Chapter 2

Bioactive Compounds Contained in Mediterranean Diet and Their Effects on Neurodegenerative Diseases

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Additional information is available at the end of the chapter

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Abstract

Neuroinflammatory processes in the brain are believed to play a crucial role in the development of neurodegenerative diseases, especially due to increased production of reactive oxygen species. The brain is susceptible to oxidative stress more than other organs due to the low activity of antioxidant defense systems. In agreement with these observations, increased oxidative stress plays an important role in the pathogenesis of neurodegenerative diseases such as Alzheimer disease, Parkinson disease, ischemic diseases and aging. The Mediterranean diet is inspired by the traditional dietary pattern of some countries of the Mediterranean basin. From ancient times, these populations were characterized by simple food habits as high intake of whole cereals (pasta, bread, rice), fruits and vegetables (up to 400 g day^{-1} in Greece), legumes and fish, olive oil as the common source of fats, poor intake of meat and dairy products and a moderate, regular wine drinking. In the present chapter, there are going to be presented some bioactive substances present in the Mediterranean diet related to the prevention of neurodegenerative diseases. These substances are able to exert important antioxidant activity (through mechanisms such as sequestration of free radicals, inhibition of the production of hydrogen peroxide, activation of endogenous defense mechanisms.

Keywords: Mediterranean diet, neurodegenerative diseases, Alzheimer disease, Parkinson disease, melatonin, hydroxytyrosol

1. Introduction

Neurodegeneration in Parkinson's, Alzheimer disease, and other neurodegenerative diseases seems to be multifactorial, in that a complex set of toxic reactions leads to the demise of neurons. Complications include: inflammation, glutamatergic neurotoxicity, increases in iron

and nitric oxide, depletion of endogenous antioxidants, reduced expression of trophic factors, dysfunction of the ubiquitin-proteasome system, and expression of proapoptotic proteins leads to the demise of neurons [1].

At pathological level, almost all neurodegenerative diseases share common features such as the generation of misfolded protein deposits, metal ion deregulation, and exposure to oxidative stress [2, 3]. In Alzheimer disease the extracellular senile plaques are consisted on amyloid-β peptides derived from the mutations in genes encoding the amyloid precursor protein while the intracellular tangles are from hyperphosphorylated Tau protein. In Parkinson disease the accumulation of intracytoplasmic Lewy bodies is mainly composed of α-synuclein and ubiquitin [4].

Alzheimer's disease is responsible of 70% cases of dementia in elderly people. Between 2000 and 2013, United States of America death rates for dementia increased 21% for men and 31% for women. Among individuals 85 age old or older, dementia-associated death rates for women and men were ~4% and 3.2%, respectively [5]. Risk factors include hypercholesterolemia, obesity, diabetes, and cardiovascular factors, such as hypertension, and inflammation [6].

Nowadays, neurodegenerative diseases are not curable and treatments have limited effectiveness. Hence, increasing interest for effective preventive measures has been recently shown in the scientific literature [7]. Prevention of neurodegenerative diseases and search for new drugs are the great challenges of scientific research, because the symptoms appear in the human being only when the degeneration is advanced. Mechanisms involved in neurodegenerative diseases are complex and multifactorial. However, these mechanisms present common pathways, including: mitochondrial dysfunction, intracellular Ca^{2+} overload, oxidative stress and inflammation. Often multiple pathways coexist, restricting benefits from therapeutic interventions.

Neuroinflammatory processes in the brain are believed to play a crucial role in the development of neurodegenerative diseases, especially due to increased production of reactive oxygen species. The brain is susceptible to oxidative stress more than other organs due to the low activity of antioxidant defense systems. In agreement with these observations, increased oxidative stress plays an important role in the pathogenesis of neurodegenerative diseases such as Alzheimer disease, Parkinson disease, ischemic diseases and aging [8].

Several models of diet have been proposed but, until now, the highest attention of researchers, clinicians, and institutions has been focused on the Mediterranean diet. This diet has been promoted as a model for healthy eating and it has been widely recognized to have favorable effects on lipid profile and to provide a significant source of antioxidants and vitamins [9].

The Mediterranean diet is inspired by the traditional dietary pattern of some countries of the Mediterranean basin. From ancient times, these populations were characterized by simple food habits as high intake of whole cereals (pasta, bread, rice), fruits and vegetables (up to 400 g day^{-1} in Greece), legumes and fish, olive oil as the common source of fats, poor intake of meat and dairy products and a moderate, regular wine drinking. The intake of saturated animal fats is relatively low, and moderate fish consumption gives enough polyunsaturated fatty acids [9, 10].

Valls-Pedret et al. and Ngandu et al. provide a strong level of scientific evidence for the beneficial effects of the Mediterranean diet on cognitive functions [11, 12]. Several clinical, epidemiological and experimental studies suggest that consumption of the Mediterranean diet reduces the

incidence of certain pathologies related to oxidative stress, chronic inflammation and immune system diseases such as cancer, atherosclerosis, cardiovascular disease and neurodegenerative diseases [13]. These reductions can be partially attributed to different bioactive compounds present in the Mediterranean diet (omega 3 fatty acids, polyphenols, resveratrol or melatonin). In fact, the five most important adaptations induced by the Mediterranean dietary pattern are [7]:

1. Lipid lowering effect,
2. Protection against oxidative stress, inflammation and platelet aggregation,
3. Modification of hormones and growth factors involved in the pathogenesis of cancer,
4. Inhibition of nutrient sensing pathways by specific amino acid restriction, and
5. Gut microbiota-mediated production of metabolites influencing metabolic health.

There is negative correlation between cognitive functions, saturated fatty acids and protective effect against cognitive decline with increased fish consumption, high intake of monounsaturated fatty acids and polyunsaturated fatty acids (PUFA), particularly n-3 PUFA [14]. Similarly, polyunsaturated and omega-3 fatty acids as docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) supplements are associated with increased cognitive function, due to the cumulating of factors that ultimately favor membrane permeability and neuronal functioning [15].

There are numerous epidemiological studies relating the Mediterranean diet with the prevention of neurodegenerative diseases and minor cognitive decline [14, 16]. However, other studies did not observe such relationship. Anastasiou et al. suggest that adherence to the Mediterranean diet is associated with better cognitive performance and reduced dementia in Greek elderly population [17]. Hardman et al. demonstrate that the relationship between Mediterranean diet score and cognition was only significant when medication use was taken into account.

In the present chapter, there are going to be presented some bioactive substances present in the Mediterranean diet related to the prevention of neurodegenerative diseases. These substances are able to exert important antioxidant activity (through mechanisms such as sequestration of free radicals, inhibition of the production of hydrogen peroxide, activation of endogenous defense mechanisms (catalase, superoxide dismutase), chelation of metals, etc.). However, many other biologically plausible mechanisms may be responsible for their protective effect [18, 19] as follows:

- Modulation of gene expression.
- Detoxification of carcinogens.
- Induction of cell death.
- Protection of DNA.
- Modification of cellular communication.
- Modification of the hormonal profile.
- Modulation of the lipid profile.
- Stimulation of the immune system.

- Anti-inflammatory effect.
- Effects on hemostasis.
- Hypocholesterolemic effect.
- Hypotensive effect.
- Antimicrobial activity

2. Bioactive substances in the Mediterranean diet

2.1. Resveratrol

Resveratrol belongs to the family of stilbenes and is one of the most studied polyphenols, mostly present in grapes and wines. This stilbene was discovered in 1940 in *Veratrum grandiflorum* by Takaoka [20] and reported in high concentration in *Vitis vinifera* in 1976 by Langcake and Pryce [21], leading to the subsequent research about bioactive function of the molecule (**Figure 1**). The scientific literature has reported several benefits related to resveratrol, most of them regarding to antioxidant capacity and cardiovascular improvement. However, pharmacokinetics of the molecule and the great content on red wine and grapes reveal resveratrol as an essential compound on the Mediterranean diet regarding neuroprotection.

Despite several studies regarding pharmacokinetics of resveratrol, it is still uncertain. Many scientific researchers have reported excellent values regarding *in vitro* bioavailability of resveratrol [22]. However, these values are not in agreement with *in vivo* results, mainly due to chemical insubstantiality [23]. In fact, revisions about pharmacokinetics differ widely between

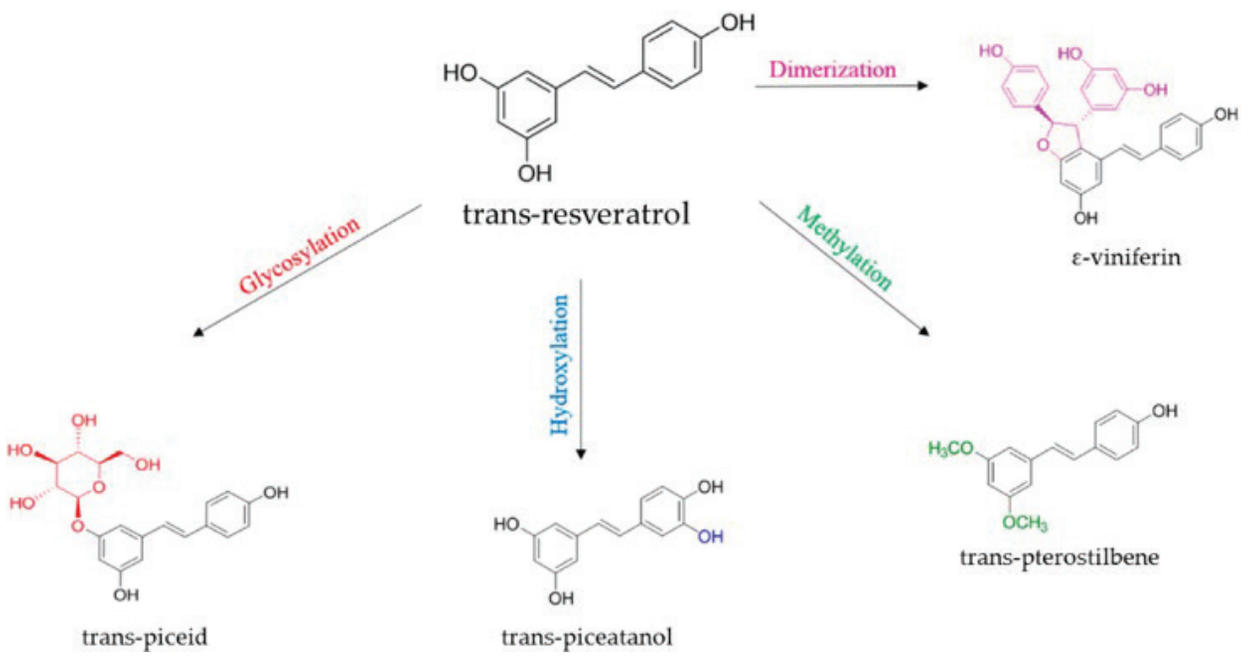

Figure 1. Resveratrol and related metabolites.

them about bioavailability of resveratrol. Fernández-Mar et al. reviewed knowledge on scientific literature, reporting a bioavailability of resveratrol over 70% [24]. Meanwhile, Ahmed et al. found a bioavailability minor than 1% after extensive revision of literature, reflecting the high discrepancies about the absorption of resveratrol [23].

Dietary sources of resveratrol comprise a wide variety of plant matrices [23]. Health benefits attributed to resveratrol were noticed by the scientific community, leading to the increment of scientific reports relating its presence in a wide range of plants. From now, resveratrol has been reported to be present in at least 72 plant derived foods [23, 25]. As reported by Fernández-Mar et al. main sources of resveratrol comprise peanuts, pistachios, different berries, dark cocoa, and grapes/wine. All of them could be included in the Mediterranean diet; however, the main source of resveratrol in the Mediterranean diet are grape and derivatives, especially red wine [26–29]. Thus, concentration of trans-resveratrol in red wine can reach 14.3 mg/L, depending on the type of grape, cultivar conditions, or vinification procedures [23, 26–29]. Resveratrol is exclusively present in seeds and skin of grapes. Therefore, concentration of resveratrol in red wine is higher than white ones, due to the vinification process which leads to more extensive contact between skin/seeds and must [24]. As commented above, not only resveratrol has been found in grapes and must.

As reviewed by Ahmed et al. [23], resveratrol can also be found in different berries and related products, namely blueberries cranberries, bilberries, lingonberries, partridgeberries, mulberries and strawberries [30–32]. However, the different technological and agronomical processes applied to berries and the slight content on resveratrol, are limiting factors for considering berries as remarkable source of that bioactive compound. Similarly, other foods containing minor amounts of resveratrol are dark cocoa, beer, and bee wax from honeycomb [33–39].

Other food with high amount of resveratrol are peanuts, in which resveratrol can be found in all edible parts of the plant. For example, peanut butter and peanut oil were found to have high quantity of trans-resveratrol reaching 16.9 μg/g in case of peanut oil [36, 37].

Resveratrol has shown different pathways that could postpone neurodegenerative diseases onset, especially Alzheimer disease [23]. In 2017, Ahmed et al. published a revision about the role of resveratrol in Alzheimer disease and other neurodegenerative diseases. They showed a total of 18 recent publications about the different action of resveratrol in human organism [23].

As a summary, resveratrol leads to:

- Inhibition of tauopathy.
- Enhancement of long-term memory formation.
- Inhibition of brain pro-inflammatory responses.
- Inactivation of astrocytes.
- Enhancement of sirtuin-1 activity.
- Protection from oxidative injury.
- Inhibition of neurotoxicity by H_2O_2.

- Inhibition of synthesis of Aβ plaque.
- Prevention of neuronal death.

Cognitive impairment is also susceptible to be treated with resveratrol, as observed in animal models. Consequently, resveratrol might also be considered as a potential anti-depressant bioactive compound [28].

Neuronal deficiency originates from multiple neurodegenerative diseases. Resveratrol seems to be quite associated to the development of specific neurodegenerative diseases as Alzheimer disease or Huntington disease and Parkinson disease [29]. The most outstanding capacity of resveratrol that influences its effectiveness for the treatment of neurodegenerative diseases is the ability to penetrate the blood-brain barrier. In fact, it has demonstrated a great neuroprotective capacity, even in administration at low doses.

The activation of sirtuin-1 pathway (SIRT1) seems to be a determinant property of resveratrol [40, 41]. Parker et al. [42] showed that by daily intake of one wine glass, it brings enough resveratrol (500 nM) to combat neuronal dysfunction caused in Huntington and Alzheimer's diseases through SIRT1 activation.

Regarding Parkinson's disease, the first advances regarding its relation with resveratrol were published in the year 2000 [43]. In mice, Karuppagounder et al. reported that daily intake of resveratrol decreased Aβ plaque in the CNS. Mayor changes were observed in the medial cortex, the striatum and the hypothalamus. Moreover, the most noticeable changes were observed deprived of the sirtuin-1 pathway, which enhances the hypothesis of reduced formation of Aβ plaque due to reduction cysteine and glutathione in the CNS [44].

One of the most studied characteristics of resveratrol is its ability to reduce oxidative injury. Reactive oxygen species (ROS) are mayor agents promoted unpaired oxidative stress, and are determinant for the production of oxidative injury and non-enzymatic lipid peroxidation. Oxidized lipoproteins stimulates apoptosis due to the union of DNA to NF-κB. Resveratrol acts inhibiting the activation of NF-κB, which reduces the possibility of oxidative injury at the Central Nervous System (CNS) [45, 46].

2.2. Melatonin

Melatonin (*N*-acetyl-5-methoxytyramine) is a characteristic neurohormone of the pineal gland, also produced as a secondary metabolite in plants (**Figure 2**). It has been shown that synthesis of melatonin is produced from tryptophan, serotonin and *N*-acetylserotonin ultimately. On the other hand, melatonin molecule can also be formed by *O*-methylation of serotonin followed by *N*-acetylation of 5-methoxytryptamine in yeast [47, 48].

The absorption of melatonin after oral intake has been previously approached by the scientific literature, reporting similar values between different researchers. Bioavailability reported values vary from 33 to 8.7% [49–51]. The absorption of melatonin is delimited by many parameters such as age, sex, season or circadian cycle. Nevertheless, there is variables such as elimination and distribution half-life that look to remains equivalent between subjects.

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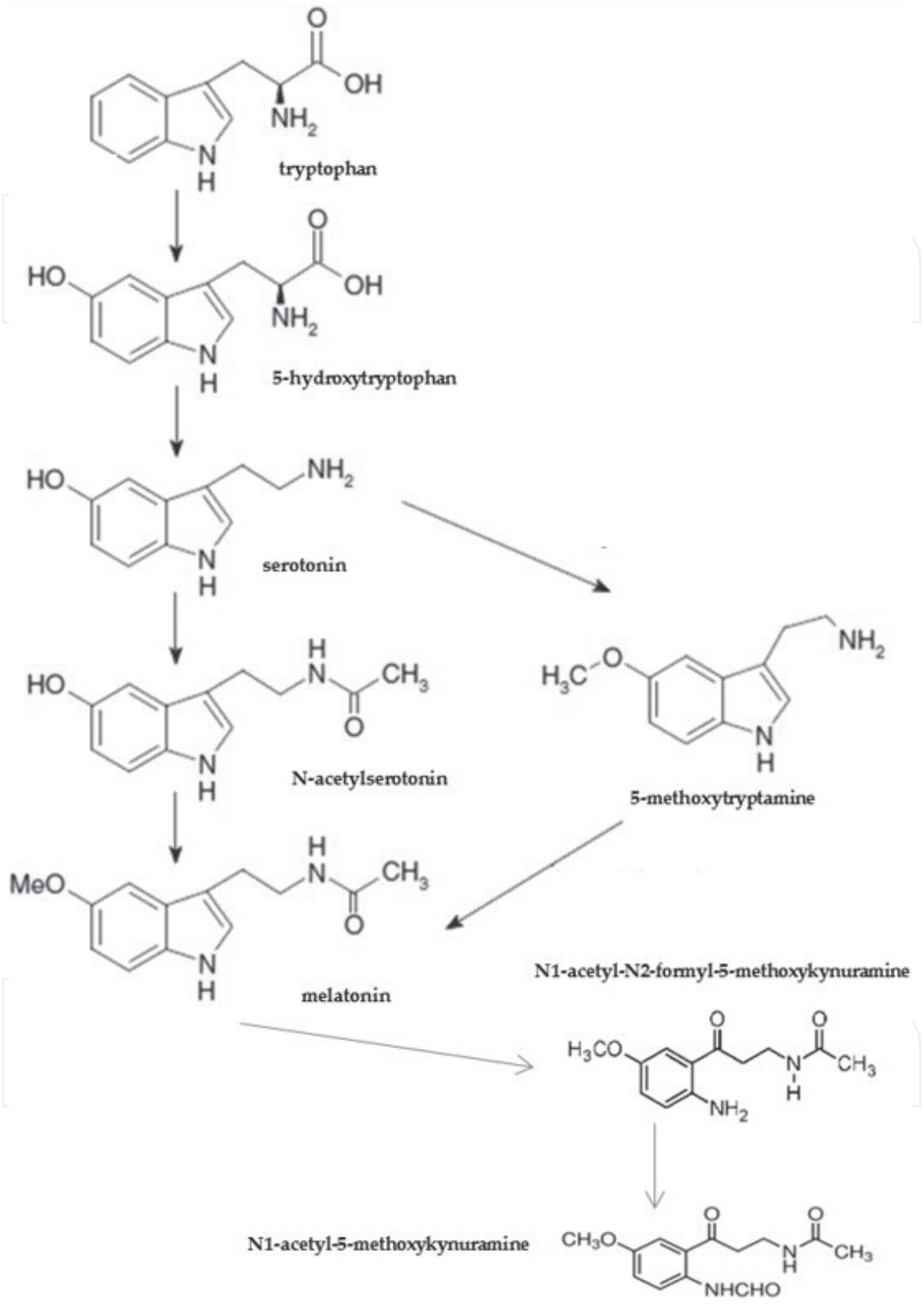

Figure 2. Melatonin and related metabolites.

Nowadays, the claim accepted by the European Food Safety Authority concerning melatonin is related to mitigation of subjective feelings of jet lag, reduction of sleep onset latency, and contribution to sleep quality. Doses of melatonin for reaching these effects are between 0.5

and 5 mg. Moreover, the effects commented before can occur if the administration of the indolamine is close to bed time on the first day [52].

Melatonin were reported in seeds such as rice and sweet corn, besides roots, leaves and fruits from different plants. In fact, melatonin has been reported in strawberries, kiwis, pineapples, bananas and apples [24]. The presence of melatonin has also been described in olive oil, extra virgin olive oil, and in sunflower oil at concentrations between 71 and 113 pg mL^{-1} [53]. Other foods from Mediterranean diet that have sown high concentration of melatonin are salmon (3.7 ng g^{-1}), chicken and lamb (2.3 ng g^{-1} and 1.6 ng g^{-1} respectively), bread's crumb and crust (341 and 138 pg g^{-1} respectively) and yogurt (126 pg g^{-1}) [54, 55].

Despite being present in many foods, main sources of Melatonin in Mediterranean diet are grapes and especially, wines. Iriti et al. showed variation in the concentration of melatonin in different varieties of grapes, such as: Nebbiolo, Croatina, Sangiovese, Merlot, Marzemino, Cabernet Franc, Cabernet Sauvignon and Barbera [56]. These authors described a concentration of melatonin ranging from 0.005 to 0.9 ng g^{-1}. Likewise, Mercolini et al. also observed the presence of melatonin in wine (0.4–0.5 ng mL^{-1}) [57].

Recently, other authors have reported melatonin in higher concentration than observed in previous reports (245–423 ng mL^{-1}). Rodríguez-Naranjo et al. carried out an investigation in 10 monovarietal wines: Cabernet Sauvignon, Petit Verdot, Prieto Picudo, Syrah and Tempranillo [58]. Despite not found in grapes and musts, melatonin and its isomers were found in finished wines derived from them. That fact, revealed that melatonin is formed during wine processing from yeasts.

Melatonin can exert diverse beneficial effects for health, having demonstrated antioxidant, anticancer, immunomodulation and neuroprotective capacity [24]. In addition, biological activities of the most important metabolites of melatonin, *N*-1-Acetyl-*N*-2-formyl-5-methoxykynuramine (AFMK) and *N*-1-Acetyl-5-methoxykynuramine (AMK), have also been reported. AFMK is a potent antioxidant, which provides protection to the DNA molecule and lipids through different many metabolic pathways. On the other hand, AMK is also a powerful antioxidant and is able to inhibit the biosynthesis of prostaglandins by binding to diazepam receptors [59–61].

Like other secondary metabolites, melatonin can stimulate endogenous antioxidant enzymes and/or capture free radicals (antioxidant capacity *in vitro* and *in vivo*) [47, 62, 63]. This neurohormone is capable of capturing reactive oxygen species, such as peroxynitrite [64]; or hydrogen peroxide in a dose-dependent manner [61]. In addition, melatonin has demonstrated antioxidant capacity in vitro by the $ABTS^{+}$ method [62]. In vivo studies have also demonstrated the antioxidant effect of melatonin. When administered in mice, it was observed that melatonin is able to reduce chronic oxidative stress related to aging [65], and that it could even reduce blood pressure in men with chronic hypertension [66].

The amphipathic nature of the molecule allows it to cross physiological barriers, so its presence has been described in the nucleus of the cytosol, in the mitochondria and in different biological membranes [67]. The importance of this fact lies in the fact that the molecule can act in the places where free radicals are formed, providing antioxidant defense from oxidative injury where they are needed.

The role of melatonin as neuroprotective agent is relevant. It has been successfully proved in sleep disorders, helping to restore circadian rhythm. Moreover, melatonin is especially effective in patients with neurodegenerative diseases [68]. Several scientific studies have been carried out with the aim for palliating consequences of diseases such as Alzheimer, Parkinson, Huntington disease or amyotrophic lateral sclerosis, obtaining satisfactory results [24].

Miller et al. widely reviewed neuroprotective capacity of melatonin, reporting a wide range of actions in the human being [69]. Regarding neurodegenerative diseases, the most susceptible to be treated by melatonin are Parkinson disease [70–72], Multiple sclerosis [73, 74], Alzheimer disease [75–77] and amyotrophic lateral sclerosis [78–81].

The different effects of melatonin that could be useful for the improvement of neurological pathologies are large [69]. Melatonin can improve the evolution of Parkinson disease by the reduction of excitotoxicity caused by the autoxidation of dopamine [70], or improving quality and length of sleep [72]. Moreover, melatonin protects from injury to mitochondria, decreasing lipid peroxidation in multiple sclerosis and Alzheimer disease [73–75] and increase antioxidant enzymes generation [74]. Melatonin has also showed capacity to protect against cognitive deficits and inhibits formation of nicotinamide and Aβ plaque [76–78]. Melatonin also is able to reduce oxidative injury by reducing carbonyls formation [79, 80], and delays the progression of amyotrophic lateral sclerosis by inhibiting MT1 reception loss [81].

2.3. Hydroxytyrosol

Hydroxytyrosol is also known as 2-(3,4-dihydroxyphenyl)-ethanol (3,4-DHPEA) and as DOPET (**Figure 3**). Hydroxytyrosol is mainly found in olive oil as secoiridoid derivatives, as acetate and in free form [82]. Both hydroxytyrosol and its derivatives arise from oleuropein (hydroxytyrosol esterified with elenolic acid), present in olives during the extraction of olive oil [24].

Wine has proven to be another important source of hydroxytyrosol in the Mediterranean diet, and is formed in wine from tyrosol during alcoholic fermentation. Hydroxytyrosol was firstly found in Italian wines by Di Tommaso et al. [83], and later in other Italian and Greek wines [84–86]. Some authors describe a higher concentration in red wines (3.66–4.20 mg L^{-1}) than in white wines (1.72–1.92 mg L^{-1}) [24, 87]. Finally, Minuti et al. obtained hydroxytyrosol concentrations between 1.8 and 3.1 mg L^{-1} in red wine [87]. Thus, scientific literature shows that wine is an important source of hydroxytyrosol in the diet, along with olive oil [24].

De La Torre et al. and Schröder et al. investigated the bioavailability of hydroxytyrosol by comparing the intake of red wine and olive oil [87–89]. The intake of red wine (250 mL) increased plasmatic concentration of hydroxytyrosol above 8 ng mL^{-1}, representing greater increase than the observed after the intake of olive oil (0.35 mg of hydroxytyrosol with the intake of wine red and 1.7 mg with the ingestion of olive oil). These authors proposed the endogenous production of hydroxytyrosol from ethanol and dopamine in response to the observed increase.

Moreover, tyramine has been proposed as another route for hydroxytyrosol formation, and could be partly responsible for the increased endogenous formation of hydroxytyrosol after the intake of red wine. Therefore, substantial content of tyramine in red wine, could lead to the increase of endogenous formation of hydroxytyrosol. However, the amount of tyramine in the red wine is not large enough to explain such increase in endogenous hydroxytyrosol [88].

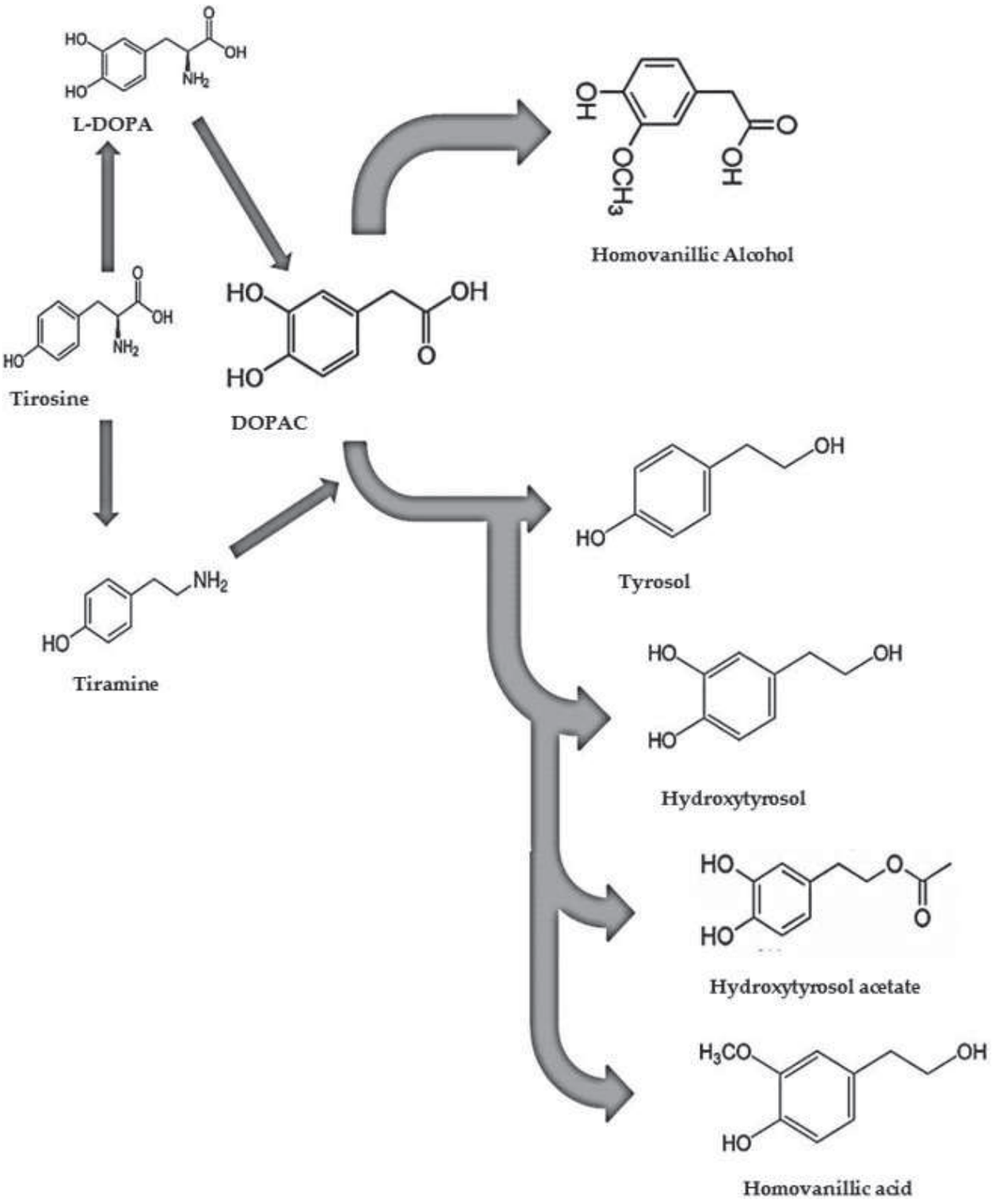

Figure 3. Hydroxytyrosol and related metabolites.

Several studies have reported beneficial effects of hydroxytyrosol, mainly after the intake of olive oil (the main source of hydroxytyrosol in the Mediterranean diet). The different effects attributed to hydroxytyrosol include: antioxidant capacity, cardioprotective effect, anticancer,

antimicrobial, neuroprotective and antidiabetic activity [24]. Numerous authors have proved their ability both to chelate oxidizing compounds [90, 91], and to increase the concentration of antioxidant enzymes [91].

Neurodegenerative diseases, such as Alzheimer's disease or Parkinson's disease, could also be improved by the ingestion of hydroxytyrosol [92, 93]. As melatonin, hydroxytyrosol has the ability to cross the blood–brain barrier. Therefore, it can go through the brain and is rapidly metabolized, acting where the oxidative attack is produced [24].

Different studies evaluating the effects of hydroxytyrosol, showed the great neuroprotective capacity of the molecule. Hydroxytyrosol considerably inhibits LDL efflux in a dose-dependant way, both *in vivo* and *in vitro*. That fact offers an initial knowledge for more studies as potential effects of hydroxytyrosol as neuroprotective compound [93]. Marhuenda et al. reported a descend on the formation of neuroprostanes and F_2-dihomo-isoprostanes after the intake of red wine [28]. These effect was related to the content on hydroxytyrosol, more than other compounds from red wine matrix. Moreover, an oleuropein-enriched extract showed neuroprotective capacity by establishing a non-covalent complex with the amyloid–β–peptide, so can be decisive in many neurodegenerative diseases as Alzheimer's or Parkinson's disease. Therefore, hydroxytyrosol, being the main degradation molecule from oleuropein, can be proposed as a promising neuroprotective compound [92].

2.4. Polyphenols

Polyphenols comprises a large and heterogeneous group of phytochemicals containing phenol rings. They are mainly divided into flavonoids, phenolic acids, stilbenes, and lignans. Mayor flavonoids are flavones, flavonols, flavanols, flavanones, isoflavones, and anthocyanins [94] (**Table 1**).

Polyphenols can induce antioxidant enzymes such as glutathione peroxidase, catalase and superoxide dismutase that decompose hydroperoxides, hydrogen peroxide and superoxide anions, respectively. Moreover, they can also inhibit the expression of enzymes such as xanthine oxidase [95]. Dietary polyphenols have been shown to play important roles in human health. In fact, high intake of fruits, vegetables and whole grains, which are rich in polyphenols, has been related to reduced risk of many chronic diseases including cancer, cardiovascular disease, chronic inflammation and many degenerative diseases [96].

Health benefits of catechins and proanthocyanidins are related to their antioxidant character and free radical scavenger activity. Moreover, they can switch mechanisms involved in different pathologies such as: hypertension, inflammation, proliferation cellular, thrombogenesis, hypertriglycemia, hypercholesterolemia and neurodegenerative diseases or neuroinflammation [94].

Studies conducted on cell cultures stimulated with lipopolysaccharide show that the administration of quercetin, catechin and epigallocatechin gallate blocks the inflammatory response by inhibiting NOSi and the expression of cyclooxygenase (COX-2), as well as the production of NO, the release of pro-inflammatory cytokines, and the generation of ROS, in astrocytes and in microglia [97]. These extracts of phytochemicals have also been shown to inhibit MAPKs such

		Main food sources
Flavonoids	Anthocyanins	Cherries, red wine, olives, hazelnuts, almonds, black elderberry, black chokeberry, blueberries
	Flavonols	Grapefruit/pomelo juice, oranges, orange juice, grapefruit juice
	Flavanols	Dark chocolate red wine, apples, peaches, cocoa powder, nuts, dark chocolate
	Isoflavones	Soy flour, beans soy paste, roasted soy bean,
	Flavanones	Grapefruit/pomelo juice, oranges, orange juice, grapefruit juice
	Flavones	Virgin olive oil, oranges, whole grain wheat-flour bread, refined-grain wheat-flour bread, whole grain wheat four, black olives
Stilbenes	Resveratrol	Grapes, red wine, nuts
Phenolic acids	Benzoic acid	Olives, virgin olive oil, red wine, walnuts, pomegranate juice, red raspberry
		Coffee, maize oil, potatoes
Lignans	Cinnamic acid	Virgin olive oil, whole grain rye flour, bread from whole grain rye flour, flaxseed

Table 1. Main food sources of polyphenols [101].

as p38 or ERK1/2, which regulate NOSi and TNF-α, in addition to the activation of glial cells [97]. Mendel et al. suggest that catechins, may protect brain from aging and reduce the incidence of dementia, Alzheimer disease and Parkinson disease [98]. Moreover, Geiser et al. indicate that both anti-aggregation and antioxidant characteristics of catechins may alter mRNA expression to reduce feed-forward mechanisms and promote non-amyloidogenic processing [99].

In vivo studies show that chronic administration of epicatechin in combination with physical exercise, improves spatial memory, due to the increase in the Akt protein that activates the endothelial nitric oxide synthase (NOSe) enzyme, stimulate the angiogenesis, as well as the increase in neuronal density in regions such as the dentate gyrus of the hippocampus [100].

Other group of polyphenols which has showed several benefits are anthocyanins. Several studies have shown beneficial effects of anthocyanins on health, and the high antioxidant capacity due to their capacity to protect from free radicals by the donation of hydrogen atoms. The role of anthocyanins in neurodegenerative diseases is strongly linked to oxidative attack protection. Anthocyanins can modulate cognitive and motor function, enhancing memory, and preventing age-related decline in neural function [102]. Extracts rich in anthocyanins and proanthocyanidins exhibited greater neuroprotective activity than extracts rich in other polyphenols. Moreover, many individual anthocyanins interfered with rotenone neurotoxicity, which can be related with increased memory [103].

Finally, mayor food containing anthocyanins are berries that can effectively reverse age-related deficits in certain aspects of working memory. Anthocyanins and other flavonoids can prevent neuroinflammation, by the activation of synaptic signaling, and improving blood flow to the brain. It appears that some dietary anthocyanins can cross the blood–brain barrier, allowing the compounds to have a direct beneficial effect [100]. Anthocyanins suppress mitochondrial oxidative stress-induced apoptosis by preserving mitochondrial GSH and inhibiting cardiolipin oxidation and mitochondrial fragmentation [104].

3. Conclusion

Neurodegenerative diseases are a public health problem and the possibilities of delaying their evolution constitute a challenge for research. Considering the relationship between oxidative stress and neuroinflammation with neurodegenerative diseases, monitoring a diet rich in bioactive substances with antioxidant activity and polyunsaturated fatty acids of the omega-3 series, with a proven antiinflammatory and neuroprotective effect, could slow down the evolution of the disease, improve cognitive deterioration, delay the decline of motor symptoms and improve the quality of life of patients. An example of this type of diet is the Mediterranean diet, which is characterized by the consumption of fruits, vegetables, legumes, nuts, olive oil, moderate consumption of red wine and blue fish that incorporate bioactive substances with beneficial effects on health.

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