Review

Ellagic Acid (EA): A Green Multi-Target Weapon Reducing Oxidative Stress and Inflammation Thus Preventing and Ameliorating Alzheimer Disease (AD) Condition

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Review

Ellagic Acid (EA): A Green Multi-Target Weapon Reducing Oxidative Stress and Inflammation Thus Preventing and Ameliorating Alzheimer Disease (AD) Condition

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Abstract: Oxidative stress (OS), generated by overrun of reactive species of oxygen and nitrogen (RONS), is the key cause of several human diseases. In particular, with inflammation, OS is responsible for the onset and the development of the clinical signs and the pathological hallmarks of Alzheimer disease (AD). AD is a multifactorial chronic neurodegenerative syndrome indicated by a form of progressive dementia associated with aging. While one-target drugs only soften its symptoms while generating drug resistance, multi-target polyphenols from fruits and vegetables, such as ellagitannins (ETs), ellagic acid (EA), and urolithins (UROs), having potent antioxidants and radical scavenging effects capable to counteract OS, could be new green options to treat human degenerative diseases, thus representing hopeful alternatives and/or adjuvants to one-target drugs to ameliorate AD. Unfortunately, in *vivo* ETs are rather not absorbed, while providing mainly ellagic acid (EA), which due to its trivial water-solubility, first pass effect, metabolism in the intestine to give UROs, or irreversible binding to cellular DNA and proteins is in turn very low bioavailable, thus failing as therapeutic *in vivo*. Up-to-day, only UROs have confirmed the beneficial effect demonstrated *in vitro*, by reaching tissues to the extent necessary for having therapeutic outcomes. Unfortunately, upon administration of food rich in ETs or ETs and EA, UROs formation is affected by extreme interindividual variability that renders them unreliable as novel clinically usable drugs. Large attention has been therefore paid specifically to multitarget EA, which is incessantly investigated as such or nanotechnologically manipulated to be a potential "lead compound" with protective action towards AD. A brief overview of the multi-factorial and multi-target aspects that characterize AD, and polyphenols activity respectively, as well as of the traditional and/or innovative clinical treatments available to treat AD constitutes the opening of this work. Upon focus on the pathophysiology of OS, and on EA chemical features and mechanisms leading to its antioxidant activity, an all-round updated analysis on the current EA-rich foods and EA involvement in the field of AD has been provided. The possible clinical usage of EA to treat AD has been shown reporting results by its applications *in vivo* and clinical trials. A critical view about the need for a more extensive use of the most rapid diagnostic methods to detect AD from its early symptoms has also been included in this work.

Keywords: Alzheimer disease (AD); one-target vs. multi-target drugs; oxidative stress (OS); reactive oxygen and nitrogen species (RONS); antioxidant effects; radical scavenging activity; ellagitannins (ETs); ellagic acid (EA); urolithins (UROs); *in vitro* and *in vivo* EA applications; AD diagnosis

1. Introduction

Alzheimer-Perusini disease, mainly known as Alzheimer's disease (AD), presenile dementia of the Alzheimer type, primary degenerative dementia of the Alzheimer type, and for simplicity Alzheimer, is the most common form of progressively disabling degenerative dementia, with onset

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mainly in presenile age, specifically over 65 years[1]. It is estimated that approximately 50-70% of cases of dementia are due to the AD condition, while 10-20% are due to vascular dementia[2]. Some data from the World Alzheimer Report 2023 produced by Alzheimer's Disease International established that in the next 25 years, the number of people living with dementia worldwide could increase from 55 million to 139 million. Furthermore, the costs associated with the disease could jump from 1.3 trillion dollars in 2019 to over 2.8 in 2030. The most frequent early symptom is represented by a difficulty in remembering recent events, followed by other symptoms which may appear by ageing, including aphasia, disorientation, sudden changes in mood, depression, inability to take care of oneself, and behavioural problems. Also, confusion, irritability and aggressiveness, mood swings, difficulty speaking, both short- and long-term memory loss and progressive sensory dysfunction further aggravate the already detrimental condition of patients suffering by AD [3,4].The subject tends to isolate himself from society and family and gradually, basic mental abilities are lost. It seems that, about 70% of the AD developmental would be genetic with several genes usually involved. But the exact cause and progression of AD are not still well understood. It is well established that AD is a well-unshakable neuronal disfunction, whose primary causes could be associated with toxin insults, heredity, metabolism, or even attack by infectious pathogens[5]. Several research indicates that AD is closely correlated with amyloid plaques and neurofibrillary tangles found in the brain, but the root cause of this degeneration is unknown[6]. Other well-explored factors, contributing to cognitive neurodegeneration driving to AD comprise excessive acetylcholine esterase enzymes (AChE), β amyloid (βA) precursor protein-cleaving enzyme 1 (BACE-1), glycogen synthase kinase 3 β (GSK-3 β), monoamine oxidases (MAOs), metal ions in the brain, N-methyl-D-aspartate (NMDA) receptor, and phosphodiesterases (PDE). It is anyway extensively recognized that OS, as well as the formation of free radical and not radical RONS, are strongly involved in the progression of brain aging and, in the onset, and evolution of AD. In addition, impaired bioenergetics, mitochondrial abnormalities, and neuroinflammatory processes are implicated too. Collectively, one-hundred years after the AD discovery, the scientific community is quite firm that, although the pathogenesis of AD is not yet fully understood, it is surely a multifactorial disease caused by both genetic, environmental, and endogenous factors (Figure 1), like other neurodegenerative disorders [7]. The excessive incorrect folding and aggregation of proteins often related to the ubiquitin-proteasomal system (UPS) are also accountable to AD.

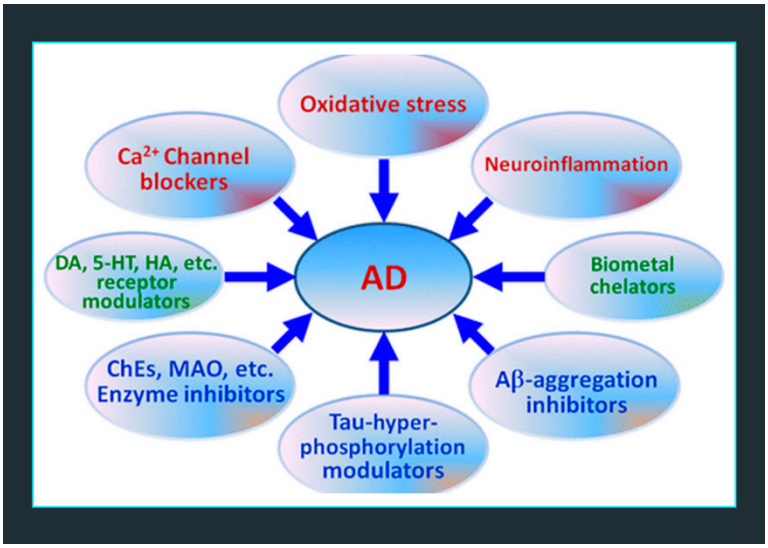

Figure 1. Some of the endogenous factors and possible biological targets involved in AD pathology. Readapted with PERMISSION/LICENSE GRANTED AT NO CHARGE by ACS Chemical Neuroscience (American Chemical Society) from [8].

Particularly, the increasing of RONS causes mitochondria and DNA damaging, with increased production of toxic Aβ causing in turn severe DNA repair dysfunctions. Currently, approved therapeutic treatments used to treat AD provide only little and temporarily benefits to symptoms

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and can partially slow the progression of the disease. Increasing insights, coupled with further ongoing discoveries about AD multi-factorial pathogenesis, have provided the rationale for the search for new therapies, which directly could target AD molecular causes [7]. New drug candidates with promising potential to modify the disease are now in the pipeline and have reached testing in clinical trials [9]. On the index date of January 1, 2023, there were 187 trials assessing 141 unique treatments for AD. Phase 3 included 36 agents in 55 trials; 87 agents were in 99 Phase 2 trials; and Phase 1 had 31 agents in 33 trials. The most common drugs, comprising 79% of drugs in trials, were those proposed as disease-modifying therapies, and 28% of candidate therapies were those using repurposed agents. Collectively, current Phase 1, 2, and 3 trials will require 57,465 participants [9]. Unfortunately, although nowadays over 500 clinical trials have been conducted to identify a possible effective treatment for AD, no treatment has yet been identified, capable to halt or reverse the disease[10]. The widespread and increasing diffusion of AD in the population, and the limited and non-resolving efficacy of the available therapies, as well as the enormous resources necessary for its diagnosis, management in terms of social, emotional, organizational and economic, make AD one of the diseases with the most serious social impact in the world [11]. This lack of pathogenesis-targeting therapies is principally due to the limiting effects of the blood–brain barrier (BBB), which keeps out of the brain about 99% of all "foreign substances". Later their discovery, nanoparticles (NPs) have been successfully used for targeted delivery into many organs, including the brain[12]. In this context, new nano dimensional agents and/or formulations of existing drugs could be promising options for the possible diagnosis and treatment of various neurological disorders, including AD. Furthermore, it has been reported that drugs hitting a single molecular target are not effective for the treatment of diseases like the complex neurodegenerative syndromes, like diabetes, cardiovascular diseases, and cancer, which involve multiple pathogenic factors [13]. On the contrary, drugs that could cover up different pharmacological approaches could offer more possible ways of overcoming the problems that could arise from the use of single-target drugs, often well-functioning in *vitro* but not in *vivo* experiments. On this worrying scenario concerning the poor available arsenal of drugs and/or nano-drugs to treat AD, the several multitarget health effects of many fruits and vegetables could represent an appealing alternative treatment option. In fact, it has been demonstrated that foods including muscadine grape, berries as pomegranate, strawberry, raspberry, blackberry, nuts such as chestnuts, walnuts, almonds, pecans, pistachios, herbs such as *Camellia sinensis*, seeds including berries seeds, and their derived foods and/or beverages possess recognized healthy and/or preventive effects against several complex human diseases, thus evidencing their multitarget behaviour [14]. Such effects have been associated mostly with their high content in antioxidant molecules, mainly of polyphenol type [14–16], such ellagitannins (ETs) as well as gallic acid (GA) and ellagic acid (EA), which are produced by their hydrolysis *in vivo* (Figure 2) [17]. By limiting the hyperproduction of RONS they counteract OS, recognized as the foremost prompting factor of several human discomforts.

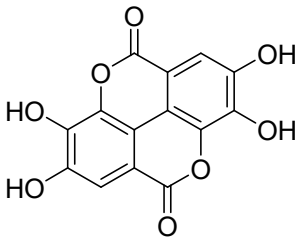

Figure 2. Chemical structure of ellagic acid (EA).

Particularly, the stringent correlation existing between the consumption of ETs-rich foods and the deriving ameliorating effect vs. several human degenerative diseases is extensively reported[17,18]. As examples, documented findings assert an association between the consumption of ET-rich foods and greater cardiovascular health [19,20], or among the consumption of fruits and vegetables and minor incidence of coronary heart disease [21]. Much empirical data guided to the hypothesis that ETs might be exploited to prevent chronic and degenerative diseases such as cancer,

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diabetes, cardiovascular diseases, and central nervous system (CNS) disorders, including AD [22]. Nonetheless, in Europe, EFSA has not been still approved for them any kind of health claims [14]. As abovementioned, ETs are capable to provide EA by hydrolysis, which is rationally considered the bioactive fragment of ETs possessing one of the strongest antioxidant power capable to counteract OS [17], confirmed already 10 years ago in a study by Kilic[23]. *In vitro* radical scavenging and antioxidant capacity of EA were clarified using different analytical methodologies such as total antioxidant activity determination by ferric thiocyanate, hydrogen peroxide scavenging, 1,1-diphenyl-2-picryl-hydrazyl free radical (DPPH) scavenging, 2,2′-azino-bis(3-ethylbenzthiazoline-6-sulfonic acid) (ABTS) radical scavenging activity and superoxide anion radical scavenging, ferrous ions (Fe^{2+}) chelating activity and ferric ions (Fe^{3+}) reducing ability[23]. . Being endowed with this relevant capability to combat OS, nowadays considered the key cause of all diseases, and therefore being gifted with the capacity to ameliorate human degenerative diseases, food chemists consider both ETs and EA as nutraceuticals (NTs). NTs are defined compounds which possess both the canonical nutritional values and several additional health benefits, so that the dietary intake of foods containing these components often translates in relevant beneficial biological effects. This review aims at more largely driving the researchers' attention towards EA as actual possible multi-target treatment option for AD. A brief overview on the multi-factorial and multi-target aspects that characterize AD, and polyphenols such as EA respectively, open this work. Upon a focus on the pathophysiology of OS, on EA chemical features and on the mechanisms of its antioxidant activity, an all-round updated analysis concerning the EA-rich foods and EA involvement in the field of AD has been provided. The possible clinical usage of EA to treat AD has been shown reporting results by its applications in vivo and clinical trials. A critical view about the need for a more extensive use of the most rapid diagnostic methods to detect AD from its early symptoms has also been included in this work.

2. Multifactorial Nature of Neurodegenerative Diseases: Alzheimer Disease (AD)

Neurodegenerative diseases (NDs) have long been viewed as among the most mysterious and challenging issues in biomedicine [12]. While moving from descriptive phenomenology to mechanistic analysis, researchers have become progressively aware that the major processes involved in their onset are complex and multifactorial, including both genetic, environmental, and endogenous factors[24,25]. Such NDs comprehend, among others, Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (HD), as well as amyotrophic lateral sclerosis (ALS). As in other neurodegenerative conditions, the pathogenic cascade driving to AD includes protein incorrect folding and aggregation, OS and RONS formation, metal dyshomeostasis, mitochondrial dysfunction, and phosphorylation impairment, all occurring concurrently. Figure 3 summarizes the concomitant multiple factors conducting to the onset of the AD conditions, while Figure 4 evidence how some of these factors can damage directly the neurons causing their death or can trigger a detrimental cascade of events anyway leading to the death of neurons.

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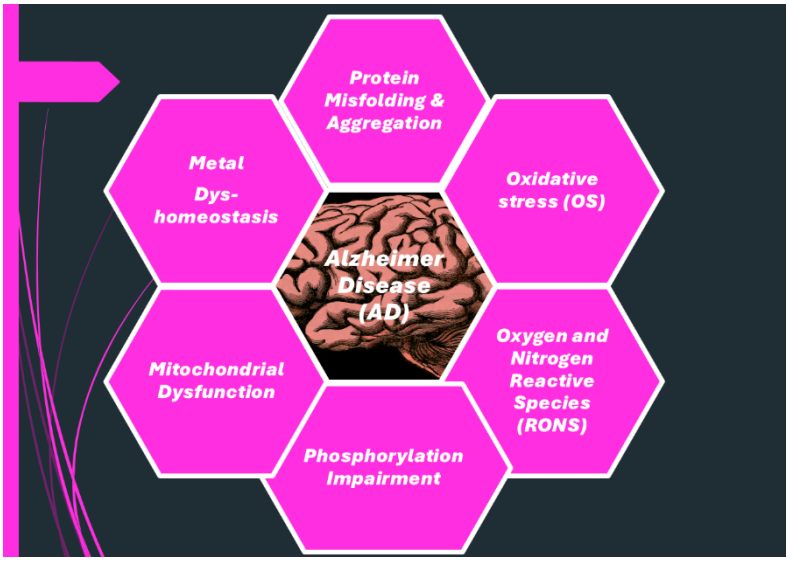

Figure 3. Multifactorial pathogenic cascade leading to the onset and development of AD.

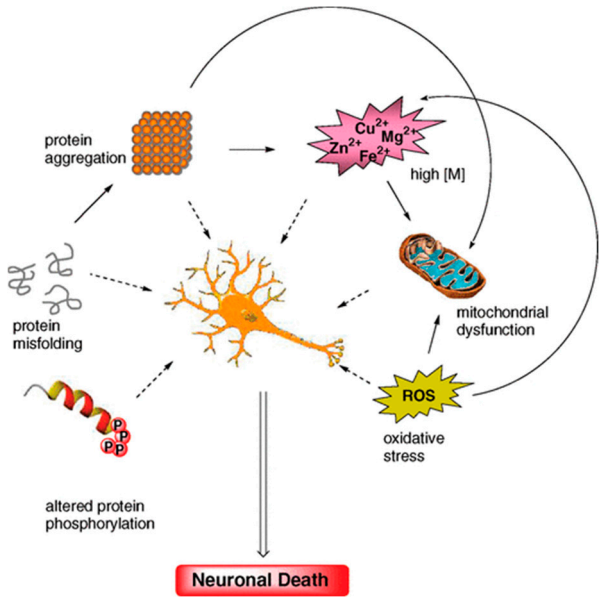

Figure 4. Schematic pathways of the multifactorial events leading to neuronal death. General mechanisms, such as protein misfolding and aggregation, oxidative stress (OS), metal (M) dyshomeostasis, mitochondrial dysfunction, and altered protein phosphorylation, have been identified in several neuronal disorders. Readapted with PERMISSION/LICENSE GRANTED AT NO CHARGE by ACS Chemical Neuroscience (American Chemical Society) from [7].

Protein wrong folding followed by self-association and subsequent deposition of aggregated, anyway supported by OS, RONS uncontrolled increasing and metal dyshomeostasis, has been observed in the brain tissues of patients affected by AD [26]. Findings suggest that protein assemblies produced by different amyloidogenic proteins share common structural and histological morphologies and might trigger similar neurotoxic mechanisms. The biophysical behaviour of these proteins, leading to their incorrect folding, aggregation, and deposition, has prompted scientists to group these kinds of neurological disorders under the common name of "conformational diseases" [27]. It is worth noting that amyloid oligomers such as amyloid-precursor protein (A) and R-synuclein have been widely reported to permeabilize both cell and mitochondrial membranes, thus impairing their functions [28]. They are therefore probably responsible for the subsequent calcium

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dysregulation, membrane depolarization, and deficiency of mitochondrial functions, which have been identified as a common feature of AD [29].

2.1. More in Deep in The Multifactorial Causes of AD: Reactive Oxygen and Nitrogen Species (RONS)

The role of RONS in many NDs was deemed to be as essential as the role of microorganisms in infectious diseases. In normal conditions, RONS generation is kept under control by the antioxidant defences and repair systems of cells[30]. On the contrary, when overproduced, the detoxification systems of cells fail to maintain RONS physiological levels. They accumulate, thus causing the onset of OS and inflammation. Irremediable damage to DNA, lipids, and proteins happens, thus promoting aging, age-related diseases, and several degenerative human disorders[30]. To respond to the answer "Is OS a cause or a consequence of the neurodegenerative cascade in AD?" has been and remain a daily challenge for experts in the field, which would need urgently a solution. At present, scientists agree almost unanimously to affirm that imbalance of intracellular oxidation state is an early event in the neurodegeneration and is therefore likely to be one of the major factors of neurodegenerative disorders. Neuronal tissue is particularly sensitive to OS, and the possible imbalance in pro-oxidant *vs* antioxidant homeostasis in central nervous system (CNS), can result in the production of several potentially toxic RONS, including both radical and nonradical species that participate in the initiation and/or propagation of radical chain reactions injuring neurons. Table 1 reports the possible sources of RONS, which can be endogenous, both enzymatic and non-enzymatic, as well as exogenous.

Table 1. Endogenous and exogenous sources of ROS and the main reactive species of RONS, which can be in turn produced.

Endogenous Sources		Exogenous Sources	Reactive Species
Enzymatic	Non-Enzymatic		
			$O_2^{\bullet-}$
		Air	H_2O_2
NOX	Mitochondria	Water pollution	•OH
MPO	Respiratory chain	Tobacco	•OOH
Cytochrome	Glucose auto-	Alcohol	ONOO•
P450	oxidation	Heavy/transition	NO_2•
Lipoxygenase	NAD•	metals	NO•
Angiotensin II	Semiquinone	Drugs	$ONOOCO_2^-$
Xanthene	radicals	Industrial solvents	NO^{2+}
oxidase	Radical	Cooking	ONOOH
Cyclooxygenase	pyridinium	Radiation	N_2O_3
FpH•	Hemoproteins	EPFRs	$ONOO^-$
		BC-PFRs	$ONOOCO_2^-$
			$CO_3^{\bullet-}$

MPO = myeloperoxidase; NOX = NADPH oxidase; NAD = nicotinamide adenine dinucleotide; Fp = flavoprotein enzymes; EPFRs = environmental persistent free radicals present in particulate matter; BC-PFRs = biochar-related persistent free radicals.

The following Figure 5 schematizes specifically the main endogenous processes by which ROS can be created in cells and the detrimental effects they can have on health [30], including DNA damage, lipids, and protein peroxidation, telomere reduction, aging, and death.

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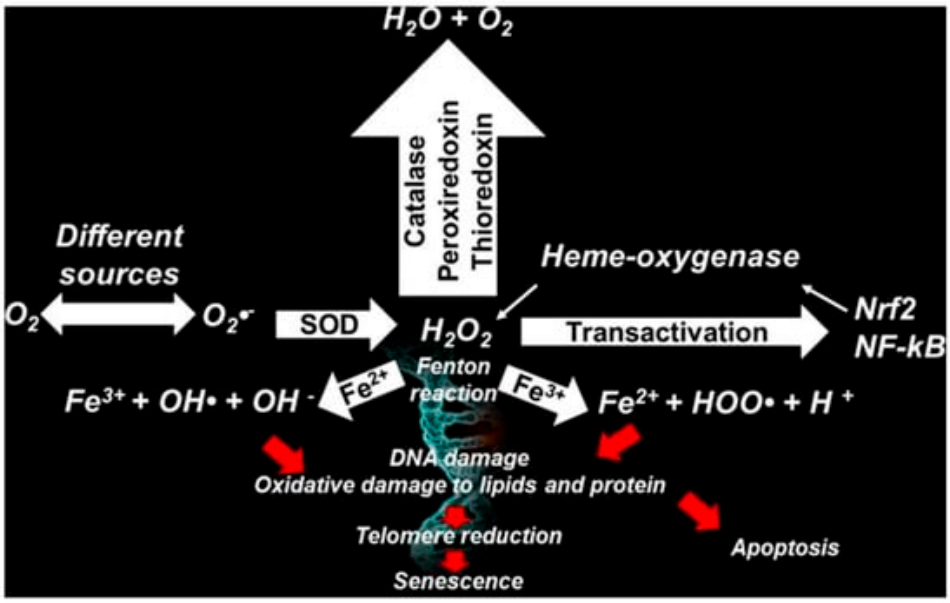

Figure 5. Schematic pathways of ROS production and their main effects on biological systems. Nrf2 = erythroid nuclear transcription factor-2; NF-kB = transcription factor involved in cellular responses to stimuli such as stress, cytokines, free radicals, heavy metals, ultraviolet irradiation, oxidized low-density lipoproteins (LDL), etc. Reproduced from our article [30].

In AD, OS has been found in every family of biological molecules within neurons, spanning from lipids to DNA and proteins. Anyway, several clinical studies have revealed that the simple administration of one or a few one-target antioxidants had modest success in the treatment of neurodegeneration. It has been reported that in AD, it exists also a direct cause and effect relationship between metal abnormalities and increased oxidative damage. Transition metals such as iron, copper, or other redox active metals are essential in many biological reactions, but the alterations in their homeostasis may result in increased free radical production. Moreover, while all the disease-specific proteins bear metal-binding motifs, metal ions favour the fibril generation, and the protein deposition found in AD (Section 2, Figure 4). Furthermore, in addition to be a cause of OS in neurons, metal-mediated OS is linked also to mitochondrial dysfunction, where ROS can be generated, as well. Morphological, biochemical, and molecular abnormalities in mitochondria in various tissues affected by AD have been signalled. Although the chronological hierarchy of events and underlying causes in AD about mitochondrial dysfunction and OS are not yet fully clarified, there is unequivocable evidence that both participates to the evolution of the others, setting in motion a self-sustaining, amplifying cycle that can ultimately activate the initiation of neuronal death processes as shown in the following Figure 6.

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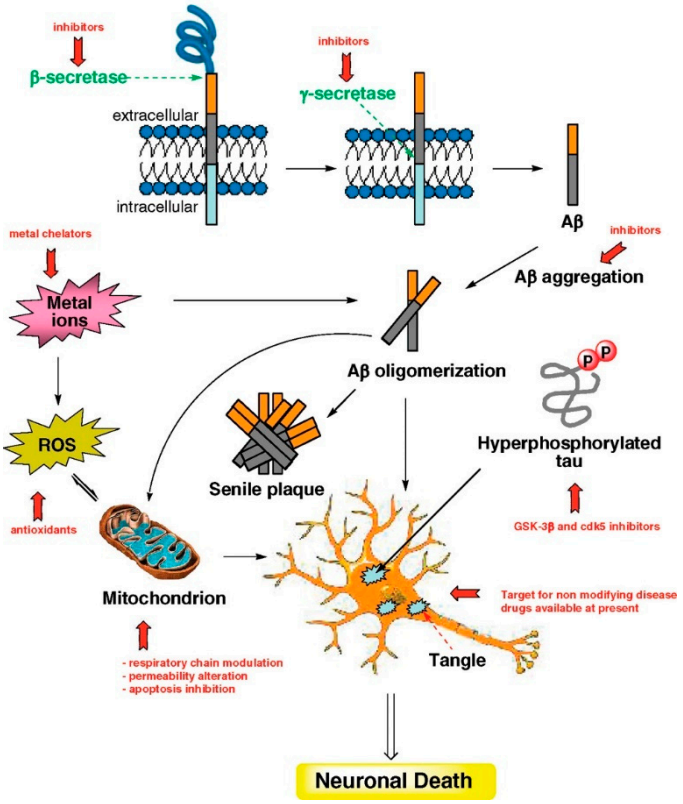

Figure 6. Possible molecular causes of neuronal death and protective cyclic mechanisms in AD. The central event in AD pathogenesis is an imbalance between Aβ production and clearance. The enhanced activity of β- and γ-secretases leads to increased release of amyloidogenic Aβ42, which forms oligomers and then extracellular deposits (senile plaques). In this regard, one way to confront AD pathogenesis may be to combat the oligomerization processes by means of small molecules. A role for metal ions and ROS in the Aβ oligomerization has also been advanced. Therefore, also metal chelation and antioxidants are two general mechanisms to be considered in the search for disease-modifying anti-AD drug candidates. Also, β- and γ-secretase inhibitors may be promising lead compounds because they tackle an early event in AD pathogenesis. Mitochondrial dysfunction plays a fundamental role in the neuronal death associated with AD, as it is likely that intracellular Aβ could compromise the function of this organelle. τ hyperphosphorylation leading to tangle formation is regarded as a downstream event but could contribute to reinforcing neuronal dysfunction and cognitive impairment. Readapted with PERMISSION/LICENSE GRANTED AT NO CHARGE by ACS Chemical Neuroscience (American Chemical Society) from [7].

Also, the endoplasmic reticulum (ER) is an important apoptotic checkpoint. It has been shown that, in AD, apoptosis induced by badly bent proteins involves ER impairment. Another common mechanism shared by NDs concerns the alteration of the phosphorylation state of some key proteins participating in the pathogenic cascades. Besides the well-recognized hyperphosphorylated state of τ protein in the neurofibrillary tangles observed in AD brain, other specific altered patterns of kinase and phosphatase activities are associated with alteration in the phosphorylation state of disease-specific proteins, which are different for PD, ALS, and HD. Extensive molecular evidence demonstrated the cell-type specificity in neuronal disorders and the selective neuron degeneration in AD. However, none of these general mechanisms alone are sufficient to explain the high number of biochemical and pathological abnormalities of AD, which encompass a multitude of cross-related cellular and biochemical changes that cannot be adequately addressed by following treatments based on one-molecule, one-target paradigm. In our opinion, there should be a growing interest and an urgent need for the development of multi target directed ligands (MTDLs) to provide real disease-modifying drug candidates for such ND.

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3. One-Target Drugs vs. Multi-Target Therapies in the Treatment of Degenerative Diseases

The scientific knowledge about the pathogenesis of several human diseases has advanced enormously in recent decades. Therefore, the sector of drug discovery has gradually shifted from seeking an entirely human phenotype-based approach to a more reductionist approach based on single molecular targets. This change has led to a type of drug research, still extensively followed, aimed mainly at the discovery of small molecules able to modulate the biological function of a single given target, believed to be fully responsible for a certain disease. Efforts in this sense have been devoted to achieving drug molecules selective for a certain protein, and many ligands endowed with outstanding *in vitro* selectivity and efficacy are today available. Although such one-molecule, one-target paradigm has led to the discovery of many successful drugs, and it will probably remain a milestone for years to come, it should be noted that a highly selective ligand for a given target in *vitro*, does not always result in a clinically efficacious drug in *vivo* (Table 2).

Table 2. In *vitro* and in *vivo* outcomes of the one-molecules/one target paradigm approach.

In vitro	*In vivo*
High Selectivity Strong efficacy Tendency to develop resistance	Not recognizing the target by the ligand *in vivo* Not reaching of the site of action by the ligand One target interaction is not enough to have a sufficient impact on the complex diseased system

The low correspondence between results in *vitro* and those in *vivo* in the case of NDs, is mainly due to the multifactorial nature of human degenerative diseases. In these cases, the cells can often find ways to compensate for a single protein, whose activity is affected by the one-target drug administered, by taking advantage of the redundancy of the system, including the existence of parallel pathways [31]. Drugs hitting a single target may be inadequate for the treatment of diseases like neurodegenerative syndromes such as AD, diabetes, cardiovascular diseases, and cancer, which involve multiple pathogenic factors [32]. Different pharmacological approaches are necessary to overcoming the problems that arise from the use of single-target drugs (Table 2, column 1). When a single target medicine is not sufficient to effectively treat a disease, alternative approaches aiming at hitting more than one impaired process correlated to the disorder should be considered. Figure 7 shows some alternative medical approaches.

Figure 7. Alternative approaches to the one-molecule/one-target drug one. MMT= multimodal therapy; MCM = multiple-compound medication. (Single compounds hitting multiple targets can be abbreviated also as MTDLs).

The three most adopted approaches (MMT, MCM and MTDLs) reported in Figure 7 have charted in Table 3 with related advantages and disadvantages.

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Table 3. Alternative multi-target approaches.

Approaches	Advantages	Disadvantages	Ref.
MMT	Attack the multifaceted discomfort from multiple mechanisms	Compliance problems by patients Undesired in *vivo* drug-drug interactions In *vivo* unbeneficial side effects Different bioavailability, pharmacokinetics metabolism of the single drugs	[33]
MCM	Attack the multifaceted discomfort from multiple mechanisms	Undesired in *vitro* and in *vivo* drug-drug incompatibility hampering single formulation	[34]
	Simpler dosing regimens	Different bioavailability, pharmacokinetics, metabolism of the single drugs in the cocktail	
	↑ Patient compliance	Unbeneficial side effects in *vivo* Undesired in *vivo* drug-drug interactions	
MTDLs	Unique bioavailability pharmacokinetics, metabolism (ADMET profile) Simpler pharmacokinetic and ADMET optimization	Complex ADMET Complex pharmacokinetic	[35]
	↓ Risk of possible drug-drug interactions Simplified therapeutic regimen in relation to MMT		

MMT= multimodal therapy; MCM = multiple-compound medication; MTDLs = multi-target direct ligands; ADMET = absorption, distribution, metabolism, excretion and toxicity.

The multiple-medication therapy (MMT) (Figure 7), also known as combination therapy, may be used as alternative option to one-target therapy. It is usually composed of two or three different drugs singularly administrated, thus combining different therapeutic mechanisms[36]. A second approach might be the use of a multiple-compound medication (MCM), also referred to as a "single-pill drug combination", which implies the incorporation of different drugs into the same formulation. Finally, a very appealing strategy is now appearing assumes that a single compound may be able by *per se* to hit multiple targets, because comprehend in the same molecule more than one pharmacophore. Clearly, therapy with a single drug that has multiple biological properties would have inherent advantages over MMT or MCM as reported in Table 3. There is, therefore, a strong indication that the development of single compounds able to hit multiple targets might disclose new avenues for the treatment of major NDs, such as AD, for which new effective cures are an urgent need and an unmet goal. In the past, Morphy and Rankovic pleasingly discussed this approach in three articles, which anyway were mostly concerned with non-NDs [37–39]. In this context, we are convinced that the definition "multi-target-directed ligands" (MTDLs) more completely describes these compounds. Effectively, MTDLs should succeed in treating complex diseases, because of their ability to interact with the multiple targets thought to be responsible for the disease pathogenesis. The excellent perspective by Morphy and Rankovic [37] covered several aspects of the design strategy leading to MTDLs for different areas such as inflammation, dopaminergic D2-receptors, histaminergic H1-receptors, serotoninergic receptors, angiotensin system, peroxisome proliferators activated receptors, kinases, and nitric oxide releasing conjugates. Although more attention to the achievements of MTDLs also for NDs is increasing, there is still a paucity of review literature dealing

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with complex diseases associated with neurodegeneration, which we hope to compensate for, by our present work.

3.1. Alzheimer's Disease (AD) and Currently Available Medicines and/or Treatments in Development

Among the NDs above reported, AD stands out as the fourth leading cause of death in the Western countries and the most common cause of acquired dementia in the elderly population. As shown in Figure 8, two main forms of AD are recognized, both characterized by neuronal death.

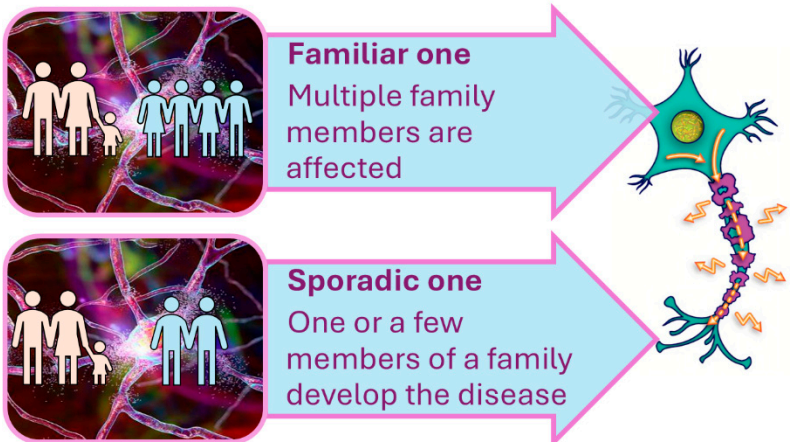

Figure 8. The main possible forms of AD.

In line with an increase in average life expectancy of humans, the number of affected persons is expected to triple by 2050, with immense economic and personal tolls [35]. In parallel with this increase, the speed of drug research has accelerated noticeably in recent decades, but not enough. However, the number of therapeutic options on the market remains strongly restricted. Worryingly, the currently registered drugs for AD, i.e. acetylcholinesterase inhibitors (AChEIs) are not able to alter or prevent disease progression. They are instead palliative in alleviating disease symptomatology[40]. On this scenario, being AD a multifactorial disease whose insights and discoveries about its pathogenesis are progressively ongoing, the rationale exists for the discovery and study of multi-target drugs directly targeting different AD molecular causes at once.

3.1.1. Current AD Therapies

Although the path of the events leading to the AD onset is far to be completely clarified, the cholinergic hypothesis was the oldest one and had the strongest influence on the development of clinical treatment strategies for AD. Acetylcholine (Ach) is released in the synaptic cleft where it activates both postsynaptic and presynaptic cholinergic receptors [nicotinic (N) and muscarinic (M)], leading to an increase of cholinergic transmission, which results in cognition improvement. Anyway, ACh is removed from the synapse by the action of the enzyme acetylcholinesterase (AChE), which therefore has been become the target for the development and approval of acetylcholinesterase inhibitors (AChEIs) for AD treatment as visualized in Chart 1 and reported in Table 4.

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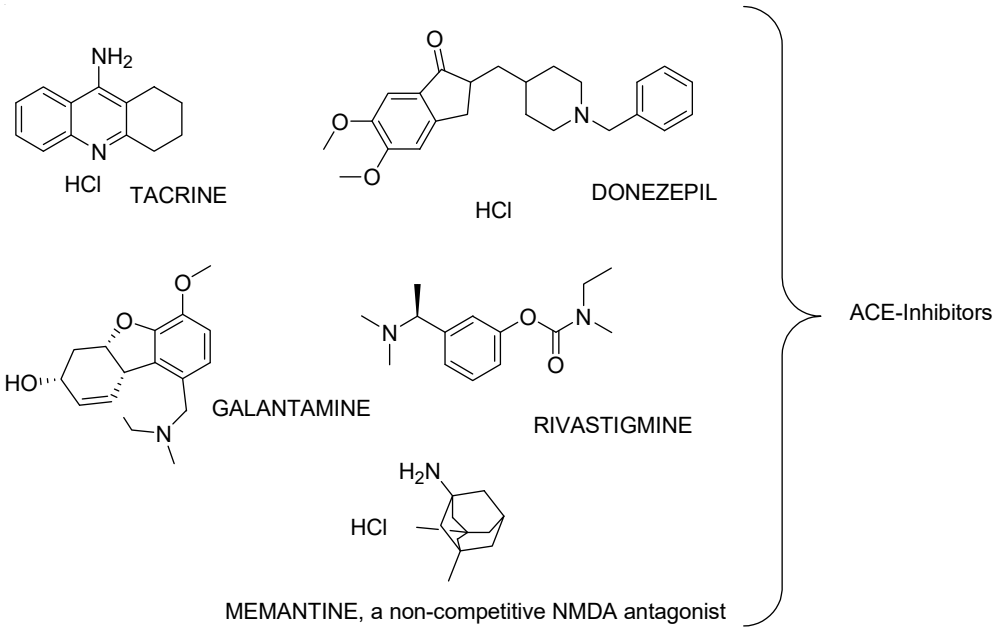

Chart 1. Structure of traditional AChEIs.

The acetylcholinesterase inhibitor (AChEI) tacrine (Chart 1) was the first drug to be approved for the treatment of AD, now rarely used because of its hepatotoxicity. Later, three other AChEIs, donepezil, rivastigmine, and galantamine reached the market, becoming the standard for AD therapy, only later complemented by memantine, a noncompetitive NMDA antagonist (Chart 1). Table 4 include the advantages and disadvantage connected to the use of such therapeutics.

Table 4. Current old and more recent one-target therapeutics approved for AD.

Family	Subfamily	Drugs	Advantages	Disadvantages	Ref.
Old AChEI		Tacrine °,* Denezepil * Rivastigmine * Galantamine *	↑ Cognitive, behavioural, functional impairments	Hepatotoxic Unable to address the molecular mechanisms that underlie the pathogenic processes Not able to resolve the causes	[41]
	Non-competitive NMDA antagonist	Memantine *			

IChEI = acetylcholinesterase inhibitors; ↑ = improved, higher, ameliorated; * approved standards of AD therapy; ° nowadays rarely used.

Although the diffused clinical practice, the debate on the effective activity of AChEIs medications endures. So, the search for novel AChEIs, such as inhibitors of the "non-classical function" of AChE have rehabilitated interest in expanding their potential as real disease-modifying agents. Current AD drug development programs focus primarily on agents with anti-amyloid disease-modifying properties, and several studies have been carried out on molecules capable to reduce amyloid pathology (Table 5). Classes of therapeutic modalities currently in the advanced stage of clinical trial testing comprise forms of immunotherapy which uses several drugs (Table 5), including also medicaments with anti-amyloid properties. Nontraditional dementia therapies, such as those using the HMG-CoA reductase inhibitors, including mainly statins[42], such as atorvastatin, simvastatin, fluvastatin, pravastatin, rosuvastatin and lovastatin are now being evaluated also for their clinical benefits in AD as disease-modifying treatments [42].

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Table 5. Summary of recent pharmacological interventions against AD.

Class of Drugs	Compounds	Mechanism	Subjects	Trial Phase	Summary	[Ref]
Anti-amyloid therapy						
Secretase inh.	Verubecestat	BACE1 inh.	PTM AD	II/III	↓Efficacy	[43,44]
	Atabecestat		P AD		↓ Cognition Psychiatric disorder	[45]
	Lanabecestat		MCI to mild AD	III	↓ Cognition ↓ Weight loss Psychiatric disorder	[46]
	LY3202626		Mild AD		↓ Efficacy	[47]
	Umibecestat		Cognitively healthy APOE4 carriers	II/III	Completed Failed analysis due to ↓ number of events	[48]
	Elenbecestat		MCI to moderate AD	III	↓ Efficacy Nightmare	[49,50]
	Semagacestat	γ-secretase inh.	Mild to moderate AD		↓ Efficacy Skin cancer, ↓ weight Hematologic disorder Infection	[51]
	Avagacestat		MCI		↓ Efficacy Non-melanoma cancer, GIT symptoms	[52]
	Tarenflurbil	γ-secretase modulator	Mild AD		↓ Efficacy Anaemia infection	[53]
Aβ aggregation inhibitor	PBT1	MPAC	MCI to moderate AD	II	Rescue of cognitive decline in severely affected patients (ADAS-cog ≥25) Visual impairment	[54]
	PBT2	MPAC	MTM AD		↓ Efficacy ↑ Individual variance	[55,56]
Aβ immunotherapy	ACI-24	Aβ vaccine	Adults with Down syndrome		↓ Immunogenicity	[57]
	CAD106		Mild AD		↓ Efficacy	[57]

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	UB-311	Monoclonal antibody	MCI to mild AD	III	No published data	[57]
	ABVac40				Ongoing	[57]
	BAN2401				↓ Efficacy among APOE4 carriers	[58]
	Gantenerumab		PTM AD		↓ Efficacy	[59]
	Aducanumab		Monoclonal antibody		Termination ↓ Change in efficacy FDA approval for now	[60,61]
Anti-τ therapy						
Phosphatase modifier	Selenate	PP2A activator	MTM AD	II	↓ Efficacy	[62,63]
Kinase inhibitor	Roscovitine	CDK5 inh.	5XFAD mice	*In vivo*	Prevention of τ phosphorylation	[64,65]
	Flavopiridol		CD1 mice		Rescue of cognitive decline	[64,65]
	Tideglusib	GSK3β inh.	MTM AD	II	↓ Efficacy transaminase increase	[66]
	Lithium		MCI		Rescue of cognitive decline	[67–69]
τ aggregation inh.	MB	Disrupts polymerization	MTM AD		↑ Cognition	[70]
	LMTX			III	↓ Efficacy	[71]
	Curcumin	↓ β-sheet in τ	CHE	II	↑ Working memory (short-term course)	[72]
Microtubule stabilizer	EpoD	↑ Microtubule bundling	Mild AD	I	Discontinuation Frequent adverse effects No published data	[73]
	NAP	Protects microtubules from katanin disruption	MCI	II	↑ Cognition and functionalities	[74,75]
	TPI-287	Stabilizes microtubules	MTM AD	I	Rescue of cognitive Decline Anaphylactoid reactions	[76]

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τ immunotherapy	AADvac1	τ Vaccine	Mild AD	II	Completed No published data	[77]
	ACI-35		MTM AD	I	Safe and tolerated	[78]
	Aβ 3–10-KLH		3 × Tg-AD mice	*In vivo*	↑ Cognition	[79]
	BIIB092	Monoclonal antibody	Early AD	II	Ongoing	[80]
	ABBV-8E12					[81,82]
	RO7105705		PTM AD			[82,83]
	BIIB076		Healthy volunteers, MCI	I	Safe and tolerated	[84]
	LY3303560		Early AD	II	Completed No available data	[85]
	JNJ-63733657			II	Ongoing	[86]
	UCB0107		Healthy volunteers	I		[87,88]
Anti-neuroinflammatory therapy						
Microglia modulator	Thymoquinone	TLR4 inh.	AD mice induced by $AlCl_3$	*In vivo*	Rescue of cognitive impairment	[89]
	Ethyl pyruvate					[89]
	TAK-242				↑ Cognition	[90]
	GW2580	CSF1R inh.	APP/PS1 mice		Recovery of short-term memory and behavioural deficit	[91]
	JN-J527		P301S mice		↑ Functionalities	[92]
	PLX3397		5XFAD mice		Recovery of spatial and emotional memory deficit	[93]
Astrocyte modulator	Stattic	STAT3 inh.	5XFAD mice		Rescue of learning and memory impairment	[94]
	FK506	Calcineurin/NFAT inh.	MCI to AD	II	Not yet recruiting	[95]
	SB202190	P38 MAPK inh.	Wip1-deficient mice	*In vivo*	Rescue of learning and memory impairment	[96]

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	PD169316		Aβ-injected mice		Rescue of spatial memory and learning impairment	[96]
	MW108		H τ mice		Rescue of cognitive impairment	[97]
	NJK14047		5XFAD mice		↑ Cognition	[98]
	MRS2179	P2Y1R inh.	APPPS1 mice		↑ Spatial learning	[99]
	BPTU					[99]
Insulin resistance management	Intranasal insulin therapy	Intranasal supplement	MCI to moderate AD	II	↑ Cognition ↑ Modulation by APOE4 genotype	[100,101]
			MCI to AD	II/III	↓ Efficacy	[102]
	Liraglutide	Incretin receptor agonist	Mild AD		Delay of cognitive impairment	[103]
	Metformin	Biguanide	MCI	II	↓ Recall memory decline	[104]
			MCI to early AD		↑ Executive functionalities	[105]
	Gemfibrozil	PPAR-α agonist	MCI	I	Completed No published data	[106]
	Pioglitazone	PPAR-γ agonist	Mild AD	II	↑ Cognition	[107]
			MCI	III	↓ Efficacy	[108,109]
	T3D-959	PPAR-δ/γ agonist	STZ-induced AD	*In vivo*	↓ Neuroinflammation	[110]
Microbiome therapy	Sodium oligomannate	Dysbiosis of gut microbiota	MTM AD	III	↑ Cognition	[111,112]
Neuroprotective agents						
Antiepileptics	Levetiracetam	SV2A receptor	MCI	III	Ongoing	[113]
	Gabapentin	VGCCs inh.	MTS AD	IV		[114]
NMDAR modification	Sodium benzoate	DAAO inh.	MCI to mild AD	II	↑ Cognition	[115]
			MCI		↑ Cognition and functionalities	[116]
			MTS AD with BPSD		↑ Cognition in female	[117]

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	Riluzole	Glutamate modulator	Mild AD		Completed No published data	[118]
	Troriruzole				Ongoing	[119]
Omega 3 FA supplements	DHA	Anti-oxidative effect	MTM AD	III	↓ Efficacy	[120]
			CHE	II	Ongoing	[121]
	Icosapent ethyl			III		[122]

Inh. = inhibitor; PTM = prodromal to mild; FA = fatty acids; ↓ = slow, reduce, decreased, lower, lack of; ↑ = higher, improved, enhanced; BACE1—β-secretase1, APOE4—apolipoprotein E type 4, PBT1—clioquinol, PBT2—second-generation clioquinol, MPAC—metal protein attenuating compound, ADAS-cog—Alzheimer's Disease Assessment Scale–Cognitive Subscale, MB—methylene blue, EpoD—Epothilone D, NAP—davunetide, TPI-287—abeotaxane, DHA—docosahexaenoic acid; MTM = mild to moderate; MTS = moderate to severe; CHE = cognitively healthy elderly; DAAO = D-amino acids oxidase; MTS = magnetic transcranial stimulation; MCI = mild cognitive impairments; BPSD = behavioural and psychological symptoms of dementia.

3.1.2. Versus Disease-Modifying Therapies in Alzheimer's Disease [123]

The long-expected era of disease-modifying therapy (DMT) for AD has finally arrived and will substantially influence how the disease is perceived and managed. Unfortunately, the new treatments closest to extensive clinical implementation (Figure 9), will pose challenges for rightful access. No national health-care system is ready to deliver these drugs to more than a fraction of patients who might be eligible.

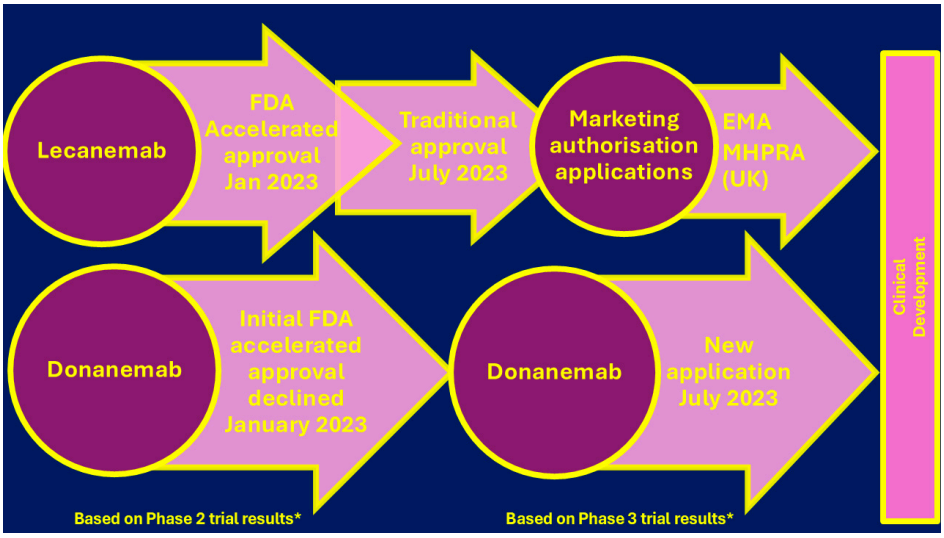

Figure 9. Developmental root to the clinical implementation of new active principles (PA) for MDTs. FDA = food and drug administration; EMA = European medical agency; MHPRA = Medicine and Healthcare Products Regulatory Agency; * refers to donanemab.

These active principles (APs) include lecanemab and donanemab, which are intravenous monoclonal antibodies capable to remove βA plaques from the brain, thus slowing cognitive and functional decline. Paradoxically, lecanemab and donanemab have revealed side-effects, mainly amyloid-related imaging abnormalities (ARIA) in about 21% and 39% of patients, respectively[124]. While usually asymptomatic and transient, ARIA requires close monitoring. Symptoms and signs of ARIA can be non-specific, including blurred vision, headaches, and unsteadiness, or can include focal deficits such as dysphasia. However, many patients with ARIA can be re-dosed safely after a period off treatment[124].

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3.1.3. Multi-Target Therapy (MTT) for AD

However, the adoption of MMT, MCM and MDTLs (or MTSM) might result in more effective treatment strategies for AD, due to the multifactorial nature of this disorder. MMT has already proven successful in the treatment of other complex diseases such as cancer, HIV, and hypertension. Due to the possibility of attacking several targets simultaneously, exploiting synergy, and minimizing the individual toxicity of the administered single drugs, maximum efficacy has been achieved. With similar outcomes and advantages, MCMs, were fought, to ameliorate the compliance of patients with AD. From 2006, the number of patented MCM, where new compounds, which revealed potentialities to ameliorate AD were administered in combination with old therapeutics (AChEIs or NDMA receptors antagonists, as well as NSAID or a combination of two) has overtaken that of single-drug entities for the potential treatment of AD[125] (Table 6).

Table 6. Some patented MCM.

Patented by	Combination Ingredients	Advantages/Finalization	Mechanism of the additional ingredient	Ref.
Myriad Genetics *	AChEI + *(R)*-flurbiprofen **	Therapeutic or prophylactic treatment of AD due to the capability of NSAIDs to reduce the incidence of AD	↓ The level of Aβ associated with plaque formation inhibit cyclooxygenase enzymes	[126]
Mayo Foundation	AChEI+Aβ-lowering agent		↓the concentration of Aβ ↓agents acting on the same level	[127]
N.R.	5-substituted-3-oxadiazolyl-1,6-naphthyridin-2(1*H*)-one + reported AChEIs	Stimulation of cerebral functions and amelioration of AD to the anti-dysmnesics effects of the additional ingredient	Negative allosteric modulators of $GABA_A$	[128]
Johns Hopkins University	ABPA + reported AChEIs	↑ Cognition properties by ABPA ↑ Memory performances ↑ Therapeutic effects for AD treatment ↓Doses of the two compounds Retained therapeutic efficacy ↓Side effects Cost saving	Specific $GABA_B$ antagonist and $GABA_C$ agonist	[129]
	MS-153 + reported AChEIs	↓Ischemia-induced neuron damage by MS-153 ↑Oral bioavailability ↑Enhanced cognitive performance in aged rats in Morris Water Maze tests of spatial memory	↓Glutamate release ↑ Glutamate uptake No blocking NMDA or AMPA receptors	[130]

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Schering Corporation	Macrocyclic lactones+ AChEIs and/or an NSAID	Ameliorate Neurodegenerative diseases such as AD	↓β-secretase ↓BACE-1 enzyme (IC_{50} value of 4-186 nM)	[131,132]
Voyager Pharmaceutical Corporation	AChEI + NMDA RA + leuprolide acetate (G-R HA)	↓AD development	↓Biosynthesis and secretion of gonadotropins	[133]
Rabinoff	CPC+5-CDPC	↑ Memory For AD therapy and prevention	Neurotrophic factors	[134]
Epix Pharmaceuticals	5-HT_4 AGO + Galantamine	↑ Memory	Modification of ACh release	[135]
Wyeth	5-HT_6 ANTA + Donazepil 5-HT_6 ANTA + Galantamine 5-HT_6 ANTA + Donazepil	↑ Memory ↓Dose of the AChEI ↓Typical side effects of AChEIs ↓Cardiovascular effect of 5-HT6 antagonist	Modulation of multiple neurotransmitter systems	[136]

↓ = slow, reduce, decreased, lower; ↑ = higher, improved, enhanced; * the same applicant published related patents, which focused on the combination of flurbiprofen derivatives, specifically with donezepil, rivastigmine and galantamine ; ** non-steroidal anti-inflammatory drug (NSAID)[130–132]; N.R. = not reported; MS-153 = (R)-(-)-5-methyl-1-nicotinoyl-2-pyrazoline; RA = receptor antagonist; G-R HA = gonadotropin-releasing hormone analogues suppress the pituitary gland's secretion of LH; CPC = glycerylphosphorylcholine; 5-CDPC = 5′-cytidine diphosphocholine; 5-HT = receptors members coupled to a G protein contributing to dopamine secretion and regulating learning and long-term memory by modification of ACh release. ANTA =antagonist; AGO = agonist; ABPA = 3-aminopropyl-(n-butyl)-phosphinic acid.

In clinic, the MMT of memantine *plus* an AChEI appears to produce an additional effect resulting in a well-tolerated, effective treatment strategy [137]. Considering the well-accepted clinical use of MMT only as a starting point, the MTDL design strategy might represent its natural evolution, and MTDLs emerge as valuable tools for better hitting the multiple targets implicated in AD aetiology [138]. Several MTDLs have been developed by academia and industry in recent years. These have been the subject of some interesting review articles, which readers particularly interested could examine at the related references [139–142]. The main design strategy usually applied to build up a possible new MTDL involve detecting the active portions of different drugs and combining them in a single structure to afford hybrid molecules[8]. In principle, each pharmacophore of these new drugs should retain the ability to interact with its specific site(s) on the target and, consequently, to produce specific pharmacological responses that, taken together, should slow or block the neurodegenerative process of AD. Specifically, it is in use to modify the molecular structure of an AChEI by inserting opportune pharmacophores (indicated as PG groups in Figure 10) already present inside other drugs, which demonstrated beneficial effects in neurodegenerative diseases, to provide the traditional drug with additional ameliorative effects, while reducing side effects of separate single drugs and enhancing the compliance of patients [8].

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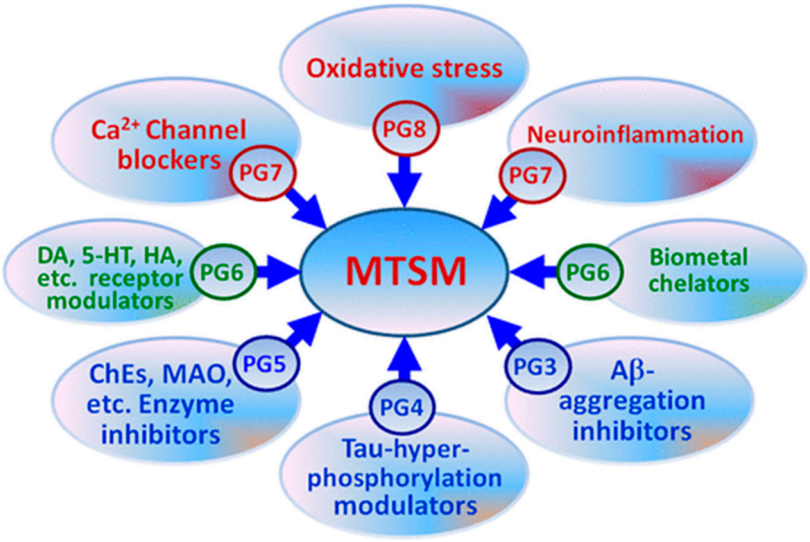

Figure 10. Ideal and efficient MTSM (equal to say MTDLs) for AD therapy, showing their corresponding pharmacophoric groups (PG). Readapted with PERMISSION/LICENSE GRANTED AT NO CHARGE by ACS Chemical Neuroscience (American Chemical Society) from [8].

4. Ellagitannins (ETs) and EA as Multi-Target Compounds: Strengths and Weaknesses

Both ETs and EA have proven, at least in *vitro*, to prevent and/or ameliorate chronic diseases such as cancer, diabetes, cardiovascular [143] and lately also neurodegenerative diseases[144,145]. It seems that these positive effects are due to their multi-target action accounting for anti-angiogenic, anti-atherogenic, anti-carcinogenic, anti-obesity, anti-inflammatory, antioxidant and anti-thrombotic properties, together with anti-neurodegenerative capability. All these gains seem to derive from their antioxidant power and therefore their capability to contain OS, the key cause of all human disorders[14,17]. Since neurodegenerative disorders including AD are multifactorial diseases, the application of the usual and extensively approached one-molecule, one-target paradigm, providing drugs able to hit only a single target, could have limited effects, mainly in *vivo*, and may also translate in the emergence of resistance. On the contrary, a compound capable to interfere with different targets involved in the cascade of the pathological events leading to a given disease could be highly effective for treating multifactorial diseases, as AD [13]. The synthetic design of such drugs may not be easy, because the obtained drugs could bind in *vivo* targets that are not involved with the disease of interest and could be not necessarily responsible for side effects. On the contrary, natural polyphenols such as ETs and EA, *per se* possessing the multifaceted health activity above reported as demonstrated by the outcomes deriving by the assumption of food containing them, are provided ready by nature and could be promising options to ameliorate/treat AD. However, they could serve at least as template molecules to be used as starting platforms to design new multi-target drugs.

4.1. Bioavailability Drawbacks Associated with ETs and EA

According to a review reported in 2020, except for an insignificant amount (e.g. 0.7–4.7 mg/100 g of berries, wet weight), the free form of EA is produced mostly in *vivo*, after the consumption of ETs-rich food, due to the physiological massive hydrolysis of ETs in the gastrointestinal tract (GIT) [17]. Anyway, even if according to some other authors, free EA makes up only a small part of the total EA pool in plants, others suggest that its portion can reach and even exceed 50% of the total content, depending on the plant species [146]. Interestingly, in the fruits of *Terminalia ferdinandiana* Exell, a native Australian plant known as the Kakadu plum, EA was found to be mostly free form, with a percentage reaching 70.6% of the total EA pool [147]. By contrast, the percentage of free EA in strawberries, as shown by the same study, reaches only 7.4% of its total content[147]. Despite early studies did not show the presence of EA in plants of the Fabaceae family, there is now evidence of relatively high levels of this phytochemical in several sprouted legumes, such as sprouted adzuki

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bean (*Vigna angularis*), some varieties of bean (*Phaseolus vulgaris* L.), cowpea (*Vigna unguiculata* (L.) Walp.), pea (*Pisum sativum* L.), and soybean *(Glycine max* (L.) Merr.)[148]. Sprouted soybeans have been found to have a considerably higher EA content than other sprouted legumes (45.6–48.9 mg/100 g vs. 8.96–18.3 mg/100 g dry weight) [148]. Although, the ratio between free and bound forms of EA in plants may vary considerably depending on the plant species, the proportion of unbound EA may also depend on the method chosen for determination, the type of storage, and processing practice [149]. Freezing fruits, as well as processing them to produce beverages and jams, may have different effects on the content of EA[146]. However, after the intake of ETs-rich foods, ETs are only slightly absorbed and reach the small intestine, where they are hydrolysed to EA by the gut microbiota action [17]. Once produced, EA is practically not absorbed, due to its trivial water solubility, unfavourable physicochemical characteristics and low bioavailability (Table 7) and reaches the large intestine untouched. A justification for EA poor bioavailability and its low concentrations in plasma and tissues is based on the EA capacity to bind permanently to cellular DNA and proteins, or to form weakly soluble complexes with calcium and magnesium ions, which greatly reduce transcellular absorption[150]. Also, still active metabolites of EA, such as methyl and dimethyl ethers or glucuronic acid conjugates, sparkly detected in plasma and urine at 1 and 5 h after ingestion, corresponded to very low concentrations as well, not sufficient to produce significant beneficial effects[17]. In large intestine, EA is metabolized to the more hydrophilic urolithins (UROs), secondary polyphenol metabolites derived from the gut microbial action [151], and/or converted to its dimethyl, as well as dimethyl glucuronate and sulphate derivatives which are excreted.

Table 7. Chemical and physical properties of EA[152,153].

Physicochemical Identifiers	Descriptive Data
Chemical Name [1]	Ellagic Acid
CAS number	476-66-4
Molecular formula	$C_{14}H_6O_8$
Molecular weight	302.194 g/mol
Hydrogen bond donor count	4
Hydrogen bond acceptor count	8
Covalently bonded unit count	1
Form/colour	Cream coloured needles from pyridine Yellow powder
Melting point	>360 °C
Density	1.667 at 18 °C
Dissociation constants	pKa_1 = 6.69 (phenol) pKa_2 = 7.45 (phenol) pKa_3 = 9.61 (phenol) pKa_4 = 11.50 (phenol)
Solubility [2]	Slightly soluble in alcohol [154] Poorly soluble in water [155] Insoluble in ether Soluble in alkalis and pyridine[152]
Vapor pressure	2.81×10^{-15} mm Hg at 25 °C
Spectral properties	UV max (ethanol): 366, 255 nm

[1] traditional IUPAC name; [2] EA water solubility = 9.3–9.7 μg/mL at pH 7.4 and 21 °C [155].

A representative structure of an ET (casuarictin), that of EA, and those of URO A, B, C, D, iso-A and iso-B have been shown in Scheme 1, which shown the path of EA formation after the intake of ETs-rich foods and its subsequent metabolism to UROs and dimethyl ether derivatives[17]. A more recent article has introduced also URO-M5 and M6 among the URO-type metabolites of EA[151]. Precisely, in this new route EA is transformed in URO-M5 which is in turn converted in URO-D, while URO-M5 is converted in URO-M6 which then provides URO-C as URO-D [151].

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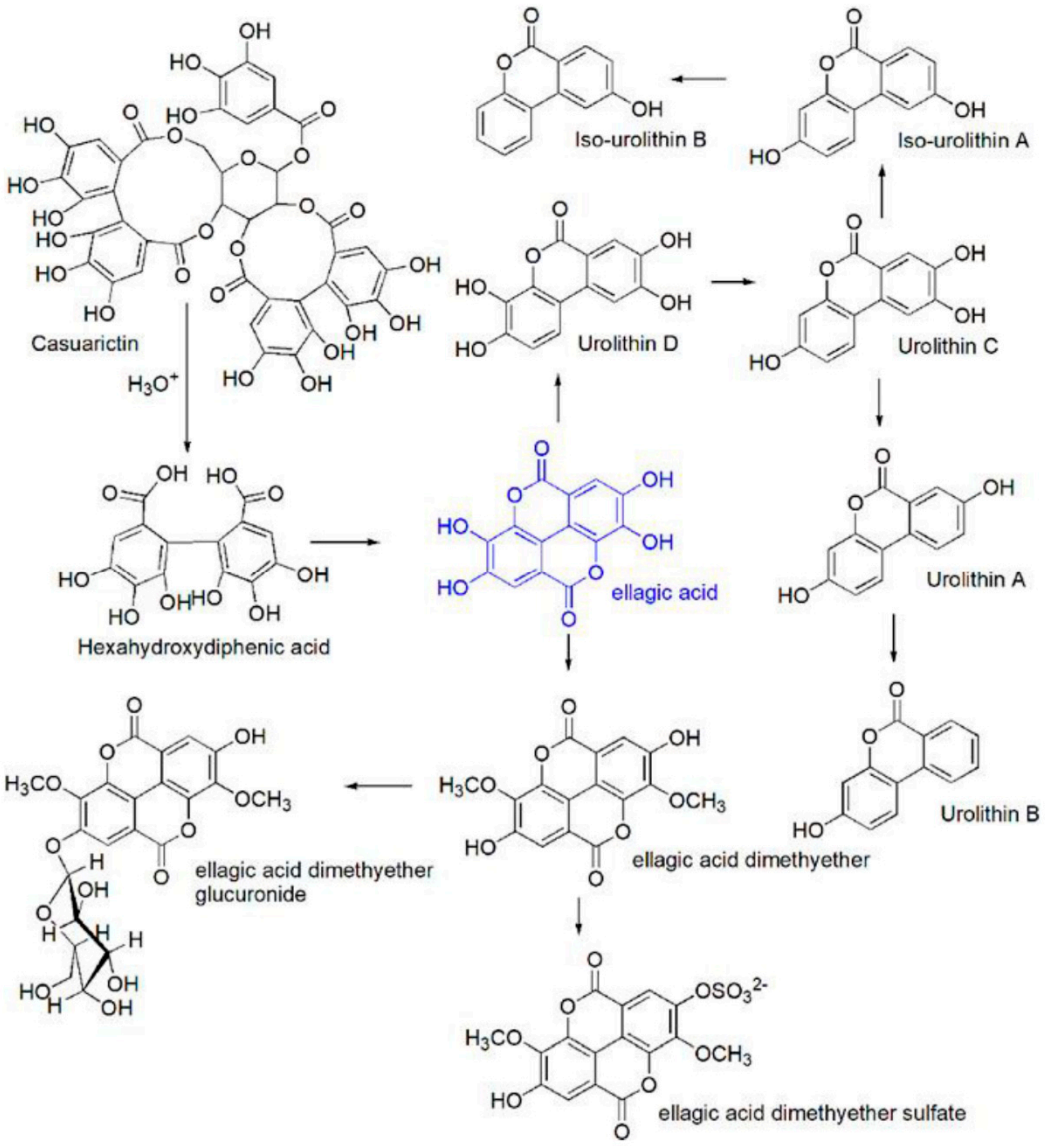

Scheme 1. Chemical structures of casuarictin, EA and the most known UROs.

In the year 2022, a study reported the existence and structure of up to 13 UROs [156]. Collectively, being ETs poorly adsorbed in GIT, they cannot reach blood and tissues where they could exert their beneficial effects but provide the bioactive EA upon hydrolysis. Nonetheless, instead to be absorbed and reaching blood and tissues where acting, due to its very low water-solubility [155], also EA undergoes a massive metabolism. Specifically, it is transformed in UROs, and in other metabolites excretable with urine and the amount of EA detected in blood and tissues observed after ETs-rich foods intake results insignificant to improve the conditions associated to chronic human diseases [146]. Due to this process, the findings obtained with ETs and EA in *vivo* studies against several human pathologies did not coincide with the promising ones observed in *vitro*, as generally happens for dietary polyphenols[14,157]. As observable in Scheme 1, UROs are dibenzopyran-6-one derivatives with different hydroxyl substitutions. UROs are more lipophilic than EA, and this has been suggested as a factor responsible for the greater urolithins absorption rate as compared to EA, thus being the only active phenolic molecules sufficiently absorbed and detectable in the circle and cells after ETs-rich foods intake[151]. URO-A and URO-B serve as the major metabolites of EA found in the gut, being URO-A as the most biologically active as compared to the rest of the EA metabolites[151]. In enterocytes and hepatocytes, UROs undergo biotransformation to UROs metabolites[146]. The main metabolites of urolithins found in plasma and urine are their glucuronyl

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and sulfate conjugates, including URO-A and URO-B glucuronide and sulfate, while the minor metabolites are URO-C and iso-URO-A glucuronide[146].

4.2. Ellagic Acid or Urolithins?

Both in *vitro* and in *vivo* studies have shown evidence that also UROs own anti-inflammatory, anti-carcinogenic, anti-glycative, antioxidant (lower than ETs and EA), antimicrobial properties, as well as preventive effects on gut and systemic inflammation. Furthermore, UROs seem also to play the role of hormone analogues [158]. Table 8 reports the most relevant studies concerning the in *vivo* effects of UROs assessed in animal models.

Table 8. Biological activities of UROs in different animal models.

Animal model	Assay conditions	Main outcomes	Ref.
	Anti-inflammatory activity		
F344 rat	Uro-A (15 mg kg^{-1} d^{-1} p.o.; HED: ~150 mg 70 kg^{-1} person) for 25 days prior to DSS-induced colon inflammation (UC colitis model)	Preservation of colonic architecture ↓iNOS, COX-2 and PTGES protein expression ↓Pro-inflammatory IL-1β and IL-4 gene expression	[20]
ICR mice	Uro-A (300 mg kg^{-1} d^{-1} p.o.; HED: ~1.5 g 70 kg^{-1} person) for 1 or 6 h prior to inducing inflammation (carrageenan-induced paw edema model)	↓Volume of paw edema ↑ORAC antioxidant activity in plasma	[159]
Wistar rats	Uro-A or Uro-B (2.5 mg kg^{-1} d^{-1} i.p.) for 3 weeks in a streptozotocin-induced type-1 diabetes model	↓Fractalkine, Prevention of cardiac dysfunction ↑Maximal rate of ventricular pressure rise and parallel ↓ in the isovolumic contraction time Recovery of cardiomyocyte contractility and Ca^{+2} dynamics and ↑velocity of shortening (only for Uro-B)	[160]
Sprague-Dawley rats	Uro-A (50 mg kg^{-1} d^{-1} p.o.) for 5 days in a cisplatin-induced nephrotoxicity model	↓Cisplatin-induced inflammatory cascade and inhibition of the proapoptotic pathway Prevention of renal dysfunction and histopathological damage	[161]
C57BL/6J or $Nrf2^{-/-}$ mice	Uro-A (20 mg kg^{-1} d^{-1} p.o.) at 0, 6, 12, 18, and 24 h before LPS-induced peritonitis in C57BL/6J mice Uro-A (20 mg kg^{-1} d^{-1} p.o.) (4 or 20 mg kg^{-1} d^{-1} p.o.) after 12 h of TNBS-induced colitis (C57BL/6 or $Nrf2^{-/-}$ mice) and every 12 h thereafter up to 72 h Uro-A (20 mg kg^{-1} d^{-1} p.o.) on the 4^{th} and 6^{th} day of DSS-induced colitis C57BL/6 model	↓LPS-induced increase in serum IL-6 and TNF-α levels.; Protection of TNBS-induced tissue damage (body weight loss, reduction of DAI score, intestinal permeability, colon shortening and weight to length ratio) and inflammation scores (reduction of neutrophil infiltration, MPO activity, and serum inflammatory markers such as IL-6, TNF-α, CXCL1, and IL-1β); Protection of DSS-induced acute colitis (↓DAI scores, colon shortening, gut permeability and increase of colon weight/length ratio); ↓inflammation (serum IL-6, IL-1β, TNF-α and colonic tissue MPO levels)	[162]
C57BL/6J mice	Uro-A (nanoparticle encapsulated) (50 mg kg^{-1} d^{-1} p.o.) for 19 days in cisplatin-induced acute kidney injury model	Attenuation of the histopathological hallmarks of cisplatin-induced acute kidney injury; ↓mortality by lower renal oxidative and apoptotic stress (Nrf2/antioxidant response element and P53 pathways)	[163]
C57BL/6 mice	Uro-A (20 mg kg^{-1} d^{-1} i.g.) for 8 weeks in surgically osteoarthritis model	Protective effect in osteoarthritis development by ↓OARSI score, ↓PI3K/AKT pathway activation and the nuclear p65 expression in chondrocytes	[164]

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Animal model	Assay conditions	Main outcomes	Ref.
C57BL/6 mice	Uro-A (50 mg kg^{-1} d^{-1} p.o.) for 3 days and 30 min before surgery in a model of ischemia reperfusion injury	↓TNFα, IL1β, MIP1α and MIP2 mRNA expression; ↑autophagy; attenuation of associated kidney injury; protection against ischemia reperfusion injury	[165]
C57BL/6 mice	Uro-A (100 mg kg^{-1} d^{-1} i.p.) for 5 days in a cisplatin-induced ischemic neuronal injury model	↓Histological damage in proximal tubular cells; ↓cisplatin-induced pro-inflammatory cytokines/chemokines (TNF-α, IL-23, IL-18 and MIP2) and attenuation of renal oxidative/nitrative stress	[166]
IL-$10^{-/-}$ C57BL/6j mice	Uro-A (0.114 mg kg^{-1} d^{-1} p.o.) for 2 days in *Campylobacter jejuni* infected, microbiota-depleted IL-$10^{-/-}$ mice as preclinical inflammation model	Improve clinical outcome and less pronounced macroscopic (less colonic shrinkage) and microscopic (less colonic histopathology and apoptosis) inflammatory sequelae of infection; ↓intestinal pro-inflammatory immune responses (IFN-γ, TNF-α, MCP-1 and NO) and systemic markers (IFN-γ, MCP-1 and IL-6); ↓abundance of macrophages, monocytes and T lymphocytes in the mucosa and lamina propria	[167]
$FUNDC1^{f/f}$ mice and cardiomyocyte-specific FUNDC1 knockout ($FUNDC1^{CKO}$) mice	Uro-A (30.0 mg kg^{-1} i.p.) prior to LPS treatment (48 h) to induce septic cardiomyopathy	Attenuate inflammation-mediated myocardial injury levels and normalization of cardiac function, including LVEF, LVDd, and FS in $FUNDC1^{f/f}$ mice, but not in $FUNDC1^{CKO}$ mice	N.R.
	Neuroprotective effect and(or) improvement of cognitive function		
Transgenic (express human amyloid β_{1-42} in the muscle tissue after a heat shock) *Caenorhabditis elegans* (CL4176)	Exposure to Uro-A (43.8 µM), Uro-B (47.2 µM), methyl-Uro-A (41.3 µM), methyl-Uro-B (44.2 µM)	Only methyl-Uro-B has a protective effect against $A\beta_{1-42}$ induced neurotoxicity and worm paralysis	[168]
Alzheimer's disease APP/PS1 transgenic mice model	Uro-A (300 mg kg^{-1} d^{-1} p.o.) for 14 days	↑of learning, ↑of memory deficits Prevention of neuronal apoptosis ↑Neurogenesis; ↓plaque Aβ deposition ↓Peri-plaque microgliosis and astro cytosis in the cortex and HPC Anti-(neuro)-inflammatory activity ↓Pro-inflammatory cytokine levels ↓Activation of NF-κB p65 subunit ↓p38 (MAPK)	[169]
ICR mice	Uro-A (150, 100 or 50 mg kg^{-1} d^{-1} p.o.) for 8 weeks in a D-gal-induced brain aging model	↓D-gal-induced cognitive impairment ↓Brain aging by suppression of miR-34a induced upregulation ↓Apoptosis induction, ↑autophagy by upregulating the SIRT1 signalling pathway and downregulating the mTOR signalling pathway	[170]
C57BL/6 mice	Uro-A (2.5 or 5.0 mg kg^{-1} d^{-1} i.p.) for 24 h and 1 h before surgery in an ischemic neuronal injury model	↓Infarction volume; reinforcement of ischemia-induced autophagy by ↑LC3-II and ↓p62 level; ↓ER stress by autophagy activation	[171,172]
ICR mice	Uro-A (1.5 or 2.0 mg kg^{-1} d^{-1} i.p.) at 1 and 24 h prior to surgery, and 1 h after surgery in an ischemic neuronal injury model (transient middle cerebral artery occlusion)	Ameliorate infarction, neurological deficit scores, and spatial memory deficits after cerebral ischemia; ↓neuron loss and ↑neurogenesis after ischemic stroke; Attenuate apoptosis by regulating apoptotic-related proteins; ↓glial activation via affecting inflammatory signaling pathways (↑AMPK and IκBα activation, and ↓Akt, NFκB p65, ERK, JNK, and p38)	[172]***

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Animal model	Assay conditions	Main outcomes	Ref.
ICR mice	Uro-A (2.5 mg kg^{-1} d^{-1} i.p.) for 8 weeks in an STZ-induced diabetic mouse model	Alleviate APP and BACE1 expressions, Tau phosphorylation, Aβ deposition, and cognitive impairment; ameliorate the high glucose-induced TGM2 expression	[173]
Cardioprotective activity			
C57BL/6J mice	Uro-A (1 mg kg^{-1} d^{-1} i.p.) at 24 and 1 h before ischemia induction in a myocardial ischemia reperfusion injury model	Improvement of cardiac function by ↓myocardial infarct size, prevention of cardiomyocyte apoptosis and ↑serum CK and LDH activities after ischemia	[174,175]
Wistar rat	Uro-A (3 mg kg^{-1} d^{-1} p.o.) combined with a high cholesterol diet supplemented with Vit. D3 for 3 days prior to the balloon injury of the aorta and 12 weeks of treatment	Improvement of aortic atherosclerotic lesions; ↓plasma lipid (total cholesterol, TGs, and LDL) and angiotensin II levels in aortic tissue	[175]
$ApoE^{-/-}$ mice	Uro-B (10 mg kg^{-1} d^{-1} p.o.; equal to 1.11 mg kg^{-1} to human) for 14 days	↓Lipid plaque deposition and oxidized-LDL uptake	[176]
C57BL/6 mice	Uro-A (20 μg d^{-1} i.p.) accompanied with a high-fat diet for 12 weeks	Anti-obesity activity by ↑systemic insulin sensitivity, ↓total and LDL cholesterol levels. In liver: ↓TGs accumulation, inflammation and elevation of mitochondrial biogenesis. In adipose tissue: ↓adipocyte hypertrophy and macrophage infiltration	[177]
Sprague Dawley rats	Uro-B (0.7 mg kg^{-1} d^{-1} i.p.) at 24 and 48 h before ischemia induction in a myocardial ischemia reperfusion injury model	↓Myocardial infarct size; ↓cardiac dysfunction after ischemia reperfusion; protection against myocardial ischemia/reperfusion injury via p62/Keap1/Nrf2 signalling pathway	[178]***
Wistar rats	Uro-A or Uro-B (2.5 mg kg^{-1} d^{-1} i.p.) four times a week for 4 weeks, in rats fed on a high-fat diet	Anti-obesity effect by ↓body weight and visceral adipose tissue mass; restore hepatic antioxidant capacity, serum lipid profile; ↓lipid accumulation; ↑faecal fat excretion. ↓LXRα and SREBP1c (lipogenesis) level; ↓PERK and IRE1α (hepatic endoplasmic reticulum stress) level; ↑PPARα expression (fatty acid oxidation)	[179,180]
C57BL/6 mice and *ob*/*ob* mice	Uro-A (30 mg kg^{-1} d^{-1} i.g.) for 10 weeks, in mice fed on a high-fat diet	↓HFD-induced and genetic obesity; ↑in energy expenditure via ↑thermogenesis in brown adipose tissue and ↑browning of white adipose tissue	[181,182]
DBA2J mice	Uro-A or Uro-A and ellagic acid (0.1 % p.o.) for 8 weeks, in mice fed on a high fat/high sucrose diet (starting 8 weeks before to induce insulin resistance)	↓Diet-induced insulin resistance via ↓fasting glucose, serum free fatty acids and TGs levels and ↑adiponectin fasting. Differential expression of genes related to mitochondrial function in liver and skeletal muscle	[182]
C57BL/6 mice	Uro-A (50 mg kg^{-1} d^{-1} i.p.) alone or in combination with chloroquine for 8 weeks in an induced by high fat and STZ-induced type 2 diabetic model	Improvement of diabetic symptoms:↓high water intake and urine volumes, ↓fasting blood glucose, glycated hemoglobin levels, plasma C-peptide, MDA and IL-1β level; ↑reduced glutathione, IL-10 content, glucose tolerance, and pancreatic function indexes such as HOMA-β; ↓mitochondrial swelling and myelin-like cytoplasmic inclusions; ↑upregulate the LC3-II and beclin1; ↓sequestosome 1 (p62) accompanied by ↓apoptotic protein cleaved caspase3 in pancreas via	[183]

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Animal model	Assay conditions	Main outcomes	Ref.
		regulating autophagy and AKT/mTOR signalling pathway	
	Other biological activities		
F344 rat	Uro-A (15 mg kg^{-1} d^{-1} p.o.; HED: ~150 mg/70 kg person) for 25 days before inducing DSS-induced colon inflammation (UC model)	Gut microbiota modulation: ↑bifidobacteria and lactobacilli	[20]
C57BL/6J mice and *Caenorhabditis elegans*	1) Uro-A (25 or 50 mg kg^{-1} d^{-1} p.o.) for 6 weeks and 8 months, respectively, in age-related muscle decline mice model 2) Exposure to Uro-A, Uro-B, Uro-C or Uro-D (50 μM) in *C. elegans* for 50 days	1) Improvement of exercise capacity via ↑muscle function manifested by greater grip strength and level of spontaneous exercise. 2) Uro-A, Uro-B, Uro-C or Uro-D extended lifespan by 45.4, 36.6, 36.0 and 19.0%, respectively	[184]
Sprague–Dawley rats	Uro-A (25 mg kg^{-1} d^{-1} p.o.) for one day after surgery, and for 4 weeks of treatment in intervertebral disc degeneration (needle-punctured tail) model	Amelioration of intervertebral disc degeneration mediated by ↓loss and destruction of disc height, and osteophyte formation	[185]
BALB/c athymic mice (nu/nu)	Uro-A (50 mg kg^{-1}, 5 days per week p.o.) for 4–5 weeks in xenograft with PC-3 and C4-2B cells model	Anticancer activity: ↓tumour growth and Ki-67 expression in both PC-3 and C4-2B xenografts; ↓AR/pAKT signalling in C4-2B tumours	[186]
Nude mice	Uro-B (40 mg kg^{-1} i.p. and s.c.) every 2 days for 30 days in a subcutaneous xenograft with HEG2 cells model	Anticancer activity: ↓average tumor volume, weight, and Ki-67 levels	[187]
C57BL/6 mice (wild type, $Nrf2^{-/-}$ and $AhR^{-/-}$)	Uro-A (20 mg kg^{-1} d^{-1} p. o.) for 7 days	Improvement of gut barrier function: activation of AhR-Nrf2-dependent pathways to upregulate epithelial tight junction proteins (Cldn4, NQO1, Ocln, ZO1, and TJP3). Cyp1A1 activity induction in colon and liver of wild type but not in $AhR^{-/-}$ mice	[162]
C57BL/6 mice	Uro-A (10 mg kg^{-1} d^{-1} i. g.) for 12–16 weeks	Angiogenic effect: ↑angiogenic pathways and markers such as VEGFA and CDH5, which were blunted in skeletal muscles; ↑skeletal muscle vascularization via silent information regulator 1 and PGC-1α pathway; ↑ATP and NAD+ levels in skeletal muscle	[188]
ICR mice	Uro-A (80 or 240 mg kg^{-1} d^{-1} p. o.) for 1 or 3 days in a purine bodies-induced hyperuricemia model	Anti hyperuricemia effect: Inhibit the increase in plasma uric acid levels and hepatic xanthine oxidase activity; ↓expression of genes associated with hepatic purine metabolism	[189,190]
C57BL/6 mice	Uro-A (10, 25, or 50 mg kg^{-1} d^{-1} p.o.) at 0, 11 and 17 days after immunization in an EAE model	Effect against autoimmune diseases: Suppression of disease progression at prevention, induction, and effector phases of preclinical EAE at the highest dose; ↓number of inflammatory cells and demyelination; lower numbers of M1-type microglia and activate dendritic cells; ↓infiltrating Th1/Th17 cells in the CNS	[190]
mdx and mdx/Utr $^{-/-}$ (DKO) mice, and *Caenorhabditis elegans* dys-1; hlh-1 strain	Uro-A (mg kg^{-1} d^{-1} p.o.) for 10 weeks in DMD mice models Exposure to Uro-A (25 μM) for 4 days in C. elegans dys-1; hlh-1 model (lacking the human DMD gene)	Improvement of muscle function by ↑mitophagy in muscular dystrophy: ↑skeletal muscle respiratory capacity, and improved MuSCs' regenerative ability, resulting in the recovery of muscle	[191]

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Animal model	Assay conditions	Main outcomes	Ref.
		function and ↑survival in DMD mouse models ↑Expression of *pink-1* and *pdr-1* mitophagy genes, with no impact on the expression of autophagy genes. Improvement in the mitochondrial network, mitochondrial respiration, citrate synthase activity, and the mitochondrial DNA over nuclear DNA (mtDNA/nDNA) ratio. Positive impact on muscle function and motility of the dystrophic worms	
Wistar rats	Uro-A or Uro-B (2.5 mg kg^{-1} d^{-1} i.p.) four times a week for 4 weeks, in rats fed on a high-fat diet	Gut microbiota modulation: modulate gut microbes related to body weight, dysfunctional lipid metabolism and inflammation	[180]

N.R. = not reported; ↑ = improvement, improved, higher; ↓ = lowered, decreased, lower; αKGDH, alpha-ketoglutarate dehydrogenase; AhR, aryl hydrocarbon receptor; AMP, adenosine monophosphate; AMPK, AMP activated protein kinase; APP, amyloid precursor protein; AR, androgen receptor; ATP, adenosine triphosphate; BACE1, β-secretase-1; CDH5, cadherin 5; CK, creatine kinase; Cldn4, claudin 4; CNS, central nervous system; COX, cyclooxygenase; CXCL1, chemokine ligand 1; CYP, cytochrome P450; DAI, disease activity index; DHT, 5α-dihydrotestosterone; DMBA, dimethylbenz[a]anthracene; DMD; Duchenne muscular dystrophy; DSS, dextran sulphate sodium; EAE, experimental autoimmune encephalomyelitis; ER, endoplasmic reticulum; ERα, estrogen receptor alpha; ERK, extracellular signal-regulated kinase; FRAP, ferric-reducing antioxidant power; FS, fractional shortening; GDX, gonadectomized; GnRH, gonadotropin releasing hormone; GR, glutathione reductase; GSH, reduced glutathione; GSSG, oxidized glutathione; HED, human equivalent dose; HOMA, homeostasis model assessment; ICR, Institute of Cancer Research; IFN, intereferon; IκBα, nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor alpha; IL, interleukin; iNOS, nitric oxide synthase; IRE1α, inositol-requiring transmembrane kinase/endoribonuclease 1α; JNK, c-Jun N-terminal kinase; Keap1, Kelch like ECH associated protein 1; LC3-II, protein levels of microtubule-associated protein 1 light chain 3-II; LDL, low-density lipoprotein; LDH, lactate dehydrogenase; LH, luteinizing hormone; LPS, lipopolysaccharide; LVDd, left ventricular diastolic; LVEF, left ventricular ejection fraction; LXRα Liver X receptor α; MAPK, mitogen-activated protein kinase; MCP-1, monocyte chemoattractant protein 1; MDA, malondialdehyde; MIP, macrophage inflammatory protein; miR, microRNA; MPO, myeloperoxidase; mTOR, mammalian target of rapamycin; NAD, nicotinamide adenine dinucleotide; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NO, nitric oxide; NQO1, NAD(P)H dehydrogenase [quinone] 1; Nrf2, nuclear factor erythroid 2-related factor 2; OARSI, Osteoarthritis Research Society International; Ocln, occludin; ODMA, O-desmethylangolensin; ORAC, oxygen radical absorbance capacity; OVX, ovariectomy; PDH, pyruvate dehydrogenase; PERK, protein kinase R-like endoplasmic reticulum kinase; PGC-1α, peroxisome proliferator-activated receptor-gamma coactivator-1-alpha; PI3K, phosphoinositide 3-kinase; PPARα, peroxisome proliferator-activated receptor α; PRL, prolactin; PTGES, prostaglandin E synthase; SIRT, sirtuin 1; SOD, superoxide dismutase; SREBP1, sterol regulatory element binding protein 1; STZ, streptozotocin; TBARS, Thio barbituric acid reactive substances; TC, total cholesterol; TERP, truncated estrogen receptor product; TG, triglycerides; TGM2, transglutaminase type 2; TJP3, tight junction protein 3; TNBS, 2,4,6-Trinitrobenzenesulfonic acid; TNF-α, tumour necrosis factor alpha; TP, testosterone propionate; UC, ulcerative colitis; Uro, urolithin; VEGFA, vascular endothelial growth factor A; ZO1, zonula occludens-1.

Due to the confirmations both *in vitro* and *in vivo* about the pharmacological properties of UROs, currently there is an extensive tendency to think that UROs, rather than EA, could be the actual bioactive molecules accountable for benefits coming from the consumption of ETs and EA rich foods[14,67]. This proposition is supported by the awareness that, although *in vitro* findings have shown that EA and UROs are almost equally active, studies *in vivo* provided trustworthy verification about this fact, only regarding UROs. Only UROs have been found in fluids, cells, and tissues and were measured, finding concentrations capable to exert the ameliorative effects already evidenced *in vitro*. On the other hand, the interest in knowing more about the possible EA activity *in vivo* has led scientists to increasingly and incessantly focus on preparing water soluble and absorbable EA

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formulations, able to defend EA and to lower or annul EA metabolism to UROs, so that it could reach cells and tissue in its pristine form [152]. The formulation of drug delivery systems, capable of transporting and releasing EA to the target site, represents a valid approach for bypassing the bad biopharmaceutical features of this polyphenol, thus allowing a better evaluation of its potential application as radical scavenger antioxidant therapeutic. In this context, from the year 2019, we studied some micro- and nanosized solutions which revealed interesting performance[192–194].

4.4. Drawbacks Associated to UROs Hamper Their Clinical Development Thus Quenching the Researcher Interest

Even if gifted with healthy properties like those of EA, UROs are not suitable for safer therapeutic purposes, due to their double faceted behaviour. They can be beneficial but, depending on their structure, environmental conditions, the type of target cells under study, age, and health state of the individuals, they could result also harmful[17]. The amount and typology of UROs produced in the gut of individuals depends also on the type of vegetables which has been introduced, the individual microbiota metabolic activity, that is typified by a highly inter-individual heterogeneity, depending on several factors and humans metabotype (0, A, B)[17]. Moreover, this highly interindividual and intra-individual process is not completely elucidated yet [34,35]. Let's imagine that even living species which do not produce UROs exist. Table 9 reports the UROs mainly found in different mammalian species after the consumption of different vegetables.

Table 9. Production of UROs in different mammalian species.

Mammalian	Source	URO Type	Refs
Rat (*Rattus norvegicus*)	Pomegranate husk	A, B, C	[195]
	Ellagic acid	A	
	Oak-flavored milk	A, B, C	
	Pomegranate extract	A, M-6, M-7	
	Geraniin (*Geranium thunbergii*)	M-5	
Mouse (*Mus musculos*)	Pomegranate extract	A	
	Pomegranate husk	A	
Baver (*Castor canadensis*)	Wood	A, B	
Complex toothed squirrel (*Trogopterus xanthipes*)	Unknown	A	
Sheep (*Ovis Aries*)	*Trifoleum Subterraneum*	A, B	
Sheep (*Ovis Aries*)	Quebracho	A	
Cattle (*Bos primigenius*)	Young oak leaves	A, Iso A, B	
Pig (*Sus scrofa domesticus*)	Acorns	A, C, D, B	
Humans (*Homo Sapiens*)	Pomegranate juice	A, C, Iso A, B	
	Pomegranate extract	A, B, C	

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Mammalian	Source	URO Type	Refs
	Walnuts	A, B, C	
	Strawberry	A, C, Iso A, B	
	Raspberry	A, C, Iso A, B	
Humans (*Homo Sapiens*)	Blackberry	A, C	[196]
Humans (*Homo Sapiens*)	Cloudberry	A	[197]
	Oak-aged red wine		
Humans (*Homo Sapiens*)	Tea	A	[195]
	Nuts	A, Iso A, B	

UROs absorption, blood and tissue concentrations, and inter-subject variability in the comebacks to UROs exposure, are arbitrary variables, which drive to various responses that, ironically, could promote adverse effects. In addition, human microbiota activity is difficult to be reproduced in animal models and cannot be easily studied and/or controlled [17].

5. EA as Template Antioxidant Molecule for the Development of New Therapeutics for AD

EA attracts the interest of researchers as promising molecule to provide benefits in neurodegenerative disorders including AD, mainly due to its anti-inflammatory and the antioxidant properties. Defining which pharmacophore/pharmacophores in EA is the actual responsible/s for its health benefits, but also for its possible collateral effects is crucial for in silico screening investigations and to design new multi-target EA-type CNS drugs. The mechanisms at the basis of the EA multifaceted bioactivity are based mainly on its antioxidant, radical scavenger and anti-ageing effects, capable to contrast OS. Collectively, EA is to counteract the detrimental RONS, which are a byproduct of physiologic aerobic metabolism. For a more precise distinction, OS refers to a torrent of destructive proceedings that frequently triggers and accompanies the molecular/cellular pathogenic events, responsible for several human disorders, including AD [144,198]. Differently, inflammation, being both the cause and the effect of RONS accumulation, is considered a pathological characteristic of the most part of human diseases including those developing in the CNS including AD.

5.1. EA Antioxidant Effects: Proposed Mechanisms of Action

Natural antioxidants are fundamentally present in vegetable food, and polyphenols, such as EA, are supposed to be more than 8000 molecules, all characterized by possessing at least a phenol moiety. EA hydroxyl groups and the lactone systems give the molecules the capacity of forming hydrogen bonds, while can also act as electron acceptors and/or hydrogen donors. Consequently, EA is endowed with the capacity to take electrons from different substrates thus promoting antioxidant redox reactions and functioning as a very efficient free radicals (FRs) scavenger[199]. The EA anion is proposed as the key species for its protective effects against OS[199]. It is predicted to be efficiently and continuously regenerated after scavenging two free radicals per cycle[199]. Chemical species able to prevent oxidation can be classified in primary antioxidants (Type I, or chain breaking) and secondary antioxidants (Type II, or preventive). EA can behaviour as both Type I and Type II antioxidant, thus exerting a multiple-function antioxidant activity (Table 10)[200].

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Table 10. Classification of antioxidants.

Antioxidant Type	Action Type	Modalities	Ref.
Type I	Free-radical scavengers Break the chain leading to FRs formation	HAT PCET SET SET-PT SPLET RAF SPLHAT	[200]
Type II	Preventive molecules Retard the oxidation process	Metal chelation Hydroperoxides decomposition to non-radical species Repairing of primary antioxidants with hydrogen or electron donation Deactivating of singlet oxygen Impounding of triplet oxygen Absorbing UV radiation	[200]

HAT = hydrogen atom transfer; PCET = proton coupled electron transfer; SET = single electron transfer; SET-PT = single electron transfer followed by proton transfer; SPLET = sequential proton loss electron transfer; RAF = radical adduct formation; SPLHAT = sequential proton loss hydrogen atom transfer.

5.1.2. Type I Scavenging Reactions

Type I scavenging reactions, which can occur between EA and FRs, follow second order kinetics and scavenging capacity, as well as its velocity, depend both on the concentration of EA and FRs. Factors which could modify their chemical structures, such as the pH, polarity, the reaction conditions, and mainly the medium could also affect EA scavenging capacity. In general, the antioxidant capacity of EA reduces strongly in solvents able to form hydrogen bonds with EA and improve in solvents favouring EA ionization to anion phenoxide[201]. The alcohols may act as acceptors of hydrogen bonds, thus decreasing EA antiradical effects by hydrogen atom transfer (HAT) reactions. On the other hand, they can favour the ionization of the EA to anion phenoxides, which can react rapidly with the peroxyl radicals, through an electron transfer, thus improving EA radical scavenging activity by SET reactions[201]. In general, the antiradical properties of different natural and synthetic Type I antioxidants possessing OH groups, derives mainly from their capacity to transfer hydrogen atoms to FRs. This process can occur by mechanisms reported in Table 11. These mechanisms generate non-radical species or new radicals, more stable and less reactive than the previous ones, thus restricting the development of OS. Table 11 reports also the chemical equations associated to these proposed mechanisms.

Table 11. Possible action mechanisms of the Type I antioxidants and related equations.

Action Mechanism	Chemical Equation	Features	Natural Compounds [200]
HAT	$H_nAntiox + {}^{\bullet}R \rightarrow H_{n-1}Antiox^{\bullet} + HR$	A key reaction mechanism	Polyphenols EA
PCET	$H_nAntiox + {}^{\bullet}R \rightarrow H_{n-1}Antiox^{\bullet} + H^{+} + {}^{\bullet} \rightarrow HR$	Exactly the same products as HAT	Flavonoids Quinone-hydroquinone
RAF	$H_nAntiox + {}^{\bullet}R \rightarrow [H_nAntiox\text{-}R]^{\bullet}$	Presence of multiple bonds peculiar of	Carotenoids Gentisic acid

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		electrophilic radicals	Rebamipide Hydroxybenzyl alcohols
SET	$H_nAntiox + {}^{\bullet}R \rightarrow H_nAntiox^{+\bullet} + R^-$	Primary pathway	EA Curcumin Carotenoids Catechins Edaravone Resveratrol
	$H_nAntiox + {}^{\bullet}R \rightarrow H_nAntiox^{+-\bullet} + R^+$	Secondary pathway	Xanthones Carotenoids Trolox Caffeic acid Genistein
SPLET	$H_nAntiox \rightarrow H_{n-1}Antiox^- + H^+$ $H_{n-1}Antiox^- + {}^{\bullet}R \rightarrow H_{n-1}Antiox^{\bullet} + R^-$	Crucial mechanism in the scavenging activity in polar environments	Trolox Curcumin Vitamin E Quercetin Epicatechin Piceatannol Resveratrol Kaempferol Esculetin Fraxetin Morin Hydroxybenzoic Dihydroxybenzoic Flavonoids Isoflavonoids Xanthones Procyanidins Edaravone GA Erodiol
SEPT	(1) $H_nAntiox + {}^{\bullet}R \rightarrow H_{n-1}Antiox^{\bullet+} + R^-$ (2) $H_{n-1}Antiox^{\bullet+} \rightarrow H_{n-1}Antiox^{\bullet} + H^+$	A two-step mechanism involving electron transfer and deprotonation as in SPLET but in a different order	Vitamin E Galvinoxyl α-tocopherol Baicalein Astaxanthin Quercetin
SPLHAT	(1) $H_nAntiox \rightarrow H_{n-1}Antiox^- + H^+$ (2) $H_{n-1}Antiox^- + {}^{\bullet}R \rightarrow H_{n-2}Antiox^{\bullet-} + HR$	Deprotonation of the antioxidant and an H transfer reaction	EA Anthocyanidins GA Esculetin α-Mangostin Propyl gallate

EA can exercise antioxidant effects mainly through three of the above-mentioned reaction mechanisms, such as SET, HAT and SPLHAT reactions. Although the result is always the inactivation of FRs to neutral, cationic, or anionic species, the kinetics and secondary reactions involved in the processes are different (Figure 11).

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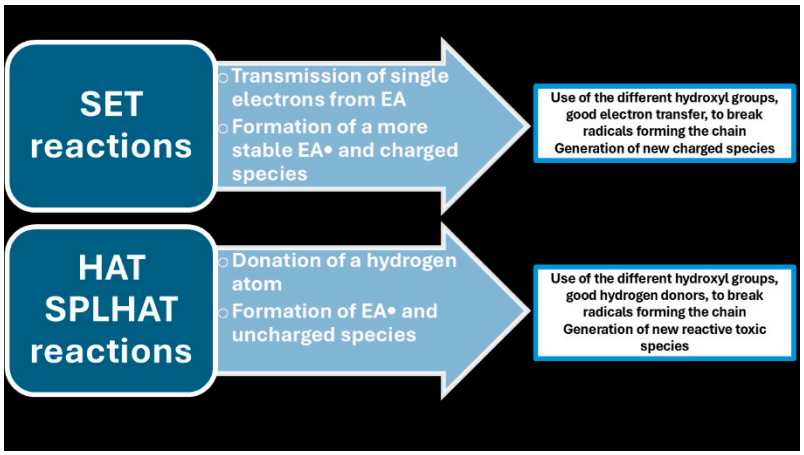

Figure 11. Antioxidant mechanism of EA.

When EA reacts, for example, with the radical specie ROO•, a hydrogen cation coming from its hydroxyls into other radical species, is transferred forming a transition state of an H-O bond with one electron. On the other hand, the hydroxyl groups can interact with the π-electrons of the benzene ring providing molecules endowed with the ability to generate free long-living radicals stabilized by delocalization, able to interfere and modify radical-mediated oxidation processes, by SET reactions.

5.1.3. Type II Scavenging Reactions

EA is also a Type II antioxidant, thus providing its protective effects against FRs by inhibiting the endogenous production of oxidants and radical hydroxyl (•OH) molecule, which is the most reactive and electrophilic specie of the oxygen-based radicals [30]. • OH is the main responsible of tissues and DNA damage and therefore, its inhibition is of prime significance for reducing OS generated from the metal-catalysed Fenton reaction and the Haber Weiss recombination (HWR), according to Equations (1)–(4), involving the reduced forms of Fe and Cu.

$$Fe\ (II) + H_2O_2 \rightarrow Fe\ (III) + OH^- + {}^\bullet OH \quad (1)$$

$$Cu\ (I) + H_2O_2 \rightarrow Cu\ (II) + H^- + {}^\bullet OH \quad (2)$$

$$Fe\ (III) + O_2\ {}^{\bullet -} \rightarrow Fe\ (II) + O_2 \quad (3)$$

$$Cu\ (II) + O_2\ {}^{\bullet -} \rightarrow Cu\ (I) + O_2\ (Fenton) \quad (4)$$

In this context, EA is an excellent antioxidant due to its capability to chelating and subtracting metal as Fe^{2+}, Fe^{3+}, and copper ions involved in the production of FRs, thus preventing the oxidation of low-density lipoproteins (LDL)[199,200,202]. EA can also interact with enzymes involved in radical generation, such as various cytochrome P450 isoforms, lipoxygenases, cyclooxygenase, and xanthine oxidase, thus inhibiting RONS over production. This capability derives from the presence of the hydrophobic benzenoid rings and from the skill of the phenolic hydroxyl groups to form hydrogen-bonding interactions [203]. Moreover, EA can act synergistically with other endogenous and exogenous antioxidants, such as ascorbic acid, β-carotene, and β-tocopherol, thus increasing their effectiveness and regulating intracellular glutathione levels[203]. Unfortunately, some of hydroxyl groups of EA, in conditions of high dosage, high concentrations of transition metal ions, alkali pH, and/or the presence of oxygen molecules, can act unexpectedly also as pro-oxidants moieties[204]. These groups may sometimes induce significant DNA damage in the presence of Cu (II) or may create ROS through the reduction of Cu (II)→Cu. The pro-oxidant activity is peculiar of small polyphenols, as EA, while is limited in large molecular-weight phenols, such as ETs. On the other hand, this apparent issue can trigger apoptosis in cancer cells[205,206].

6. EA-Rich Foods, EA Food Supplements, and EA Involvement in the Treatment of AD

As above-mentioned, the polyphenolic lactone by formula $C_{14}H_6O_8$, known as EA, as well as the intake of EA food supplements, foods rich in ETs and/or EA can translate in altering profuse signaling

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inside cells thus preventing and/or pauperizing the progression of diverse neurodegenerative abnormalities, including AD [207]. Its neuroprotective effectiveness is attributable mainly to its ROS scavenging, iron chelating properties, positive regulation of energetics of mitochondrial respiratory complex, and abundant modulation of neuronal molecular signaling pathways[208].

6.1. Most Relevant In Vitro and In Vivo Studies Using ETs and EA-Rich Plants

Table 12 summarizes the beneficial properties demonstrated *in vitro* and/or *in vivo* studies using different experimental models, or even in clinical settings, observed upon the assumption of ETs and EA-rich plants.

Table 12. List of plants reported for the presence of ETs and EA and the medicinal properties observed upon their assumption.

Family	Plant	Plant part	Model	Medicinal properties	Refs.
Apocynaceae	*Decalepis hamiltonii*	Roots	*In vivo*	Anticancer	[209]
	Macrosiphonia longiflora	Xylopodium	Clinical	Anti-inflammatory	[210]
Juglandaceae	*Carya illinoinensis*	Kernels and shells	*In vivo*	Toxicological effect Antioxidant	[211]
	Juglans regia	Kernels	N.D.	N.D.	[212]
Malvaceae	*Thespesia lampas*	Roots	*In vitro* *In vivo*	Antioxidant Hepatoprotective	[213]
	Sterculia striata	Nut		Antioxidant	[214]
Sapindaceae	*Dimocarpus longan*	Seeds	*In vitro*	Antioxidant Antimicrobial	[215]
	Nephelium lappaceum	Husk		Antioxidant	[216]
Rosaceae	*Geum rivale*	Aerial	N.D.	N.D.	[217]
	Rubus parvifolius	Whole plant	*In vivo*	Hepatoprotective Antioxidant	[218]
	Sanguisorba officinalis		*In vitro*	Antiadipogenic	[219]
Phyllanthaceae	*Emblica officinalis*	Fruits	*In vitro* *In vivo* Clinical	Antioxidant Antihepatotoxic Anti-inflammatory Antidiabetic	[220]
Myrtaceae	*Phyllanthus acuminatus*	Leaves	*In vitro*	Antioxidant Cytotoxic	[221]
	Myrciaria dubia	Fruit	*In vitro*	Antioxidant	[222]
	Psidium friedrichsthalianum			Antioxidant Metabolomic	[223]
	Syzygium calophyllifolium			Antioxidant Antibacterial	[224]
	Syzygium cumini			Antidiabetic Antioxidant	[225]
	Myrciaria floribunda			Antioxidant	[226]

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	Eugenia uniflora	Leaves	*In vitro* *In vivo*	Anti-inflammatory Antioxidant Antibacterial	[227]
	Myrtus communis		N.D.	N.D.	[228]
	Campomanesia adamantium	Leaves and root	*In vitro*	Apoptotic death of leukemic cells	[229]
	Eucalyptus globulus	Bark, stem, leaves Fruit	*In vitro*	Antioxidant Bioherbicide	[230]
	Acca sellowiana	Fruits, pulp, peel		Antimicrobial	[231]
Euphorbiaceae	*Chrozophora senegalensis*	Leaves and stem	*In vitro* *In vivo*	Cytotoxicity Antimalarial	[232]
	Acalypha hispida			Anti-inflammatory Antioxidant	[233]
	Gymnanthes lucida	Leaves	*In vitro*	Antimicrobial Cytotoxic	[234]
	Euphorbia pekinensis	Root	*In vitro* *In vivo*	Antidiabetic	[235]
	Euphorbia supina	Herb	*In vitro*	Antioxidant	[236]
Lythraceae	*Sebastiania chamaelea*	Whole plant	*In vitro* *In vivo*	Cytotoxicity Antimalarial	[232]
	Trapa taiwanensis	Fruit		Antioxidant Hepatoprotective	[237]
	Woodfordia fruticose	Flower	*In vivo*	Antiulcer	[238]
	Lafoensia pacari	Leaves	*In vitro* *In vivo*	Cytotoxicity Wound healing	[239]
	Lagerstroemia speciosa	Leaves and stem		Antiviral	[240]
Combretaceae	*Terminalia chebula*	Fruit		Antioxidant Antibacterial Neuroprotective	[241]
	Terminalia bellirica	Fruit		Antioxidant Hepatoprotective Antidiabetic	[242]
Cistaceae	*Cistus laurifolius*	Leaves	*In vitro*	Antioxidant Prostaglandin inh. Antimicrobial	[243]
Lecythidaceae	*Barringtonia racemosa*	Leaves and stems		Antioxidant	[244]
Bixaceae	*Cochlospermum angolensis*	Bark		Antioxidant Antidepressant	[245]
Fabaceae	*Delonix elata*	Stem and bark		Antioxidant Hepatoprotective	[246]
Moraceae	*Ficus glomerata*	Fruit and leaf		Antioxidant Gastroprotective	[247]
Gentianaceae	*Gentiana scabra*	Rhizome		Antioxidant Hepatoprotective	[248]

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Geraniaceae	*Geranium carolinianum*	Aerial		Anti-hepatitis B virus	[249]
Irvingiaceae	*Irvingia gabonensis*	Seed	N.D.	N.D.	[250]
Anacardiaceae	*Mangifera indica*	Flower and fruit	*In vitro*	Antioxidant Antiplatelet aggregation	[251]
Moringaceae	*Moringa oleifera*	Leaves	*In vitro* Clinical	Antioxidant Antimicrobial Photoprotective	[252,253]
Polygonaceae	*Polygonum chinense*	Whole plant	*In vitro*	Antiviral	[254]
Vitaceae	*Vitis rotundifolia*	Fruit		Antioxidant	[255,256]
Tamaricaceae	*Tamarix aphylla*	Leaves and stem	N.D.	N.D.	[257]
Punicaceae	*Punica granatum*	Husk, fruit, and seeds	*In vitro* *In vivo*	Antioxidant Anti-inflammatory Vasculo-protective	[258,259]

N.D. = Not determined; inh. = inhibitor.

From information reported in Table 12, it appears unequivocable that the clinical interest in the possible beneficial properties of EA-rich plants is very limited. Particularly, among the studies here considered (56), the clinical ones represent only 5%, and *in vivo* ones are largely under half percent (25%) of the *in vitro* ones (70%) (Figure 12).

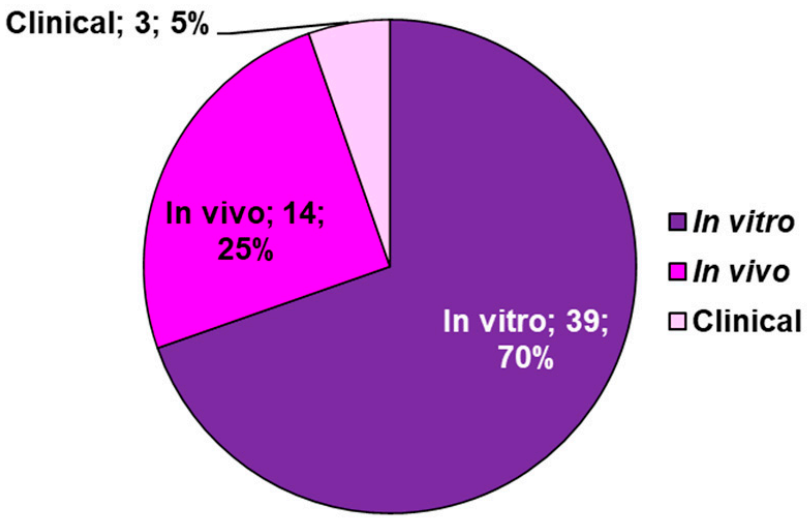

Figure 12. Percentages of *in vitro, in vivo* and clinical reports on the pharmacological activity of EA containing plants among 56 studies considered.

Collectively, practically all studies, regardless they were conducted *in vitro, in vivo*, or in clinical setting, revealed mainly antioxidants and anti-inflammatory effects. Although among the considered studies, a neuroprotective action was mentioned in only one case [241], as already extensively claimed in this review, inflammation and OS evidenced in all other studies are detrimental processes pivotal in the onset and development of AD, thus confirming the high potentialities of EA and EA-rich plants to at least prevent AD arrival. Anyway, other *in vitro* studies exist reporting on the neuroprotective effects of *Punica granatum* [260] and *Cochlospermum. angolensis* bark extracts[245]. The administration of *P. granatum* reduced Aβ deposition by a specific non-competitive inhibition of BACE1 activity[260]. Bark extracts exerted potent radical scavenging activity thus limiting OS,

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reduced cholinesterase activities, while potentiating monoaminergic functions by reducing MAO activity and preserving biogenic amine[245]. Moreover, the *in vivo* administration of pomegranate extracts (POMx) 6.25 mL/L in the drinking water for 3 months [261] to C57BL/6 APPswe/PS1dE9 transgenic mice (male) reduced microgliosis, AD progression, while improved spatial learning, motor functions, memory performance and behavioural performance by decreasing the concentration of TNF-α, NFAT and cytokine, reducing Aβ production and IkB degradation, while inhibiting production of NF-kB. Similarly, the administration of pomegranate juice (PJ) 6.25 mL/L in the drinking water for 6 to 12.5 months of age to C57BL/6 APPsw/Tg2576 trans-genic mice (male) reduced the amyloid deposition in the hippocampus, while improved learning and memory abilities, motor functions and behavioural performance by dipping Aβ42 concentrations[262]. Table 13 reports results of quantitative analyses of the ETs and EA content in various fruits, nuts, and beverages. It is important knowing that among ETs-rich food as an *in vivo* source of EA, punicalagin, found predominantly in pomegranate, sanguiin H-6 in strawberry and raspberry, vescalagin in oak-aged wines and spirits, and pedunculagin in walnuts, are the ETs providing the highest amounts of EA.

Table 13. Content of the main ET (most represented) and the mean content of ETs, expressed as mg/100 g of fresh weight (FW) for foods or mg/100 mL for beverages[14]. The mean content of EA, expressed as mg/100 g (FW), with the exceptions mentioned in the footnotes. Free or total EA values depending on the food source are reported usually without any specifications.

Food sources		ET	ETs *	EA *	Refs.
Alcoholic beverages	Cognac	Vescalagin	4.3 mg/100 mL	1.13 mg/100 mL	[14]
	Oak-age red wine			0.94 mg/100 mL	[154]
	Rum		2.97 mg/100 mL	0.21 mg/100 mL	
	Walnut liquor			1.22 mg/100 mL	[14]
	Whisky		0.15 mg/100 mL	0.82 mg/100 mL	
				0.12 mg/100 mL	[154]
Fruits and fruit products	Apple	Casuarictin	195 mg/100 g	DNQ	[154]
	Arctic blackberry			17.15 mg/100 g	[14]
	Arctic bramble			390 mg/100 g	[154]
	Bilberry			DNQ	
	Blackberry	Sanguiin H-6 Lambertianin C Sanguiin H-2 Lambertianin A Lambertianin D	175 mg/100 g	43.67 mg/100 g	[14]
	Blackcurrant			DNQ	[154]
	Bog-whortleberry			DNQ	

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Boysenberry			70 mg/100 g Seeds: 30 mg/g	
Cherry			DNQ	
Chokeberry			DNQ	
Cloudberry	Sanguiin H-6 Lambertianin C	262 mg/100 g	15.30 mg/100 g 644 mg/100 g	[14]
Cloves			DNQ	
Cranberry			DNQ	
Evergreen blackberry			60 mg/100 g Seeds: 21 mg/g	[154]
Gooseberry			DNQ	
Guava			DNQ	
Highbush blueberry			1.40 mg/100 g	[263]
Java plum			DNQ	
Kakadu plum			**Whole fruit** 826 mg/100 g DW (F) 1470 mg/100 g DW (T) **Puree** 615 mg/100 g DW (F) 1331 mg/100 g DW (T)	[264]
Kiwi			DNQ	
Mango			**Seeds** 1.2 mg/g	[154]
Marionberry			73 mg/100 g	
Muscadine grape	Sanguiin H-5	4.6 mg/100 mL (juice)	**Whole fruit** 0.92 mg/100 g **Juice** *Black grape* 0.90 mg/100 mL *Green grape* 0.93 mg/100 mL	[263] [14]
Pomegranate	Punicalagin	**Whole fruit**	861 mg/100 g	[265]

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		Punicalin Pedunculagin Casuarin Castalagin Vescalagin Granatin B Pomegraniins A Pomegraniins B	55 mg/100 g **Juice** 202 mg/100 mL	**Whole fruit** 9.67 mg/100 g	[263]
				Juice from concentrate 17.28 mg/100 mL **Pure juice** 2.06 mg/100 mL	[14]
				External peels 2853 mg/100 g DW	[265]
				Internal marcs 85 mg/100 g	[192]
	Raspberry	Sanguiin H-6 Lambertianin C Sanguiin H-10 Sanguiin H-2	244 mg/100 g 76 mg/100 g (jam)	719 mg/100 g	[154]
				Black 38.00 mg/100 g Red 2.12 mg/100 g	[14]
				Yellow 190 mg/100 g Wild 270 mg/100 g	[266]
				Juice: 0.84 mg/100 mL Jam: 1.14 mg/100 g	[14]
				Seeds Black 6.7 mg/g Red 8.7 mg/g	[154]
	Strawberry	Agriimonin Sanguiin H-6 Pedunculagin Lambertianin C Sanguiin H-10 Casuarictin	53 mg/100 g 24 mg/100 g (jam)	1.24 mg/100 g	[14]
				75 mg/100 g cv. Honeoye 77.6 mg/100 g cv. Jonsok 79.9 mg/100 g cv. Polka 68.3 mg/100 g	[154]
	Strawberry guava			DNQ	[267]
Herbs and Spices	Common sage			DNQ	[267]
	Evening primrose			DNQ	[267]
	Wild turnip top			1.32 mg/100 g	[14]

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Nuts	Brazil nut			DNQ	[154]
	Cashews				
	Chestnut	Castalagin	1.33 mg/100 g	735.44 mg/100 g	[14]
	Japanese walnut			15.67 mg/100 g	
	Peanut			DNQ	[154]
	Pecan	Pedunculagin	5358 mg/100 g	33 mg/100 g	[154]
	Walnut	Pedunculagin	1604 mg/100 g	28.5 mg/100 g	[14]
				Dehulled 5.90 mg/100 g	[14]
				59 mg/100 g	[154]

DNQ = Detected but not quantified; DW = dry weight; * mean content.

Despite its very low bioavailability, more interest was demonstrated in the evaluation of effects of isolated EA both on stressors associated to the AD and on AD symptoms. Table 14 reports some relevant *in vitro* studies which revealed the effects of isolated EA against several stressors found in AD and/or recognized as engaged in the onset and development of AD.

Table 14. *In vitro* neuroprotective role of EA by its effects against various types of stressors observed in AD.

Stressor	Experimental model	EA concentration	Observations	Refs.
Aβ	Primary murine cortical microglia	10 μM/L	Inhibited microglial activation via attenuation of TNF-α, and NFAT activity	[268]
	SH-SY5Y cells	2 mg/mL	Prevented Aβ neurotoxicity by promoting Aβ aggregation into fibrils with significant oligomer loss	[269]
		0.1–0.4 mM	Suppressed proinflammatory and disease aggravation markers	[270]
D-gal	SH-SY5Y cells	0.01–10μM	Increased cell proliferation and GSH concentration, while decreasing concentrations of ROS, MDA, TNF-α, β-GAL, and AGEs	[271]
ATRA and TPA	SH-SY5Y cells	30–100 μM	EA induced cell detachment, decreased cell viability, and induced apoptosis	[272]
		50 μM	EA decreased cell detachment, loss of viability, and activation of apoptosis	[273]
Cadmium	Rat primary astrocytes	30 μM	Decreased ROS production and astrocyte cell death	[274]

Rotenone	PC12 pheochromocytoma	10 μM	Decreased ROS and RNS production, PARP1, HSP70, and α-synuclein aggregation	[275]
OGD/R	Primary culture of rat cortical neurons	10 and 30μg/mL	Decreased the number of apoptotic/necrotic cells, and remedied the decrease in the ratio of Bcl-2/Bax expression	[276]
Tumor	Human glioblastoma and rat glioma cell line	5.5 mg or 10 mg	Chitosan-EA composite films induced the accumulation of the tumor suppressor protein p53 and increased caspase-3 activation, which preceded induction of apoptosis	[253]
		5.5 mg or 10 mg	EA induced apoptosis in cancer cells as well as suppressing angiogenesis in dose-dependent manner	[251]
Antidepressant	AChE, BuChE, and MAO-A		EA exhibited appreciable MAO-A inhibition activity compared with cholinesterase inhibitors	[245]

Aβ = β-amyloid; AChE = acetylcholinesterase; AGE = advanced glycation end-product; ATRA = all-*trans* retinoic acid; BuChE = butyrylcholinesterase; D-gal = d-galactose; EA = ellagic acid; GSH = reduced glutathione; HSP70 = heat shock protein 70; MAO-A = monoamine oxidase A; MDA = malondialdehyde; NFAT = nuclear factor of activated T-cells; OGD/R = oxygen-glucose deprivation and reoxygenation; PARP = poly(ADP-ribose) polymerase; RNS = reactive nitrogen species; ROS = reactive oxygen species; TPA = 12-*O*-tetradecanoylphorbol-13-acetate; β-GAL = β-galactose.

In addition, the administration *in vitro* of commercial EA, was able to decrease the oxidative DNA damage and free radicals' concentration [270,277] by limiting dopamine oxidation, as well as the concentrations of neurotoxins, oxygen superoxide and H_2O_2, and exerting potent radical scavenging activity. Additionally, a reduction in AChE activity detrimental in AD was observed [270]. Another study reported that EA administration reduced the production and toxicity of Aβ oligomers, by decreasing Aβ oligomerization, the soluble Aβ42 levels and the Aβ42 toxicity in SH-SY5Y neuroblastoma cells used as *in vitro* model[269]. Also, EA *in vitro* administration was able to improve the monoaminergic functions by reducing the MAO-A activity [245].

Table 15 and 16 summarize the *in vivo* assessment of the neuroprotective effects of EA in various AD animal models and animal models of pathologic conditions present in the AD developmental. Specifically, in Table 15, the biomarkers which were evaluated and the positive variations observed in the pathology processes were included, while the involved mechanisms of action of EA were inserted in Table 16.

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Table 15. *In vivo* neuroprotective effects of EA in various AD animal models.

Neurotoxin/Cause * Concomitant Pathology +	Animals	Time	EA (mg/kg)	Administration	Biomarkers	Observations	Refs
DOX *	Male Sprague Dawley rats	14 d	10	Oral	Brain MDA, TNF-α, iNOS, caspase-3, COX, cholinesterase GSH, monoamines	↓MDA, ↓TNF-α, ↓iNOS, ↓caspase-3 ↓COX, ↓cholinesterase ↑GSH, ↑monoamines	[278]
SA *	Male Wistar rats	21 d	10 and 30	Oral	MDA, NO, PCO, TNF-α, IL-1β TAC, GSH, GPx	↓MDA, ↓NO, ↓TNF-α, ↓IL-1β ↓PCO↑TAC, ↑GSH, ↑GPx	[279]
As induced Neuroinflammation *	Wistar rats	11 d	20 and 40	Oral	Total ROS, DNA fragmentation BAX, IL-1β, TNF-α, IFN-γ, MMP	↓Total ROS, ↓TNF-α, ↓IFN-γ ↓DNA fragmentation, ↓BAX, ↓Bcl-2 ↓IL-1β, ↑MMP	[280]
ACR *	Male Wistar rats	30 d	30	Oral	MDA, NO, IL-1β, TNF-α SOD, GPx, CAT	↓MDA, ↓NO, ↓TNF-α, ↓IL-1β ↑Glutathione, ↑SOD, ↑GPx, ↑CAT	[281]
Cup *	C57BL/6J mice	4 wk	40 and 80	Oral	Oligodendrocyte apoptosis IL-11, IL-17, SDF-1a, *Cxcl12*	↓Apoptosis, ↓macrophage activity ↓IL-17, ↑IL-11 ↑Mature oligodendrocyte population	[282]
TCDD *	Sprague Dawley female rats	13 wk	1	Oral	Superoxide anion, LPO DNA single-strand breaks	↓Superoxide anion, ↓LPO ↓DNA single-strand breaks	[283]
	Male Wistar rats	10 d	50		Antioxidant enzyme activities Glutathione concentrations	↑SOD, ↑CAT, ↑GSH, ↑GPx	[284]
CCl_4-induced brain injury *	Male Wistar rats	8 wk	10	Intraperitoneal	TNF-α, NF-κB, Nrf2, caspase-3 VEGF, Bcl-2 protein expression MDA, CAT, GSH concentrations	↓VEGF, ↓NF-κB, ↓TNF-α, ↓Bcl-2 ↓MDA, ↑Caspase-3, ↑Nrf2 ↑CAT, ↑GSH	[285]

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Scopolamine+diazepam *	Male Wistar rats and mice	10 d	10, 30, and 100		Elevated plus maze and passive avoidance	↓Amnesia and restored memory dysfunction	[286]
6-OHDA *	Wistar rats	10 d	50	Oral	Stride length and cylinder tests TNF-α, IL-1β concentrations	↓Contralateral rotation, ↓TNF-α ↓IL-1β, ↑Stride-length	[287]
	Male Wistar rats	14 d	50		MDA, SOD, GPx, stride-length, Bar decent latency Frequency bands' power of pallidal EEG	↓MDA, ↓stride-length ↓Bar decent latency ↓Frequency bands' power of pallidal EEG ↑SOD, ↑GPx	[288]
		10 d			Tail-flick and hot-plate tests Morris water maze test	↓OS	[289]
		1 wk	50		Rotational test Elevated narrow beam test OS, MAO-B, S100, Nrf2 DNA damage, HO-1 assessment	↓MDA, ↓ROS, ↑Nrf2, ↑HO-1 ↓DNA fragmentation, ↑MAO-B	[290]
PTZ *	Swiss male albino mice	14 d	20 and 40		Onset of convulsions Brain GABA concentration	↑Onset of convulsions ↑Brain GABA concentration	[291]
	Swiss male albino mice	33 d	50		Homocysteine, Aβ1–42, GABA, Glutamate, 4HNE, GSH, GR, GPx, TNF-α, IL-6, cyt C	↑GABA, ↑GSH, ↑GR, ↑GPx ↓Glutamate, ↓homocysteine ↓4HNE, ↓cyt C, ↓p53, ↓Bax, ↓Bcl-2 ↓Caspase-3, ↓caspase-9 ↓DNA damage	[292]
D-gal-induced Aging *	Male Sprague Dawley rats	8 wk	50	Oral	Antioxidative Anti-inflammatory Anti-apoptotic potential	↑SOD, ↑CAT, ↑GPx, ↑TAC ↓MDA, ↓TNF-α, ↓IL-6, ↓IL-1β	[293]

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Diabetic neuropathy *	Female Wistar rats	28 d	50		CAT, PON-1, TAS, TOS, OSI, MDA, NO	↓MDA, ↓TOS, ↓OSI, ↓NO ↑CAT, ↑PON-1, ↑TAS	[294]
	Wistar rats	4 wk	35		↑Brain oxidative stress markers Nitrite, LDH, TNF-α, AChE, eNOS	↓Brain OS, ↓nitrite, ↓TNF-α ↓AChE, ↓LDH	[295]
Sporadic Alzheimer disease *	Wistar rats	5 wk	50		OS, AchE pool, Aβ plaque Inflammatory response ↑Synaptic plasticity ↑Mitochondrial energetics	↓OS, ↓proinflammatory markers ↑Synaptophysin	[270]
Ischemic stroke/reperfusion/hypoperfusion *	Male Sprague Dawley rats	2 d	10 and 30		Photothrombotic nerve injury Neurological function score	↓Volume of cerebrum infarction ↓Neurological deficit scores ↑Neuronal viability ↑Cell nuclear viability	[276]
	Male Wistar rats	10 d	100		↑Blood pressure, heart rate, MDA EEG determination	↓MDA, restored the heart rate ↓Blood pressure	[296]
	Ischemic stroke/reperfusion/hypoperfusion	14 d	50		MDA and thiol (-SH) group	↓MDA, ↓thiol (-SH)	[297]
TBI *	Male Wistar rats	7 d	100	Oral	Passive avoidance memory HPC LTP, IL-1β, IL-6 BBB permeability	↓Memory, ↓IL-1β, ↓IL-6 ↓HPC LTP impairments ↓BBB permeability	[298]
		4 d		Intraperitoneal	PAT, HPC LTP BBB permeability, TNF-α	↓Neurologic severity score ↓BBB permeability ↓Cognition ↓HPC LTP abnormalities, ↓TNF-α	[299]
Depression +	Female albino mice	14 d	25, 50, and 100	Oral	Forced swimming test	Antidepressant-like effects ↑ Serotonergic and noradrenergic	[300]

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			Tail suspension test	systems functionalities	
	Mice	1, 2.5, and 5		EA (2.5 mg/kg) ↓Immobility time ↑HPC BDNF concentration	[301]
	Male albino mice	25, 50, and 100	↑Plus-maze test GABAergic and serotonergic systems in antianxiety activity	↑Percentage of time spent ↑Entry into the open arms	[302]

MMP = mitochondrial membrane potential; OS = oxidative stress; for other abbreviations see Appendix A.

Table 16. Results obtained by *in vivo* administration of EA to differently induced AD animal models or to animal models with induced pathologies concomitant to AD as depression, and brain inflammation.

Dosage/Route of Administration	Animals (sex)	Animal model	*In vivo* effects	Molecular/cellular mechanism	Refs.
100 mg/kg/day by gavage 14 days after TBI	Wistar rats (male)	Traumatic brain injury (TBI)	↓Neuroinflammation ↓Cognition defects ↓Motor deficiencies ↑Memory, ↑HPC LTP	↓IL-1β ↓IL-6 ↓ BBB permeability ↓TNF-α protein	[298]
100 mg/kg/day i.p. for 7 days	Adult Wistar rats (male)	Bilateral intra-HPC microinjection of Aβ_{25-35}	↑Learning and memory abilities ↑Motor functions ↑Behavioural performance ↑Learning and recognition memory ↑Neuronal protection ↑Spatial memory, ↓OS ↓Lipid peroxidation	Modulation of NF-κB/Nrf2/TLR4 signalling pathway ↓AChE activity ↓[NF-κB] ↓[Nrf2] ↓[TLR4] ↓[MDA] ↑CAT ↑GSH activity	[303]
50 mg/kg/day per os For 30 days	Adult Wistar rats (either sex)	Streptozotocin induced sporadic AD	↓Biochemical abnormalities ↓Mitochondrial dysfunction, ↓OS ↓Aβ plaque, ↑Neuroprotection ↓Irregular locomotor behaviour	↓[GFAP] ↓[CRP] ↓[Aβ] ↓AchE levels ↑synaptophysin expression ↓[MDA] ↑GSH activity ↑[BMA]	[304]

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17.5–35.0 mg/kg per os + fluoxetine 20 mg/kg/i.p	Swiss adult male albino mice	Immobilization-stressed animals *	↓Antidepressant-like activity ↓Immobility periods No effect on locomotor activity ↓Plasma nitrite levels	Modulation of the adrenergic/serotonergic central system ↓NOS activity	[305]
25, 50, 100 mg/kg p er os acute and chronic 14 days administration	Adult female albino mice		↓Depressive-like symptoms ↓Immobility periods No effect on locomotor activity	Modulation of the serotonergic/noradrenergic central system (5-HT1, 5-HT2, 5-HT3), (α-1, α-2)	[300]
1–5 mg/kg Acute administration	Mice		↓Immobility time ↓Depressant-like symptoms	↑HPC BDNF level	[301]

BBB = Blood–brain barrier; * to induce depression as an AD concomitant pathologic status. Abbreviations are specified in Appendix A.

It is universally recognized that inflammation and OS are pivotal to the onset and the development of the clinical signs and the pathological hallmarks that typify AD [14]. Increased levels of pro-inflammatory cytokines such as TNF-α, IL-1β, IL-6 and interferon g (IFN-g) reduce the Aβ phagocytosis in AD affected brain, interfering with the physiological mechanisms of plaque removal and then worsening astrogliosis and neural death that support the progression of the disease [14,17]. On the other hand, over accumulation of RONS and developmental of OS, caused by metal ions imbalance, contribute to the development and progression of AD. Specifically, they promote amyloid-β (Aβ) overproduction, cause τ hyperphosphorylation, disrupt organelles, causing endoplasmic reticulum (ER) stress; mitochondrial and autophagic dysfunctions, which impair synaptic functions, thus leading to a chronic neurodegeneration and cognitive deficits, such as seen in AD patients[306]. Other abnormalities observable in CNS, including malondialdehyde and 4-hydroxy-2-nonenal altered levels, increase lipid peroxidation and pervasive protein oxidation, determine high levels of nitro-tyrosine and increase amounts of 8-hydroxy-2-deoxyguanosine link OS to AD[307]. Even if adjusting metal balance by supplementing chelators of the metal ions may be potential in ameliorating AD pathologies, the possible therapeutic benefits of dietary multifaceted molecules such as EA capable to both contrast inflammation and OS in AD have been and are currently under intense investigation. It has been reported that in *vitro*, EA from *Punica granatum* inhibits the activity of the b-secretase (BACE1), a cleaving enzyme involved in the production of Aβ from amyloid precursor protein (APP), with a relative specificity[308]. Accordingly, in *vivo* administration of pomegranate juice (which is particularly enriched in EA and punicalagin, source of EA) to APP/PS1 transgenic mice, an animal model of AD, elicited a significant amelioration in spatial learning and motor functions and a marked reduction of the endogenous level of Aβ peptide (Aβ42), TNF-a, NFAT and microgliosis in the hippocampus[309,310]. Although apparently in contrast with such results, also Feng and colleagues concluded that EA could be neuroprotective in patients suffering from AD because of its ability to promote endogenous mechanisms of protection aimed at reducing the bioavailability of the soluble form of Aβ protein in the bio-phase [269]. Kiasalari and co-workers confirmed that in *vivo*, EA ameliorates behavioural skills and neuronal defects, provoked by microinjection of Aβ peptide in the CNS[303]. The anti-inflammatory and antioxidant properties of EA were further confirmed in a Streptozotocin (STZ) intra-cerebral injected animal model of AD (SAD rats), which developed detrimental hallmarks that mimic those observed in the sporadic form of AD[270]. The in *vivo* EA treatment in these animals revealed a marked reduction in AChE activity paralleled by the restoration of the synaptic pool of ACh. EA also caused a significant reduction of the Aβ deposition, a reduced OS and neural apoptosis. Summing up, although further studies are needed to confirm the hypothesis of the neuroprotective action of EA in AD, the results from both in *vitro* and in *vivo* experiments assert rational justifications for looking to

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EA as a compound of great interest for potential applications as a memory restorative agent in the treatment of dementia and AD[270]. Finally, in a relatively recent study by our colleagues, it has been demonstrated that the oral administration of a new oral EA micro-dispersion (EAm), with increased EA solubility, although did not modify animal weight and behavioral skills, significantly recovered changes in "*ex-vivo, in vitro*" parameters in old animals, when compared to young ones[193]. Moreover, EAm treatment significantly reduced CD45 signal in both young and old cortical lysates and it diminished GFAP immunopositivity in young mice. Finally, EAm treatment significantly reduced IL1β expression in old mice. These results suggest that EAm is beneficial to aging and represents a nutraceutical ingredient for elders[193].

8. Conclusions, Perspective for the Future and Authors Opinions

Currently available dementia services worldwide are inadequately resourced and staffed, mainly community based and strongly fragmented. On the contrary, multidisciplinary teams and facilities will be needed to administer correctly and safely all new therapies which are arising for AD, and their correct delivery will require an accurate molecular diagnosis of AD. In the UK, only about 60% of people potentially with dementia receive even a clinical diagnosis of dementia. Despite the guidance from the National Institute for Heath and Care Excellence recommends structural imaging, there is wide variation in imaging use between centres.

8.1. Imaging Analyses Available to Confirm the Presence of AD

There is wide variation in the proportion of patients receiving a scan. More worryingly, among people which have a scan, the majority had only a computed tomography (CT) scanning of head, which combines special x-ray equipment with sophisticated computers to produce multiple images or pictures of the brain to look for and rule out other causes of dementia, such as a brain tumor, subdural hematoma or stroke, with only 26% having an MRI. Specifically, the magnetic resonance imaging (MRI) uses a powerful magnetic field, radio frequency pulses and a computer to produce detailed pictures that can detect brain abnormalities associated with mild cognitive impairment (MCI) and can be used to predict which patients with MCI may eventually develop AD. Although in the early stages of AD, an MRI scan of the brain may be normal, in later stages, MRI may show a decrease in the size of different areas of the brain (mainly affecting the temporal and parietal lobes). Anyway, less than 2% of patients have molecular confirmation of their disease using CSF biomarkers, as included in NICE guidance, or an amyloid positron emission tomography (PET) scan analysis, which is a diagnostic examination that uses small amounts of radioactive material (called a radiotracer) to diagnose and determine the severity of a variety of diseases. A combined PET/CT exam fuses images from a PET and CT scan together to provide detail on both the anatomy (from the CT scan) and function (from the PET scan) of brain. A PET/CT scan can help differentiate Alzheimer's disease from other types of dementia. Another nuclear medicine test called a single-photon emission computed tomography (SPECT) scan could be also used for this purpose. Additionally, using PET scanning and a new radiotracer called C-11 PIB, scientists have recently imaged the build-up of beta-amyloid plaques in the living brain. Radiotracers similar to C-11 PIB are currently being developed for use in the clinical setting.

8.2. An Opportunity to Change

Although NICE guidelines are not available for the investigation and management of people with mild cognitive impairment, the advent of new therapies provides an opportunity for change. The recent availability of disease-modifying drugs for AD might bring an influx of people into clinical services including both those with AD, those with other dementias, and individuals concerned about their risk of developing dementia and/or AD. Clear referral criteria and equitable pathways from primary care to specialist services will be required. Access must not be limited to those living near specialist centres, and health systems must also ensure access for minorities and individuals living alone. "Time is brain" should be adopted. Diagnostic delays for AD might adversely affect outcomes

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of the new disease-modifying therapies. If disease progression can be slowed, then initiating treatment as early as possible could result in maximal benefit. The clinical implementation of these new drugs will, at least initially, likely resemble the methodology used in clinical trials. Greater access to diagnostic tests will be required, and demand for MRI could be a major bottleneck. It is likely that more scanners will be needed, and also a more efficient use of existing scanners, including the development of shorter, focussed protocols; and neuroradiological expertise for scan interpretation, and for the detection of amyloid-related imaging abnormalities (ARIA).

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Appendix A

Usually: abbreviations included in the main text, Figures and Tables should be already specified at their first mention or in the captions, as well as in footnotes of Figures and Tables, respectively. Anyway, in this Appendix A, we have provided the full list of all possible abbreviations meetable in the manuscript with their significance.

Aβ, β-amyloid.
AChE, acetyl cholinesterase.
ACR, acrylamide.
AD, Alzheimer disease.
AGE, advanced glycation end-product.
ASD, amorphous solid dispersion.
ATRA, all-*trans* retinoic acid.
BBB, blood–brain barrier.
BDNF, brain-derived neurotrophic factor.
BP, blood pressure.
BuChE, butyrylcholinesterase.
C_{max}, maximum concentration in plasma.
CA, cornus ammonis.
CAAdP, cellulose acetate adipate propionate.
Ca^{2+}-EA-ALG NP, ellagic acid encapsulated in calcium-alginate nanoparticles.
CAT, catalase.
Ch/β-GP, chitosan/β-glycerophosphate.
CMCAB, carboxymethyl cellulose acetate butyrate.
CNS, central nervous system.
COX, cyclooxygenase.
Cup, cuprizone.
cyt C, cytochrome c.
DG, dentate gyrus.
d-gal, d-galactose.
DOX, doxorubicin.
EA, ellagic acid.
EA-NP, ellagic acid nanoparticle.
EEG, electroencephalographic.
eNOS, endothelial nitric oxide synthase.
EPM, elevated plus-maze.

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Erβ, estrogen receptor β.
ET, ellagitannin.
FST, forced swimming test.
GABA, γ-aminobutyric acid type.
GFAP, glial fibrillary acidic protein.
GPx, glutathione peroxidase.
GSH, reduced glutathione.
HPMCAS, hydroxy-propyl-methyl cellulose acetate succinate.
HPC, hippocampus/hippocampal.
HO-1, heme oxygenase-1.
iNOS, nitric oxide synthase.
LDH, lactate dehydrogenase.
LPO, lipid peroxidation.
LTP, long-term potentiation.
MAO, monoamine oxidase.
MAPK, mitogen-activated protein kinase.
MDA, malondialdehyde.
MFB, medial forebrain bundle.
Nrf2, nuclear factor erythroid 2-related factor-2.
OLG, oligodendrocyte.
PCL, poly(ε-caprolactone).
PCO, protein carbonylation.
PCPA, *p*-chlorophenylalanine.
PD, Parkinson disease.
PDI, protein disulfide isomerase.
PI3K, phosphoinositide 3-kinase.
PON-1, paraoxonase.
PTZ, pentylenetetrazol.
PVP, polyvinylpyrrolidone.
RAGE, receptor of advanced glycation end-products.
ROS, reactive oxygen species.
SA, sodium arsenite.
SAD, sporadic Alzheimer disease.
SNc, substantia nigra pars compacta.
SNO, *S*-nitrosylation.
SNO-PDI, *S*-nitrosylation of protein disulfide isomerase.
SOD, superoxide dismutase.
SSB, single-strand break.
STZ, streptozotocin.
TAC, total antioxidant capacity.
TBI, traumatic brain injury.
TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin.
ThT, thioflavin T.
TOS, total oxidant status.
TST, tail suspension test.
β-gal, β-galactosidase.
5-HT, 5-hydroxytryptamine.
6-OHDA, 6-hydroxydopamine.

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