



# Exploring the Therapeutic Potential of Phytochemicals in Alzheimer's Disease: Focus on Polyphenols and Monoterpenes

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Alzheimer's disease (AD) is a chronic, complex neurodegenerative disorder mainly characterized by the irreversible loss of memory and cognitive functions. Different hypotheses have been proposed thus far to explain the etiology of this devastating disorder, including those centered on the Amyloid- $\beta$  (A $\beta$ ) peptide aggregation, Tau hyperphosphorylation, neuroinflammation and oxidative stress. Nonetheless, the therapeutic strategies conceived thus far to treat AD neurodegeneration have proven unsuccessful, probably due to the use of single-target drugs unable to arrest the progressive deterioration of brain functions. For this reason, the theoretical description of the AD etiology has recently switched from over-emphasizing a single deleterious process to considering AD neurodegeneration as the result of different pathogenic mechanisms and their interplay. Moreover, much relevance has recently been conferred to several comorbidities inducing insulin resistance and brain energy hypometabolism, including diabetes and obesity. As consequence, much interest is currently accorded in AD treatment to a multi-target approach interfering with different pathways at the same time, and to life-style interventions aimed at preventing the modifiable risk-factors strictly associated with aging. In this context, phytochemical compounds are emerging as an enormous source to draw on in the search for multi-target agents completing or assisting the traditional pharmacological medicine. Intriguingly, many plant-derived compounds have proven their efficacy in counteracting several pathogenic processes such as the A $\beta$  aggregation, neuroinflammation, oxidative stress and insulin resistance. Many strategies have also been conceived to overcome the limitations of some promising phytochemicals related to their poor pharmacokinetic profiles, including nanotechnology and synthetic routes. Considering the emerging therapeutic potential of natural medicine, the aim of the present review is therefore to highlight the most promising phytochemical compounds belonging to two major classes, polyphenols and monoterpenes, and to report the main findings about their mechanisms of action relating to the AD pathogenesis.

**Keywords:** Alzheimer's disease, phytochemicals, polyphenols, monoterpenes, multi-target therapy, neurodegeneration, neuroinflammation, amyloid- $\beta$  aggregation

## INTRODUCTION

Alzheimer's disease (AD) is one of the most common age-related diseases. It currently affects over 40 million people worldwide, accounting for up to 70% of all cases of dementia (Sengupta et al., 2016; Bhatti et al., 2019; Zhang et al., 2021). The AD syndrome is characterized by the progressive deterioration of cognitive abilities accompanied by an irreversible neuronal loss (Selkoe and Hardy, 2016). The AD clinical symptomatology, described for the first time by Alois Alzheimer in 1907 (Alzheimer, 1907), includes memory impairment, behavioral alterations, language deficits, and other symptoms (Querfurth and LaFerla, 2010). AD represents a devastating brain disorder with a significant burden for health systems. Unfortunately, the few drugs approved for the AD treatment are only limited to a slight relief of symptoms but are not able to arrest the onset and progression of the AD-related neurodegeneration (Husna Ibrahim et al., 2020; Jeremic et al., 2021). For these reasons, much attention is still being given to drug development and to a deeper understanding of the AD pathophysiological processes. Many efforts are currently made by researchers from around the world to find new molecular targets for the development of effective therapies. However, one of the major limitations of any treatment is the fact that at the time of the clinical diagnosis an irreversible brain atrophy has already occurred and the cascade of events leading to neurodegeneration is well developed (Perrin et al., 2009; Holtzman et al., 2011).

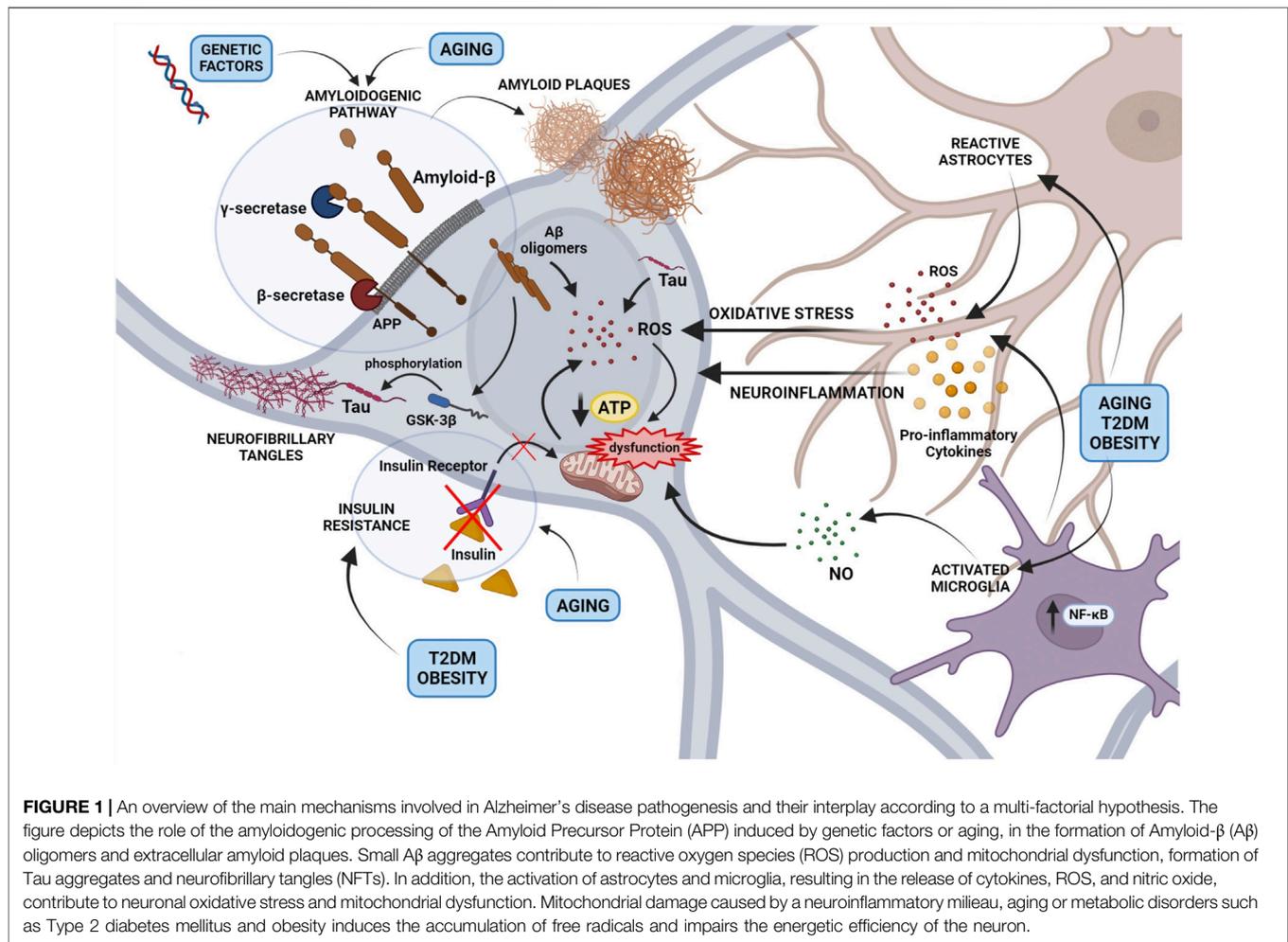
The formation of AD lesions develops over two or 3 decades, resulting in a preclinical period in which the AD neuropathology is present without any cognitive symptoms. At the moment of the clinical diagnosis, the brain of AD patients is mainly characterized by large extracellular deposits of aggregated Amyloid- $\beta$  ( $A\beta$ ) peptides, also called amyloid plaques, and by degenerating neurons containing neurofibrillary tangles (NFTs), which are mainly composed of the microtubule-associated protein Tau in a hyperphosphorylated form (Selkoe and Hardy, 2016; Trejo-Lopez et al., 2021). Beside these two principal hallmarks, additional changes may be observed, including amyloid deposition at the vascular level (amyloid angiopathy), neuroinflammation, and a significant shrinkage of the hippocampus and entorhinal cortex, detectable at the MRI scan, in comparison to the brain of unaffected people (Serrano-Pozo et al., 2014).

The knowledge about the etiology of AD remains still incomplete. Three genes whose mutations induce an aberrant processing of the amyloid precursor protein (APP) and the consequent increase of the  $A\beta$  production, the APP, Presenilin 1 (PS1) and Presenilin 2 (PS2) genes, have been identified as the main determinants of the early-onset autosomal dominant AD (Serretti et al., 2007; Fernandez et al., 2014). Regarding the late-onset forms of familial AD, non-dominant genetic factors have been found to account for most of the cases (Kwok et al., 2020). By contrast, still little is known about the origins of the  $A\beta$  deposition and neurodegeneration occurring in the sporadic AD, which represents the greatest proportion of all AD cases (Efthymiou and Goate, 2017). Nonetheless, the inheritance of the  $\epsilon 4$  allele of the Apolipoprotein (APO) E gene, which is associated with both increased  $A\beta$  deposition and tau

pathology (Shi et al., 2017; Shi et al., 2021), constitutes the strongest genetic risk factor for sporadic AD, determining the age at onset of the disease and strictly influencing its progression (Cerf et al., 2011; Hashimoto et al., 2012; Koffie et al., 2012). The increasing age is instead considered the major non-genetic risk factor, with genetic and environmental factors influencing the onset and severity of the disease (Zhang et al., 2021).

At present, the most accepted etiological hypothesis of AD is the so-called "amyloid cascade hypothesis," which considers the aggregation of the  $A\beta$  peptide and its accumulation in brain tissues as the main trigger of the AD neurodegenerative cascade (Selkoe and Hardy, 2016). According to this hypothesis, the intracellular and extracellular deposition of  $A\beta$  aggregates triggers a sequence of deleterious events that contribute to the AD pathogenesis, including gliosis, oxidative stress, Tau hyperphosphorylation, neuronal death, and synaptic loss (Braak and Braak, 1994). However, the "amyloid cascade hypothesis" has progressively undergone an extensive debate because of its inability to fully describe the complex pathogenesis of AD and the continuous failure of  $A\beta$ -targeted therapies. Moreover, it has been shown that the Tau pathology could cause neurodegeneration and neuroinflammation regardless of the  $A\beta$  pathology (Kametani and Hasegawa, 2018; Laurent et al., 2018). Meanwhile, several other hypotheses have been proposed, including those centered on the impairment of cholinergic transmission, mitochondrial dysfunction, oxidative stress, neuroinflammation, and brain insulin resistance. However, the common limitation of these hypotheses is that, similarly to the "amyloid cascade hypothesis," they overemphasize a single specific mechanism, underestimating other mechanisms. In this regard, it is worth noting that much information about the pathological features of AD arises from the numerous genetic and toxin-induced rodent models of AD that have been developed in the last decades. These models, despite replicating some AD symptoms and being useful for testing the efficacy of anti-AD drugs, are not sufficient for modeling the complexity of the AD pathology and, importantly, are incapable to explain the origins of the sporadic forms of AD.

A "multifactorial hypothesis" of AD assumes that multiple etiological factors may converge in a common pathological manifestation (**Figure 1**). This seems to be the most convincing model able to explain why all the drugs developed under the "one-molecule, one-target" paradigm have displayed poor therapeutic potential. In addition, although how the complex interplay among different mechanisms contribute to the AD etiology remains still poorly understood, a multifactorial hypothesis is probably the most suitable to describe the onset of sporadic AD taking also note of aging as the most important risk factor. In this view, a therapeutic strategy targeting simultaneously different pathways considered as determinants of the AD pathogenesis seems to be the most promising approach to modify the disease progression. In this context, plant-derived compounds are emerging as an enormous source to draw on in the search for multi-target agents completing or assisting the traditional pharmacological medicine. The attempt of this review is therefore to highlight the most promising



phytochemicals for the AD treatment belonging to two major classes, polyphenols and monoterpenes, and to describe their mechanisms of action.

## MAIN PATHOGENIC MECHANISMS IN AD

### $A\beta$ Aggregation and Toxicity

The  $A\beta$  aggregation has been extensively investigated in the last 2 decades (Selkoe, 1991; Selkoe and Hardy, 2016) and most efforts to prevent or slow down the AD progression have been centered thus far on the inhibition of this process. The extracellular deposits of  $A\beta$  aggregates, namely the neuritic plaques, are the primary hallmarks found in the brain of the patients diagnosed with AD (Selkoe and Hardy, 2016). However, the  $A\beta$  aggregation and accumulation start at the cellular level many years before the clinical diagnosis of AD (Morris et al., 1996; Brannstrom et al., 2014).

The  $A\beta$  peptide, consisting of 39–43 amino acid residues, is produced in the brain upon the cleavage of the APP by proteolytic enzymes. The APP, which has been reported to be involved in many important physiological functions of neurons (Priller et al.,

2006), is a large transmembrane protein physiologically undergoing a non-amyloidogenic processing consisting in the sequential cleavage by  $\alpha$ - and  $\gamma$ -secretases (Selkoe, 2002). Importantly, the cleavage site for the  $\alpha$ -secretase lies within the  $A\beta$  sequence of the APP and hence precludes the  $A\beta$  formation. In the so-called “amyloidogenic pathway” the APP is instead processed first by the  $\beta$ -secretase, also known as  $\beta$ -site APP Cleaving Enzyme 1 (BACE-1), and then by the  $\gamma$ -secretase, which generates monomeric  $A\beta$  fragments. The most abundant species are the  $A\beta_{1-40}$  and  $A\beta_{1-42}$  (Seubert et al., 1993), the latter being the most prone to aggregate into structures with a  $\beta$ -sheet conformation and, hence, the most toxic (Bressler et al., 1996; Folch et al., 2018). The total  $A\beta$  burden depends on the balance between production and clearance or degradation rates (Hardy, 1997; George-Hyslop and Rossor, 2001). The  $A\beta$  clearance may occur through the transport into the cerebrospinal fluid, the blood across the blood-brain barrier (BBB), and the removal by brain-resident macrophages (Yoon and Jo, 2012). The  $A\beta$  degradation is ensured by some proteases, such as cathepsin and the insulin-degrading enzyme (IDE), which cleave the  $A\beta$  into smaller soluble fragments (Miners et al., 2011; Kurochkin et al., 2018).

Both A $\beta_{1-40}$  and A $\beta_{1-42}$  have been shown to interact with several receptors including the N-Methyl-D-Aspartate (NMDA),  $\alpha$ -Amino-3-hydroxy-5-Methyl-4-isoxazole Propionic acid (AMPA), nicotinic Acetylcholine (nACh), and muscarinic Acetylcholine (mACh) receptors (Tozaki et al., 2002; Snyder et al., 2005; Liskowsky and Schliebs, 2006; Gu et al., 2009), and to induce a synaptic transmission impairment through Ca<sup>2+</sup> dysregulation and the blockage of ion channels and neurotransmitters (Peña et al., 2006; Pannaccione et al., 2020). The aggregation of A $\beta_{1-42}$  monomers first gives rise to soluble oligomeric species, which further assemble to form insoluble aggregates known as fibrils accumulating in the brain parenchyma and other tissues (Chen et al., 2017). In an alternative aggregation pathway known as secondary nucleation, the fibrils act as a catalytic surface for the formation of new aggregates (Arosio et al., 2015). The toxicity of A $\beta_{1-42}$  aggregates is directed to different cell types and affects a myriad of cellular functions. Oxidative stress, mitochondrial dysfunction, astrocytic and microglial activation, membrane perturbation, and loss of ionic homeostasis are, at the cellular level, some of the events downstream the A $\beta_{1-42}$  aggregation and accumulation (Selkoe and Hardy, 2016). All these processes converge in the disruption of neuronal network, synaptic dysfunction, neuroinflammation, and neurodegeneration, leading in turn to the loss of cognitive abilities and, ultimately, in the severe dementia typical of the late stages of AD (Palop et al., 2007; Busche et al., 2015; Zott et al., 2018; Li and Selkoe, 2020; de Oliveira et al., 2021).

According to the so-called “cellular phase,” an extension of the amyloid cascade hypothesis proposed by De Strooper and Karran (De Strooper and Karran, 2016), the dysfunction of the neuro-glial-vascular unit along with the impairment of astrocytic and microglial homeostatic functions mainly contribute to precipitate AD in a clinical disease. Importantly, although the neuro-glial-vascular dysfunction and subsequent cerebrovascular damage are also believed to precede and even contribute to the disruption of A $\beta$  homeostasis, the soluble A $\beta$  aggregates spreading throughout the brain may in fact form insoluble deposits at the vascular level and compromise the vascular function and BBB integrity (Xu et al., 2016; Soto-Rojas, et al., 2021). Unsurprisingly, such a condition, known as cerebral amyloid angiopathy exacerbates the AD pathology (Shabir et al., 2018). Glial cells seem to play a key role in this process, since both astrocytes, the predominant form of glial cells in the central nervous system (CNS), and microglia, the major phagocytic cells in the brain, are involved in the tight regulation of A $\beta$  clearance and degradation. Importantly, the capability of astrocytes and microglia to internalize and degrade A $\beta$  (Guénette, 2003; Hansen et al., 2018) is strictly correlated with their aberrant activation during the AD progression (Bates et al., 2009; Ries and Sastre, 2016). Moreover, A $\beta$  has been recognized to exert oxidative stress in astrocytes by altering astrocytic Ca<sup>2+</sup> homeostasis and mitochondrial function (Abramov et al., 2004; Verkhatsky et al., 2017; Piccialli et al., 2020). In turn, the A $\beta$ -induced dysregulation of ionic homeostasis in astroglial cells may crucially contribute to their pathological remodelling (Boscia et al., 2017; Verkhatsky et al., 2017; Piccialli et al., 2020).

## Tau Hyperphosphorylation and Toxicity

Multiple lines of evidence suggest that the hyperphosphorylation and aggregation of the protein Tau may be a major trigger of AD neurodegeneration. Tau, the main component of NFTs, is a microtubule stabilizer protein that normally undergoes a myriad of post-translational modifications, including phosphorylation (Goodson and Jonasson, 2018). Different kinases have been demonstrated to be involved in Tau phosphorylation, including the glycogen synthase kinase 3 $\beta$  (GSK-3 $\beta$ ), protein kinase A, p38 mitogen activated protein kinase (MAPK), extracellular signal-related kinases (Erk1/2), and c-Jun N-terminal kinases (JNK) 1/3 (Martin et al., 2013). In AD, an imbalance between kinase and phosphatase activities causes Tau hyperphosphorylation. It is known that A $\beta$  aggregates may induce Tau hyperphosphorylation by enhancing the activity of several kinases including GSK-3 $\beta$  and MAPKs. Moreover, A $\beta$  triggers the activation of caspase-3 and calpain-1, which can cleave Tau at the C-terminus generating small fragments able to induce neurite degeneration and neuronal death (Gamblin et al., 2003; Bloom, 2014; Chen et al., 2018). Interestingly, the activation of the JNK pathway induces caspase activation, further promoting Tau cleavage (Sahara et al., 2008). Tau hyperphosphorylation leads to its aggregation and dissociation from microtubules (Wang et al., 2013; Gao et al., 2018). The dissociation from microtubules and the formation of NFTs in turn cause the impairment of the axonal transport, cytoskeletal and mitochondrial dysfunction, oxidative stress, and synaptic loss (Hoover et al., 2010) and, moreover, increase the cytosolic content of tau further promoting its aggregation and fibrillization. Similarly to A $\beta$ , aggregated Tau forms  $\beta$ -sheet-containing amyloid fibrils, known as paired helical filaments (Mandelkow et al., 2007). Another noteworthy feature of Tau is its ability to spread throughout the brain by moving from 1 cell to another, anatomically connected, cell hence perfectly exemplifying the prion-like propagation characteristic of several proteinopathies (Dujardin and Hyman, 2019). Importantly, Tau can affect mitochondrial function by inducing ROS production, reducing mitochondrial respiration and causing the impairment of mitochondrial transport along neuronal axons (David et al., 2005; Dubey et al., 2008). Although Tau toxicity is considered a major driver of AD neurodegenerative cascade, there is still a significant gap in the knowledge of the molecular mechanisms underlying tau-mediated neuroinflammation. Nonetheless, very recently it has been demonstrated that Tau induces a pro-inflammatory response in microglia by activating p38 MAPK, whose blockade, instead, promotes microglial phagocytic function and reverses Tau toxicity (Perea et al., 2018; Perea et al., 2022).

## Oxidative Stress and Mitochondrial Dysfunction

Oxidative stress and mitochondrial dysfunction are prominent features of many neurodegenerative diseases including AD (Butterfield, 2002; Butterfield and Boyd-Kimball, 2018; Sharma and Kim, 2021). Reactive oxygen species (ROS) and reactive nitrogen species (RNS), which exist in both radical

and non-radical forms, are very reactive molecules that may influence cell functions and viability depending on their concentration. Mitochondria are widely recognized as a major source of ROS, since reactive species are physiologically produced through mitochondrial respiration. In particular, the leak of protons from some complexes of the mitochondrial electron transport chain and their interaction with oxygen ( $O_2$ ), normally occurring during the process of energy production, provide the majority of ROS in the cell. Physiologically, ROS and RNS concentration is maintained at low levels by enzymatic and non-enzymatic factors. Among the enzymes, the superoxide dismutase (SOD) plays a crucial role in antioxidant processes by converting the superoxide radical  $O_2^{\bullet-}$ , a very reactive species, to  $H_2O_2$ , a more stable form of ROS. Glutathione peroxidase (GPx) and catalases, in turn, limit the accumulation of  $H_2O_2$  by producing water and oxygen. Glutathione (GSH), which acts as a cofactor of GPx, is also a non-enzymatic antioxidant able to quickly inactivate reactive species by itself. At physiological concentrations, ROS play a key role as second messengers, by oxidizing the-SH group on the cysteine residues of proteins and hence regulating their post-translation modifications, activity, and trafficking. In particular, ROS have been associated to an increased activity of MAPK pathways, such as those involving Erk1/2, JNK, and p38 MAPK. Moreover, ROS may impact the activity of several transcription factors sensitive to redox changes including the Hypoxia Inducible Factor-1 $\alpha$  (HIF-1 $\alpha$ ) and the nuclear factor erythroid 2-related factor 2 (Nrf2).

The brain is particularly susceptible to oxidative stress because of the high content of lipids, although the different brain cell types do not display the same vulnerability to oxidative damage. Glial cells are indeed more resistant to oxidative injury, while neurons, especially those in the amygdala and hippocampus, are more sensitive. In neuronal cells, a rise in intracellular ROS levels causes protein degradation, DNA damage, and lipid peroxidation. In this context, mitochondria are a major target of ROS/RNS damages (Hung et al., 2018). Indeed, in addition to induce protein carbonylation, lipid peroxidation, and mitochondrial DNA damage (Marchi et al., 2012), ROS and RNS directly trigger the opening of the permeability transition pore (PTP), which in turn amplifies free radical signals. In addition, the exposure to reactive species can result in a decrease in the enzymatic activity of the complexes of the respiratory chain, thus reducing the efficacy of the production of ATP and further increasing the generation of ROS (Zorov et al., 2014). The occurrence of a severe mitochondrial dysfunction in the brain of AD patients has been extensively demonstrated (Abate et al., 2020). In particular, high levels of sporadic mutations in mitochondrial DNA were found in AD brains along with deficiencies in mitochondrial DNA repair mechanisms (Lin et al., 2002; Singh et al., 2015; Nissanka and Moraes, 2018). Alongside, many components of the antioxidant system have been shown to be particularly affected during the AD progression. At molecular level, both oxidative stress and mitochondrial failure have been linked to A $\beta$ , although it is still unclear whether the A $\beta$  aggregation and accumulation are predominantly the cause or rather a consequence of oxidative stress (Cheignon et al., 2018). Undoubtedly, A $\beta$  oligomers may induce ROS production through several mechanisms. First, the

A $\beta$  peptide is oxidative *per se* because of the peculiar chemical/electrostatic features of its secondary structure. For the same reason, the A $\beta$  insertion into the lipid bilayer of the neuronal plasma membrane induces lipid peroxidation in a direct manner (Butterfield, 2002). Furthermore, A $\beta$  oligomers induce an increase of intracellular  $Ca^{2+}$  levels promoting its accumulation in mitochondria (Calvo-Rodriguez et al., 2019), which in turn induces the opening of the mPTP, release of mitochondrial ROS, and apoptotic cell death (Esteras and Abramov, 2020).

On the other hand, many experimental data suggest that oxidative stress and mitochondrial dysfunction induce an increase in the amyloidogenic cleavage of the APP and an aberrant A $\beta$  production (Misonou et al., 2000; Perez Ortiz and Swerdlow, 2019). Indeed, it was shown that oxidizing agents can increase the expression of the APP (McCarty et al., 2021), and the expression and activity of BACE-1 (Tamagno et al., 2002; Tong et al., 2005; Zhang et al., 2016). Moreover, both *in vitro* and *in vivo* studies pointed out the A $\beta$  peptide as a target molecule of metal-catalyzed oxidation (Näslund et al., 1994; Kowalik-Jankowska et al., 2004; Inoue et al., 2009). However, whether A $\beta$  oxidation impacts on its aggregation and/or its binding to plasma membranes remains to be elucidated.

## Neuroinflammation

Neuroinflammation is a physiological process aimed at protecting the CNS from several injuries and involves several types of cells and mediators. A growing amount of evidence has revealed that a sustained inflammatory state in the brain is a major contributor in the AD pathogenesis (Dhapola et al., 2021). Furthermore, neuroinflammation is a well-documented downstream event of the A $\beta$  accumulation (Akiyama et al., 2000). Accordingly, several studies reported high levels of inflammatory markers in the brain of AD patients, elevated levels of cytokines and chemokines in serum and cerebrospinal fluid, and microgliosis (Zhang F et al., 2013; Dursun et al., 2015; Hesse et al., 2016). Importantly, the increase of these markers seems to be correlated with the cognitive impairment occurring in AD (Solfrizzi et al., 2006; Westin et al., 2012).

The neuroinflammatory process is characterized by the activation of glial cells, especially astrocytes and microglia that, once activated, trigger the release of cytokines and chemokines such as interleukin-1 $\beta$  (IL-1 $\beta$ ) and interleukin-6 (IL-6), and other pro-inflammatory mediators including the nuclear factor- $\kappa$ B (NF- $\kappa$ B), nitric oxide (NO), tumor necrosis factor (TNF)- $\alpha$ , TNF- $\beta$ , adhesion molecules, and enzymes like cyclooxygenase-2 (COX-2) (Akiyama et al., 2000). The role of activated microglial cells is crucial in neuroinflammation since they can exert both neurotoxic and neuroprotective effects depending on the phenotype they acquire upon activation (Woodburn et al., 2021). Importantly, it has been demonstrated that soluble A $\beta$  oligomers can activate microglia and the production of pro-inflammatory cytokines (Selkoe and Hardy, 2016; Yang et al., 2017). On the other hand, it has been reported that neuroinflammation and the subsequent impairment of the neuro-glial-vascular unit, which is mainly composed of neuronal, glial, and vascular cells supporting the BBB (Harder

et al., 2002), occur before the disruption of the A $\beta$  homeostasis (Zlokovic, 2011). Indeed, the BBB disruption and increased permeability have been shown to occur in the early phase of the AD pathology (van de Haar et al., 2016). The increased leakage from the BBB may impair the A $\beta$  clearance and lead to microglial activation, hence amplifying the inflammatory response (Janota et al., 2016).

NF- $\kappa$ B nuclear transcription factor plays a crucial role in neuroinflammation, as it is the master regulator of the transcription of pro-inflammatory genes. Moreover, it has also been proposed as a molecular factor underlying some sporadic forms of AD (Chen et al., 2012). NF- $\kappa$ B is responsible for the activation of uncontrolled microglia, with subsequent ROS production, and pro-inflammatory cytokine and glutamate release, which in turn induce neuronal damage (Spencer et al., 2012). In particular, microglia stimulate the formation of NO by the inducible NO synthase (iNOS). NO, in turn, triggers neurodegenerative processes since it reduces the ATP synthesis by blocking the neuronal mitochondrial respiration at the cytochrome C oxidase level, hence inducing the production of ROS. Another crucial role is played by those signaling pathways involving MAPKs. The p38 MAPK, which is activated by the ROS produced upon microglial activation, was shown to activate NF- $\kappa$ B (Kheiri et al., 2018). Importantly, it has been reported that the A $\beta$ -induced oxidative stress leads to the activation of p38 MAPK and subsequent tau hyperphosphorylation (Giraldo et al., 2014).

In addition, decreased levels of Nrf2, a transcription factor negatively regulated by NF- $\kappa$ B (Liu et al., 2008) that is involved in antioxidants response mechanisms (Nair et al., 2008), have been reported in the brains of AD patients (Ramsey et al., 2007). Based on the evidence that an Nrf2 deficiency increases the levels of pro-inflammatory mediators, there is a growing interest in finding any Nrf2 pharmacological activators.

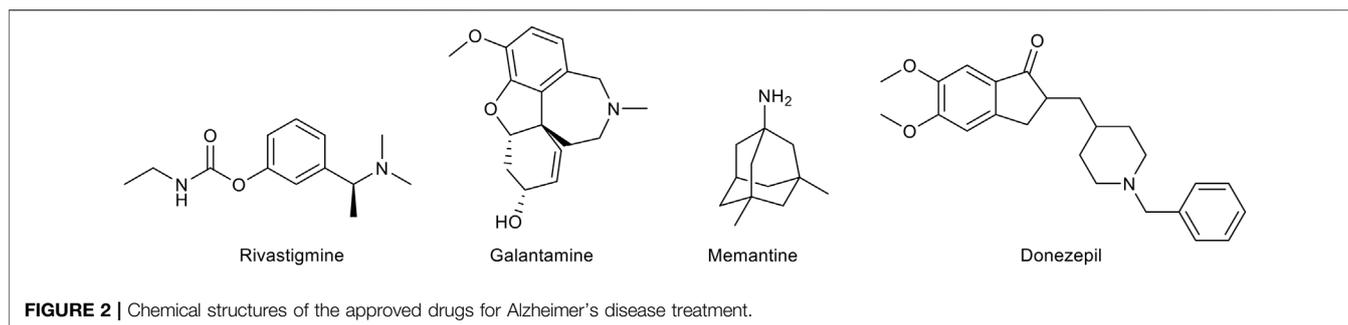
## Brain Insulin Resistance

Many age-related brain abnormalities at molecular and cellular levels have been identified as contributing factors of sporadic AD. Among those attracting particular attention, the impairment of brain glucose/energy metabolism induced by metabolic disorders such as obesity, diabetes and hyperinsulinemia, has been widely accepted to be implicated in the AD progression (de la Monte, 2017; Ettcheto et al., 2020). The deterioration of systemic glucose metabolism, which may range from chronic, mild glucose intolerance to type 2 diabetes mellitus (T2DM), has been found to be present before the clinical appearance of sporadic AD, hence suggesting that an early and severe brain hypometabolism may contribute to the neuropathological changes leading to AD (Cunnane et al., 2011). Despite its ability to uptake glucose in an insulin-independent manner, the brain is in fact an insulin-sensitive organ widely expressing insulin receptors (IR), especially in those regions considered crucial for cognition and feeding (Milstein and Ferris, 2021). Accordingly, it is now clear that both insulin and its analogue, the insulin-like growth factor 1 (IGF-1), can influence brain energy homeostasis, neuronal survival, and learning and memory processes (Kapogiannis and Mattson,

2011). For this reason, insulin resistance, which consists in a lower insulin activity at the cellular level accompanied by an impaired metabolism of carbohydrates, lipids, and proteins (DeFronzo et al., 2015), can have a crucial impact on cognitive functions. High fat diet (HFD) feeding, obesity and T2DM are the main causes of insulin resistance and are all recognized as risk factors for late-onset AD (Terzo et al., 2021). T2DM is a complex chronic disorder highly prominent in older people, characterized by the chronic increase in blood glucose levels, impaired insulin secretion by pancreatic  $\beta$ -cells, and insulin resistance (DeFronzo et al., 2015). T2DM is also associated to hyperlipidaemia, resulting from the use of lipids instead of glucose, and to subsequent microvascular and macrovascular complications (Vesa et al., 2020). Importantly, epidemiological studies indicate that T2DM is associated to an increased risk to develop AD in comparison to normal people (Biessels et al., 2006).

Obesity is a multifactorial disorder of energy metabolism often associated with other pathological conditions including dyslipidemia, hypertension, and stroke (Hall et al., 2015). Obesity may induce brain insulin resistance through several mechanisms: 1) in obesity conditions the adipose tissue loses its ability to store fatty acids, thereby inducing their accumulation in other tissues including the brain, which consequently develop insulin resistance (Engin, 2017); 2) in the adipose tissue of obese people, macrophages become pro-inflammatory and produce inflammatory cytokines, which crossing the BBB induce central inflammation and subsequent brain insulin resistance (De Souza et al., 2005; Zatterale et al., 2020); 3) nutrients overload induces a mitochondrial fatty acids and glucose accumulation leading to mitochondrial dysfunction, subsequent ROS production, and oxidative stress, which in turn contribute to the reduction of insulin signaling and inflammation (Marin-Royo et al., 2019).

Insulin resistance has also been found in association with AD independently on coincident T2DM (Bosco et al., 2011). In the brain of AD patients, IRs and IGF-1 receptors were found to be significantly reduced along with a decrease of many components of the insulin signaling cascade (Steen et al., 2005). This evidence led to consider AD as a brain diabetes or a "Type 3 diabetes". Although there is evidence supporting some roles of insulin in regulating the brain glucose uptake, it is well known that the brain preferentially expresses the insulin-insensitive glucose transporters 1 and 3, while the insulin-sensitive glucose transporter 4 (GLUT4) is limited to specific brain regions such as the hippocampus and hypothalamus (Leloup et al., 1996; Reno et al., 2017). However, insulin signaling crucially affects many aspects of mitochondrial metabolism, which in turn plays a central role in controlling cellular metabolism and nutrient sensing. For this reason, brain insulin resistance induces the impairment of mitochondrial metabolism and, subsequently, the reduction of the ATP production, mitochondrial dyshomeostasis and increased ROS production (Sripetchwandee et al., 2018). It is also worth noting that insulin resistance leads to a reduced A $\beta$  degradation by IDE, hence promoting the A $\beta$  accumulation (Ho et al., 2004; Zhao et al., 2004; Petrov et al., 2015). In addition, the impairment of



**FIGURE 2** | Chemical structures of the approved drugs for Alzheimer's disease treatment.

insulin signaling induces an increased activation of GSK-3 $\beta$ , which phosphorylates Tau, hence leading to Tau hyperphosphorylation (Hong and Lee, 1997; Planel et al., 2007; Zhang et al., 2018; Wei et al., 2021).

## THE SEARCH FOR DISEASE-MODIFYING STRATEGIES IN ALZHEIMER'S DISEASE: MULTI-TARGET THERAPIES AND LIFE-STYLE INTERVENTIONS

As mentioned above, there is a limited number of drugs for the treatment of AD. The pharmacological agents currently used for the therapy of the AD-associated dementia comprise three acetylcholinesterase (AChE) inhibitors, donepezil, rivastigmine, and galantamine (Figure 2). The only non-AChE inhibitor drug, memantine, is a NMDA receptor antagonist (Figure 2). All these drugs are used in clinical practice for mild to severe dementia and provide a symptomatic relief alleviating to some extent the cognitive symptomatology. However, despite useful in improving the quality of life of the patients, they are not able to interrupt or delay the AD progression. This evidence has prompted the search for effective disease-modifying agents.

To date, the majority of the disease-modifying strategies for AD have been based on A $\beta$ -focused approaches aimed at interfering with the A $\beta$  production, deposition and clearance. In particular, some drugs targeting the A $\beta$  peptide have been developed to control the APP proteolytic cleavage by  $\beta$ - and  $\gamma$ -secretases. Different BACE-1 inhibitors entered clinical trials because of the excellent results in preclinical studies. However, these trials proved unsuccessful due to the lack of effectiveness, as for the BACE-1 inhibitor Lanabecestat (Miranda et al., 2021), or because of a cognitive worsening in the patients, as in the case of Umibecestat (Neumann et al., 2018). Similarly,  $\gamma$ -secretase inhibitors failed clinical trials because of many side effects (Miranda et al., 2021). As alternative approaches, the inhibition of the A $\beta$  aggregation and the destabilization of pre-existing A $\beta$  aggregates have also been considered. Two drugs able to inhibit the A $\beta$  aggregation, tramiprosate and colostrinin, showed promising results in the early phases of clinical trials to fail successively in displaying any efficacy (Bilikiewicz and Gaus, 2004; Aisen et al., 2007).

Beside the anti-aggregating molecules, other therapeutic strategies have included active or passive immunization against the A $\beta$  peptide, consisting in the administration of A $\beta$  antigens and anti-A $\beta$  monoclonal antibodies, respectively. Unfortunately, although most of the A $\beta$ -targeted drugs tested in clinical trials unveiled promising results in reducing the A $\beta$  burden, they did not prove a significant efficacy against the cognitive decline, hence raising the question of whether targeting solely the A $\beta$  peptide could really impact on the AD pathogenesis. Since Tau neurofibrillary tangles are the other key pathological hallmark of AD, many pharmacological strategies have been directed to the Tau pathology, by addressing Tau hyperphosphorylation through Tau kinase inhibitors such as GSK-3 $\beta$  inhibitors, or its aggregation by means of anti-aggregating molecules (Long and Holtzman, 2019). Indeed, although it was postulated that the altered A $\beta$  metabolism precedes the Tau-related pathology and neuronal degeneration, many reports showed that Tau hyperphosphorylation is a primary factor in AD independently on A $\beta$ , and that the formation of amyloid plaques and neurofibrillary tangles may in fact act in parallel or in combination to contribute to the development of AD (Bloom, 2014). On the other hand, since Tau neurofibrillary tangles and amyloid plaques are not unique to AD but are also characteristic of the aging brain as well as of other diseases, it has been proposed that both these hallmarks may be pathological manifestations of other underlying mechanisms causing the disease.

According to the assumption that aging constitutes a predominant risk factor for AD, many studies have highlighted that increased levels of oxidative stress, mitochondrial dysfunction, neuroinflammation, and metabolic alterations, which are prominent features of aging, may all be critical in the initiation of the neurodegeneration occurring in AD (Song et al., 2021). In addition, a broad range of comorbidities and the underlying biological mechanisms have been shown to affect the AD pathogenesis and progression, including obesity, diabetes, cardiovascular diseases, stroke, and depression (Santiago and Potashkin, 2021). In the light of this evidence, the conventional approach based on the use of single-target drugs is currently switching toward a multi-target strategy able to interfere with different aspects of the AD pathogenesis (Oset-Gasque and Marco-Contelles, 2018). From one side, the multi-target approach may be achieved through a combination therapy, in which a cocktail of multiple single-target agents is administered. Such strategy, however, retains some limitations,

including the higher risk of drug-drug interactions, which in turn may affect the metabolism of the administered drugs and, hence, alter their efficacy and/or toxicity. From the other side, the pharmacological research is paying growing attention on the development of pleiotropic ligands interacting with two or more therapeutic targets at the same time. To this aim, a new drug design strategy is being considered, which consists in the combination of different pharmacophores to obtain hybrid molecules with the ability to modulate different pathways.

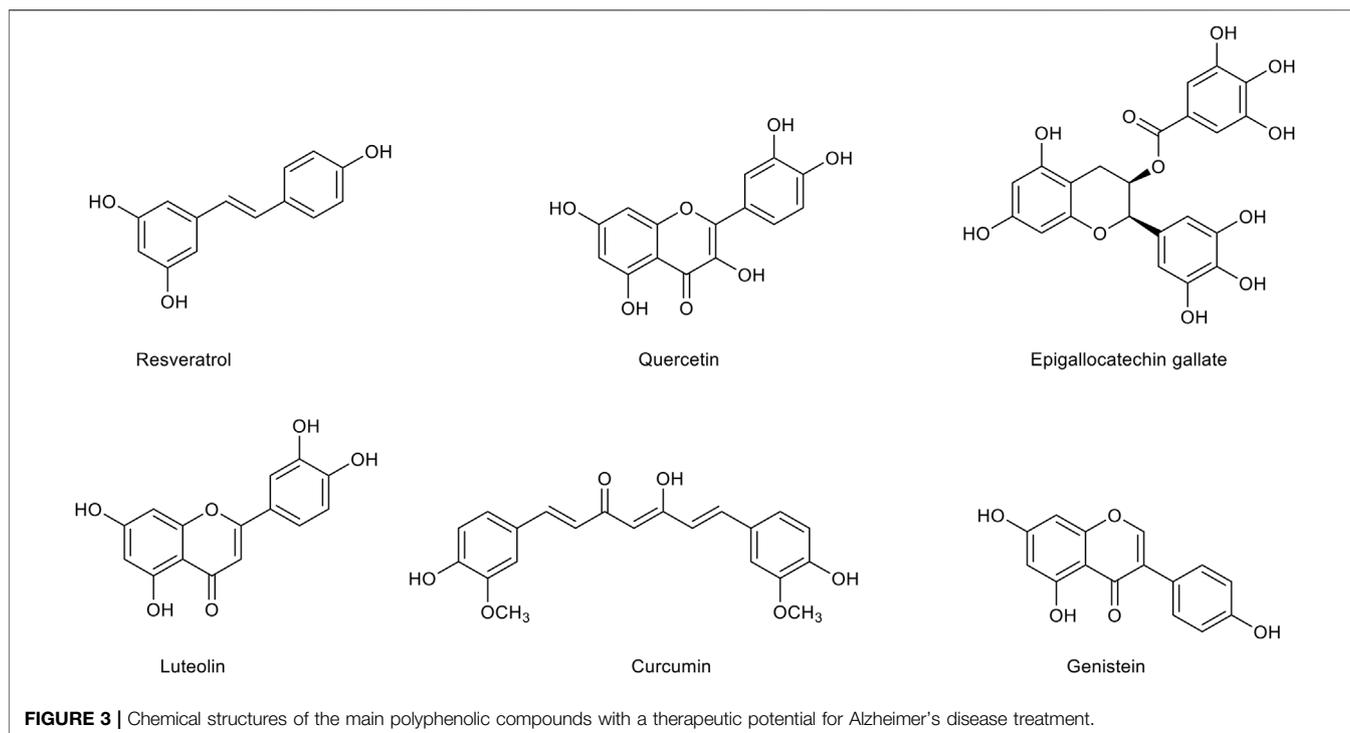
A great emphasis has also been placed on non-pharmacological interventions able to prevent or reduce AD severity. Many observational studies on AD animals and human subjects evidenced that life-style interventions including physical exercise, caloric restriction and nutritional supplements with antioxidant compounds are effective in reducing the modifiable AD risk factors, such as those raising from aging processes or any comorbidities (Bhatti et al., 2019; Dominguez et al., 2021). Novel strategies conceived to prevent the AD onset are focusing on dietary changes and nutritional supplements (Dominguez et al., 2021). In particular, there is a growing body of evidence supporting the ability of dietary polyphenols, such as those found in the Mediterranean diet, to interfere with different AD-related pathomechanisms and to slow down age-related cognitive deficits hence reducing the risk of dementia (Casamenti and Stefani, 2017; Bagetta et al., 2020). Epidemiological studies indicate that the consumption of flavonoids, a large family of polyphenol compounds, may ameliorate the AD pathology and provide a symptomatic benefit especially due to their anti-inflammatory and antioxidant activities (Devi et al., 2021; Hole and Williams, 2021).

## PLANT-DERIVED NATURAL COMPOUNDS AS MULTI-TARGET DISEASE-MODIFYING AGENTS

Natural products have played a dominant role over the centuries in the search for new therapeutic agents for the treatment of a wide range of human diseases. Natural compounds may indeed help in the discovery of new lead compounds or serve as structural mimics for synthetic analogues. Recently, a great emphasis on testing natural medicine for the AD therapy has been developed. Of note, galantamine, a tertiary alkaloid first isolated from *Galanthus nivalis* L. (Amaryllidaceae), is currently included in the AD therapy for its cholinesterase inhibitory properties and its ability to enhance the cholinergic function and ameliorate memory deficits (Heinrich, 2010; Anand and Singh, 2013). Rivastigmine, instead, is a semi-synthetic drug approved by the FDA as a cholinesterase inhibitor recommended for mild-to-moderate AD (Marucci et al., 2021). Based on this promising evidence and on the growing need for natural alternatives with less adverse effects in comparison to pharmaceutical drugs, phytochemical compounds are gaining attention as possible components of preventive or combination therapies aimed at counteracting the AD neurodegeneration (Jurcau, 2021; Lye et al., 2021). Many findings have already been provided by the literature about the efficacy of several

natural compounds including polyphenols and monoterpenes in affecting different pathogenic mechanisms of AD thanks to their antioxidant and anti-inflammatory properties, and to the ability to modulate the A $\beta$  aggregation and toxicity. Many of them have also been demonstrated to act as multi-target agents with reported fewer side effects in comparison to their synthetic counterparts (Rahman et al., 2021).

A huge number of phenolic compounds have displayed the capability to interfere with the aggregation of the A $\beta$  peptide by targeting one or multiple steps (Ma et al., 2020; Stefanescu et al., 2020). In particular, the action of natural inhibitors can be directed to 1) the assembly of A $\beta$  monomers, producing small aggregates; 2) the remodeling of A $\beta$  oligomers, leading to the formation of off-pathway species; 3) the inhibition of the secondary nucleation (Najarzadeh et al., 2019). These actions are underlain by the direct interaction of the compounds with the A $\beta$  peptide through covalent or non-covalent bindings (Henriquez et al., 2020; Ma et al., 2020). In particular, the phenolic moieties can establish  $\pi$ - $\pi$  stacking with the aromatic residue of the A $\beta$  or establish hydrophobic or hydrogen bonding interactions through phenolic hydroxyl groups (Fan et al., 2020). It was also demonstrated that the higher the number of catechol moieties the more the inhibitory activity increases (Tsunoda et al., 2018). Biophysical and docking studies also demonstrated that a guaiacol moiety is required for the anti-aggregating activity of polyphenolic inhibitors (Tomaselli et al., 2019). As mentioned above, the presence of anti-inflammatory and antioxidant properties is another crucial feature of natural compounds contributing to their therapeutic potential (Uddin et al., 2021). Many phytochemicals including flavonoids and other polyphenols, terpenoids, and carotenoids have indeed the ability to target multiple signaling pathways responsible for microglial activation and the subsequent release of pro-inflammatory mediators, or those involved in the activation of NF- $\kappa$ B and p38 MAPK (Spilisbury et al., 2012; Spagnuolo et al., 2018; Jin et al., 2019; Olajide and Sarker, 2020). Other natural products are able to activate Nrf2, a mechanism that has been shown to underlie at least in part their anti-inflammatory activity. Overwhelming evidence has also highlighted the use of natural compounds with a strong antioxidant activity as a promising approach for the AD treatment (Guan et al., 2021; Walia et al., 2021). However, evidence of their efficacy has been quite limited thus far possibly due to a poor bioavailability or to the time point in which the treatment is undertaken (Forman and Zhang, 2021). For these reasons, many debates have developed on how the bioavailability of these compounds may be improved and whether a dietary supplementation with natural antioxidant could be more useful than their employment for a therapeutic intervention (Fusco et al., 2007; Feng and Wang, 2012; Denzer et al., 2016; Pallauf et al., 2017). Among phytochemicals, flavonoids are largely known for their antioxidant activity as they can act directly as reactive oxygen scavengers by donating hydrogen. Nevertheless, flavonoids display a low circulating concentration if compared to well-characterized ROS scavengers, hence suggesting that their antioxidant potential could be due to different mechanisms such as the modulation of intracellular pathways involved in



oxidative stress (Reiber et al., 1993; Borges et al., 2018). Importantly, many natural substances, especially polyphenols, have been shown to be effective in counteracting the main pathophysiological mechanisms of T2DM hence offering potential benefits for reducing the risk of both diabetes and AD (Blahova et al., 2021). These substances may represent a complementary approach, along with life-style intervention such as exercise and nutrition, aimed at enhancing glucose control, lowering insulin resistance and improving insulin sensitivity.

## Polyphenols

Polyphenols (Figure 3) are a heterogeneous group of chemical substances naturally synthesized by the secondary metabolism of plants characterized by one or more aromatic rings bearing one or more hydroxyl groups. Flavonoids, the most diffuse phenolic compounds, are attracting growing attention for their multiple benefits. Indeed, many studies have correlated flavonoid intake with the improvement of cognition, attenuation of neuroinflammation and oxidative stress (Cichon et al., 2021). Although there is still uncertainty about their pharmacokinetics properties, flavonoids and other polyphenols are currently investigated as possible therapeutic agents in the AD treatment. Indeed, while on one hand many studies demonstrated that nano-encapsulation of flavonoids may overcome pharmacokinetic limitations and improve their bioavailability, on the other hand these compounds are also considered as attractive molecular scaffolds for the development of more potent and specific therapeutics.

Resveratrol, a polyphenol typically found in the skin of grapes (*Vitis vinifera* L., Vitaceae), has gained increasing interest for its therapeutic potential in metabolic diseases and for its

ameliorative effect on cognitive decline. Indeed, resveratrol displays different pharmacological effects, including anti-inflammatory, antioxidant and anti-diabetic effects. Resveratrol has been shown to exert an inhibitory activity on neuroinflammation in several studies (Candelario-Jalil et al., 2007; Lu et al., 2010; Potter et al., 2013; Zhang R et al., 2013; Wang et al., 2015). In particular, it has been shown to inhibit the production of pro-inflammatory factors such as NO, TNF- $\alpha$  and IL-1 $\beta$  in both astrocytic and microglial cells (Yao et al., 2015; Zhao et al., 2018). *In vivo* studies have demonstrated that resveratrol is able to improve cognition and reduce amyloid plaque formation in Tg6799 mice (Chen et al., 2019), to inhibit microglial activation in APP/PS1 mice (Capiralla et al., 2012), and to decrease the amount of insoluble A $\beta$  in the hippocampus of AD rats, with positive effects on BBB integrity (Zhao et al., 2015). Moreover, resveratrol has been demonstrated to affect the A $\beta$  production by inhibiting the activity of  $\beta$ -secretase (Choi et al., 2011; Koukoulitsa et al., 2016) and to modulate the A $\beta$  clearance through several mechanisms (Zhang et al., 2014). Further studies have shown that resveratrol is able to inhibit the A $\beta$  aggregation from lower molecular weight (MW) oligomers into higher MW oligomers and to disrupt pre-formed A $\beta$  aggregates (Fu et al., 2014; Ghobeh et al., 2014). The beneficial effects of resveratrol in metabolic disorders such as insulin resistance and T2DM have also been characterized. Data from the literature indicate that resveratrol ingestion is able to stimulate glucose uptake by increasing the translocation of GLUT4 (Szkudelski and Szkudelska, 2011). Moreover, resveratrol has been suggested to counteract the HFD-induced insulin resistance (Mendez-del Villar et al., 2014). Interestingly, the treatment with resveratrol in

streptozotocin (STZ)-injected diabetic rats has been able to counteract many pathogenic mechanisms, including oxidative stress, inflammation and synaptic loss, and to prevent memory impairment by modulating cholinergic transmission (Tian Z. et al., 2016; Tian et al., 2016 Y.). In a clinical trial, the treatment with resveratrol of patients with mild-to-moderate AD induced a decrease of A $\beta$  levels in cerebrospinal fluid and a reduction of neuroinflammation biomarkers (Moussa et al., 2017). However, a pilot study carried on elderly subjects has revealed that the chronic use of resveratrol selectively improves psychomotor speed without significantly ameliorate memory function (Anton et al., 2018). Nonetheless, this result could be connected to the poor penetration of the BBB and an overall low oral bioavailability. Therefore, formulations of resveratrol with an improved bioavailability could increase its efficacy. In particular, the nano-encapsulation in lipid carriers or liposomes as well as the insertion into polymeric particles could ameliorate both pharmacodynamics and pharmacokinetics of resveratrol (Andrade et al., 2018). Moreover, some efforts have been made to synthesize various analogues of resveratrol with a more potent biological activity (Lee et al., 2012; Lu et al., 2013; Biscussi et al., 2020).

Quercetin, a ubiquitous flavonoid widely distributed in fruits and vegetables, has been found to exert strong anti-aggregating and anti-inflammatory activities. Quercetin has been proven to effectively inhibit the A $\beta$  aggregation by destabilizing the oligomeric species of misfolded proteins and inhibiting the fibril growth (Matsuzaki et al., 2007). Quercetin is also able to reduce iNOS-mediated NO production in lipopolysaccharide (LPS)-treated BV2 microglial cells by suppressing NF- $\kappa$ B activation (Kang et al., 2013). Moreover, quercetin has been demonstrated to attenuate the inflammation mediated by IL-1 $\beta$  in astrocytes and neuronal cultures by inhibiting the release of IL-6 and IL-8 (Sharma et al., 2007). The anti-inflammatory activity of quercetin has also been thought to underlie its positive effect on cognitive function in APP/PS1 mouse model of AD, where it also reduces A $\beta$  plaques and Tau phosphorylation (Lv et al., 2018). In 3xTg-AD mice, quercetin decreases the amount of the extracellular A $\beta$ , improves astrogliosis and microgliosis, and preserves cognitive function (Sabogal-Guáqueta et al., 2015; Barreca et al., 2016). The putative antioxidant potential of quercetin has also been considered for its use in AD treatment since it has both a direct antioxidant activity, due to two pharmacophores present in the molecule able to scavenge free radicals, and the ability to modulate antioxidant pathways. Indeed, quercetin has been shown to act as a scavenger of both ROS and RNS (Boots et al., 2008), to increase the expression of SOD and GSH (Ishige et al., 2001), and to positively modulate Nrf2 signaling (Arredondo et al., 2010; Molaei et al., 2020; Yu et al., 2020). Both *in vitro* and *in vivo* studies have shown that quercetin exerts beneficial effects on diabetes. In particular, it has been shown that quercetin reduces blood glucose levels, increases plasma insulin levels and positively affects memory and learning functions in streptozotocin (STZ)-induced diabetic rats (Khaki et al., 2010; Srinivasan et al., 2018; Yang and Kang, 2018). Unfortunately, despite its promising therapeutic potential, a clinical approach with the use of

quercetin has been quite limited probably due to its poor permeability of the BBB, low bioavailability, and rapid metabolism (Cai et al., 2013). However, several studies using multiple nanoparticles formulations have shown that the use of nanotechnology may significantly improve the brain delivery of quercetin and enhance its bioavailability (Kumari et al., 2010; Bagad and Khan, 2015; Najafabadi et al., 2018).

Luteolin, a flavone widely distributed in herbs and vegetables, has emerged as an interesting phytochemical able to mitigate many pathogenic mechanisms responsible for AD, including neuroinflammatory processes and the impairment of brain glucose metabolism. Luteolin seems to be a modulator of immune reactions for its very efficient anti-inflammatory properties in peripheral macrophages, compared to those of other flavonoids including its analogue quercetin (Comalada et al., 2006). Interestingly, luteolin exerts an anti-inflammatory effect also in LPS-activated microglia where it has been found to significantly reduce the expression of iNOS and COX-2 and to downregulate pro-inflammatory cytokines and the production of NO (Zhu et al., 2011). This finding has been confirmed in *in vivo* studies. In particular, it has been shown that a dietary administration of luteolin reduces microglial activation in senescent mice (Burton et al., 2016). This effect has been explained by the ability of luteolin to suppress in a dose-dependent manner the expression of pro-inflammatory and pro-apoptotic genes hence shifting the microglial transcriptome toward an anti-inflammatory phenotype (Dirscherl et al., 2010). Recently, it has been reported that luteolin is able to improve memory deficits in a mouse model of AD by inhibiting astrocyte overactivation and neuroinflammation and by reducing endoplasmic reticulum (ER) stress (Kou et al., 2021). In agreement, luteolin has been demonstrated to improve cognitive abilities in a mouse model of vascular dementia by modulating the expression of pro-inflammatory and pro-apoptotic proteins and by stimulating neurogenesis (Siracusa et al., 2017; Cordaro et al., 2020). Very interesting, it has been shown that the combination of luteolin with another anti-inflammatory compound, the palmitoylethanolamide is able to reduce iNOS and GFAP expression and protect glial cells against the A $\beta$  injury in both *in vitro* and *ex vivo* experimental models (Paterniti et al., 2014). The effective anti-inflammatory activity of luteolin has also been suggested to contribute to its protective effect against insulin resistance (Daily et al., 2021). Indeed, luteolin has been shown to improve insulin sensitivity in many cell types, including adipocytes and endothelial cells (Ding et al., 2010; Deqiu et al., 2011). In agreement, a diet supplemented with luteolin has been demonstrated to ameliorate obesity and insulin resistance in mice (Xu et al., 2014). In obese mice, luteolin improves cognitive deficits by alleviating neuroinflammation, oxidative stress and neuronal insulin resistance (Liu et al., 2014). Interestingly, the combination of luteolin with the L-theanine amino acid prevents AD-like symptoms by improving the hippocampal insulin signaling and decreasing neuroinflammation in A $\beta$ -infused rats (Park et al., 2018).

Epigallocatechin gallate (EGCG), the main polyphenolic constituent of the tea plant *Camelia sinensis* (L.) Kuntze

(Theaceae), is considered the major responsible for the beneficial effects of green tea. Many *in vitro* and *in vivo* studies have demonstrated that EGCG and its metabolites may exert significant neuroprotective activities. Several experimental data have highlighted the ability of EGCG to interfere with the A $\beta$  aggregation. EGCG can bind weakly and in a non-specific manner to A $\beta$  monomers while it displays higher affinity toward oligomers (Ahmed et al., 2017). Electron microscopy studies have shown that EGCG can inhibit the A $\beta$  secondary nucleation and intervene in the early steps of the A $\beta$  aggregation inducing the formation of spherical, off-pathway aggregates. (Ehrnhoefer et al., 2008; Ahmed et al., 2017). It is still unclear, instead, whether EGCG is able to disassemble preformed fibrils. On the other hand, it has been demonstrated that EGCG may disrupt A $\beta$  protofibrils by forming  $\pi$ - $\pi$  and hydrogen bonding interactions (Zhan et al., 2020; Li M et al., 2021). In transgenic APP<sub>SWE</sub> Tg2576 mice, the intraperitoneal treatment with EGCG for 2 months is associated to a significant reduction of the A $\beta$  levels, although it has been suggested that this result arises from the ability of EGCG to modulate the APP cleavage pathway (Rezai-Zadeh et al., 2005). In particular, experimental studies have provided evidence that EGCG increases the  $\alpha$ -cleavage of APP (Rezai-Zadeh et al., 2005; Ettcheto et al., 2020). EGCG has also displayed an anti-inflammatory activity in several studies by reducing TNF- $\alpha$ , IL-1 $\beta$ , IL-6, and iNOS levels and rescuing neurogenesis through mechanisms involving NF- $\kappa$ B (Cheng-Chung Wei et al., 2016; Seong et al., 2016). It has also been demonstrated that EGCG exerts a positive effect on cognitive function by promoting ROS scavenging (Schroeder et al., 2009) and counteracting the A $\beta$ -induced mitochondrial apoptotic processes (Fukutomi et al., 2021). Importantly, it has recently been reported that EGCG treatment ameliorates mitochondrial respiration deficits in children affected by Down syndrome (Scala et al., 2021). A recent meta-analysis of 17 studies performed on animal models of AD has demonstrated that EGCG can rescue cognitive impairment and A $\beta$  pathology through the combination of its anti-inflammatory, antioxidant, and antiaggregating activities (Zhang et al., 2020). EGCG has been also shown to act as an anti-diabetic agent especially due to its significant anti-inflammatory and antioxidant activities. In particular, EGCG is able to increase glucose tolerance and the glucose-stimulated insulin secretion in obese mice (Ortsäter et al., 2012) and to affect diabetes-related comorbidities such as diabetic neuropathy (Raposo et al., 2015). Interestingly, EGCG treatment improves insulin sensitivity and memory deficits in APP/PS1 mice fed with a HFD (Ettcheto et al., 2020). Unfortunately, clinical results on the efficacy of EGCG in ameliorating cognitive functions have not reflected the therapeutic potential emerged in pre-clinical studies. In fact, EGCG treatment displays some limitations such as the high rate of metabolism and subsequent degradation, which in turn prevent a sufficient concentration in human plasma (Pervin et al., 2019). On the other hand, EGCG displays to permeate the BBB at low micromolar levels (Pervin et al., 2017).

Curcumin, a polyphenol extracted from the rhizomes of *Curcuma longa* L. (Zingiberaceae), possesses a variety of pharmacological properties. Growing evidence has

demonstrated that curcumin can significantly improve cognitive functions in AD by reducing oxidative damage, inflammation and A $\beta$  aggregation. In particular, it has been reported that curcumin inhibits the formation of A $\beta$ <sub>1-40</sub> and A $\beta$ <sub>1-42</sub> fibrils *in vitro* in a dose-dependent manner and destabilizes preformed fibrils (Ono et al., 2004; Yang et al., 2005; Hamaguchi et al., 2010). Different studies have shown that curcumin is able to bind monomeric species and low MW oligomers (Fu et al., 2014) and to induce major structural changes in the A $\beta$ <sub>1-42</sub> aggregates (Mithu et al., 2014). More recently, it has been demonstrated that curcumin and its derivatives are able to intercalate among A $\beta$  chains in the first stage of the A $\beta$  aggregation and to form hydrogen bonding and hydrophobic interactions with the A $\beta$  peptide, leading to more disordered amyloid structures (Doytchinova et al., 2020). Interestingly, *in vivo* studies have shown that the systemic treatment with curcumin reduces pre-existing plaques in ~8-month-old APP<sub>swe</sub>/PS1dE9 mice, suggesting its ability to disaggregate A $\beta$  deposits (Garcia-Alloza et al., 2007). Curcumin effects have also been investigated in *in vitro* and *in vivo* models of neuroinflammation. In particular, curcumin has been demonstrated to inhibit NF- $\kappa$ B and MAPK activation in LPS-stimulated microglia (Porro et al., 2019; Zhang et al., 2019). These findings have been confirmed by the results obtained in an animal model of AD showing that the treatment with curcumin ameliorates neuroinflammation and cognitive decline upon exposure to LPS (Sorrenti et al., 2018). In an *in vitro* study, curcumin has been shown to decrease in a concentration-dependent manner the expression of IL-1 $\beta$ , IL-6 and TNF- $\alpha$  in the A $\beta$ -activated microglia by inhibiting Erk1/2 and p38 MAPK pathways (Shi et al., 2015). Curcumin is also capable to control oxidative stress. In particular, the antioxidant activity of curcumin seems to derive from its  $\beta$ -diketone structure and phenolic groups, which confer the ability to scavenge free radicals (Ak and Gülçin, 2008). In neuronal cultures exposed to pro-oxidant conditions, curcumin exerts a strong neuroprotective effect by counteracting the toxicity of H<sub>2</sub>O<sub>2</sub> and Fe<sup>3+</sup> (Morales et al., 2017). In rat pheochromocytoma cells (PC12) exposed to A $\beta$  toxicity, curcumin has been shown to inhibit oxidative damage (Park et al., 2008). The therapeutic potential of curcumin has been further confirmed by several studies on animal models of insulin resistance. Indeed, curcumin has been demonstrated to increase the activity of insulin receptors in rats and activate insulin pathways (Li et al., 2010), and to delay T2DM by improving  $\beta$ -cell function and reducing insulin resistance (Chuengsamarn et al., 2012). Interestingly, the use of curcumin as such in clinical studies does not display a significant efficacy against AD, although the drug is well-tolerated (Ringman et al., 2012). This evidence has been explained with its poor ability to pass the BBB and its very low oral bioavailability (Begum et al., 2008). Therefore, in the last years many curcumin analogues with improved aqueous solubility, pharmacokinetics, bioavailability and stability have been synthesized. Importantly, these compounds show greater efficacy than curcumin hence appearing as promising agents for the AD treatment (Anand et al., 2008; Airolidi et al., 2011; Yanagisawa et al., 2011). Meanwhile, strategies to enhance

curcumin delivery have also been evaluated. In particular, curcumin-containing nanoliposomes as well as other delivery systems have been designed and show to be very effective in reducing the A $\beta$  fibrils formation (Taylor et al., 2011; Lazar et al., 2013; Mourtas et al., 2014; Shahbaz et al., 2021).

Genistein is a naturally occurring isoflavone mainly found in soybean, green peas, legumes, and peanuts. Mechanistically, genistein potentially inhibits the activity of tyrosine protein kinases and of a DNA topoisomerases. Additionally, owing to the presence of numerous phenolic moieties in its structure, genistein exerts potent anti-oxidant effects (Gong et al., 2015). Therefore, genistein can modulate several pathogenetic mechanisms in AD including A $\beta$  metabolism, inflammation and cholinergic system dysfunction. Accordingly, genistein can reduce the production of A $\beta$  by inhibiting BACE-1 (Youn et al., 2018). Furthermore, Hirohata et al. (2012) observed that genistein can directly bind the A $\beta$ <sub>25-35</sub> fragment preventing the formation of its aggregates. Genistein can reduce the neurotoxicity induced by A $\beta$ <sub>1-42</sub> by inhibiting kinesin AP180T (AP180) and Ras homolog family member A (RhoA) and, therefore, A $\beta$  accumulation (Yu et al., 2010).

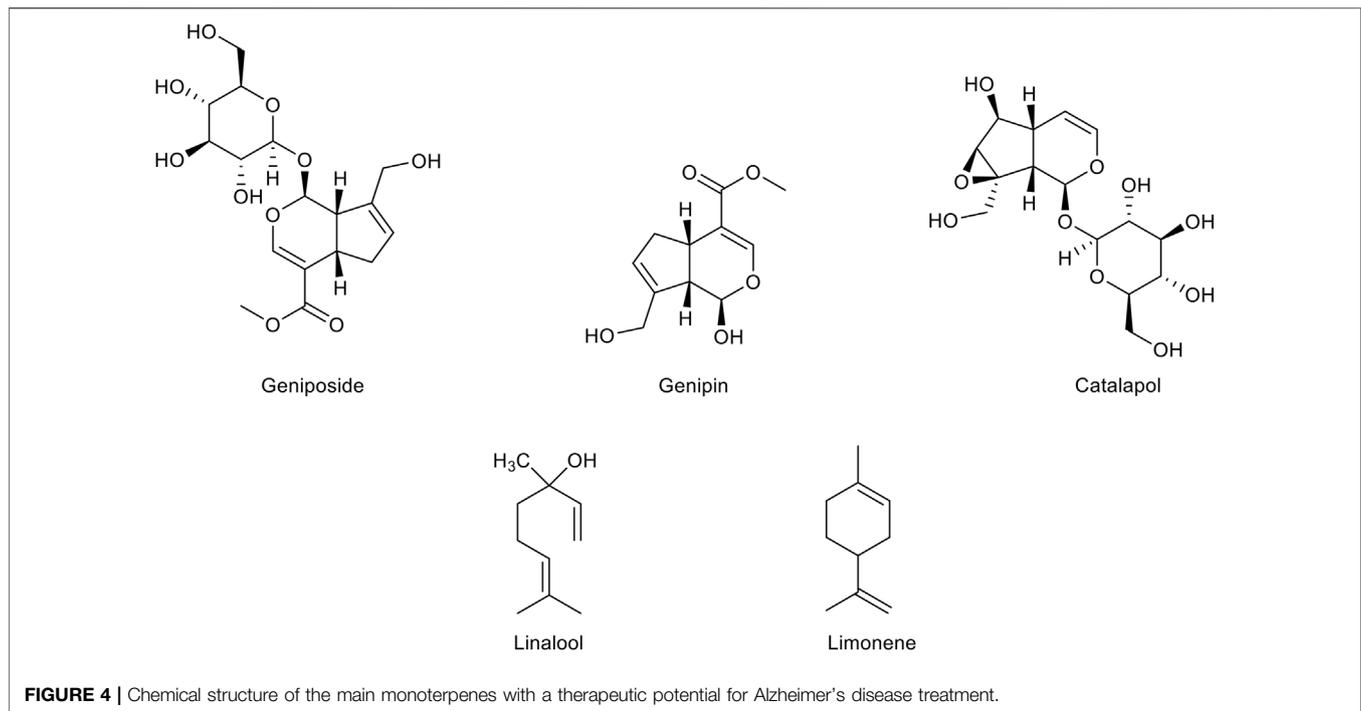
Neuroinflammation is responsible for an abnormal secretion of pro-inflammatory cytokines that trigger detrimental signaling pathways leading to protein aggregation in the AD brain. In this context, Valles et al. (2010) demonstrated that the increased levels of IL-1 $\beta$  and TNF- $\alpha$  induced by A $\beta$  were modulated treating astrocytes with genistein (Valles et al., 2010). In addition, genistein can inhibit the activity of NF- $\kappa$ B signal pathway mediated by Toll-like receptor (TLR4) (Zhou et al., 2014). Accordingly, genistein blocks the binding of NF- $\kappa$ B to the DNA thus antagonizing the neuroinflammatory effect in AD (Seo et al., 2018). Interestingly, in diabetic mice genistein (Pedersen et al., 1996; Wang et al., 2016), as well as some of its derivatives (Qiang et al., 2014), can improve cognitive dysfunction by inhibiting the activity of AChE and by the modulation of Ca<sup>2+</sup> homeostasis in cholinergic neurons (Jhamandas et al., 2001).

## Monoterpenes

Monoterpenes (Figure 4), a group of isoprene derivatives also known as isoprenoids, are found as secondary metabolites in many aromatic plants. These plant-derived compounds, already known for their very effective antibacterial and antifungal activities, are now emerging as potential therapeutic agents in multiple disorders for their antioxidant activity. Many monoterpenes display a free radical scavenging ability, which seems to arise from the presence of the conjugated double bonds typical of the isoprenoid structure. In addition, the growing knowledge about supplementary activities of monoterpenes such as anti-inflammatory, anti-cholinesterase, and anti-nociceptive activities, is highlighting their therapeutic potential in several neurodegenerative diseases including AD.

Geniposide, a major iridoid glycoside of *Gardenia jasminoides* J. Ellis (Rubiaceae) fruits, displays a significant neuroprotective potential. First, geniposide exerts both antioxidant and anti-apoptotic effects. In particular, geniposide has been demonstrated to protect PC12 and SH-SY5Y cells from oxidative damage and

apoptotic processes, by modulating the MAPK signaling pathways and caspases expression and by increasing the levels of SOD and GPx (Liu et al., 2006; Liu et al., 2007; Yin et al., 2010a; Yin et al., 2010b; Sun et al., 2013). Interestingly, geniposide protects primary hippocampal neurons from the A $\beta$ <sub>1-42</sub> toxicity by improving mitochondrial axonal trafficking and function and ameliorating synaptic damage (Li et al., 2014; Sun et al., 2014; Zhao et al., 2016; Zhang et al., 2017). Increasing studies have emphasized the ability of geniposide to act as an agonist of the GLP-1 receptor (GLP-1R) and to trigger different neuroprotective mechanisms upon GLP-1R activation, including the induction of insulin secretion, the increase of intracellular cyclic Adenosine Monophosphate (cAMP) levels and the activation of IDE gene expression (Liu et al., 2006; Liu et al., 2009; Liu et al., 2012; Yin et al., 2012; Li et al., 2018). Based on these results, geniposide is attracting growing interest among researchers. Therefore, a substantial number of studies have been performed in mouse models of AD and amyloidosis, significantly reinforcing the therapeutic potential of this substance in counteracting the neurodegenerative processes of AD. In STZ-induced diabetic rats the intragastric administration of geniposide has been demonstrated to improve insulin resistance and blood glucose levels, to increase the expression of IDE and to decrease A $\beta$ <sub>1-42</sub> levels (Liu et al., 2013). In agreement, the intracerebroventricular (ICV) injection of geniposide in STZ-treated rats was able to improve learning and memory deficits, attenuate Tau hyperphosphorylation and prevent subcellular and synaptic abnormalities by reducing the activity of GSK-3 enzyme (Gao et al., 2014). In agreement, further results have shown that geniposide counteracts the increase of Tau phosphorylation induced by the insulin deficiency in AD mice treated with STZ, by promoting GSK-3 $\beta$  phosphorylation and subsequent inactivation (Zhang et al., 2015). In APP/PS1 transgenic mice, the treatment with geniposide ameliorates memory deficits by significantly suppressing oxidative damage, mitochondrial function, and MAPK signaling overactivation (Lv et al., 2014; Zhao et al., 2017). Other studies performed in APP/PS1 have suggested that the inhibitory effect of geniposide on Tau hyperphosphorylation and A $\beta$ <sub>1-42</sub> production is due to an increase of leptin signaling (Liu et al., 2015; Liu et al., 2017). Very interestingly, the aglycone of geniposide, genipin, which can be produced through the metabolism of geniposide by intestinal microflora enzymes, has recently been reported to possess several pharmacological properties, such as anti-inflammatory, anti-diabetic and anti-depressive effects (Li et al., 2016). Genipin has been found to exert a strong anti-inflammatory activity in several models of inflammation by targeting iNOS and NF- $\kappa$ B. In particular, it has been demonstrated that genipin inhibits the increase of NO production and iNOS, COX-2, IL-1 $\beta$  and IL-6 expression in LPS-activated BV2 microglial cells (Araki et al., 2014). Besides, genipin has also been shown to inhibit inflammation by downregulating chemokines, chemokine receptors and interferon-induced protein expression (Li et al., 2012). Genipin has also displayed the ability to protect neuronal cells against the cytotoxicity of A $\beta$ , H<sub>2</sub>O<sub>2</sub> and rotenone by preventing widespread damage induced by the increase of ROS and RNS production (Yamazaki et al., 2001; Hughes et al., 2014). Moreover, it has recently been reported that genipin reduces Tau phosphorylation and fibrillation in Tau-overexpressing cells and decreases the A $\beta$  generation in neuronal cells overexpressing the



Swedish mutant APP, by inhibiting BACE-1 expression (Li F et al., 2021).

Catalpol, an iridoid glycoside extracted from the roots of *Rehmannia glutinosa* (Gaertn.) DC. (Plantaginaceae), has been shown to interfere with different mechanisms underlying many pathological conditions such as diabetes, atherosclerosis, and ischemic injury (Cai et al., 2016; Liu et al., 2016; Xue et al., 2016; Yan et al., 2018; Bai et al., 2019; Chen et al., 2020; He et al., 2021). Many reports have demonstrated that catalpol is protective against the oxidative stress and mitochondrial dysfunction induced by several neurotoxins including rotenone, MPP(+) and D-galactose, by increasing the activity of antioxidant factors, preventing the complex I activity reduction, and counteracting the lipid peroxidation (Mao et al., 2007; Tian et al., 2007; Zhang et al., 2007). Several *in vitro* studies have also shown that catalpol is able to protect astrocytes from H<sub>2</sub>O<sub>2</sub> damage and to suppress neuroinflammation by inhibiting NF- $\kappa$ B activation and reducing iNOS activity in LPS-treated astrocytes and in mice with acute systemic inflammation induced by LPS (Bi et al., 2008; Zhang et al., 2009; Bi et al., 2013). Catalpol has also been reported to protect neuronal and glial cells by A $\beta$ <sub>1-42</sub> toxicity by preventing astrocytic and microglial activation and the release of pro-inflammatory factors such as ROS, NO and TNF- $\alpha$ , and by attenuating the mitochondrial-dependent neuronal apoptosis (Jiang et al., 2008; Liang et al., 2009). A large number of pharmacological studies performed in different mouse models have confirmed the neuroprotective potential of catalpol. In particular, in mice intraperitoneally injected with D-galactose to reproduce senescence, catalpol is able to improve cholinergic function, reduce inflammatory cytokines levels, prevent mitochondrial dysfunction, and improve learning and memory

deficits. Catalpol has also been found to promote the activity of endogenous antioxidant enzymes and decrease ROS and NOS production (Zhang et al., 2007; Zhang X. et al., 2008; Zhang X. L. et al., 2008; Zhang et al., 2010; Zhang X et al., 2013). In mice injected with D-galactose and A $\beta$ , the treatment with catalpol is able to inhibit oxidative stress and to reduce A $\beta$  levels by regulating the activity of SOD, GPx and by increasing the expression of IDE, which is involved in the A $\beta$  degradation (Huang et al., 2016). In addition, it has been shown that catalpol is able to reduce the BBB damage and subsequent hyperpermeability induced by A $\beta$ <sub>1-42</sub> fibrils and to increase the A $\beta$  clearance (Liu et al., 2018). Interestingly, in neuronal cells overexpressing the Swedish mutant APP, catalpol has been found to increase the expression of the  $\alpha$ -secretase, through an Erk/cAMP-response element binding protein (CREB) pathway, hence promoting the non-amyloidogenic processing of the APP and reducing the generation of A $\beta$  (Wang et al., 2018). The anti-inflammatory activity of catalpol has also been associated to its anti-hyperglycemic effect in STZ-induced diabetic rats (Huang et al., 2010) and ameliorates insulin resistance induced by HFD by suppressing the NF- $\kappa$ B pathway (Zhou et al., 2015).

Linalool is a major component of essential oils from many aromatic plants. Despite its lower antioxidant activity compared to other monoterpenes due to the lack of conjugated double bonds, linalool has been shown to improve the antioxidant potential of many essential oils by acting in synergy with other components (Wojtunik-Kulesza et al., 2019). The neuroprotective effect of linalool has been suggested in several *in vitro* and *in vivo* experimental models of neurodegeneration. Indeed, linalool has been shown to counteract the increase of ROS

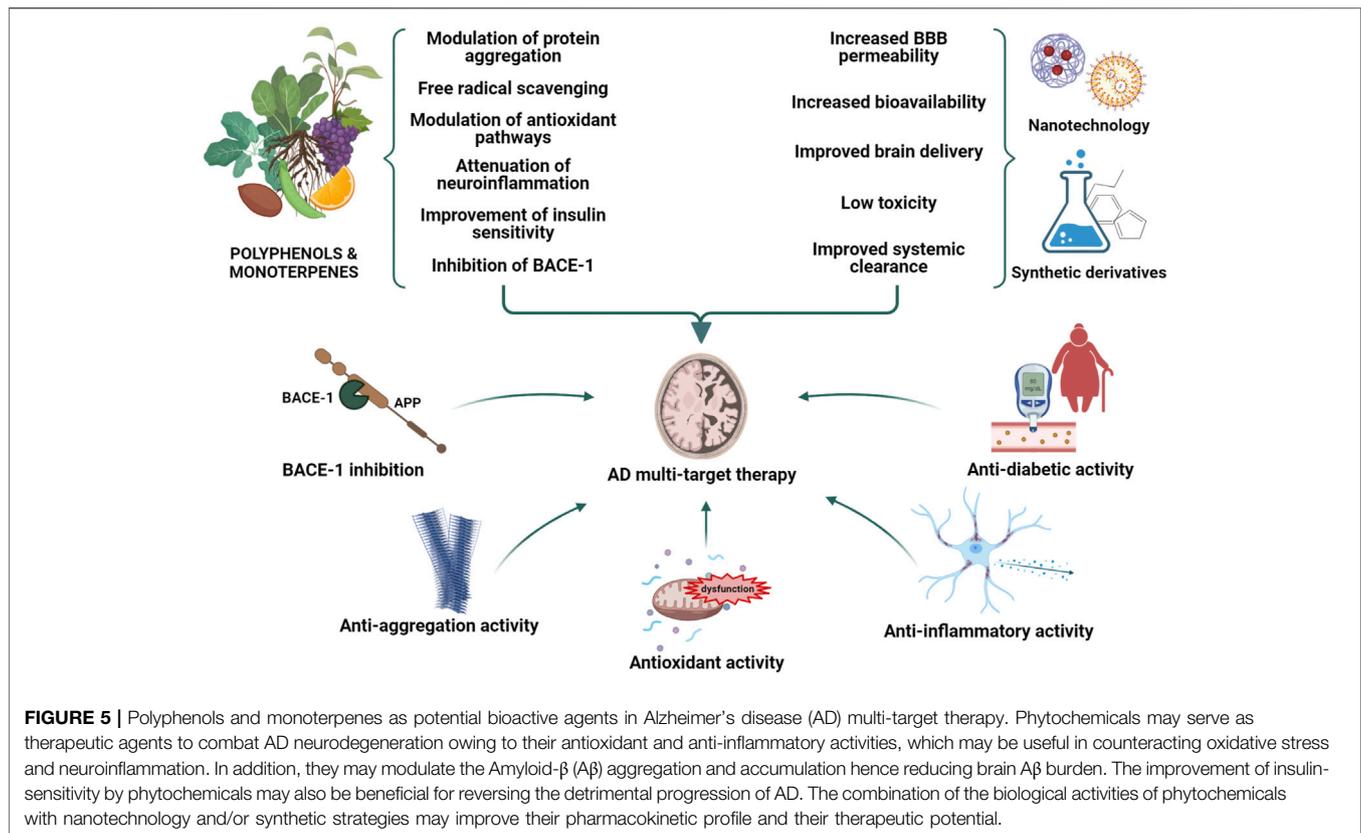
production and mitochondrial  $\text{Ca}^{2+}$  levels, to preserve mitochondrial integrity, and to reduce lipid peroxidation in immortalized neuronal cells exposed to glutamate (Sabogal-Guáqueta et al., 2019). Moreover, linalool significantly counteracts cell death and COX-2 increase in organotypic hippocampal slices exposed to NMDA (Sabogal-Guáqueta et al., 2019). In line with these results, it has been demonstrated that linalool is able to interfere with the glutamatergic transmission, hence displaying an anticonvulsant effect (Brum et al., 2001). Interestingly, the intraperitoneal administration of linalool counteracts the  $\text{A}\beta$ -induced hippocampal injury and ameliorates cognitive deficits in  $\text{A}\beta$ -treated mice. Specifically, linalool attenuates caspase activation, oxidative stress, and the reduction of Nrf2 expression induced by  $\text{A}\beta$  (Xu et al., 2017). In addition, the chronic administration of linalool has been reported to reduce  $\beta$ -amyloidosis, astrogliosis and microgliosis and to improve spatial and learning memory in triple transgenic AD mice (3xTg-AD). These neuroprotective effects correlate with reduced levels of p38 MAPK, NOS2, COX-2, and IL-1 $\beta$  (Sabogal-Guáqueta et al., 2016). In line with these reports, *in vitro* results from our laboratory have shown that linalool is able to counteract the mitochondrial dehydrogenase activity reduction, increase of intracellular levels of ROS, and caspase-3 activation in PC12 cells exposed to  $\text{A}\beta_{1-42}$  oligomers. In agreement, *Lavandula angustifolia* and *Coriandrum sativum* essential oils containing linalool as major component have also displayed antioxidant and anti-apoptotic effects, hence confirming the beneficial potential of linalool in synergistic combination with other components (Caputo et al., 2021).

Limonene, a monocyclic monoterpene abundantly found in the genus *Citrus* (Rutaceae), displays several biological properties including antioxidant, anti-inflammatory and anti-nociceptive activities (Roberto et al., 2010; d'Alessio et al., 2013; Piccinelli et al., 2017). Recently, limonene has been investigated by the scientific community for its pharmacological effects in various chronic diseases including AD, multiple sclerosis, and epilepsy (Eddin et al., 2021). Recent reports have shown that limonene may exert a beneficial effect in neurodegenerative diseases due to its antioxidant and anti-inflammatory activities. Like many other monoterpenes, limonene has been found to exert an anti-AchE activity (Szwajgier and Baranowska-Wójcik, 2019; Piccialli et al., 2021). A recent study performed in a *Drosophila* model of AD has shown that limonene is able to counteract the  $\text{A}\beta_{1-42}$ -induced neurotoxicity by decreasing ROS levels and hence preventing Erk phosphorylation. Moreover, limonene induces a significant decrease in the number of activated glial cells and in the expression of NO, thus also proving to exert an anti-inflammatory effect (Shin et al., 2020). In addition, limonene has been demonstrated to suppress oxidative stress and inflammation by inhibiting COX-2, iNOS, and NF- $\kappa$ B in doxorubicin-treated rats (Rehman et al., 2014). Interestingly, limonene also displays an efficacy in preventing or alleviating metabolic disorders in HFD-fed mice (Jing et al., 2013). In STZ-induced diabetic rats it exerts an anti-hyperglycemic effect, increases the activity of antioxidant enzymes such as SOD and GSH, and reduces the

levels of lipid peroxidation, hence displaying a therapeutic potential in preventing diabetes complications (Murali et al., 2013; Bacanlı et al., 2017). Very recently, a study from our group has shown that limonene is able to counteract the reduction of mitochondrial dehydrogenase activity, increase of intracellular ROS levels and nuclear morphology alterations induced by  $\text{A}\beta_{1-42}$  oligomers in primary cortical neurons (Piccialli et al., 2021). In the same study, the antioxidant activity of limonene has been crucial in preventing the increase of outward transient potassium currents, which were shown to play a critical role in triggering caspase activation and apoptotic cell death (Pannaccione et al., 2007). Moreover, our results also confirmed that limonene is able to exert an anti-AchE activity almost comparable to that of galantamine (Piccialli et al., 2021), thus highlighting its multi-target therapeutic potential.

## TRANSLATING PHYTOCHEMICALS INTO PHARMACEUTICALS: ONGOING CHALLENGES

The natural compounds described above are only a short collection of all the plant-derived natural compounds showing beneficial effects in AD. Likely, the amount of attracting molecules to be tested against neurodegeneration is expected to increase considering the growing interest in this research field. However, although they appear as an encouraging alternative route compared to many synthetic drugs failing to definitively cure AD, natural products have failed as well to display impressive efficacy in clinics. Indeed, while there are a massive number of mechanistic studies suggesting the therapeutic potential of natural compounds in AD and other neurodegenerative diseases, clinical results from human trials have been mostly insufficient or disappointing. The discrepancies between pre-clinical research and clinical results suggest that scientific literature may probably overestimate the potential benefits of natural compounds on cognitive impairment. Nevertheless, the lack of significant results may stem from complex reasons. The first critical hindrance to the clinical use of natural compounds is the difficulty in extrapolating the dose required in humans from that providing a biological effect in *in vitro* or *in vivo* studies. This problem, in turn, arises from the different responsiveness of cell cultures and animal models to the activity of certain agents, and the necessity, given a broad spectrum of targets and activities for a single compound, to decipher which target is mechanistically more valid to reach the desired therapeutic effect and, based on that target, to identify the adequate dose. Additional *in vitro* and *in vivo* studies should be performed to validate the use of natural compounds in combination with other agents or drugs, a strategy that might boost their efficacy and succeed in providing more relevant results. Another crucial issue is represented by the pharmacokinetic properties of natural compounds that determine their bioavailability, an aspect gaining complexity when it comes to evaluating the efficacy of dietary supplementation with polyphenols, in which the overall



dietary intake may be critical. As mentioned above, the major pharmacokinetic limitations leading to clinically irrelevant results include the poor ability to cross the BBB and rapid metabolism. In this regard, transformation and absorption at the gut level deserve much attention, especially in the evaluation of the use of polyphenols in a dietary intervention, since the composition of gut microbiota may strongly influence and even drive their pharmacological effects. Moreover, dietary polyphenols have recently been demonstrated to have a clinically relevant impact on many essential functions of human body, including the regulation of immune system and gut microbiota (Grosso, 2018; van der Merwe, 2021)—an aspect that further complicates the validation of certain natural compounds as pharmaceuticals for AD therapies. Lastly, significant limitations affecting the overall therapeutic potential of phytochemicals are also related to the design of clinical trials. Indeed, the identification of the exact mechanism of action and, hence, of a therapeutic target is of crucial importance for an accurate selection of the participants, which in turn may strongly affect the success of a clinical trial. Therefore, although the ongoing strategies to overcome the aforementioned limitations, namely the synthesis of derivatives with improved pharmacokinetic profiles and nanotechnology, may help achieve the auspicious results further efforts with implemented multi-disciplinary approaches are needed to realize the pharmaceutical potential of natural compounds. Nonetheless, they remain an attractive opportunity to optimistically look to in the search for new effective AD treatments.

## CONCLUSION

AD, along with many other age-related diseases, is the object of unceasing investigation due to its irreversibility and the lack of effective treatments. Considered the urgent need to find new neuroprotective strategies, many different routes have been approached. Natural products, which have been used for their medicinal properties since ancient times, have recently been researched for their ability to interfere with many biological processes and for their nutritional potential, both implicated in their therapeutic power. In the last decades several mechanistic and pilot studies have suggested the protective effect of natural products and their bioactive components against AD. In particular, many phytochemicals have been proven to exert significant antioxidant and anti-inflammatory effects. More recently, their ability to modulate the  $A\beta$  aggregation and to interfere with the amyloid cascade has also been demonstrated. Intriguingly, a major plus of many natural compounds is their effectiveness in regulating multiple molecular pathways, thus emerging as suitable agents for a multi-target therapeutic approach (Figure 5). To date, although preclinical investigations have suggested their neuroprotective potential, the clinical use of many promising plant-derived compounds has proven unsuccessful, especially due to their poor pharmacokinetic profile. To overcome this issue, both synthetic and nanotechnological strategies are currently taken into consideration. However, to translate pre-clinical results into clinics further issues should be addressed,

including a better identification of the optimal dosage and formulation in order to obtain at the same time the strongest effect and the safest profile. A nutraceutical intervention with specific diets containing natural antioxidant and anti-inflammatory agents is also under investigation for its potential efficacy in preventing or reducing the risk of developing age-related neurodegenerative diseases. Nonetheless, the validation of a dietary supplementation with multi-active phytochemical compounds to treat or prevent AD also requires the examination of many critical issues such as those concerning the mutual influence between the dietary intake of such compounds and the regulation of many important functions of human body that may in turn affect the healthy state of the patients. Undoubtedly, the approval of a therapeutic approach centered on natural products is still in its infancy. Further efforts are needed to optimize the clinical

relevance of phytochemicals and to realize their pharmaceutical potential.

## AUTHOR CONTRIBUTIONS

Conceptualization, IP and AP; Writing—review and editing, IP, VT, LC, SDE, RC, VDF, and AS; Writing—original draft preparation, IP, AS, and AP; Supervision, AP.

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