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Review

Ellagic Acid: A Green Multi-Target Weapon That Reduces Oxidative Stress and Inflammation to Prevent and Improve the Condition of Alzheimer's Disease

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Abstract: Oxidative stress (OS), generated by the overrun of reactive species of oxygen and nitrogen (RONS), is the key cause of several human diseases. With inflammation, OS is responsible for the onset and development of clinical signs and the pathological hallmarks of Alzheimer's 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 antioxidant and radical scavenging effects capable of counteracting 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 not absorbed, while providing mainly ellagic acid (EA), which, due to its trivial water-solubility and first-pass effect, metabolizes in the intestine to yield UROs, or irreversible binding to cellular DNA and proteins, which have very low bioavailability, thus failing as a therapeutic in vivo. Currently, only UROs have confirmed the beneficial effect demonstrated in vitro by reaching tissues to the extent necessary for therapeutic outcomes. Unfortunately, upon the administration of food rich in ETs or ETs and EA, URO formation is affected by extreme interindividual variability that renders them unreliable as novel clinically usable drugs. Significant attention has therefore been paid specifically to multitarget EA, which is incessantly investigated as such or nanotechnologically manipulated to be a potential "lead compound" with protective action toward AD. An overview of the multi-factorial and multi-target aspects that characterize AD and polyphenol activity, respectively, as well as 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's chemical features and mechanisms leading to its antioxidant activity, an all-around updated analysis of the current EA-rich foods and EA involvement in the field of AD is provided. The possible clinical usage of EA to treat AD is discussed, reporting results of its applications in vitro, in vivo, and during clinical trials. A critical view of the need for more extensive use of the most rapid diagnostic methods to detect AD from its early symptoms is also included in this work.

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

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1. Introduction

1.1. Methods

To select the literature material useful to edit this review, we used keywords like those reported in the keywords section. Specifically, in Scopus, PubMed, and PubChem databases, we used the following keywords: Alzheimer's disease; one-target drugs, multi-target drugs; oxidative stress; reactive oxygen and nitrogen species; antioxidant effects; radical scavenging activity; ellagitannins; ellagic acid; urolithins; in vitro and in vivo ellagic acid applications; and Alzheimer's disease early diagnosis. Using this method, several reviews and experimental works were collected, whose number was immediately reduced by removing duplicates. The remaining works were further reduced to the 310 references used in this study by removing the obsolete ones and then by dividing the residuals into experimental and review works. The first ones were used to obtain the most updated information and recent advances concerning Alzheimer's disease (AD), the current drugs available to treat its symptoms, and the possible new curative options under investigation, including polyphenols. The review articles were also used to obtain information on the advantages and disadvantages of ellagitannins, ellagic acid, and urolithins in terms of biomedical applications, their main sources, and the mechanisms of their antioxidant powers as the basis of their beneficial properties. On the contrary, the experimental studies provided us with data useful to organize the tables containing information about the most relevant findings achieved with the in vivo and in vitro applications of urolithin and ellagic acid (EA).

1.2. Background

1.2.1. Alzheimer's Disease

Alzheimer–Perusini disease, mainly known as Alzheimer's disease (AD), presenile dementia of the Alzheimer's type, primary degenerative dementia of the Alzheimer's type, and, for simplicity, Alzheimer's, is the most common form of progressively disabling degenerative dementia, with onset 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 USD 1.3 trillion in 2019 to over 2.8 in 2030. The most frequent early symptom is represented by difficulty in remembering recent events, followed by other symptoms that may appear with aging, 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 from 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 AD development is genetic, with several genes usually involved. However, the exact cause and progression of AD are still not well understood. It is well established that AD is a well-unshakable neuronal dysfunction whose primary causes could be associated with toxin insults, heredity, metabolism, or even attack by infectious pathogens [5]. Several research studies indicate 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 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 phosphodiesterase (PDE). It is extensively recognized that OS, as well as the formation of free radicals 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. Collectively, one hundred years after AD discovery, experts in the field are confident in asserting that, even if AD's pathogenesis is not yet entirely understood, it is a multifactorial disorder whose causes can be genetic, environmental, and endogenous (Figure 1), like other neurodegenerative diseases [7]. The excessive incorrect folding and aggregation of proteins often related to the ubiquitin–proteasomal system (UPS) are also accountable to AD.

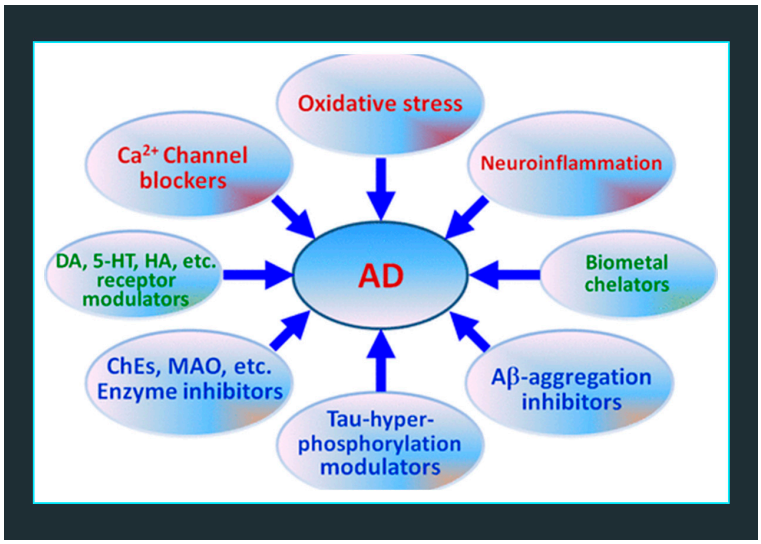


Figure 1. Some of the endogenous factors and possible biological targets involved in AD pathology. Readapted with PERMISSION/LICENSE GRANTED AT NO CHARGE by ACS Chemical Neuroscience (American Chemical Society) from [8].

Particularly, the increase in RONS causes mitochondria and DNA damage, 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 temporary benefits to symptoms 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 that could directly target the molecular causes of AD [7]. New drug candidates with promising potential to modify the disease are now under clinical trials [9]. On 1 January 2023, 141 exclusive treatments for AD were under investigation in 187 trials. Specifically, 36 agents were in 55 Phase 3 trials, 87 agents were in 99 Phase 2 ones, and 31 agents were in 33 Phase 1 ones. Among these, 79% of drugs in trials were those proposed as disease-modifying therapies, while 28% of therapies under experimentation were those using repurposed agents. Jointly, existing Phase 1, 2, and 3 trials have a need for 57,465 participants [9]. Unfortunately, although over 500 clinical trials have been conducted to identify a possible effective treatment for AD, no treatment has yet been identified capable of halting or reversing 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 and management in terms of social, emotional, organizational, and economic aspects, 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". After 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 striking a single molecular target are not suitable to treat disorders like neurodegenerative and cardiovascular ones, diabetes, cancer, etc., which embrace multiple factors of pathogenesis [13]. On the contrary, drugs that involve different pharmacological approaches could provide more potential methods of overcoming the obstacles that could occur upon the use of single-target drugs, often well-functioning in vitro but not in vivo experiments.

1.2.2. Medical Potentialities of Fruits and Vegetables

In this worrying scenario concerning the poor available arsenal of drugs and/or nanodrugs 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 such as pomegranates, strawberries, raspberries, and blackberries; nuts such as chestnuts, walnuts, almonds, pecans, and pistachios; herbs such as *Camellia sinensis*, seeds including berry seeds; and their derived foods and/or beverages possess recognized healthy and/or preventive effects against several complex human diseases, thus evidencing their multitarget behavior [14]. Such effects have been mostly associated with their high content of antioxidant molecules, mainly polyphenols [14–16], such ellagitannins (ETs), as well as gallic acid (GA) and ellagic acid (EA), which are produced via 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.

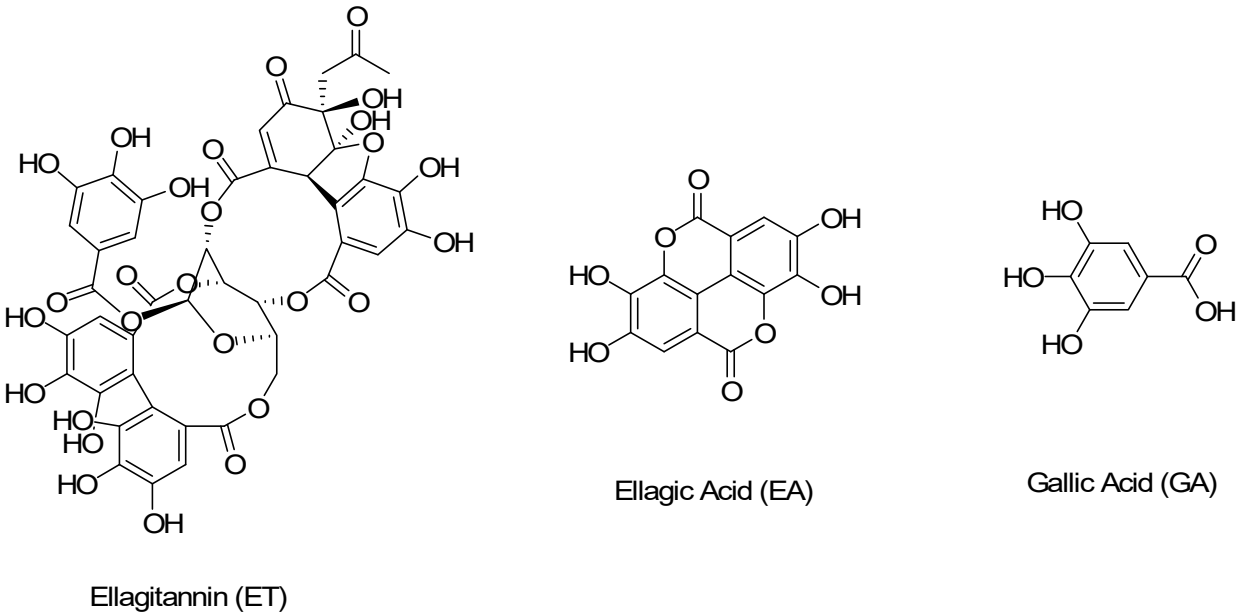


Figure 2. Chemical structure of ellagitannins (ETs), ellagic acid (EA), and gallic acid (GA).

Particularly, the strong correlation existing between the intake of foods containing high amounts of ETs and the subsequent beneficial effect vs. several human degenerative diseases is extensively reported [17,18]. As examples, documented findings assert the existence of an association between the eating of foods rich in ETs and stronger cardiovascular health [19,20], or between the intake of fruits and vegetables and minor occurrence of coronary heart disease [21]. Much experimental data led to the assumption that ETs might be used to prevent difficult-to-treat disorders such as those of diabetes, cancer, cardiovascular

diseases, and the central nervous system (CNS), including AD [22]. Nonetheless, in Europe, the European Food Safety Agency has not still approved any kind of health claims concerning ETs [14]. As mentioned above, ETs are capable of providing EA via hydrolysis, which is rationally considered the bioactive fragment of ETs. Indeed, possessing one of the strongest antioxidant powers, it is the molecule capable of counteracting OS to an extent that can be helpful in preventing and/or ameliorating AD conditions [17], as confirmed 10 years ago in a study by Kilic [23]. The in vitro radical scavenging and antioxidant capacity of EA was clarified using different analytical methodologies such as total antioxidant activity determination via ferric thiocyanate, hydrogen peroxide scavenging, 1,1-diphenyl-2-picrylhydrazyl free radical (DPPH) scavenging, 2,2′-azino-bis(3-ethylbenzthiazoline-6-sulfonic acid) (ABTS) radical scavenging activity and superoxide anion radical scavenging, ferrous ion (Fe^{2+}) chelating activity, and ferric ion (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 as compounds that possess both canonical nutritional values and several additional health benefits. In this regard, a diet of NTs-rich foods often triggers relevant positive biological effects. Anyway, despite this definition, as mentioned above and more deeply discussed later, ETs are not absorbed in vivo and are not capable of reaching tissues and organs, thus being unsuitable as molecules or template molecules to develop new treatments for human diseases. Specifically, they are hydrolysed in the gastrointestinal tract (GIT), thus providing, among other molecules, EA, which, possessing the strongest antioxidant effects and beneficial properties, represents an excellent platform to develop new drugs for AD. Unfortunately, EA also undergoes massive metabolism to urolithins (UROs) in the intestine, which are still endowed with appreciable beneficial properties, but studies have demonstrated that UROs are not advisable for harmless therapeutic purposes due to their double-faced behaviour. They can induce beneficial effects, but on the basis of their chemical structure, environmental settings, the sort of target cells under study, the individual's age, and their health state, they could also lead to harmful consequences [17]. In this scenario, EA remains the polyphenolic small molecule that attracts the interest of researchers as a promising molecule to provide benefits in neurodegenerative disorders, including AD. In this context, the main challenges of researchers in the field include defining which pharmacophore/pharmacophores in EA can be actually responsible/s either for its health benefits or for its possible collateral effects. Also, the incessant development of new EA dosage forms capable of improving its bioavailability and in silico screening investigations to design new multi-target EA-type CNS drugs are the goals of chemists, pharmacologists, and practitioners.

1.3. Our Aims

Given the above-reported considerations, this review aimed at more largely driving researchers' attention toward EA as an actual possible multi-target treatment option for AD.

The main purpose of this manuscript is to stimulate major interest in EA and to increase research on it as a promising platform to develop more effective compounds for AD, including EA nano-formulation, to solve its bioavailability drawbacks. Solving important issues or filling gaps in this field was not in the scope of this review, whose main goal was to provide all-round knowledge about AD as a multifactorial neurodegenerative disease and its supposed causes, as well as polyphenols and mainly EA, in addition to their antioxidant mechanisms responsible for their beneficial effects on AD.

1.4. Summary

A brief overview of the multi-factorial and multi-target aspects that characterize AD, as well as polyphenols such as EA, respectively, open this work. Focusing on the pathophysiology of OS, EA chemical features, and the mechanisms of its antioxidant activity, an all-around updated analysis concerning EA-rich foods and EA involvement in the field of AD is provided. The possible clinical usage of EA to treat AD is shown, reporting results by its applications in vivo and clinical trials. A critical view of the need for more extensive use of the most rapid diagnostic methods to detect AD from its early symptoms is also included in this work.

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

For years, neurodegenerative disorders (NDs) have been considered the most mysterious and challenging problems in medicine and 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 genetic, environmental, and endogenous factors [24,25]. Such NDs comprehend, among others, amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), Parkinson's disease (PD), Alzheimer's disease (AD), Huntington's disease (HD), multiple system atrophy (MSA), tauopathies (TPs), and prion diseases PRD). As in other neurodegenerative conditions, the pathogenic cascade driving AD includes protein non-correct folding and combination, RONS non-controlled production, and, consequently, the onset of OS, metal dyshomeostasis, mitochondrial impairments, and phosphorylation dysfunctions, all occurring concomitantly. Figure 3 summarizes the concomitant multiple factors leading to the onset of AD conditions, while Figure 4 evidences how some of these factors can directly damage neurons, causing their death or potentially triggering a detrimental cascade of events anyway, leading to the death of neurons.

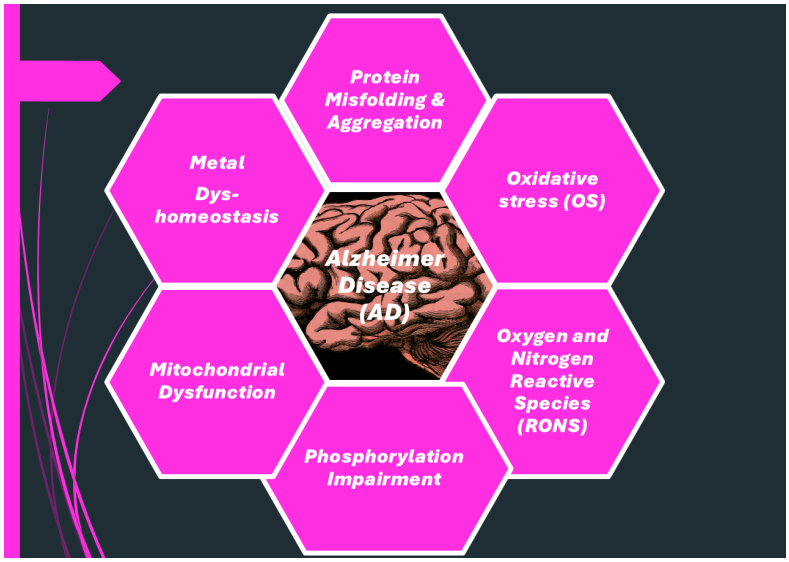


Figure 3. Multifactorial pathogenic cascade leading to the onset and development of AD.

Protein misfolding, followed by self-association and the subsequent deposition of aggregation supported by OS, increase in uncontrolled RONS, and metal dyshomeostasis, has been observed in the brain tissues of patients affected by AD [26]. The findings suggest that protein assemblies produced by different amyloidogenic proteins share common structural and histological morphologies and might trigger similar neurotoxic mechanisms.

The biophysical behavior 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 subsequent abnormal calcium regulation, depolarization of membranes, and reduced mitochondrial functions, which have been commonly detected in AD conditions [29].

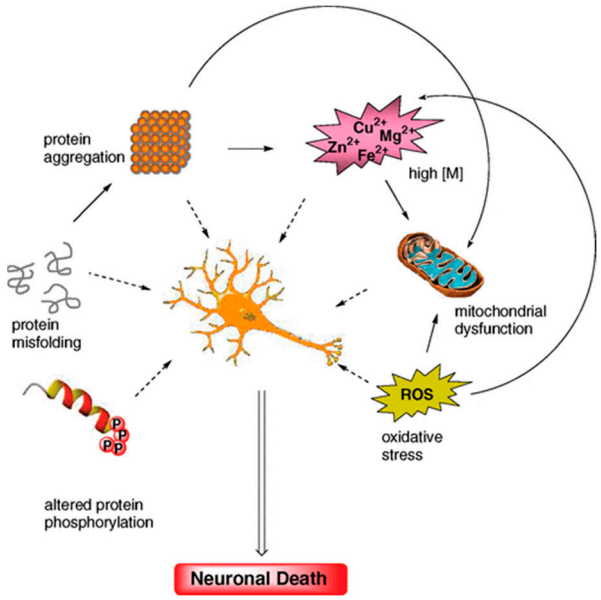


Figure 4. Schematic routes of the multifactorial events leading to neuronal death. General mechanisms, such as protein non-correct folding and aggregation, OS, metal (M) dyshomeostasis, mitochondrial impairments, and distorted protein phosphorylation, have been found in several neuronal disorders. Readapted with PERMISSION/LICENSE GRANTED AT NO CHARGE by ACS Chemical Neuroscience (American Chemical Society) from [7].

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

The role of RONS in many NDs is essential. While the physiological production of RONS generation is controlled well by the antioxidant fortification and repair systems of cells [30], when overproduced, they disrupt the cell's detoxification systems, which fail to maintain RONS levels within the correct parameters. As a result, they could reach high concentrations, thus causing OS and inflammation. Irremediable damage to nucleic acids, lipids, and proteins happens, thus encouraging aging, age-related disorders, and most degenerative human diseases [30]. To respond to the answer "Is OS a cause or a consequence of the neurodegenerative cascade in AD?" has been and remains a daily challenge for experts in the field, which urgently requires a solution. At present, scientists agree almost unanimously to affirm that the unbalanced intracellular state of oxidation is the first event in neurodegeneration and is one of the most important factors in neurodegenerative disorders. Neurons are particularly vulnerable to OS, and the possible inequity in pro-oxidant/antioxidant homeostasis in the central nervous system (CNS) can translate into the further production of several potentially toxic RONS, including both radical and nonradical species, that contribute to the onset and/or propagation of radical chain reactions damaging 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, in turn, be produced.

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

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

Figure 5 specifically schematizes 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, lipid and protein peroxidation, telomere reduction, aging, and death.

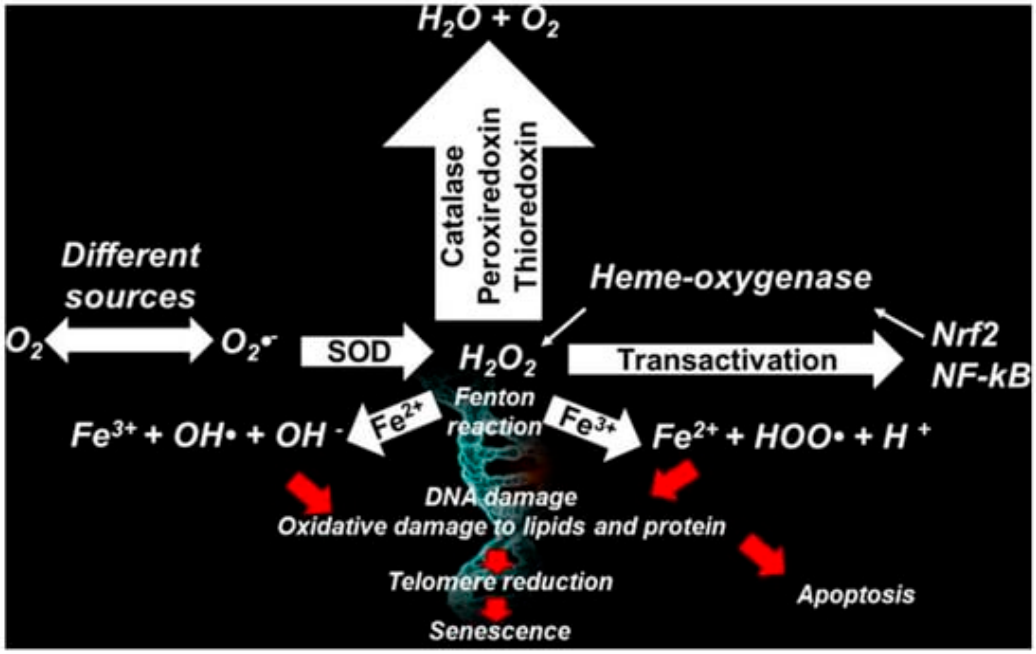


Figure 5. Schematic pathways of ROS production and their main effects on biological systems. Nrf2 = erythroid nuclear transcription factor-2; NF-kB = transcription factor involved in cellular responses to stimuli such as stress, cytokines, free radicals, heavy metals, ultraviolet irradiation, oxidized low-density lipoproteins (LDL), etc. Reproduced from our previous articles [17,30].

In AD, OS has been detected in every family of molecules within neurons, including lipids, DNA, and proteins. 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, a direct cause/effect relationship

between metal impairments and heightened oxidative damage exists. Transition metals such as iron, copper, or other redox active metals are pivotal in several biological reactions, but their homeostasis alteration may drive increased free radical production. Moreover, while all the disease-specific proteins exhibit metal-binding items, metal ions promote the generation of fibrils, and the deposition of proteins found in AD (Section 2, Figure 4). Furthermore, metal-mediated OS is not only a cause of OS in neurons but also of mitochondrial impairments, where RONS can also be produced. Morphological, biochemical, and molecular irregularities in mitochondria present in different tissues of AD patients have been signalled. Although the chronological hierarchy of events and underlying causes in AD concerning mitochondrial dysfunction and OS are not yet fully elucidated, there are unequivocable marks that both support the development of the others, actuating a self-sustaining, intensifying cycle that ultimately triggers neuronal death processes, as shown in Figure 6.

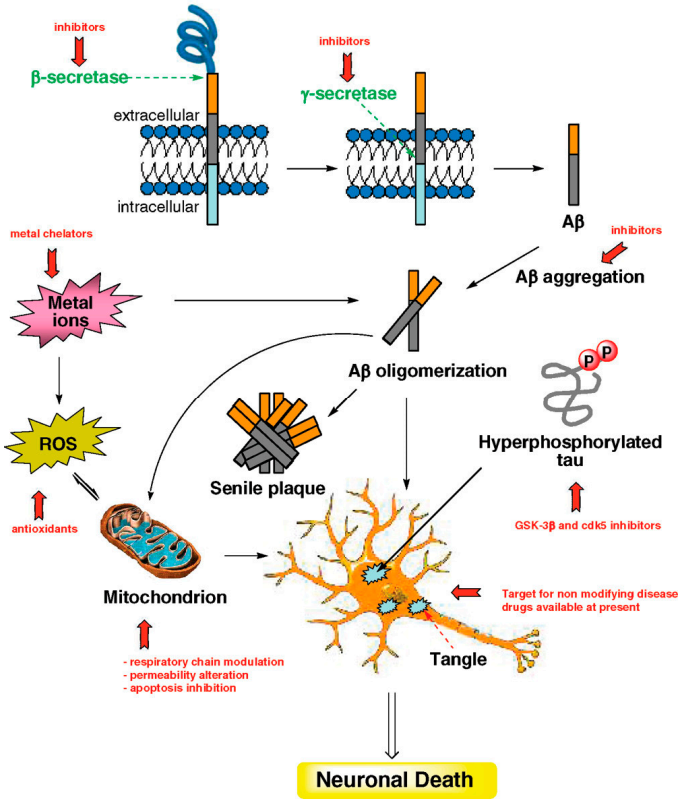


Figure 6. Possible molecular causes of neuronal death and protective cyclic mechanisms in AD. The central event in AD pathogenesis is an imbalance between Aβ production and clearance. The enhanced activity of β- and γ-secretases leads to increased release of amyloidogenic Aβ42, which forms oligomers 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. The role of metal ions and ROS in Aβ oligomerization has also been advanced. Therefore, 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 essential apoptotic factor. It has been shown that, in AD, apoptosis provoked by badly bent proteins encompasses ER impairment. Moreover, the alteration of the state of phosphorylation of some pivotal proteins involved in the pathogenic cascades represents an additional mechanism usually shared by NDs. In addition to the extensively recognized hyperphosphorylated state of τ protein in the neurofibrillary tangles observed in AD brain, other specific impaired kinase and phosphatase activities are coupled to alterations in the phosphorylation state of disease-specific proteins, which are specific for PD, ALS, and HD. Several molecular evidence demonstrated a cell-type specificity in neuronal disorders and selective neuron degeneration in AD. Nevertheless, these general mechanisms alone are not sufficient to explain the high number of biochemical and pathological abnormalities of AD. Collectively, disfunctions in AD incorporate a multitude of cross-related cellular and biochemical changes that cannot be effectively addressed by using treatments based on a one-molecule, one-target paradigm. In our opinion, there is a growing interest and urgent need for the development of multi-target directed ligands (MTDLs) to provide real disease-modifying drug candidates for this ND.

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

Scientific knowledge about the pathogenesis of several human diseases has advanced enormously in recent decades. Therefore, the sector of drug discovery has gradually moved from pursuing a completely human phenotype-based tactic to a simpler approach based on single molecular targets. This revolution has led to a type of drug research still extensively followed, which is focused on the discovery of small molecules capable of regulating the biological function of a single target alleged to be fully responsible for a given disease. The research in this direction has been finalized to discover drug molecules selective for a given protein. Nowadays, many ligands endowed with outstanding in vitro selectivity and efficacy are available. Unfortunately, it should be noted that a highly selective ligand for a certain target in vitro is not always also 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	Does not recognize the target by the ligand in vivo
	Does not reach the site of action of the ligand
	One-target interaction is not enough to have a sufficient impact on the complex diseased system

The low correspondence between the results in vitro and those in vivo in the case of NDs is mainly due to the multifactorial nature of human degenerative diseases. In NDs, the cells often find strategies to make up for a single protein, whose activity is influenced by the one-target drug administered due to the redundancy of the system, including the existence of parallel pathways [31]. Drugs striking a single target are commonly inadequate to treat diseases like neurodegenerative ones, including AD, diabetes, cardiovascular disorders, and cancer, which involve multiple pathogenic factors [32]. Different pharmacological strategies are necessary to overcome the problems that arise from the use of single-target drugs (Table 2, column 1). When a single-target drug is not appropriate to successfully cure a disease, alternative options aiming at hitting more than one impaired process correlated to the disorder should be considered. Figure A1 in Appendix A at the end of this manuscript shows some alternative medical approaches.

The three most commonly adopted approaches (MMT, MCM, and MTDLs) reported in Figure A1 are charted in Table 3 with related advantages and disadvantages.

Table 3. Alternative multi-target approaches.

Approaches	Advantages	Disadvantages	Ref.
MMT	Attack the multifaceted discomfort via multiple mechanisms	Compliance problems in patients	[33]
		Undesired in vivo drug–drug interactions	
		In vivo unbeneficial side effects	
		Different bioavailability and pharmacokinetic metabolism of the single drugs	
MCM	Attack the multifaceted discomfort via multiple mechanisms	Undesired in vitro and in vivo drug–drug incompatibility hampering single formulations	[34]
	Simpler dosing regimens	Different bioavailability, pharmacokinetics, and 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 and metabolism (ADMET profile)	Complex ADMET Complex pharmacokinetic	[35]
	Simpler pharmacokinetic and ADMET optimization		
	↓ 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; ↑ = improved; ↓ = reduced.

The multiple-medication therapy (MMT) (Figure A1), also known as combination therapy, may be used as an 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 tactic could concern the use of a multiple-compound medication (MCM), also referred to as a "single-pill drug combination", which involves the inclusion of different drugs into the same dosage form. Finally, a very appealing strategy is now appearing, which assumes that a single compound may be able to hit multiple targets per se because it comprehends in the same molecule more than one pharmacophore. Obviously, there are a series of multiple advantages over MMT or MCM inherent to possible therapies using a single multitarget drug (Table 3). Indeed, there is a solid suggestion that the development of single compounds able to strike multiple targets might reveal new opportunities 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 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 disease pathogenesis. The excellent perspective by Morphy and Rankovic [37] covered several aspects of the design strategy leading to MTDLs for differ-

ent 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 for NDs is increasing, there is still a paucity of review literature dealing with complex diseases associated with neurodegeneration, which we hope to compensate for in our present work.

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

Among the NDs reported above, AD stands out as the fourth leading cause of death in Western countries and the most common cause of acquired dementia in the elderly population. As shown in Figure A2 (Appendix A), two main forms of AD are recognized, both characterized by neuronal death.

In line with an increase in the 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]. In this scenario, where AD is a multifactorial disease and 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 simultaneously.

3.1.1. Current AD Therapies

Although the path of the events leading to AD onset is far from being completely clarified, the cholinergic hypothesis is 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 in 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 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.

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

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

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

The acetylcholinesterase inhibitor (AChEI) tacrine (Chart 1) was the first drug to be approved for the treatment of AD but is 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 noncom-

petitive NMDA antagonist (Chart 1). Table 4 includes the advantages and disadvantages connected to the use of such therapeutics.

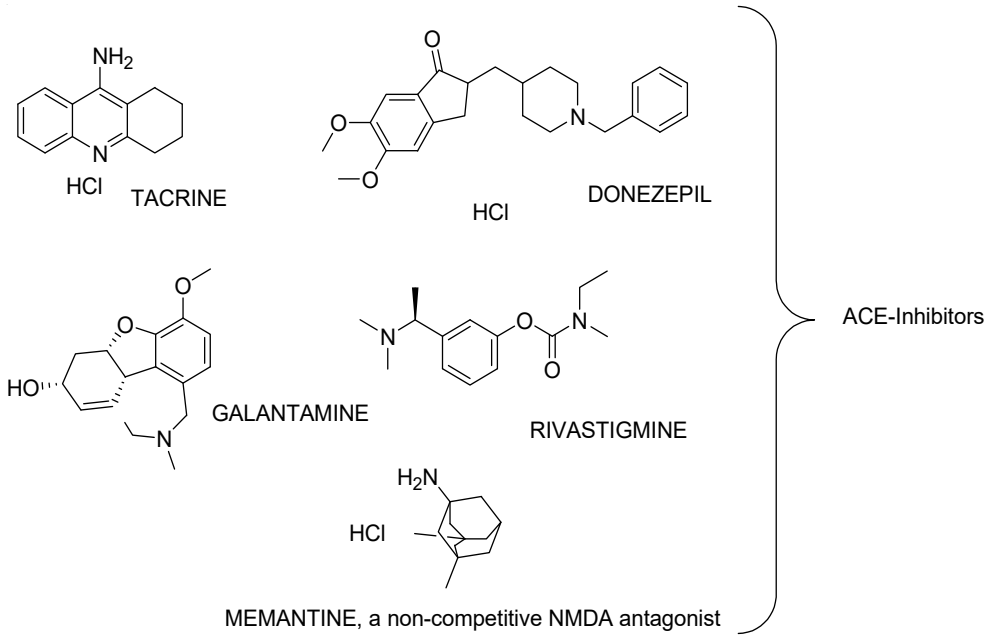


Chart 1. Structure of traditional AChEIs.

Despite the diffused clinical practice, the debate on the effective activity of AChEI medications endures. So, the search for novel AChEIs, such as inhibitors of the "non-classical function" of AChE, has 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 of reducing amyloid pathology (Table 5). Classes of therapeutic modalities currently in the advanced stage of clinical trial testing comprise forms of immunotherapy that use several drugs (Table 5), including medicaments with anti-amyloid properties. Nontraditional dementia therapies, such as those using HMG-CoA reductase inhibitors, mainly including statins [42], such as atorvastatin, simvastatin, fluvastatin, pravastatin, rosuvastatin, and lovastatin, are now being evaluated for their clinical benefits in AD as disease-modifying treatments [42].

Table 5. Summary of recent pharmacological interventions against AD.

Class of Drugs	Compounds	Mechanism	Subjects	Trial Phase	Summary	[Refs]
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	II	↓ 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		Rescue of cognitive decline in severely affected patients (ADAS-cog ≥ 25) visual impairment	[54]
	PBT2	MPAC	MTM AD		↓ Efficacy ↑ Individual variance	[55,56]

Table 5. *Cont.*

Class of Drugs	Compounds	Mechanism	Subjects	Trial Phase	Summary	[Refs]
			Anti-amyloid therapy			
Aβ immunotherapy	ACI-24	Aβ vaccine	Adults with Down syndrome	II	↓ Immunogenicity	[57]
	CAD106		Mild AD		↓ Efficacy	[57]
	UB-311				No published data	[57]
	ABVac40		MCI to mild AD		Ongoing	[57]
	BAN2401	Monoclonal antibody		III	↓ 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]

Table 5. *Cont.*

Class of Drugs	Compounds	Mechanism	Subjects	Trial Phase	Summary	[Refs]
			Anti-τ therapy			
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]
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]

Table 5. *Cont.*

Class of Drugs	Compounds	Mechanism	Subjects	Trial Phase	Summary	[Refs]
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		APP/PS1 mice		↑ Cognition	[90]
	GW2580	CSF1R inh.			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	Static	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]
	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]

Table 5. *Cont.*

Class of Drugs	Compounds	Mechanism	Subjects	Trial Phase	Summary	[Refs]
Anti-neuroinflammatory therapy						
Insulin resistance management	Liraglutide	Incretin receptor agonist	Mild AD	II	Delay of cognitive impairment	[103]
	Metformin	Biguanide	MCI		↓ 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 Oligo-mannate	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]
	Riluzole	Glutamate modulator	Mild AD		Completed No published data	[118]
	Troriruzole		MTM AD		Ongoing	[119]
Omega 3 FA supplements	DHA	Anti-oxidative effect		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 acid oxidase; MCI = mild cognitive impairments; BPSD = behavioral 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 A3, Appendix A) will pose challenges for rightful access. No national healthcare system is ready to deliver these drugs to more than a fraction of patients who might be eligible.

These active principles (APs) include lecanemab and donanemab, which are intravenous monoclonal antibodies capable of removing 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 of treatment [124].

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 used to ameliorate the compliance of patients with AD. Since 2006, the number of patented MCMs, where new compounds that 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 MCMs.

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	↓ Level of Aβ associated with plaque formation inhibits cyclooxygenase enzymes	[126]
Mayo Foundation	AChEI + Aβ-lowering agent		↓ 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 savings	Specific $GABA_B$ antagonist and $GABA_C$ agonist	[129]

Table 6. *Cont.*

Patented by	Combination Ingredients	Advantages/Finalization	Mechanism of the Additional Ingredient	Ref.
Johns Hopkins University	MS-153 + reported AChEIs	↓ Ischemia-induced neuron damage via 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]
Schering Corporation	Macrocyclic lactones+ AChEIs and/or an NSAID	Ameliorates 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 drugs (NSAIDs) [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 = glyceryl phosphorylcholine; 5-CDPC = 5′-cytidine di-phosphocholine; 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)-phosphine acid.

In the 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 etiology [138]. Several MTDLs have been developed by academia and industry in recent years. These have been the subject of some interesting review articles, and particularly interested readers could examine the related references [139–142]. The main design strategy usually applied to build up a possible new MTDL involves 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, 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 7) already present inside other drugs, which demonstrated beneficial effects in neurodegenerative diseases, to provide the traditional drug with additional ameliorative effects while reducing the side effects of separate single drugs and enhancing the compliance of patients [8].

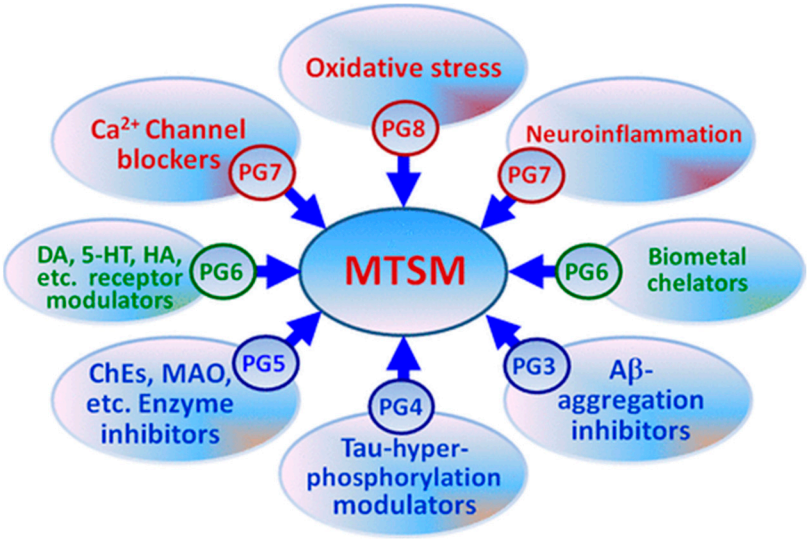


Figure 7. Ideal and efficient MTSMs (equal to, say, MTDLs) for AD therapy, showing their corresponding pharmacophoric groups (PG). Readapted with PERMISSION/LICENSE GRANTED AT NO CHARGE by ACS Chemical Neuroscience (American Chemical Society) from [8].

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, and those of the cardiovascular system [143], and, lately, 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 of interfering with different targets involved in the cascade of pathological events leading to a given disease could be highly effective for treating multifactorial diseases, such 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 not necessarily be responsible for side effects. On the contrary, natural polyphenols such as ETs and EA, per se possessing the multifaceted health activity reported above as demonstrated by the outcomes deriving by the assumption of food containing them, are provided readily 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

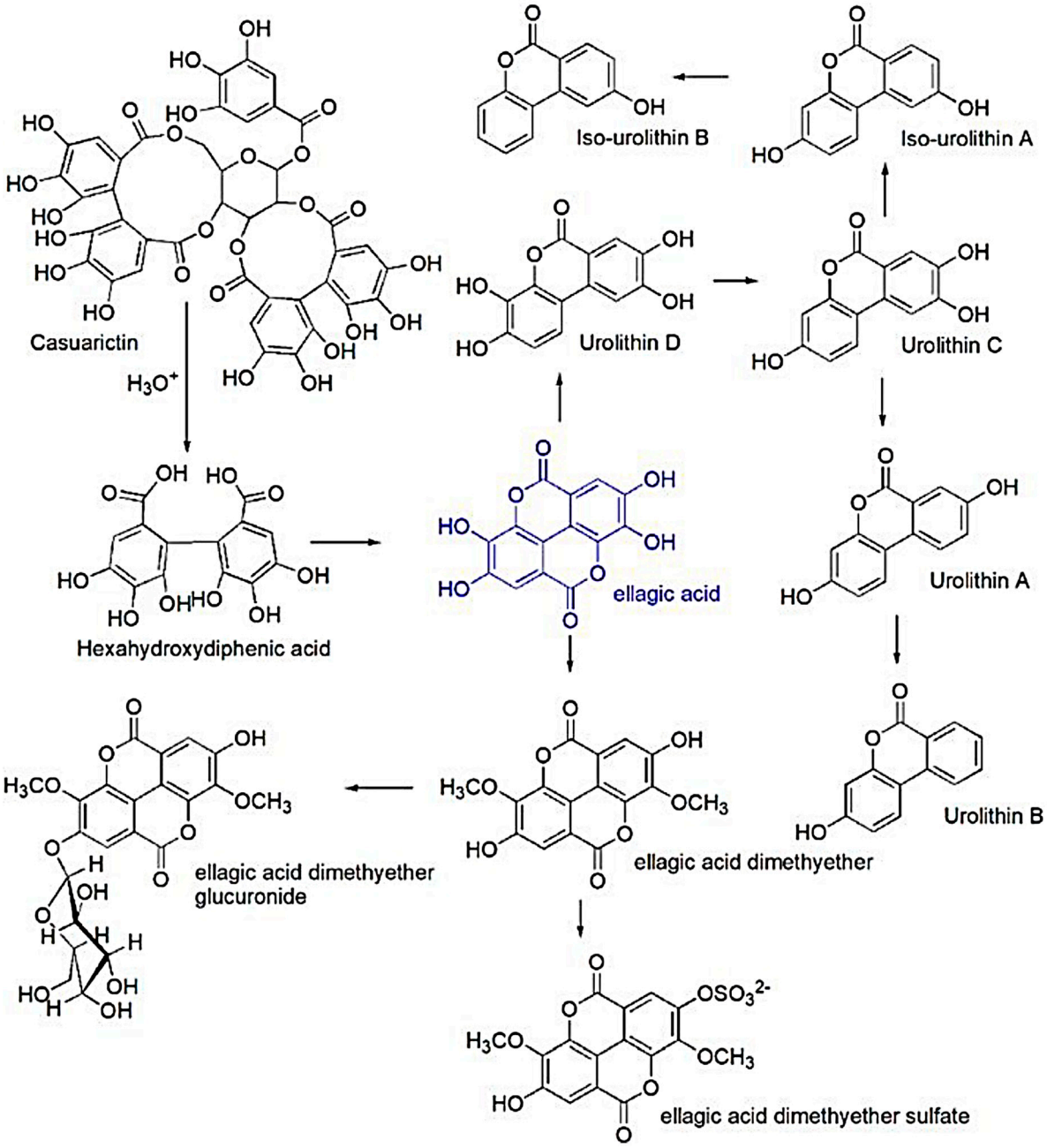
According to a review reported in 2020, except for an insignificant quantity (e.g., 0.7–4.7 mg/100 g of berries, wet weight), the free form of EA mainly has its origin in vivo, after the consumption of ETs-rich food, due to the physiological massive hydrolysis of ETs in the gastrointestinal tract (GIT) [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. 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 [146]. By contrast, the percentage of free EA in strawberries, as shown by the same study, reached only 7.4% of its total content [146]. Despite early studies not showing 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 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.) [147]. 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) [147]. 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 the processing practice [148]. Freezing fruits, as well as processing them to produce beverages and jams, may have different effects on the content of EA. However, after the intake of ETs-rich foods, ETs are only slightly absorbed and reach the small intestine, where they are hydrolyzed to EA by the gut's microbiota action [17]. Once produced, EA is practically not absorbed due to its trivial water solubility, unfavorable physicochemical characteristics, and low bioavailability (Table A1, Appendix A) and reaches the large intestine untouched. A justification for EA's poor bioavailability and its low concentrations in plasma and tissues depends mainly on its tendency to tie up permanently cellular nucleic acids and proteins or to form weakly solvable aggregates with the ionic form of calcium and magnesium, which greatly reduce transcellular absorption [149]. Also, still-active metabolites of EA were sparsely detected in fluids at 1 and 5 h after ingestion, thus corresponding to very low concentrations as well, not enough to supply substantial positive effects [17]. In the large intestine, EA is metabolized to the more hydrophilic urolithins (UROs), secondary polyphenol metabolites derived from the gut microbial action [150], and/or converted to its dimethyl, as well as dimethyl glucuronate and sulphate derivatives, which are excreted.

A representative structure of an ET (casuarictin); that of EA; and those of URO A, B, C, D, iso-A, and iso-B are shown in Scheme 1, which shows 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 also introduced URO-M5 and M6 among the URO-type metabolites of EA [150]. Precisely, in this new route, EA is transformed into URO-M5, which is in turn converted into URO-D, while URO-M5 is converted into URO-M6, which then provides URO-C as URO-D [150].

In the year 2022, a study reported the existence and structure of up to 13 UROs [151]. Collectively, since ETs are 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 of being absorbed and reaching blood and tissues, due to its very low water solubility [152], EA also 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 is insignificant in improving the conditions associated with chronic human diseases. 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 [14,153]. As observable in Scheme 1, UROs are dibenzopyran-6-one derivatives with different hydroxyl substitutions. UROs are more lipophilic than EA, and this characteristic is responsible for their greater absorption rate respect to EA, thus being the only active phenolic molecules sufficiently absorbed and detectable in the circle and cells after ETs-rich food intake [150]. URO-A and URO-B are the major metabolites of EA

found in the gut, where URO-A is the most biologically active compared to the rest of the EA metabolites [150]. In enterocytes and hepatocytes, UROs undergo biotransformation to UROs metabolites. UROs' main metabolites detected in plasma and urine consist of their glucuronic and sulfate conjugates, such as URO-A and URO-B glucuronide and sulfate, while the minor metabolites are URO-C and iso-URO-A glucuronide.



Scheme 1. Chemical structures of casuarictin, EA, and the most commonly known UROs. The scheme is a reproduction of the original one produced by authors [17].

4.2. Ellagic Acid or Urolithins?

Apparently promising, in vitro and in vivo experiments have also revealed that UROs have anti-inflammatory, anti-carcinogenic, anti-glycative, antioxidant (even if lower than ETs and EA), and antimicrobial properties. They exert preventive effects on gut and systemic inflammation and also seem to play the role of hormone analogues [154]. Table 7 reports the most relevant studies concerning the in vivo effects of UROs assessed in animal models.

Table 7. 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 proteins ↓ proinflammatory IL-1β, IL-4	[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	[155]
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 ↓ Cardiac dysfunction ↑ Maximal rate of ventricular pressure ↓ Reduction in the isovolumic contraction time Recovery of cardiomyocyte contractility and Ca^{2+} dynamics ↑ Velocity of shortening (only for Uro-B)	[156]
Sprague Dawley rats	Uro-A (50 mg kg^{-1} d^{-1} p.o.) for 5 days in a cisplatin-induced nephrotoxicity model	↓ Cisplatin-induced inflammation Inhibition of the proapoptotic pathway Prevention of renal impairments and histopathological damage	[157]
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 4th and 6th day in DSS-induced colitis C57BL/6 model	↓ LPS-induced increase in serum ↓ IL-6 and TNF-α levels Protection of TNBS-induced tissue damage ↓ Neutrophil infiltration, MPO activity, serum inflammatory markers (IL-6, TNF-α, CXCL1, and IL-1β) Protection of DSS-induced acute colitis ↓ DAI scores, colon shortening, gut permeability, and ↑ colon weight/length ratio ↓ Inflammation (IL-6, IL-1β, TNF-α, and colonic tissue MPO levels)	[158]
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	↓ Histopathological hallmarks of cisplatin-induced acute kidney injury ↓ Mortality by lower renal OS and apoptotic stress (Nrf2/antioxidant response element and P53 pathways)	[159]
C57BL/6 mice	Uro-A (20 mg kg^{-1} d^{-1} i.g.) for 8 weeks in surgical osteoarthritis model	Protective effect in osteoarthritis development by ↓ OARSI score, ↓ PI3K/AKT pathway activation, and the nuclear p65 expression in chondrocytes	[160]
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 ↑ Autophagy; attenuation of associated kidney injury	[161]
C57BL/6 mice	Uro-A (100 mg kg^{-1} d^{-1} i.p.) for 5 days in a cisplatin-induced ischemic neuronal injury model	Protection from ischemia–reperfusion injury ↓ Histological damage in tubular cells ↓ Cisplatin-induced TNF-α, IL-23, IL-18, MIP2 ↓ Renal oxidative/nitrative stress ↑ Clinical outcome	[162]
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	↓ Colonic shrinkage ↓ Colonic histopathology and apoptosis ↓ Inflammatory sequelae of infection ↓ Intestinal IFN-γ, TNF-α, MCP-1, and NO ↓ Systemic IFN-γ, MCP-1, and IL-6 ↓ Abundance of macrophages, monocytes, and T lymphocytes in the mucosa and lamina propria	[163]
$FUNDC1^{f/f}$ 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	↓ 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.

Table 7. *Cont.*

Animal Model	Assay Conditions	Main Outcomes	Ref.
Neuroprotective effect and(or) improvement in cognitive function			
Transgenic (express human amyloid $\beta_{1–42}$ 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)	Protective effect against A$\beta_{1–42}$ induced neurotoxicity and worm paralysis	[164]
Alzheimer's disease APP/PS1 transgenic mice model	Uro-A (300 mg kg^{-1} d^{-1} p.o.) for 14 days	↑ Learning, ↑ 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 ↓ Proinflammatory cytokine levels ↓ Activation of NF-κB p65 subunit ↓ p38 (MAPK)	[165]
ICR mice	Uro-A (150, 100 or 50 mg kg^{-1} d^{-1} p.o.) for 8 weeks in a D-gal-induced aging brain 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	[166]
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 via ↑ LC3-II and ↓ p62 level ↓ ER stress by autophagy activation Ameliorate infarction, neurological deficit scores, and spatial memory deficits after cerebral ischemia	[167,168]
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)	↓ Neuron loss and ↑ neurogenesis after ischemic stroke ↓ Apoptosis by regulating apoptotic-related proteins ↓ Glial activation ↑ AMPK and IκBα activation ↓ Akt, NFκB p65, ERK, JNK, and p38	[168]
ICR mice	Uro-A (2.5 mg kg^{-1} d^{-1} i.p.) for 8 weeks in an STZ-induced diabetic mouse model	Alleviated APP and BACE1 expressions, Tau phosphorylation, Aβ deposition, and cognitive impairment ↑ High glucose-induced TGM2 expression	[169]
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	↑ Cardiac function ↓ Myocardial infarct size Prevention of cardiomyocyte apoptosis ↑ Serum CK and LDH activities after ischemia	[170,171]
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	↑ Aortic atherosclerotic lesions ↓ Total cholesterol, TGs, and LDL and angiotensin II levels in aortic tissue	[171]
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 Anti-obesity activity via ↑ systemic insulin sensitivity	[172]
C57BL/6 mice	Uro-A (20 μg d^{-1} i.p.) accompanied with a high-fat diet for 12 weeks	↓ Total and LDL cholesterol In liver: ↓ TGs accumulation, inflammation and ↑ mitochondrial biogenesis In adipose tissue: ↓ adipocyte hypertrophy and macrophage infiltration	[173]

Table 7. *Cont.*

Animal Model	Assay Conditions	Main Outcomes	Ref.
	Cardioprotective activity		
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 from myocardial ischemia/reperfusion injury via p62/Keap1/Nrf2 signalling pathway	[174]
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 a high-fat diet	Anti-obesity effect by ↓ body weight and visceral adipose tissue mass Restored hepatic antioxidant capacity, serum lipid profile	[175,176]
C57BL/6 mice and *ob/ob* mice	Uro-A (30 mg kg^{-1} d^{-1} i.g.) for 10 weeks in mice fed a high-fat diet	↓ Lipid accumulation, ↑ faecal fat excretion ↓ LXRα and SREBP1c, ↓ PERK and IRE1α ↑ PPARα expression ↓ HFD-induced and genetic obesity ↑ Energy expenditure via ↑ thermogenesis in brown adipose tissue and ↑ browning of white adipose tissue	[177,178]
DBA2J mice	Uro-A or Uro-A and ellagic acid (0.1% p.o.) for 8 weeks in mice fed 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	[178]
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 high-fat and STZ-induced type 2 diabetic model	↑ Diabetic symptoms ↓ High water intake and urine volumes ↓ Fasting blood glucose, glycated haemoglobin levels, plasma C-peptide, MDA and IL-1β level ↑ Reduced glutathione, IL-10 content, glucose tolerance, and pancreatic function indexes (HOMA-β) ↓ Mitochondrial swelling and myelin-like cytoplasmic inclusions ↑ LC3-II and beclin1 ↓ Sequestosome 1 (p62) ↓ Apoptotic protein cleaved caspase3 in pancreas via regulating autophagy and AKT/mTOR signalling pathway	[179]
	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	↑ Exercise capacity via ↑ muscle function ↑ Grip strength, ↑ spontaneous exercise Uro-A, Uro-B, Uro-C, or Uro-D extended lifespan by 45.4, 36.6, 36.0, and 19.0%, respectively	[180]
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	↑ Intervertebral disc degeneration ↓ Loss and destruction of disc height and osteophyte formation	[181]
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	↓ Tumor growth and Ki-67 expression in both PC-3 and C4-2B xenografts ↓ AR/pAKT signalling in C4-2B tumors	[182]
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 cell model	↓ Average tumor volume, weight, and Ki-67 levels	[183]

Table 7. *Cont.*

Animal Model	Assay Conditions	Main Outcomes	Ref.
	Other biological activities		
C57BL/6 mice (wild type, Nrf2$^{-/-}$ and AhR$^{-/-}$)	Uro-A (20 mg kg^{-1} d^{-1} p.o.) for 7 days	↑ Gut barrier function Activation of AhR-Nrf2-dependent pathways to ↑ Cldn4, NQO1, Ocln, ZO1, TJP3 Cyp1A1 activity induction in colon and liver of wild type but not in AhR$^{-/-}$ mice	[158]
C57BL/6 mice	Uro-A (10 mg kg^{-1} d^{-1} i.g.) for 12–16 weeks	↑ Angiogenic pathways and markers such as VEGFA and CDH5 ↑ Skeletal muscle vascularization via silent information regulator 1 and PGC-1α pathway ↑ ATP and NAD+ levels in skeletal muscle	[184]
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	↓ Plasma uric acid levels and hepatic xanthine oxidase activity ↓ Expression of genes associated with hepatic purine metabolism	[185,186]
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: ↓ Disease progression at prevention, induction, and effector phases of preclinical EAE at the highest dose ↓ Inflammatory cells and demyelination ↓ Numbers of M1-type microglia Activate dendritic cells ↓ Infiltrating Th1/Th17 cells in the CNS	[186]
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)	↑ Muscle function via ↑ mitophagy in muscular dystrophy ↑ Skeletal muscle respiratory capacity ↑ MuSCs' regenerative ability Recovery of muscle function ↑ Survival in DMD mouse models ↑ Expression of *pink-1* and *pdr-1* mitophagy genes, with no impact on the expression of autophagy genes ↑ Mitochondrial network, mitochondrial respiration, citrate synthase activity ↑ mtDNA/nDNA) ratio Positive impact on muscle function and motility of the dystrophic worms	[187]
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 a high-fat diet	Gut microbiota modulation: modulated gut microbes related to body weight, dysfunctional lipid metabolism, and inflammation	[176]

N.R. = not reported; ↑ = improvement, improved, higher; ↓ = lowered, decreased, lower; αKGDH, alpha-ketoglutarate dehydrogenase; AhR, aryl hydrocarbon receptor; 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; DMD; Duchenne muscular dystrophy; DSS, dextran sulphate sodium; EAE, experimental autoimmune encephalomyelitis; ER, endoplasmic reticulum; ERK, extracellular signal-regulated kinase FS, fractional shortening; HED, human equivalent dose; HOMA, homeostasis model assessment; ICR, Institute of Cancer Research; IFN, interferon; 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; 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; ORAC, oxygen radical absorbance capacity; 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; PTGES, prostaglandin E synthase; SIRT, sirtuin 1; SREBP1, sterol regulatory element binding protein 1; STZ, streptozotocin; TG, triglycerides; TGM2, transglutaminase type 2; TJP3, tight junction protein 3; TNBS, 2,4,6-Trinitrobenzenesulfonic acid; TNF-α, tumor necrosis factor alpha; 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 effective bioactive molecules accountable for the beneficial outcomes deriving from the intake of foods rich in ETs and EA [14,67]. This proposition is assisted by the awareness that, although in vitro findings have demonstrated that EA and UROs are almost equally active, in vivo studies only provided trustworthy verification about this fact with regard to UROs. Only UROs have been found in fluids, cells, and tissues and were measured, finding concentrations capable of exerting the ameliorative effects already evidenced in vitro. On the other hand, the poor in vivo reliability of UROS (see the next paragraph for details), the greatest antioxidant effects peculiar to EA, which could be of greater help in ameliorating neurodegenerative disorders, including AD, have stimulated the interest of researchers in knowing more about the possible EA activity in vivo if absorbed. This has led scientists to increasingly and incessantly focus on preparing water soluble and absorbable EA formulations able to defend EA and to lower or annul EA metabolism to UROs so that it could reach cells and tissue in pristine form [188]. 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 a radical scavenger antioxidant therapeutic. In this context, after the year 2019, we studied some micro- and nanosized solutions, which revealed interesting performance [189–191].

4.3. Drawbacks Associated with UROs Hamper Their Clinical Development, Thus Quenching Researchers' Interest

Although gifted with beneficial characteristics like those of EA, UROs are not appropriate for secure therapeutic use due to their double-faced behaviour. Depending on their chemical structure, environmental settings, the class of target cells studied, individual age, and their health state, they could also be dangerous [17]. The amount and typology of UROs produced in the gut of individuals also depend on the type of vegetables that have been introduced and the individual microbiota metabolic activity—that is, typified by a highly inter-individual heterogeneity, depending on several factors and human metabotypes (0, A, and B) [17]. Moreover, this highly interindividual and intra-individual process is not completely elucidated yet [34,35]. Let us imagine that even living species that do not produce UROs exist. Table 8 reports the UROs mainly found in different mammalian species after the consumption of different vegetables.

Table 8. Production of UROs in different mammalian species.

Mammalian	Source	URO Type	Refs
Rat (*Rattus norvegicus*)	Pomegranate husk	A, B, C	[192]
	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	

Table 8. *Cont.*

Mammalian	Source	URO Type	Refs
Humans (*Homo Sapiens*)	Pomegranate juice Pomegranate extract Walnuts Strawberry Raspberry	A, C, Iso A, B A, B, C A, B, C A, C, Iso A, B A, C, Iso A, B	[192]
Humans (*Homo Sapiens*)	Blackberry	A, C	[193]
Humans (*Homo Sapiens*)	Cloudberry Oak-aged red wine	A	[194]
	Tea Nuts	A A, Iso A, B	[192]

URO absorption, blood and tissue concentrations, and inter-subject variability in the comebacks to URO exposure are arbitrary variables that drive various responses that, ironically, could promote adverse effects. In addition, human microbiota activity is difficult to reproduce 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 a promising molecule to provide benefits in neurodegenerative disorders, including AD, mainly due to its anti-inflammatory and antioxidant properties. Defining which pharmacophore/pharmacophores in EA are actually responsible/s for its health benefits and its possible collateral effects is crucial for in silico screening investigations and designing new multi-target EA-type CNS drugs. The mechanisms at the basis of the EA multifaceted bioactivity are mainly based on its antioxidant, radical scavenger, and anti-aging effects, capable of contrasting OS. Collectively, EA is capable of counteracting the detrimental RONS, which are a byproduct of the physiologic aerobic metabolism. For a more precise distinction, OS refers to a torrent of destructive proceedings that frequently trigger and accompany the molecular/cellular pathogenic events responsible for several human disorders, including AD [144,195]. Differently, inflammation, being both the cause and the effect of RONS accumulation, is considered a pathological characteristic of most human diseases, including those developing in the CNS, including AD.

5.1. Antioxidant Effects of EA: Proposed Mechanisms of Action

Natural antioxidants are fundamentally present in vegetable food, and polyphenols, such as EA, are supposed to comprise 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 to form hydrogen bonds and 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 radical (FR) scavenger [196]. The EA anion is proposed as the key species for its protective effects against OS [196]. It is predicted to be efficiently and continuously regenerated after scavenging two free radicals per cycle [196]. Chemical species able to prevent oxidation can be classified into primary antioxidants (Type I, or chain-breaking) and secondary antioxidants (Type II, or preventive). EA can behave as both Type I and Type II antioxidants, thus exerting multiple-function antioxidant activity (Table 9) [197].

Table 9. Classification of antioxidants.

Antioxidant Type	Action Type	Modalities	Ref.
Type I	Free radical scavengers Break the chain, leading to FR formation	HAT PCET SET SET-PT SPLET RAF SPLHAT	[197]
Type II	Preventive molecules Retard the oxidation process	Metal chelation Hydroperoxide decomposition to non-radical species Repair primary antioxidants with hydrogen or electron donation Deactivate singlet oxygen Impound triplet oxygen Absorb UV radiation	[197]

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.

5.1.1. 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, depending both on the concentration of EA and FRs. Factors that could modify their chemical structures, such as the pH, polarity, reaction conditions, and 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 [198]. The alcohols may act as acceptors of hydrogen bonds, thus decreasing EA antiradical effects via 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 peroxyl radicals through electron transfer, thus improving EA radical scavenging activity via SET reactions [198]. In general, the antiradical properties of different natural and synthetic Type I antioxidants possessing OH groups mainly derive from their capacity to transfer hydrogen atoms to FRs. This process can occur via the different mechanisms reported in Table A2 (Appendix A). 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 A2 also reports the chemical equations associated with these proposed mechanisms. EA can mainly exercise antioxidant effects through three of the reaction mechanisms reported in Table A2, 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 A4, Appendix A).

When EA reacts, for example, with the radical species 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 and able to interfere and modify radical-mediated oxidation processes via SET reactions.

5.1.2. Type II Scavenging Reactions

EA is also a Type II antioxidant, thus providing protective effects against FRs by inhibiting the endogenous production of oxidants and radical hydroxyl (•OH) molecule, which is the most reactive and electrophilic species of oxygen-based radicals [30]. •OH is

mainly responsible for tissues and DNA damage and, therefore, its inhibition is of prime significance for reducing OS generated from the metal-catalysed Fenton reaction and Haber Weiss recombination (HWR), according to Equations (1)–(4), involving the reduced forms of Fe and Cu.

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

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

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

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

In this context, EA is an excellent antioxidant due to its capability to chelate and subtract metal such as Fe^{2+}, Fe^{3+}, and copper ions involved in the production of FRs, thus preventing the oxidation of low-density lipoproteins (LDL) [196,197,199]. 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 [200]. 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 [200]. Unfortunately, some of the 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 also act unexpectedly as pro-oxidant moieties [201]. 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, such as EA, but is limited in large-molecular-weight phenols, such as ETs. On the other hand, this apparent issue can trigger apoptosis in cancer cells [202,203].

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

As above-mentioned, the polyphenolic lactone with the formula $C_{14}H_6O_8$, known as EA, as well as the intake of EA food supplements and foods rich in ETs and/or EA can translate into altering profuse signaling inside cells, thus preventing and/or pauperizing the progression of diverse neurodegenerative abnormalities, including AD [204]. Its neuroprotective effectiveness is mainly attributable to its ROS scavenging, iron chelating properties, positive regulation of energetics of mitochondrial respiratory complex, and abundant modulation of neuronal molecular signaling pathways [205].

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

Table 10 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.

Given the information reported in Table 10, it appears unequivocally that the clinical interest in the possible beneficial properties of EA-rich plants is very limited. Particularly, among the studies considered here (56), the clinical ones represent only 5%, and in vivo ones largely comprise under half a percent (25%) of the in vitro ones (70%) (Figure A5, Appendix A). Collectively, practically all studies, regardless of whether they were conducted in vitro, in vivo, or in clinical settings, mainly revealed antioxidants and anti-inflammatory effects.

Table 10. List of plants reported to exhibit the presence of appreciable concentrations of ETs and EA with demonstrated beneficial medicinal properties upon their incorporation by humans or animals.

Family	Plant	Plant Part	Model	Medicinal Properties	Refs.
Apocynaceae	*Decalepis hamiltonii*	Roots	In vivo	Anticancer	[206]
	Macrosiphonia longiflora	Xylopodium	Clinical	Anti-inflammatory	[207]
Juglandaceae	*Carya illinoinensis*	Kernels and shells	In vivo	Toxicological effect Antioxidant	[208]
	Juglans regia	Kernels	N.D.	N.D.	[209]
Malvaceae	*Thespesia lampas*	Roots	In vitro In vivo	Antioxidant Hepatoprotective	[210]
	Sterculia striata	Nut	In vitro	Antioxidant	[211]
Sapindaceae	*Dimocarpus longan*	Seeds		Antioxidant Antimicrobial	[212]
	Nephelium lappaceum	Husk		Antioxidant	[213]
Rosaceae	*Geum rivale*	Aerial	N.D.	N.D.	[214]
	Rubus parvifolius	Whole plant	In vivo	Hepatoprotective Antioxidant	[215]
	Sanguisorba officinalis		In vitro	Antiadipogenic	[216]
Phyllanthaceae	*Emblica officinalis*	Fruits	In vitro In vivo Clinical	Antioxidant Antihepatotoxic Anti-inflammatory Antidiabetic	[217]
	Phyllanthus acuminatus	Leaves	In vitro	Antioxidant Cytotoxic	[218]
Myrtaceae	*Myrciaria dubia*	Fruit	In vitro	Antioxidant	[219]
	Psidium friedrichsthalianum			Antioxidant Metabolomic	[220]
	Syzygium calophyllifolium			Antioxidant Antibacterial	[221]
	Syzygium cumini			Antidiabetic Antioxidant	[222]
	Myrciaria floribunda			Antioxidant	[223]
	Eugenia uniflora	Leaves	In vitro In vivo	Anti-inflammatory Antioxidant Antibacterial	[224]
	Myrtus communis		N.D.	N.D.	[225]
	Campomanesia adamantium	Leaves and root	In vitro	Apoptotic death of leukemic cells	[226]
	Eucalyptus globulus	Bark, stem, leaves Fruit	In vitro	Antioxidant Bioherbicide	[227]
	Acca sellowiana	Fruits, pulp, peel		Antimicrobial	[228]
Euphorbiaceae	*Chrozophora senegalensis*	Leaves and stem	In vitro In vivo	Cytotoxicity Antimalarial	[229]
	Acalypha hispida			Anti-inflammatory Antioxidant	[230]
	Gymnanthes lucida	Leaves	In vitro	Antimicrobial Cytotoxic	[231]
	Euphorbia pekinensis	Root	In vitro In vivo	Antidiabetic	[232]

Table 10. *Cont.*

Family	Plant	Plant Part	Model	Medicinal Properties	Refs.
Euphorbiaceae	*Euphorbia supina*	Herb	In vitro	Antioxidant	[233]
	Sebastiania chamaelea	Whole plant	In vitro In vivo	Cytotoxicity Antimalarial	[229]
Lythraceae	*Trapa taiwanensis*	Fruit		Antioxidant Hepatoprotective	[234]
	Woodfordia fruticose	Flower	In vivo	Antiulcer	[235]
	Lafoensia pacari	Leaves	In vitro In vivo	Cytotoxicity Wound healing	[236]
	Lagerstroemia speciosa	Leaves and stem	In vitro	Antiviral	[237]
Combretaceae	*Terminalia chebula*	Fruit		Antioxidant Antibacterial Neuroprotective	[238]
	Terminalia bellirica	Fruit		Antioxidant Hepatoprotective Antidiabetic	[239]
Cistaceae	*Cistus laurifolius*	Leaves		Antioxidant Prostaglandin inh. Antimicrobial	[240]
Lecythidaceae	*Barringtonia racemosa*	Leaves and stems		Antioxidant	[241]
Bixaceae	*Cochlospermum angolensis*	Bark		Antioxidant Antidepressant	[242]
Fabaceae	*Delonix elata*	Stem and bark		Antioxidant Hepatoprotective	[243]
Moraceae	*Ficus glomerata*	Fruit and leaf		Antioxidant Gastroprotective	[244]
Gentianaceae	*Gentiana scabra*	Rhizome		Antioxidant Hepatoprotective	[245]
Geraniaceae	*Geranium carolinianum*	Aerial		Anti-hepatitis B virus	[246]
Irvingiaceae	*Irvingia gabonensis*	Seed	N.D.	N.D.	[247]
Anacardiaceae	*Mangifera indica*	Flower and fruit	In vitro	Antioxidant Antiplatelet aggregation	[248]
Moringaceae	*Moringa oleifera*	Leaves	In vitro Clinical	Antioxidant Antimicrobial Photoprotective	[249,250]
Polygonaceae	*Polygonum chinense*	Whole plant	In vitro	Antiviral	[251]
Vitaceae	*Vitis rotundifolia*	Fruit		Antioxidant	[252,253]
Tamaricaceae	*Tamarix aphylla*	Leaves and stem	N.D.	N.D.	[254]
Punicaceae	*Punica granatum*	Husk, fruit, and seeds	In vitro In vivo	Antioxidant Anti-inflammatory Vasculo-protective	[255,256]

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

Although among the considered studies, a neuroprotective action was mentioned in only one case [238], 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. However, other in vitro studies exist reporting on the neuroprotective effects of *Punica granatum* [257] and *Cochlospermum. angolensis* bark extracts [242]. The administration of *P. granatum* reduced Aβ deposition via a specific non-competitive inhibition of BACE1 activity [257]. Bark extracts exerted potent radical scavenging activity, thus limiting OS and reducing cholinesterase activities while potentiating monoaminergic functions by reducing MAO activity and preserving biogenic amines [242]. Moreover, the in vivo administration of 6.25 mL/L of pomegranate extracts (POMx) in the drinking water for 3 months [258] to C57BL/6 APPswe/PS1dE9 transgenic mice (male) reduced microgliosis and AD progression and improved spatial learning, motor functions, memory performance, and behavioural performance by decreasing the concentration of TNF-α, NFAT, and cytokines; reducing Aβ production and IkB degradation; and inhibiting the production of NF-kB. Similarly, the administration of 6.25 mL/L of pomegranate juice (PJ) in the drinking water for 6 to 12.5 months of age to C57BL/6 APPsw/Tg2576 transgenic mice (male) reduced amyloid deposition in the hippocampus and improved learning and memory abilities, motor functions, and behavioural performance with dipping Aβ42 concentrations [259]. Table 11 reports the results of quantitative analyses of the ETs and EA content in various fruits, nuts, and beverages. It is important to know that among ET-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 11. 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 is expressed as mg/100 g (FW), with the exceptions mentioned in the footnotes. Free or total EA values depending on the food source are usually reported 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		2.97 mg/100 mL	0.94 mg/100 mL	[260]
	Rum			0.21 mg/100 mL	[14]
	Walnut liquor			1.22 mg/100 mL	
	Whisky		0.15 mg/100 mL	0.82 mg/100 mL	
				0.12 mg/100 mL	[260]
Fruits and fruit products	Apple			DNQ	[260]
	Arctic blackberry	Casuarictin	195 mg/100 g	17.15 mg/100 g	[14]
	Arctic bramble			390 mg/100 g	[260]
	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	[260]
	Bog-whortleberry			DNQ	
	Boysenberry			70 mg/100 g Seeds: 30 mg/g	
	Cherry			DNQ	
	Chokeberry			DNQ	

Table 11. *Cont.*

Food Sources		ET	ETs *	EA *	Refs.
Fruits and fruit products	Cloudberry	Sanguiin H-6	262 mg/100 g	15.30 mg/100 g	[14]
		Lambertianin C		644 mg/100 g	
	Cloves			DNQ	[260]
	Cranberry			DNQ	
	Evergreen blackberry			60 mg/100 g Seeds: 21 mg/g	
	Gooseberry			DNQ	
	Guava			DNQ	[261]
	Highbush blueberry			1.40 mg/100 g	
	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)	[262]
	Kiwi			DNQ	[260]
	Mango			**Seeds** 1.2 mg/g	
	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	[14,261]
	Pomegranate	Punicalagin Punicalin Pedunculagin Casuarin Castalagin Vescalagin Granatin B Pomegraniins A Pomegraniins B	**Whole fruit** 55 mg/100 g **Juice** 202 mg/100 mL	861 mg/100 g	[263]
				Whole fruit 9.67 mg/100 g	[261]
				Juice from concentrate 17.28 mg/100 mL **Pure juice** 2.06 mg/100 mL	[14]
				External peels 2853 mg/100 g $_{DW}$	[263]
				Internal marcs 85 mg/100 g	[189]
	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	[260]
				Black 38.00 mg/100 g	[14]
				Red 2.12 mg/100 g	
				Yellow 190 mg/100 g	[264]
				Wild 270 mg/100 g	
				Juice: 0.84 mg/100 mL	[14]
				Jam: 1.14 mg/100 g	
				Seeds Black 6.7 mg/g	[260]
				Red 8.7 mg/g	

Table 11. *Cont.*

Food Sources		ET	ETs *	EA *	Refs.
Fruits and fruit products	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	[260]
				cv. Jonsok 79.9 mg/100 g	
				cv. Polka 68.3 mg/100 g	
	Strawberry guava			DNQ	[265]
Herbs and Spices	Common sage			DNQ	[265]
	Evening primrose			DNQ	[265]
	Wild turnip top			1.32 mg/100 g	[14]
Nuts	Brazil nut	Castalagin	1.33 mg/100 g	DNQ	[260]
	Cashews				
	Chestnut			735.44 mg/100 g	[14]
	Japanese walnut			15.67 mg/100 g	
	Peanut			DNQ	[260]
	Pecan	Pedunculagin	5358 mg/100 g	33 mg/100 g	[260]
	Walnut	Pedunculagin	1604 mg/100 g	28.5 mg/100 g	[14]
				Dehulled 5.90 mg/100 g	[14]
				59 mg/100 g	[260]

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

Despite its very low bioavailability, more interest was demonstrated in the evaluation of the effects of isolated EA both on stressors associated with AD and on AD symptoms. Table 12 reports some relevant in vitro studies that 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 12. In vitro neuroprotective role of EA in terms of 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	[266]
	SH-SY5Y cells	2 mg/mL	Prevented Aβ neurotoxicity by promoting Aβ aggregation into fibrils with significant oligomer loss	[267]
		0.1–0.4 mM	Suppressed proinflammatory and disease aggravation markers	[268]
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	[269]
ATRA and TPA	SH-SY5Y cells	30–100 μM	EA induced cell detachment, decreased cell viability, and induced apoptosis	[270]
		50 μM	EA decreased cell detachment, loss of viability, and activation of apoptosis	[271]

Table 12. *Cont.*

Stressor	Experimental Model	EA Concentration	Observations	Refs.
Cadmium	Rat primary astrocytes	30 μM	Decreased ROS production and astrocyte cell death	[272]
Rotenone	PC12 pheochromocytoma	10 μM	Decreased ROS and RNS production and PARP1, HSP70, and α-synuclein aggregation	[273]
OGD/R	Primary culture of rat cortical neurons	10 and 30 μg/mL	Decreased the number of apoptotic/necrotic cells and remedied the decrease in the ratio of Bcl-2/Bax expression	[274]
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	[250]
		5.5 mg or 10 mg	EA induced apoptosis in cancer cells as well as suppressed angiogenesis in dose-dependent manner	[248]
Antidepressant	AChE, BuChE, and MAO-A		EA exhibited appreciable MAO-A inhibition activity compared with cholinesterase inhibitors	[242]

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 radical concentration [268,275] by limiting dopamine oxidation and the concentrations of neurotoxins, oxygen superoxide, and H_2O_2 and exerting potent radical scavenging activity. Additionally, a reduction in AChE activity detrimental to AD was observed [268]. Another study reported that EA administration reduced the production and toxicity of Aβ oligomers by decreasing Aβ oligomerization, soluble Aβ42 levels, and Aβ42 toxicity in SH-SY5Y neuroblastoma cells used as in vitro model [267]. Also, EA in vitro administration was able to improve monoaminergic functions by reducing MAO-A activity [242].

Tables 13 and 14 summarize the in vivo assessment of the neuroprotective effects of EA in various AD animal models and animal models of pathologic conditions present in AD development. Specifically, in Table 13, the biomarkers evaluated, and the positive variations observed in the pathology processes are included, and the involved mechanisms of action of EA are included in Table 14.

Table 13. In vivo neuroprotective effects of EA in various AD animal models. Words having this symbol (* and $^{+}$) belong to the category indicated in the titles having that symbol.

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	[276]
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	[277]
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	[278]
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	[279]
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	N.A.
TCDD *	Female Sprague Dawley rats	13 wk	1	Oral	Superoxide anion, LPO DNA single-strand breaks	↓ Superoxide anion, ↓ LPO ↓ DNA single-strand breaks	[280]
	Male Wistar rats	10 d	50		Antioxidant enzyme activities Glutathione concentrations	↑ SOD, ↑ CAT, ↑ GSH, ↑ GPx	[281]
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	[282]
Scopolamine + diazepam *	Male Wistar rats and mice	10 d	10, 30, and 100	Oral	Elevated plus maze and passive avoidance	↓ Amnesia and restored memory dysfunction	[283]
6-OHDA *	Wistar rats	10 d	50		Stride length and cylinder tests TNF-α, IL-1β concentrations	↓ Contralateral rotation, ↓ TNF-α ↓ IL-1β, ↑ Stride-length	[284]

Table 13. *Cont.*

Neurotoxin/Cause * Concomitant Pathology +	Animals	Time	EA (mg/kg)	Administration	Biomarkers	Observations	Refs
6-OHDA *	Male Wistar rats	14 d	50	Oral	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	[285]
		10 d			Tail-flick and hot-plate tests Morris water maze test	↓ OS	[286]
		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	[287]
PTZ *	Swiss male albino mice	14 d	20 and 40		Onset of convulsions Brain GABA concentration	↑ Onset of convulsions ↑ Brain GABA concentration	[288]
	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	[289]
D-gal-induced Aging *	Male Sprague Dawley rats	8 wk	50		Antioxidative Anti-inflammatory Anti-apoptotic potential	↑ SOD, ↑ CAT, ↑ GPx, ↑ TAC ↓ MDA, ↓ TNF-α, ↓ IL-6, ↓ IL-1β	[290]
Diabetic neuropathy *	Female Wistar rats	28 d	50	Oral	CAT, PON-1, TAS, TOS, OSI, MDA, NO	↓ MDA, ↓ TOS, ↓ OSI, ↓ NO ↑ CAT, ↑ PON-1, ↑ TAS	[291]
	Wistar rats	4 wk	35		↑ Brain oxidative stress markers Nitrite, LDH, TNF-α, AChE, eNOS	↓ Brain OS, ↓ nitrite, ↓ TNF-α ↓ AChE, ↓ LDH	[292]

Table 13. *Cont.*

Neurotoxin/Cause * Concomitant Pathology +	Animals	Time	EA (mg/kg)	Administration	Biomarkers	Observations	Refs
Sporadic Alzheimer disease *	Wistar rats	5 wk	50	Oral	OS, AchE pool, Aβ plaque Inflammatory response ↑ Synaptic plasticity ↑ Mitochondrial energetics	↓ OS, ↓ proinflammatory markers ↑ Synaptophysin	[268]
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	[274]
	Male Wistar rats	10 d	100		↑ Blood pressure, heart rate, MDA EEG determination	↓ MDA, restored the heart rate ↓ Blood pressure	[293]
	Ischemic stroke/ reperfusion/ hypoperfusion	14 d	50	Oral	MDA and thiol (-SH) group	↓ MDA, ↓ thiol (-SH)	[294]
TBI *	Male Wistar rats	7 d	100		Passive avoidance memory HPC LTP, IL-1β, IL-6 BBB permeability	↓ Memory, ↓ IL-1β, ↓ IL-6 ↓ HPC LTP impairments ↓ BBB permeability	[295]
		4 d		Intraperitoneal	PAT, HPC LTP BBB permeability, TNF-α	↓ Neurologic severity score ↓ BBB permeability ↓ Cognition ↓ HPC LTP abnormalities, ↓ TNF-α	[296]
Depression +	Female albino mice	14 d	25, 50, and 100	Oral	Forced swimming test Tail suspension test	Antidepressant-like effects ↑ Serotonergic and noradrenergic system functionalities	[297]
	Mice		1, 2.5, and 5			EA (2.5 mg/kg) ↓ Immobility time ↑ HPC BDNF concentration	[298]
	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	[299]

MMP = mitochondrial membrane potential; OS = oxidative stress; for other abbreviations, see Abbreviation section; ↑ = improvement, improved, higher; ↓ = lowered, decreased, lower; N.A. = not available.

Table 14. Results obtained by in vivo administration of EA to differently induced AD animal models or to animal models with induced pathologies concomitant to AD such 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	[295]
100 mg/kg/day i.p. for 7 days	Adult Wistar rats (male)	Bilateral intra-HPC microinjection of A$\beta_{25–35}$	↑ Learning and memory abilities ↑ Motor functions ↑ Behavioral performance ↑ Learning and recognition memory ↑ Neuronal protection ↑ Spatial memory, ↓ OS ↓ Lipid peroxidation	Modulation of NF-κB/Nrf2/TLR4 signaling pathway ↓ AChE activity ↓ [NF-κB] ↓ [Nrf2] ↓ [TLR4] ↓ [MDA] ↑ CAT ↑ GSH activity	[300]
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 behavior	↓ [GFAP] ↓ [CRP] ↓ [Aβ] ↓ AchE levels ↑ synaptophysin expression ↓ [MDA] ↑ GSH activity ↑ [BMA]	[301]
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	[302]
25, 50, 100 mg/kg per os acute and chronic 14-day 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)	[297]
1–5 mg/kg acute administration	Mice		↓ Immobility time ↓ Depressant-like symptoms	↑ HPC BDNF level	[298]

BBB = blood–brain barrier; * to induce depression as a concomitant pathologic AD status; ↑ = improvement, improved, higher; ↓ = lowered, decreased, lower; Abbreviations are specified in Abbreviation section.

It is universally recognized that inflammation and OS are pivotal to the onset and development of the clinical signs and the pathological hallmarks that typify AD [14]. Increased levels of proinflammatory cytokines such as TNF-α, IL-1β, IL-6, and interferon g (IFN-g) reduce the Aβ phagocytosis in the AD-affected brain, interfering with the physiological mechanisms of plaque removal and then worsening astrogliosis and neural death, supporting the progression of the disease [14,17]. On the other hand, the overaccumulation of RONS and the development of OS, caused by metal ion imbalance, contribute to the development and progression of AD. Specifically, they promote amyloid-β (Aβ) overproduction, cause τ hyperphosphorylation, disrupt organelles, and cause endoplasmic reticulum (ER) stress and mitochondrial and autophagic dysfunctions, which impair synaptic functions, thus leading to chronic neurodegeneration and cognitive deficits, such as those seen in AD patients [303]. Other abnormalities observable in CNS, including malondialdehyde and 4-hydroxy-2-nonenal altered levels, increased lipid peroxidation, and pervasive protein oxidation, determine high levels of nitro-tyrosine and increased amounts of 8-hydroxy-2-deoxyguanosine link OS to AD [304]. Even if adjustment of metal balance by supplementing chelators of the metal ions may have potential in ameliorating AD pathologies, the possible therapeutic benefits of dietary multifaceted molecules such as EA capable of 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 relative specificity [257]. Accordingly, in vivo administration of pomegranate juice (which is particularly enriched in EA and punicalagin, a 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 in the endogenous level of Aβ peptide (Aβ42), TNF-a, NFAT, and microgliosis in the hippocampus [258,259]. Although apparently in contrast with such results, Feng and colleagues also 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 [267]. Kiasalari and co-workers confirmed that in vivo, EA ameliorates behavioural skills and neuronal defects, provoked by the microinjection of Aβ peptide in the CNS [300]. The anti-inflammatory and antioxidant properties of EA were further confirmed in a Streptozotocin (STZ) intracerebral injected animal model of AD (SAD rats), which developed detrimental hallmarks that mimic those observed in the sporadic form of AD [268]. 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 in Aβ deposition, 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 EA as a compound of great interest for potential applications as a memory restorative agent in the treatment of dementia and AD [268]. 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 it 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 [190]. Moreover, EAm treatment significantly reduced the 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 benefits aging and represents a nutraceutical ingredient for elders [190].

7. Conclusions, Perspectives for the Future, and Authors' Opinions

Currently, available dementia services worldwide are inadequately resourced and staffed, mainly community-based, and highly fragmented. On the contrary, multidisciplinary teams and facilities will be needed to correctly and safely administer all new therapies that 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 Health and Care Excellence recommends structural imaging, there is wide variation in imaging use between centres.

7.1. 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 who have a scan, the majority had only a computed tomography (CT) scanning of the 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, 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, an MRI may show a decrease in the size of different areas of the brain (mainly affecting the temporal and parietal lobes). Moreover, less than 2% of patients receive 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 the 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 also be 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.

7.2. 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 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 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 a more efficient use of existing scanners,

including the development of shorter, focused protocols and neuroradiological expertise for scan interpretation and the detection of amyloid-related imaging abnormalities (ARIA).

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Abbreviation

The following abbreviations are used in this manuscript:

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.
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.

Appendix A

Table A1. Chemical and physical properties of EA [188,305].

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-colored needles from pyridine Yellow powder
Melting point	>360 °C
Density	1.667 at 18 °C

Table A1. *Cont.*

Physicochemical Identifiers	Descriptive Data
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 [260] Poorly soluble in water [152] Insoluble in ether Soluble in alkalis and pyridine [188]
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 [152].

Table A2. Possible action mechanisms of the Type I antioxidants and related equations.

Action Mechanism	Chemical Equation	Features
HAT	$H_nAntiox + {}^{\bullet}R \rightarrow H_{n-1}Antiox^{\bullet} + HR$	A key reaction mechanism
PCET	$H_nAntiox + {}^{\bullet}R \rightarrow H_{n-1}Antiox^{\bullet} + H^+ + {}^{\bullet} \rightarrow HR$	Exactly the same products as HAT
RAF	$H_nAntiox + {}^{\bullet}R \rightarrow [H_nAntiox\text{-}R]^{\bullet}$	Presence of multiple bonds peculiar of electrophilic radicals
SET	$H_nAntiox + {}^{\bullet}R \rightarrow H_nAntiox^{+\bullet} + R^-$ $H_nAntiox + {}^{\bullet}R \rightarrow H_nAntiox^{+\ -\bullet} + R^+$	Primary pathway Secondary pathway
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
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
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

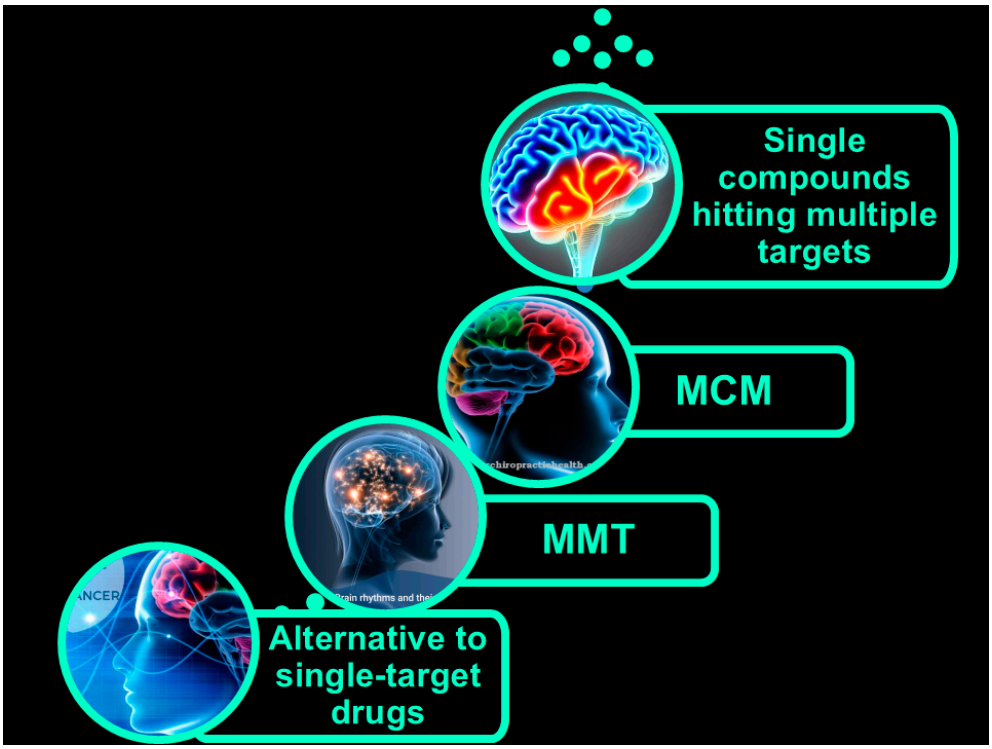

Figure A1. Alternative approaches to the one-molecule/one-target drug. MMT = multimodal therapy; MCM = multiple-compound medication (single compounds hitting multiple targets can also be abbreviated as MTDLs).

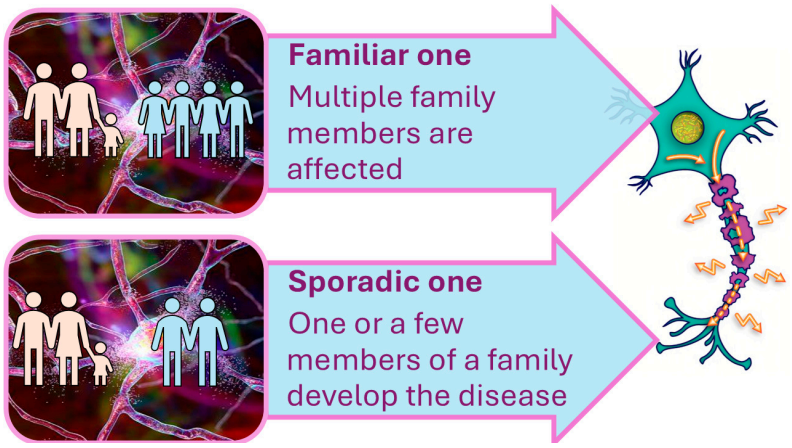

Figure A2. The main possible forms of AD.

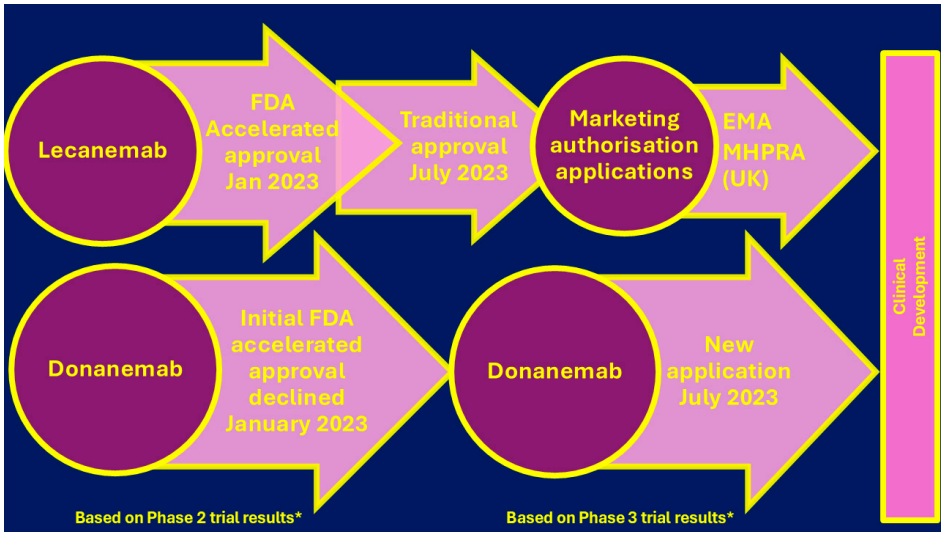

Figure A3. Developmental root to the clinical implementation of new active principles (PA) for MDTs. FDA = Food and Drug Administration; EMA = European Medical Agency; MHPRA = Medicine and Healthcare Products Regulatory Agency; * refers to donanemab.

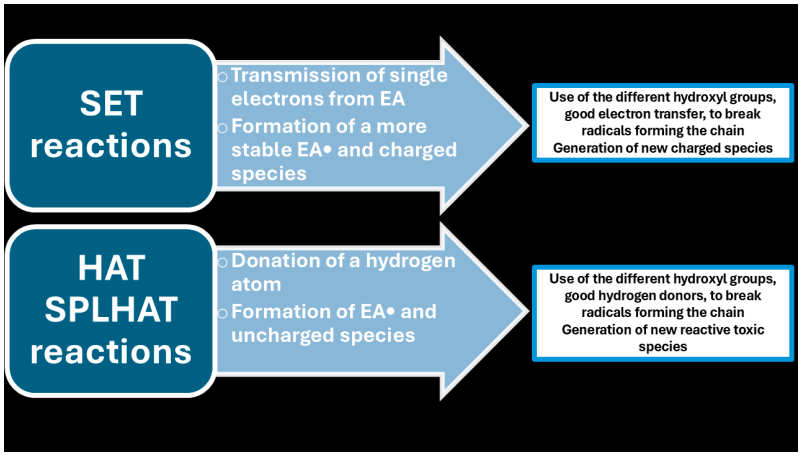

Figure A4. Antioxidant mechanism of EA.

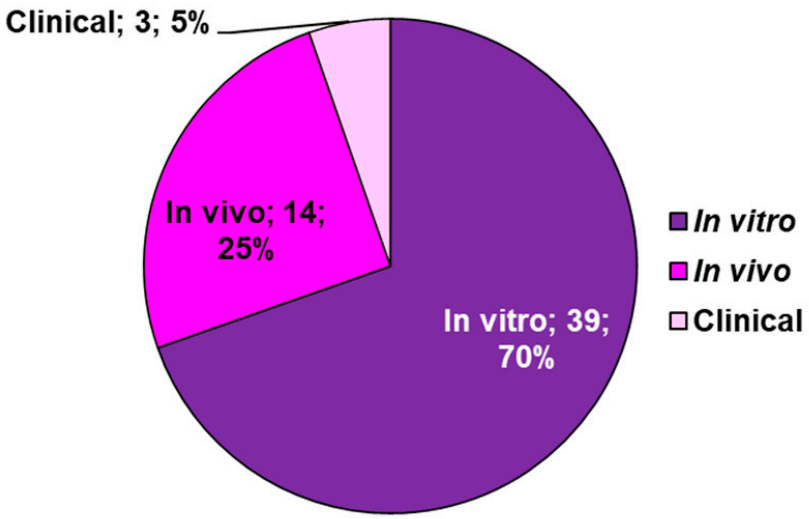

Figure A5. Percentages of in vitro, in vivo, and clinical reports on the pharmacological activity of EA-containing plants among 56 studies considered.

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