation and final products, seeing how the approval of a health claim that can be displayed on the product label is a most inviting prospect.

A notable amount of scientific papers on this topic have been published last year, therefore this work will be aimed at highlighting particular research or review papers that are representative of the whole spectrum of strategies that have been used to demonstrate the correlation between the consumption of specific foods and neuroprotection. It goes without saying that the methodologies of investigation are constantly evolving, and their number and variety enhance the probability of reaching relevant results in a relatively short time.

A recent work (Duplantier et al., 2021) gathered data supporting the potential beneficial effects of foods belonging to the Mediterranean diet, to Dietary Approaches to Stop Hypertension (DASH), and to Mediterranean-DASH Intervention for neurodegenerative delay on the onset of cognitive pathologies such as AD. In particular, five randomized clinical trials and twenty-seven observational studies, conducted over the course of the last twenty and ten years respectively, were analyzed and reviewed. Regrettably, as mentioned by the authors themselves, these studies are still quite limited in number, follow different methodologies and are also difficult to interpret in light of the short timespan in which they were conducted, especially considering the chronic and degenerative nature of the target pathology (Duplantier et al., 2021). Still, it is undoubtable that there is an increasing demand for a new type of food education, featuring evidence-based and clinically tested dietary regimens, validated over the course of much longer timespans.

A recent review paper also highlighted the connection between early nutrition and the onset of neurodegenerative diseases

later in life (Milosevic et al., 2021). Nutrition during pregnancy also seems to play an important role: it is recommended to avoid so-called "junk food" and to prefer foods containing micro- and macro-nutrients that promote resistance to oxidative stress and a healthy development of gut microbiota. The authors of this paper also rightly note that neurodegenerative diseases often correlate with individual epigenetic modifications. In this case, a precision diet involving nutraceutical substances may promote a reversal of such epigenetic modifications and, hopefully, prevent the onset and progression of the pathology (Milosevic et al., 2021). Again, further interdisciplinary studies involving larger cohorts will be crucial to identify both qualitatively and quantitatively the possible effects of better nutrition on the prevalence of these chronic pathologies. Further research would thus solidify the hypotheses that have been proposed regarding the role of single bioactive molecules present in a variety of foods.

Indeed, numerous recent studies have gathered a significant amount of evidence supporting the neuroprotective efficacy of small molecules as nutraceuticals (Nabavi et al., 2020). As an example, the Mediterranean diet includes several foods that are particularly rich in these nutrients, such as vitamins, omega-3 fatty acids, folate, and polyphenols (Liu et al., 2021).

The recent observation of the potential neuroprotective effects of the already mentioned hydroxytyrosol is particularly interesting from the point of view of the labeling of functional foods. This compound is a polyphenol found in extra virgin olive oil, a fundamental component of the Mediterranean diet. In particular, hydroxytyrosol is contained in the fruits and leaves of olive trees and olive oil and its products (Chen et al., 2021). A great number of research papers regarding its role in neuroprotection have been published in recent years (Chen et al., 2021), showing once again the increasing importance of functional foods in the future of healthy diets. The structure of this compound, described by many as a potential multi-target ligand (Chen et al., 2021) for the treatment of neurodegenerative pathologies, paves the way for the discovery of novel therapeutic agents. Hydroxytyrosol exerts neuroprotective activity by mediating a decrease of cell death, preventing cytotoxicity and oxidative stress, and it can also inhibit monoamine oxidase and catechol-O-methyl transferase enzymes, down-regulate matrixmetalloproteinases and protect from neurotoxicity caused by metal ions (**Figure 1**) (Chen et al., 2021). The design of compounds based on small natural molecules that showed similar and hopefully improved bioactivity is, in fact, a tried and tested avenue of research with truly promising results (Poliseno et al., 2021), which may constitute a new weapon to fight pathologies such as AD.
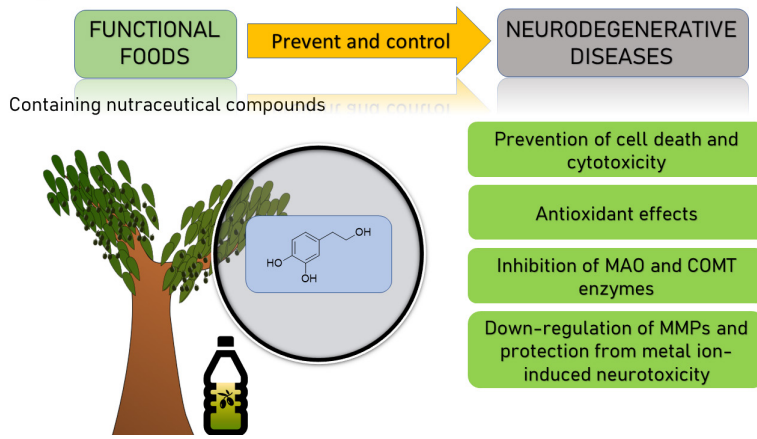
Perspective

Figure 1 │ Role of functional foods in neuroprotection.
COMT: Catechol-omethyl transferase; MAO: monoamine oxidase; MMPs: matrixmetalloproteinases.

On the other hand, it must be remarked that small, food-derived bioactive substances could also prove to be toxic. The neurotoxicity of some compounds could indeed be responsible for the onset of neurodegenerative diseases. As an example, amino acid β-N-methylamino-L-alanine (BMAA) was investigated for its toxic effects, seeing the high prevalence of so-called Guamanian amyotrophic lateral sclerosis/parkinsonism dementia complex in the indigenous population of Guam (Chernoff et al., 2017; Dunlop et al., 2021). Moreover, the same compound was capable of inducing an AD-like phenotype in animal models (Dunlop et al., 2021). The fact that this substance is produced by numerous cyanobacteria means that its toxicity is a risk factor for populations all over the world (Dunlop et al., 2021). The literature regarding this substance was recently reviewed, suggesting further research from both analytical and clinical points of view (Dunlop et al., 2021), although some studies suggest that BMAA might not be too dangerous (Chernoff et al., 2017).

This is, however, a useful example to remind ourselves that "not all that glitters is gold", and it is always necessary to consider that, while foods may contain small molecules with nutraceutical activity, they may also bear toxic substances that must be equally studied and characterized, as is the case for numerous food contaminants, such as mycotoxins, heavy metals and pesticide residues whose presence in foods is regulated in UE in Commission Regulation (EC) No. 1881/2006 and its amendments, which set the maximum levels for certain contaminants in foodstuffs. Moreover, the same regulation mandates strict regulation of the labeling system for functional foods and encourages its standardization worldwide. The main risk that these legislative measures aim to reduce is consumer misinformation: consumers could otherwise be persuaded that a portion of healthy food can be equivalent to a drug, and this is not only false but dangerous.

This mosaic of evidence proves that a healthy nutrition might really be the key to a longer and better life, and the scientific community as a whole will have to work not only on the gathering of further evidence but also on the issue of communicating this message to the public at large, which could save (and improve) many lives in the coming decades.

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Luca Piemontese[*], Leonardo Brunetti, Rosalba Leuci
Department of Pharmacy and Pharmaceutical Sciences, University of Bari Aldo Moro, Bari, Italy
*Correspondence to: Luca Piemontese, PhD, luca.piemontese@uniba.it.
http://orcid.org/0000-0002-7980-5818 (Luca Piemontese)

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