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Multi-Target-Directed Ligands and other Therapeutic Strategies in the Search of a Real Solution for Alzheimer's Disease

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Abstract: The lack of an adequate therapy for Alzheimer's Disease (AD) contributes greatly to the continuous growing amount of papers and reviews, reflecting the important efforts made by scientists in this field. It is well known that AD is the most common cause of dementia, and up-to-date there is no prevention therapy and no cure for the disease, which contrasts with the enormous efforts put on the task. On the other hand many aspects of AD are currently debated or even unknown. This review offers a view of the current state of knowledge about AD which includes more relevant findings and processes that take part in the disease; it also shows more relevant past, present and future research on therapeutic drugs taking into account the new paradigm "Multi-Target-Directed Ligands" (MTDLs). In our opinion, this paradigm will lead from now on the research toward the discovery of better therapeutic solutions, not only in the case of AD but also in other complex diseases. This review highlights the strategies followed by now, and focuses other emerging targets that should be taken into account for the future development of new MTDLs. Thus, the path followed in this review goes from the pathology and the processes involved in AD to the strategies to consider in on-going and future researches.

Keywords: Alzheimer's Disease, Multi-Target-Directed Ligands, Hybrid Molecules, New Molecules Design, Review.

1. INTRODUCTION

There are literally thousands of reviews published on Alzheimer's disease (AD) in scientific journals. In fact, the huge amount of articles that emerged in a single searching under the title "Alzheimer's disease review" up to now, is very close to 20.000 in PubMed database. This figure shows that it is a topic of great concern (that it is, indeed!); but the fact that more than thousand articles on the subject appear yearly we can obtain another lecture such as that constantly appears new relevant information about AD.

The purpose of this review is to bring here the well-known and the least recent discoveries involving two aspects of AD: the pathology of the disease and the pharmacological targets that have been investigated recently by different research groups, many of which follow the new paradigm of Multi-Target-Directed Ligands (MTDLs). This therapeutic strategy has been followed not only in the AD research but also in other neurodegenerative diseases. This review focuses mainly on aspects concerning the pathophysiology and medicinal chemistry. Massoud and Gauthier's review brings a complementary vision of this one, as the authors explore the pharmacological aspects of AD in today's treatments [1]. The review of Mangialasche *et al*. [2], focuses on drug development taking into account their mechanism of action and their clinical trial stages, including the different clinical failures that halted the development of encouraging AD therapies. The authors concerns were whether a multifactorial disease could be resolved by a compound targeting a single mechanism of action. Other reviews that are worth mentioning are Huang and Mucke's review which gives a deep insight into ApoE protein and its relationship with AD [3], and three reviews concerning medicinal chemistry, are from Cavalli *et al*. [4], Bajda *et al*. [5], and Leon and Marco-Contelles [6]. Very recently, there are two reviews of designing of drugs with multi-target activity, one of them from Geldenhuys *et al*. [7]; and the other about the molecular networks paradigm from Csermely *et al*. [8], this novel paradigm was some time ago proposed for multi-target drug discovery [9].

The economic and social aspects of AD are studied in depth in a recent review from Knapp *et al*. [10]. These aspects should not be underestimated, as they are of great concern, considering a prevalence of 30 million affected persons worldwide and that it is believed that by 2040 AD will affect more than 80 million of people on our planet [11]. This escalation is parallel to increased life expectancy, as the estimated annual incidence and prevalence of AD increases dramatically with age. In addition, the progression of the co-morbidity with age-related diseases will be enough to threat the sanitary systems in near future. Figures of co-morbidity are significant among the more frequent pathologies affecting elderly people. Co-morbid diseases with increased prevalence in AD patients are (RR versus control subjects): eating disorders (6.4), urinary tract infection (4.9), fracture neck of femur (4.1), pneumonia (2.8), depression (1.8), ischemic stroke (1.3) [12]. There could be additional problems inherent to the fact of patient admission to hospital

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as the mean stance will increase to 78 days versus 7 days of a non-AD patient, and there is an increased risk of later in-hospital mortality. The costs for AD patients are 34% higher than those of a population without the disease. The mentioned facts have entitled AD the dubious award of "The Challenge of the Second Century" [13].

1.1. Alzheimer's Disease

AD -the most common neurodegenerative disorder in elderly population- is genetically complex, slowly progressive and irreversible [14]. This disease is characterized clinically not only by an early and progressive memory loss, but also by other cognitive and behavioral disturbances [15, 16]. There are two primary pathological hallmarks of the disease: the deposition of both extracellular parenchymal and cerebrovascular amyloid-β protein (Aβ), and intracellular neurofibrillary tangles (NFTs) of hyperphosphorylated tau (τ) protein [17, 18]. Thus, anomalous protein aggregation is a crucial event in AD and it comprises of the whole processes of the defective protein, its formation, misfolding and defects in the cellular systems responsible for defective products removal [19]. This pathogenic accumulation of proteins is thought to be the cause, or at least the main factor that leads AD to cognitive impairment and, subsequently to a selective and extensive neuronal dysfunction or death in essential areas, as the hippocampus, amygdala, entorhinal cortex, and association cortices of the frontal, temporal and parietal lobes [20]. It has recently been suggested that it could be more the functional loss than the neuronal cell loss which leads to cognitive impairment [21]; and even that the loss of synapses and dendritic spines correlates better with cognitive impairment than the mere loss of neurons [22]. Currently it is proposed that, apart from degeneration of specific neuronal populations and synapses impairment, aberrant neuronal network activity should be considered as one of the main substrates of cognitive decline in AD [3]. Thus, the initial hallmarks considered led to these new ones: cerebrovascular abnormalities and synaptic failure, but also there are other hallmarks that necessarily have to be taken into consideration, namely: oxidative stress and neuroinflammation, all closely related to each other and further related to metabolic changes in the neuronal environment [23].

AD is one of the most enigmatic and intractable issues in biomedicine [24]. There are several putative factors in AD disease that could be grouped into endogenous and environmental factors, and these include processes as diverse as age, oxidative stress and free radical formation, defects in cellular bioenergetics and mitochondrial dysfunction, lesion of Golgi apparatus and intracellular transport, molecular chaperones, neurotrophins and neuroinflammation processes, even head injury or use of anesthetics, but little is known about the implications for the pathogenesis of the disease [19], even some factors are not easily considered cause or consequence. Thus, AD is considered as a multifactorial and/or multilevel pathology (Fig. **1**), with mechanisms that are complexly interrelated in vicious cycles, leading to neuronal and functional loss in the nervous system [25]. In addition, the contribution of each known factor to the pathology, or even the relevance of other unknown factors to be discovered, marks the difficulty of how to focus the problem.

1.2. AD Etiology

1.2.1. Aβ Peptides

The pathogenic character of Aβ has given origin to the "amyloid hypothesis" that states that the formation and deposition of small peptides of Aβ forms long insoluble amyloid fibrils, which accumulate in senile plaques [24] in critical regions of the brain, leading to the onset and progression of AD [26] which in the long run will lead to increasing disabilities and finally to death.

The pathogenic Aβ peptides, together with other considered non-pathogenic peptides, are originated by the proteolytic activity on the amyloid precursor protein (APP), a normal naturally occurring transmembrane protein. The activity of secretases (α, β, or γ secretase) excises APP, producing different peptides, depending on two different pathways: the α -or non-amyloidogenic- pathway which yields soluble APPα (sAPPα); and the β secretase -or amyloidogenic- pathway, that is mediated by the sequential action of β-secretase and γ-secretase, and results in the formation of Aβ peptides [27]. The relevance of α-secretase activity on halting the disease progression has been suggested recently, because it prevents the formation of toxic peptides [28, 29]. Since γ-secretase divides its substrate at several neighboring positions, Aβ peptides are a group of peptides differing in length at the C terminus. The dominant species is the $A\beta_{1\text{-}40}$ peptide constituting 80-90% of all Aβ peptides. The second major species is the $A\beta_{1\text{-}42}$ peptide, which constitutes in normal conditions 5-10%, and is considered aggregenic and thus forms the seed for larger oligomers and fibrils and finally for the macroscopic amyloid plaques [30]. From the two identified human β-secretases, the B-site APP-cleaving enzyme 1 (BACE1), a transmembrane aspartyl protease, is the one significantly expressed in the brain and seem to be relevant by cleaving APP into Aβ [24, 31].

Among other peptide forms, both Aβ peptides mentioned above can interact with themselves forming aggregates, either as cerebral amyloid angiopathy (CAA), as in the case of Aβ1-42 being accumulated in brain vessels [32]; or as senile plaques (SP) in the case of Aβ1-40, which will be deposited later in the disease process [20]. CAA contributes in building up SP aggregates and increases the clinical decline of AD patients [33] as well as leads to an enhanced loss of vessel integrity and functioning [32]. The pathogenic mechanisms, again, are largely unknown.

Extracellular deposited insoluble Aβ plaques are not only the result of the aggregation process of a group of hydrophobic peptides of 39-43 amino acid residues [20], but also the result of the defective degradation of anomalous proteins due to deficiency of the anomalous protein deposits clearance systems, namely the ubiquitin–proteasome–autophagy system and the lysosomal system [34].

1.2.2. Tau Proteins

The other classic pathogenic hallmark of AD, NFTs of τ protein, is constituted mainly by hyperphosphorylated paired

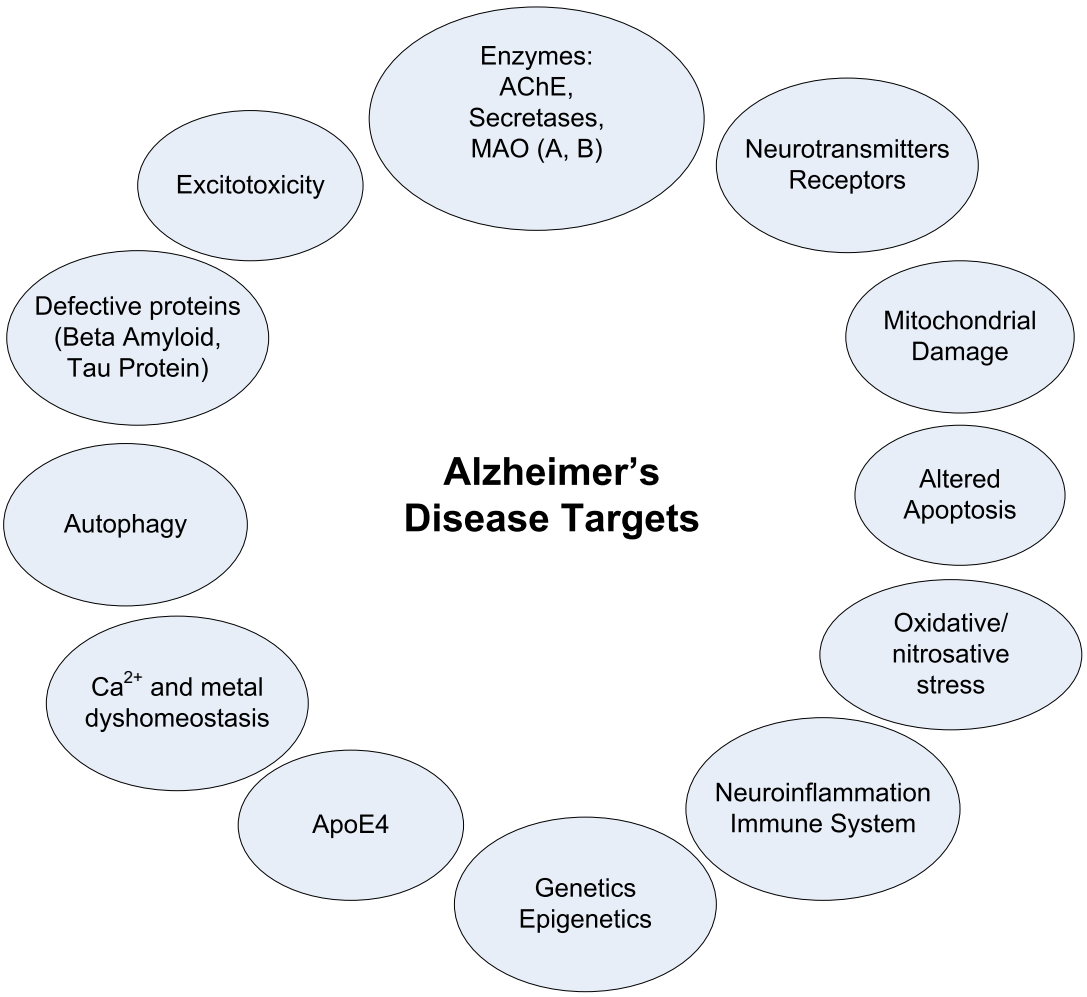

Fig. (1). Some of the main current targets in AD research.

helical filaments. Tau protein is a key microtubule-associated protein involved in the axonal trafficking, that in healthy neurons binds and stabilizes microtubules by reversible enzymatically mediated phosphorylation and dephosphorylation processes; but if τ is not dephosphorylated sufficiently, it does not bind adequately to other microtubules and polymerizes into filaments that further form NFTs [20]. The anomalous excessive phosphorylation and subsequent aggregation in intracellular tangles leads to a deadly cascade of impairment of axonal transport, synaptic alterations, microglial and astrocytic activation, progressive neuronal loss associated with multiple neurotransmitter deficiencies, and cognitive failure [24, 35]. Oligomeric and pre-aggregated forms of τ protein have been shown to be toxic *in vitro* [36]. These facts led to propose the hypothesis that has been named as "Tau hypothesis" [37].

1.2.3. Role of Peptides in the Developing Dementia

Whereas the density of amyloid plaques surprisingly does not correlate well in severity of dementia, NFTs do correlate well with the clinical symptoms, in fact now it is widely believed that there could be presence of amyloid deposits with few or no clinical manifestation [38]. The paradoxical evidences that Aβ plaques do not imply dementia and that the neurotoxic effect of these Aβ senile plaques is independent of its aggregation [39], could be explained by the investigations suggesting that the toxic agent and probable real inductor of AD pathogenesis are not the senile insoluble plaques, but the soluble Aβ peptides and oligomers instead [40]. In supporting this hypothesis, it has been found, that on one side, levels of soluble Aβ correlates with cognitive decline [41]; and on the other side, soluble peptides appear to impair synaptic structure and function [24], and that the accumulation of Aβ peptides leads to synaptic depression and aberrant excitatory neuronal activity [42, 43]. These findings lead to the conclusion that precisely some of the Aβ soluble forms are the pivotal pathogenic agents playing a role in presymptomatic early stages of AD process, well before or during the onset of plaques, although the exact Aβ species implied in the pathogenesis is to be discovered [44]. The relevance of the aggregated forms of Aβ in generating neuron impairment is also discussed, but aggregation could even act in reducing the toxicity of soluble Aβ by recruiting the peptide into the aggregates, and preventing their neurotoxicity [3]. There is however no absolute consensus about the pathogenesis of protofibrils and oligomers of Aβ40 and Aβ42, as indicated by Cerpa *et al*.,

suggesting that smaller cleavage products of APP are responsible for the neuronal dysfunction [45].

In summary, whether Aβ peptides and/or NFTs, the molecular mechanisms that conduce to learning and memory deficits remain unknown; however, the evidences point to the fact that the soluble or intermediate forms of these proteins (toxic peptides, protofibrils) which somehow interfere with cellular signaling cascades lead to cognitive impairment [46] and are thought to have cytotoxic effects on neurons [19, 37].

1.2.4. Clearance of Misfolded and Aggregated Peptides

Autophagy, a process that takes part in the cell to degrade damaged organelles and misfolded or aggregated cytoplasmic proteins, comprises of mainly three processes: macroautophagy, microautophagy and chaperone-mediated autophagy, differing in the mode of delivery to the lysosome [47]. The last two processes are relatively unknown in contrast to macroautophagy in which two pathways to induce autophagy have been identified: mammalian target of rapamycin (mTOR)- dependent and mTOR-independent signaling pathways [48]. Failure in clearance mechanisms lead to the accumulation of defective protein (previously formed, misfolded and/or aggregated) which is a crucial hallmark in AD [30]. Clearance of defective proteins implicates the collaboration between molecular chaperones and targeted protein degradation (performed by proteasome-mediated degradation), chaperone-mediated autophagy (CMA) and selective macroautophagy [49]. A failing of misfolded protein removal leads to the building-up of aggregated deposits and the development of the pathogenesis of proteinopathies [50]. The evidences of abnormal protein dynamics due to defective degradation, produced by deficiency of the clearance systems, are overwhelming in AD. Cognitive improvements in different mouse models are studied in recent reports [19, 51]. Prior to mentioning degradation of defective proteins, there are also brain clearance mechanisms of Aβ which follow two main routes [32], the direct way through the Blood-Brain Barrier (BBB), and the drainage *via* the interstitial fluid (ISF). The progressive impairment of these mechanisms, specially the first one leads, with the aging of the brain vessels, to the enhanced formation of CAA, affecting leptomeningeal arteries, cortical arteries and capillaries [33].

1.2.5. Cholinergic System

AD patients are present with impaired neural transmission of cholinergic, serotoninergic, glutamatergic, dopaminergic, and noradrenergic systems [52, 53]. Specifically the cholinergic system is closely related to the pathology and evolution of the AD disease. In AD, there is a functional impairment of basal forebrain cholinergic neurons linked with structural lesions in the same areas or regions that project to or from those areas [20, 54]. The consequences of these lesions are low levels of acetylcholine (ACh) and a loss of cholinergic transmission, resulting in learning and memory dysfunctioning. It was also found that a reduction of the acetylcholine synthesizing enzyme (choline acetyltransferase, ChAT) correlates with the grade of dementia [55]. These related events led researchers to propose the "cholinergic hypothesis" of AD, that is firmly supported by the fact that nearly all the drugs approved for AD treatment deal in one or another way with this hypothesis [56]. The links between AD disease and cholinergic system are confirmed in newly investigated evidences, and nowadays a presynaptic cholinergic hypofunction is also considered a crucial hallmark in AD [57]. Since acetylcholinesterase (AChE) (EC 3.1.1.7) catalyzes the hydrolysis of ACh into acetate and choline, AChE inhibitors are traditionally used as cholinergic agents, playing an important role in symptomatic AD treatment. In the three-dimensional structure of the enzyme the catalytic active site (CAS), constituted by three amino acids (Ser200-His440-Glu327) lies at the bottom of a long and narrow (20 x5 Å) gorge formed by 14 aromatic amino acids, where tryptophan 84 is the critical constituent of the anionic binding site [58]. The surface of the throat is known as the peripheral anionic side (PAS).

It seems that AChE is also directly implicated in AD pathogenesis influencing Aβ deposition. This has been demonstrated *in vitro,* incorporating AChE to Aβ peptides [59], and *in vivo*, injecting AChE in rat hippocampus leading to a significant cognitive impairment [60]. The experimental evidences point out that AChE acts as a molecular chaperone, accelerating the formation and increasing the neurotoxicity of amyloid fibrils and stable complexes, due to PAS, located at the entry side to the active center gorge [61, 62]. It also has been demonstrated that APP processing is regulated by the cholinergic system [20] as well as Aβ which can modulate the cholinergic system [61]. This modulation seems to be age-dependent, as aged neurons appear to be more sensitive to Aβ-mediated inhibition [63]. However, if the degenerative cholinergic loss is primary or secondary to the amyloid plaque pathology remains to be resolved [21].

The influence of neuroreceptors in AD has been intensively studied [64]. Both muscarinic and nicotinic receptors are altered in AD patients [65], and the initial stages of the disease show a clear decrease of ACh levels and nicotinic receptors [54]. The involvement of the muscarinic receptors M_1 and M_2 in AD has also been well studied [54, 55, 57, 66].

The increase of phosphorylated τ proteins in cell lines or cultured neurons can also be related to the cholinergic system [20, 67]. The APP processing can also be influenced by the cholinergic system, and affected by other endogenous and external factors, such as serotonin, glutamate, estrogen, testosterone, bradykinin, insulin, calmodulin, other neuropeptides and growth factors, copper, statins and some plant extracts [5, 20, 68].

1.2.6. The Connection Among Oxidative/Nitrosative Aberrant Signaling Pathways, Neuronal Excitotoxicity and Neuroinflammation in AD

AD pathology shows other pathogenic hallmarks like oxidative/nitrosative stress, excitotoxicity and neuro-inflammation. The "oxidative stress hypothesis" states that the increase of production of reactive oxygen species (ROS) and free radicals leads to deleterious effects on the cell components that are involved in the pathogenesis of AD [69]. The oxidative stress was initially supposed to be the result of AD pathology, but this premise has been questioned [70, 71], and a more prominent role of oxidative stress in AD

pathology is accepted [72]. In fact oxidative stress has been linked to Aβ aggregation through its relationship with BACE1 activity [73]. Nitrosative stress runs in parallel to oxidative stress and also there are products resulting from this activity, namely reactive nitrogen species (RNS), both oxidative and nitrosative stresses are now accepted as central processes in AD pathophysiology [74]. Recently it has been proposed that oxidative/nitrosative stress act as aberrant signaling pathways, resulting in progressive damage to the neuronal network [23]. On the other hand, excitotoxicity as the neuronal tissue status in which there is an excessive stimulation of ionotropic glutamate receptors, namely N-methyl-D-aspartic acid (NMDA) receptors, and an imbalance of neuronal calcium homeostasis, has been shown to conduct neuronal damage by increasing damaging free radicals and also activating nucleases, proteases and phospholipases which are considered the origin of mitochondrial dysfunction and apoptosis [23, 75]. In turn, mitochondria are well known sources of free radicals, and even in mitochondria of non-pathological cells, a low quantity of ROS is produced and maintained at a minimum by cellular defense mechanisms, but ROS can be produced in a quantity that would contribute to synaptic damage [76]. The imbalance of ROS leads to other deleterious effects that may likely end in cellular death [77] and also severely damaging mitochondria [78]. Recently it has been shown that both toxic Aβ and excessive neuronal excitation induce ROS production not only by means of mitochondria but also by the activation of NADPH oxidase, and that ROS would trigger changes in various signaling downstream pathways as mitogen-activated protein kinases (MAPK). Also, NADPH oxidase would lead to the activation of MEK1/2 or ERK1/2 and cytosolic phospholipase A_2 (cPLA2) [79]. Phospholipases A_2 are enzymes that hydrolyze fatty acids from membrane phospholipids, $cPLA_2$ is found in diverse nervous tissue cells and besides calcium is regulated by receptor mediated signaling pathways. In addition, the role of $cPLA_2$ in neurodegenerative diseases through its implication in oxidative/nitrosative signaling pathways has been clearly shown [80, 81]. Thus, there is a close relationship among Aβ toxic oligomers and excessive activation of NMDA receptors with calcium influx, cPA_2 activation, and oxidative/nitrosative aberrant signaling pathways, but also there is a direct influence of Aβ oligomers as they act on NMDA receptor trafficking [82]. In addition, oxidative/nitrosative stress contribute to protein misfolding and aggregation, therefore it is considered a pathogenic trigger of neurodegenerative processes; specifically, RNS acting through the S-nitrosylation of protein-disulphide isomerase (PDI) blocks the protective effect that this enzyme has on neurodegenerative disorders [83]. Nitrosative stress not only has been related to protein misfolding and mitochondrial dysfunction [84] but also to the mediation of cell injury and cell death after excitotoxicity [85].

Neuroinflammation is another feature of neuro-degenerative disorders, but there is little knowledge about factors determining susceptibility to neurodegeneration [86]. During neuroinflammation, nitric oxide (NO), second messenger in inflammatory signaling, is increased, producing and leading, among others, to tyrosine nitration in proteins as τ [87, 88]. Both ROS and RNS act together in neurodegeneration [89] in a vicious cycle, leading to a pro-inflammatory status, with the release of pro-inflammatory cytokines including interleukins (IL-1β, IL-6), and tumor necrosis factor α (TNFα) [90], activating microglia and astrocytes that can produce excess of NO [91]. In NO synthesis intervenes the enzyme nitric oxide synthase (NOS) of which there are three subtypes: neuronal, endothelial and inducible. In spite of the known upregulation in AD of inducible NOS (iNOS), the significance of the other subtypes of NOS (nNOS and eNOS) in AD is largely unknown [23], although a correlation has been found between nNOS in neuronal cells and neurodegeneration [92]. There are evidences of the possible synergism among nNOS and $cPLA_2$ in Aβ neurotoxicity and cyclooxygenase-2 (COX-2) should be included in the group [23].

1.2.7. Main Risk Factors for AD: Age and Genetics

AD is a genetically complex disease, thus it is quite difficult to assess the genetic influence on the apparition and progress of the disease [14]. However, in spite of its inherent difficulties this knowledge area is one of the most studied and promising in AD research till date.

One relevant aspect of AD etiology is the relationship between the age when the first symptoms appear, and the underlying genetics burden on the patient, resulting in two forms of the disease. When symptoms appear after the age of 60, patients are said to suffer from "sporadic late-onset AD" (SAD or LOAD) [3]. Besides aging, the presence of some *APOE* gene polymorphisms (namely ε4 allele) is one of the most important risk factors for developing LOAD [93, 94]. In a small number of AD patients the onset of dementia is before the age of 60, and they are classified as "early onset familial AD" (EO-FAD) patients; further, they present mutations in *APP* (amyloid precursor protein gen), *PSEN1*, and *PSEN2* (presenilin genes) [95]. However, there are many unanswered questions in AD genetics, as up to 50% of the heritability of AD remains unexplained by the known genes; and the question, if LOAD or EO-FAD are Mendelian transmitted or not, is still debated [93].

Epigenetics and AD

Suffering from AD for a given genetic burden is not always a certainty, it has been found that human monozygotic twins are likely to differ in developing the disease [96]; thus, environmental risk factors do matter significantly. Epigenetics comprise the mechanisms involved in transient and reversible changes to the chromatin regardless of the cellular differentiation status, and also those modifications concerning gene expression altering transcriptional activity in a coherent manner [97]; bringing the opportunity to environmental factors to influence how genetics will be expressed [98]. Major epigenetic mechanisms namely chromatin remodeling and histone modifications, DNA methylation, and micro RNA (miRNA) are recently described [98, 99]. With the help of those mechanisms heritable and non-heritable traits become modified without altering the DNA sequence, achieving the repression or silencing the expression of specific genes. In turn, the release from a given epigenetic repression can enhance gene expression [98]. The implication of epigenetics has been shown in the development of many diseases, among them neurodegenerative diseases, has become progressively more

evident. In the case of AD the early influence on the genome to the later developing of the disease has been proposed; for instance, the ''LEARn" (Latent Early-life Associated Regulation) model integrates environmental risk factors and the developmental basis of AD [100].

1.2.8. ApoE4

Regardless of the aforementioned evidences about the implication of ApoE on AD risk, ApoE4 is considered–an important factor in developing AD and other types of neurological pathogenesis [101]. ApoE is a polymorphic protein, with three human isoforms ApoE2, ApoE3 and ApoE4, that revealed to be crucial in neurobiological functions. Depending on the isoform considered, ApoE has either physiological functions (neurite remodeling, membrane repairing and remyelination), or pathophysiological functions (related to dendritic and synaptic alterations, Aβ clearance or deposition, glutamate receptor function or mitochondrial function) [102]. There are not only acute differences between the neurobiology and pathologic roles of different ApoE isoforms, the different cellular sources also lead to both, physiological and pathophysiological processes [103]. Thus, astrocytes and neurons express ApoE, however, ApoE expression in astrocytes is increased in the course of aging and also in response to estrogen stimulus and/or activation of liver X or NF-κB receptors, the CNS neurons appear to respond mainly to the stimulus of stress and injuries [103]. The differences also extend to the action of isoforms expressed by one or another type of cell, thus ApoE3 expression protected neuronal synapses and dendrites from excitotoxic damage in ApoE-deficient mice, regardless of its cellular origin, whereas neuronal expression of ApoE4 in cortical neurons led to cell death, after excitotoxic challenge [104]. Furthermore, ApoE isoforms respond differentially to AD hallmarks, namely Aβ and NFTs; in both cases ApoE4, on the contrary to other isoforms, increases Aβ accumulation and building up amyloid plaques [3], as well as increases τ phosphorylation and accumulation in the neurons [105]. The negative roles of ApoE4 in AD pathogenesis were also found in age-dependent and excitotoxin-induced neurodegeneration [104], impaired synaptogenesis [106] and neurogenesis [107], mitochondrial dysfunction and neurotoxicity [102], they also caused age- and τ-dependent impairment of hilar GABAergic interneurons, leading to reduced hippocampal neurogenesis and to learning and memory deficits [105].

1.3. Today's AD Therapeutic Research

Since the dawn of first symptomatic drugs some 15 years back, it can be said that currently there is no effective cure or prevention of Alzheimer's disease available and that the therapeutic approaches are symptomatic and of modest efficacy [14]. The only approved drugs that may produce real improvements in cognitive performance, fall in two categories: AChE inhibitors (AChEI), and NMDA antagonists [108], with respectively 4 and 1 drug each group [109]. The cholinergic drugs tend to restore or increase the cholinergic system deficiency by means of inhibiting acetylcholinesterase (AChE), the enzyme that degrades acetylcholine, and donepezil is a prominent component of this group [110]. There are several evidences that inhibition of AChE not only restores the cholinergic system, but also interferes with the progression of the disease [111]. On the other side, memantine attenuates the excessive NMDA glutamate receptor activity observed in AD, acting as a non-competitive, low-affinity, open-channel blocker, and it is frequently used in combination with AChE inhibitors [14].

The aforementioned drugs are clearly insufficient for an adequate AD therapy, and real solutions for the disease are eagerly awaited; unfortunately promising solutions -as the vaccination therapy attempts up to now have been, either failed in clinical phase application or are still in developing stages. So far, none of the disease modifying drugs recently developed, has demonstrated adequate efficacy in phase III studies, reducing Aβ production, preventing its aggregation, promoting Aβ clearance or targeting τ protein [112]. The poor outcomes of some Aβ targeting therapeutic agents has complicated the current advances in AD [14], although Selkoe argued that the cause of the problem might be on the trial design or the agent used, and not on the target itself [113]. Considering immunotherapy as a case of study, the first attempts to use antibodies against Aβ apparently worked well in mice, but in humans, the last clinical assay phase showed meningoencephalitis in some patients [114]. Nevertheless, immunotherapy approach is continuing, and currently studies about Aβ peptide immunotherapy and against τ protein pathology are ongoing [115]. Apart from the initial limitations of immunotherapy, cases of phase III clinical trial halting were also described for γ-secretase inhibitors, where patients showed cognitive worsening [116], or for pioglitazone, a PPARγ agonist and β-secretase inhibitor, where cardiac side effects and/or lack of efficacy, due to poor brain blood-barrier permeability, were reported in phase III trials [117, 118].

Currently, the trend of research studies is devoted to reduce these impairments or improve their causative origin [119]. Consequently, Hampel *et al.*'s disease modifying therapeutic solutions are being pursued against Aβ or τ deposition, inflammation and oxidative stress, among others [14]. On the other hand, as Standridge suggests "the paradigm that AD is pharmacologically unresponsive is shifting" and as the understanding of the molecular mechanisms of neurodegeneration progresses AD will progress, it will allow the development of more specific targets by achieving the interruption of the events that lead to this dementia [120]. However, the discovery of a remedy capable to prevent the disease progression will produce its positive results within a relatively delayed time, thus, it can be said that if a drug able to delay the disease 5 years gets approved by 2015, then it is predicted to reduce the clinical symptoms to about 40% by 2050 [117]. According to Holtzman *et al*., a major challenge for the development of therapies lies in identifying those patients at high risk for moving from a cognitively normal to an impaired status over a 3-4 year window, and to target this population for clinical trials [13].

2. NEW THERAPEUTIC STRATEGIES

2.1. Changing Paradigms

It is not so far away that the poly-pharmacology approach (that is administering a drug combination to treat a disease)

was criticized in pharmacy schools because of the plethora of side effects that these drugs could produce in patients, with little or no improvement. This induced a tendency toward more specific, more fitted-to-disease drugs. Thus, drug research has moved from a human phenotype-based endeavor to a "target-centric" or "reductionist" approach, trying to reduce drug action to individual genes, single proteins, and one modulating molecule [121], known as the term "one-disease-one-target" [122] or even "one gene, one target, one drug" [123]. The research approach in AD has followed the same trend, targeting each pathological aspect of the disease as specifically and precisely as it could be done, in the hope that it would cope or even reverse the disease. However, the fact that AD is a complex neurodegenerative disorder with a multifaceted pathogenesis [124] (Fig. **1**), complicates it to a great extent in choosing the most adequate targets, thereby restricting it to discussion only than to seek clear-cut solutions. The currently available drugs targeting as AChEs inhibitors (AChEI) and NMDA receptor antagonists (memantine), have turned out to be more palliative rather than curative [108]. According to Mudher and Lovestone, the dichotomy in selecting Aβ or τ protein as targets, has led to two kinds of "adepts", namely "baptists" (those concerned with Aβ), and "tauists" (τ protein research) [125], but in any of the cases promising drugs were not found. On the other hand, antagonizing AChE were acting not only against this target, but also on other aspects of the disease. It has been shown that AChEIs were better solutions than specific one-action drugs. Not only AD but other neurological disorders can be treated by this approach, several diseases having a multifactorial etiology are better treated with a combination of drugs (depression, schizophrenia, allergies, hypertension, inflammation conditions and metabolic diseases) [124]. Experimental studies have shown that such drug combinations also work in AD. As an example, the combination of galantamine and melatonin at sub-effective concentrations (30 and 0.3 nM, respectively) induced a synergistic protection, that was similar to the highest activity obtained separately with effective doses of melatonin or galantamine [126]. It is now well-known that the synergic effect obtained by combining different compounds, interfering simultaneously in a defined biological circuit, may increase the bioavailability of each compound at the same target [127]. There are more attempts to obtain 'multiplicative' effects by adding two drugs. Among those association of molecules there are: rivastigmine plus memantine [128], donepezil plus SLV330, a CB1 antagonist, [129], and memantine plus vitamin D [130].

2.2. Multi-Target-Directed Ligands (MTDLs)

However, despite the new hopes for healing AD, and other neurodegenerative diseases, by drug combinations acting at different levels of the neurotoxic cascade, the researchers are endeavoring to go deeper than that, and ultimately have proposed a new paradigm, emerging from a new concept -therapeutic molecules acting at different levels or targets of the disease- with different denominations: network pharmacology [8, 9, 123], multi-modal therapies [30], multifaceted [131], and more widespread MTDLs [5] or the more recently proposed term "multi-targeted designed drugs" (MTDDs) [7]. A related but more restricted concept, is that of "hybrid compounds" (Fig. **3**). Muller-Schiffmann *et al*. introduce an excellent definition for "hybrid compounds" as "the combination of two different and independently acting compounds into one covalently linked hybrid compound" that "can convey synergy from the effects of both independently acting moieties to the new composite compound, leading to a pharmacological potency greater than the sum of each individual moiety's potencies", taken into account that the moieties can be a wide variety of substances such as small molecules, polypeptides or nucleic acids [127]. Thus, hybrid compounds are designed to be MTDL molecules but not all these compounds originate through the hybrid compound strategy. This new approach in medicinal chemistry, MTDL design strategy, will develop through of single chemical compounds which are able to modulate multiple targets simultaneously (in principle with comparable affinities), with superior efficacy and safety profiles. Acting in a synergic manner on different targets, a single multifunctional drug will interfere with the networked (no matter whether sequential or not) multifactorial etiology of the disease, obtaining a real improvement throughout. In order to seek opportunity to reduce the side effects some authors [4, 121] suggested the possibility of achieving even more attractive therapies in the future. MTDLs are originated not only by the ingenuity of researchers, but also are generated in nature with examples as botulinum toxin, the prime illustration of multi-modular cooperation and site-directed activity; and bleomycin which is another natural MTDL [127, 132]. Cannabinoids, with their multi-level neuroprotective effects, can also be included as nature-generated MTDL [133].

Once the advantage of multi-targeting is clear, the next step is to decide how to combine multi-targeting in a single therapy solution. There are two possibilities, the election of molecules with in-built capacity to act on two or more targets, and/or to combine two or more pharmacophores in a single molecule. Other difficulties that are to be resolved in the MTDL strategy are to choose the most appropriate therapeutic targets (by now a question without a clear answer) and to select an adequate lead molecule to start with.

This last challenge, following previously exposed concepts, points to the AChEIs as a good option, since many AChEIs really found to be good multi-targets (Aβ inhibition, nicotinic receptor modulation, etc.), and are actually one of the first choices of researchers.

2.3. Examples of MTDL

MTDL have been present in one or another form in some compounds used in AD therapy. Thus, galantamine was found to be not only a competitive and reversible acetylcholinesterase inhibitor but also an allosteric modulator at nicotinic acetylcholine receptors [134]. Apart from its AChEI activity, donepezil has been shown to inhibit Aβ self-aggregation and BACE1 [135] and to interact with sigma-1 receptors, known for their anti-amnesic effects [136].

One of the most prominent sources of MTDL is the area of "natural products" and within them, botanical compounds are perhaps not only greater in number but also the most

Table1. Examples of Multi-Target-Directed Ligands with Origin on Natural Products and Semi Synthetic Analogs

Compound	AChE Inhibitor	Tau Hyperphos-Phorylation Inhibitor	β-amyloid Anti-Aggregation, Clearance, or Secretion	Antioxidant	Other Activities	Clinical Status (Phase)	References
Alkaloids							
Physostigmine	◆				◆nicotinic receptor agonist		[265]
Phenserine	◆		◆	◆	◆neurotrophic ◆kinase modulator ◆NMDA receptor modulator	I/III	[266] [267] [268]
Galantamine	◆				◆nicotinic receptor allosteric modulator ◆anti-apoptotic	IV	[134] [269]
Huperzines A, B	◆				◆NMDA receptor modulator ◆neuroprotective ◆anti-apoptotic	II	[270] [271]
Berberine	◆		◆	◆	◆ IMAO ◆anti-neuroinflammatory ◆cholesterol regulator ◆ insulin regulator		[272] [273]
Epiberberine	◆	◆		◆			[274]
Coptisine					◆neurotrophic ◆ IMAO-A		[274]
Groenlandicine	◆	◆	◆	◆			[274] [275]
Jatrorrhizine	◆			◆			[274]
Manzamine		◆			◆anti-neuroinflammatory ◆kinase modulator		[276]
Harmine, Harmaline	◆	◆		◆	◆ increase dopamine release ◆IMAOs ◆NMDA receptor modulators ◆kinase modulators		[277] [278]
(10-hydroxy)-Infractopicrin	◆		◆				[279]
Trigonelline	◆				◆neurotrophic ◆memory enhancement		[280] [281]
Nantenine	◆		◆		◆adrenergic α1 and serotonin 5-HT_{2A} receptors antagonist		[282]
Crebanine	◆				◆ α7-nACh receptor modulator		[283]
Nicotine			◆	◆	◆nicotinic receptor agonist ◆ neuroprotective ◆ anti-apoptotic		[271]
Caffeine					◆adenosine A_2 receptor antagonist ◆IMAO-B		[284] [285] [286]

Table 1. contd….

Compound	AChE Inhibitor	Tau Hyperphos-Phorylation Inhibitor	β-amyloid Anti-Aggregation, Clearance, or Secretion	Antioxidant	Other Activities	Clinical Status (Phase)	References
Alkaloids							
Vincamine					◆ brain circulation modulator ◆ voltage Na^+ channel modulator		[271]
Cyclobuxidine F derivatives	◆		◆				[287]
Polyphenols							
Luteolin	◆	◆	◆	◆	◆kinase modulator ◆mitochondrial protector		[288] [289] [290]
Myricetin			◆	◆	◆anti-neuroinflammatory ◆NMDA receptor modulator ◆BACE-1 inhibitor		[291] [292] [293]
Plant derived Coumarins: Decursinol, Mesuagenin	◆		◆	◆	◆anti-neuroinflammatory ◆IMAOs		[294] [295] [296]
Ensaculin	◆				◆serotonin 5-HT_{1A} agonist ◆ NMDA receptor modulator (antag.) ◆dopamine D_2 receptor antagonist	II	[297] [298]
Epigallocatechin gallate			◆	◆	◆BACE-1 inhibitor (?) ◆α-secretase inhibitor ◆kinase modulator ◆α-synuclein inhibitor ◆metal chelator ◆anti-inflammatory	II -III	[299] [300] [301] [302] [303]
Ferulic acid			◆	◆	◆BACE-1 inhibitor ◆protective against *PSEN1* expression (transgenic mice)		[304] [305] [306]
Rosmarinic acid	◆	◆	◆	◆	◆anti-apoptotic ◆neuroprotective ◆binds to muscarinic M_1, nicotinic, serotonin 5-HT_{1A}, serotonin 5-HT_{2A} and histamine H_3 receptors		[291] [307] [293] [271]
Nordihydroguaiaretic acid			◆	◆			[293]
Curcumin	◆		◆	◆	◆anti-inflammatory ◆BACE-1 inhibitor ◆α-secretase inhibitor ◆tau dimerization inhibitor ◆metal chelator ◆neuroprotective ◆ NMDA receptor modulator (antag.)	II	[308] [309] [310] [311] [312] [313]

Table 1. contd….

Compound	AChE Inhibitor	Tau Hyperphos-Phorylation Inhibitor	β-amyloid Anti-Aggregation, Clearance, or Secretion	Antioxidant	Other Activities	Clinical Status (Phase)	References
Polyphenols							
Resveratrol	◆		◆	◆	◆ SIRT1-ROCK1 signaling pathway regulator ◆BACE-1 inhibitor ◆apoptosis modulator ◆anti-inflammatory	III (n)	[314] [310] [315] [316] [317] [318]
Vitisin A, Heyncanol A	◆		◆				[319]
Hopeahainol	◆		◆	◆	◆neuroprotective		[320] [321]
Apocynin				◆	◆anti-inflammatory ◆NADPH oxidase inhibitors		[225]
Honokiol, Magnolol					◆anti-apoptotic ◆neuroprotective		[322]
Cannabinoids							
Cannabidiol				◆	◆neuroprotective ◆sedative		[271]
Terpenoids							
Niloticane	◆				◆ COX-1 inhibitor ◆ COX-2 inhibitor		[323]
Timosaponin AIII & BII	◆ (AIII)		◆(BII)	◆(BII)	◆anti-inflammatory ◆BACE-1 inhibitor (BII)		[324] [325]
Withanolide	◆		◆	◆	◆neurotrophic ◆BACE-1 inhibitor ◆α-secretase inhibitor ◆LDL receptor-related protein enhancer		[326] [327] [328] [329]
Asiatic acid	◆		◆	◆	◆BACE-1 inhibitor ◆anti-apoptotic ◆anti-inflammatory ◆α-secretase inhibitor ◆kinase modulator		[330] [329] [331]
Sage monoterpenoids	◆			◆	◆anti-inflammatory		[271]
Ginsenosides	◆		◆	◆	◆neuroprotective ◆ NMDA receptor modulator (antag.)		[271] [275]
Diverse Compounds							
Bryostatin			◆		◆α-secretase inhibitor ◆kinase modulator	I-II	[332]
Epothilone		◆			◆ microtubule stabilizer		[333]

Table 1. contd….

Compound	AChE Inhibitor	Tau Hyperphos-Phorylation Inhibitor	β-amyloid Anti-Aggregation, Clearance, or Secretion	Antioxidant	Other Activities	Clinical Status (Phase)	References
Diverse Compounds							
Geldanamycin		◆			◆ proteasome activator		[208]
Rapamycin		◆			◆immunosuppressant		[334]
Zeatin	◆			◆	◆neuroprotective		[335] [336]
Butylphtalide (NBP)		◆	◆	◆	◆αAPPs increased release ◆anti-inflammatory ◆kinase modulator ◆anti-apoptotic		[337]
Minocycline		◆	◆	◆	◆BACE-1 inhibitor ◆anti-apoptotic ◆anti-inflammatory ◆neurogenic		[338] [339] [340] [341]
Geniposide, Gardenoside					◆ memory enhancement ◆anti-apoptotic ◆neurogenic		[342] [343]
WIN-026 (KRWAR-026; INM-176)	◆		◆	◆		III	[344] [345]

relevant group of chemical compounds that are considered relevant to develop new substances (Table **1**).

2.3.1. An Example of Designed MTDL: the Path from Selegiline to Ladostigil

There are also interesting examples of MTDL design based on the combination of two or more pharmacophores acting on different targets of the disease. A good illustrative example is the case of a very promising drug for AD treatment, ladostigil (Table **2**), which emerged from selegiline [137]. Selegiline, a selective and irreversible monoamine oxidase B inhibitor (IMAO-B) that failed as antidepressant, but led to the discovery of a new therapy in (PD), also showed neuroprotective properties and is the precursor of rasagiline, [138] a less neurotoxic drug also used in PD therapy. The inhibition of MAO avoids hydrogen peroxide generation and the formation of neurotoxic free radical species. The incorporation of a carbamate moiety, the pharmacophore group of the AChE inhibitor rivastigmine, on the molecule of rasagiline, led to the design of ladostigil, which resulted in an inhibitor of both cholinesterases (AChE and BuChE) and both brain MAO (MAO-A and MAO-B). [139-141]. In addition to this inhibitory effects, ladostigil (but also rasagiline) presented other neuroprotective actions, such as to stimulate the processing of APP to the neuroprotective sAPPα. Furthermore, ladostigil protected against oxidative stress-induced neuronal apoptosis, increases antioxidant enzymes' expression and catalase activity [142]. Finally ladostigil also increased the brain-derived nerve factor (BDNF) mRNA expression, leading to improved BDNF formation and, consequently, to enhanced neuroprotective activity [143]. Thanks to the wide MTDL profile, ladostigil is not only considered as a promising candidate for AD treatment but also for other neural diseases, namely PD and amyotrophic lateral sclerosis (ALS). The last step in the path followed by Youdim's group is the attempt to incorporate into the molecule an iron chelator moiety [144], the way is paved to continue the path.

2.3.2. Natural Origin MTDL: Cannabinoids in AD Therapy

Among the substances with the ability to reduce or mitigate neurodegenerative symptoms, the group of cannabinoids has to be taken into consideration [145, 146]. The connection between the endocannabinoid system and AD has been reported consistently [119, 147-149].

The therapeutic potential of cannabinoids [150] in AD becomes apparent in several mechanisms: non-competitive AChE inhibition [151]; anti-aggregation of Aβ peptides mediated by AChE PAS inhibition or by phagocytosis of Aβ peptides mediated by CB2 receptors [152]; anti-glutamatergic effect [153]; anti-oxidant activity [147]; anti-neuroinflammatory properties [154]. It is also noteworthy

Table 2. Examples of Designed Multi-Target-Directed Ligands

Compound	Merged Pharmacophores	Additional Activities	References
Dual Acetylcholinesterase and β-amyloid inhibitors (Drugs interacting with Acetyl and/or Butyrylcholinesterases binding simultaneously to the catalytic anionic site (CAS) and the peripheral anionic site (PAS) or only to PAS)			
Xanthostigmine	Rivastigmine - xanthone hybrid		[4]
AP2238	Coumarin - dibenzylamine hybrid		[346]
IQM-622	Tacrine - 8-hydroxyquinoline hybrid		[347]
Indanone-tacrines	Tacrine - donepezil hybrid		[348]
Pyrano[3,2-c]quinoline tacrines	Tacrine - pyrano[3,2.c]quinoline hybrid		[349]
NP-61 (NP-0361) (Structure not disclosed)	Probable tacrine - indole propionamide hybrid		[350, 351, 352]
Bis(7)-tacrines	Bis-tacrines	BACE1 inhibitors	[353, 354]
Tacrine multimers			[355]
Huprine-tacrines	Tacrine - huprine hybrids	BACE1 inhibitors	[356, 357]
Donepezil-huprine derivatives	Huprine - Donepezil hybrids	BACE1 inhibitors	[358]
Indanone-dibenzylamines	AP2238 - Donepezil hybrids		[359]
N-benzylpiperidine purine derivatives	Donepezil analogues		[360]
9-substituted berberines			[361]
9-substituted berberines containing tiazole			[362]
Isaindigotone derivatives			[363]
Oxoisoaporphines			[364, 365]
Oxoisoaporphine-tacrines	Tacrine - oxoisoaporphine hybrids		[366]
Multialkoxybenzene-tacrines	Tacrine – multialkoxybenzene hybrids		[367]
2,4-disubstituted pyrimidines			[368, 369]
Piperidinium-type and 1,4-dihydropiridine derivatives			[167, 166]
Piperidine linked derivatives			[370]
Glutamic acid linked derivatives		Neuroprotective against free radicals	[371]
Benzofuran-based hybrids			[372]
Benzophenone linked derivatives			[373]
Bis-nor-meptazinols			[168]
Dual Acetylcholinesterase inhibitors and antioxidants			
Lipocrine	6-Chlorotacrine - α-lipoic acid hybrid	β-amyloid inhibitor	[374]
Memoquin and derivatives	Caproctamine - 1,4-benzoquinone hybrid	β-amyloid inhibitor Muscarinic M_2 receptor antagonist BACE1 inhibitor	[375, 376, 377, 378, 379]
Benzoquinone curcumin hybrid Benzoquinone SKF64346 hybrid			[380]
Tacrine melatonin hybrids			[381, 382]

Table 2. contd….

Compound	Merged Pharmacophores	Additional Activities	References
Dual Acetylcholinesterase inhibitors and antioxidants			
Tacrine ferulic acid hybrids			[383]
Cystamine-tacrine dimer			[384]
N-acylaminophenothiazines			[385, 386]
Dual Acetylcholinesterase inhibitors and metal chelators			
HLA20A	Carbamoylated 8-hydroxyquinolines		[387, 388]
Indanone derivatives			[389]
Tacrine-8-hydroxyquinoline hybrids PBT2		Neuroprotective Antioxidant	[347, 390]
Dual Acetylcholinesterase and β-secretase (BACE1) inhibitors			
Memoquin	Caproctamine - 1,4-benzoquinone hybrid	β-amyloid inhibitor Muscarinic M_2 receptor antagonist Antioxidant	[375, 376, 377, 378, 379]
Coumarin derivatives	AP2238 derivatives		[391]
Bis(7)-tacrine	Tacrine homodimers	Calcium channel blocker	[353, 392, 393, 354]
Tacrine-chromene hybrids		β-amyloid inhibitor	[394]
Huprine-tacrines	Tacrine - huprine hybrids		[356, 357]
Donepezil-huprine derivatives	Huprine - Donepezil hybrids		[358]
N-benzylpiperidines with BACE1 inhibitory moieties	Donepezil - BACE1 inhibitor hybrid		[395]
Quinoxaline based hybrids		Histamine H_3 receptor antagonist	[396]
Dual Acetylcholinesterase and monoaminooxidase B (MAO-B) inhibitors			
Ladostigil	Rasagiline - rivastigmine hybrid	Neuroprotective metal chelator β-amyloid modulator	[397] [398] [141]
Propargylamino -benzylpiperidine hybrids	MAOB pharmacophore – CAS AChE pharmacophore hybrid		[399]
Dual Acetylcholinesterase inhibitors and acetylcholine receptor ligands			
Caproctamine		Muscarinic M_2 receptor antagonist	[400]
Huprine X (3-Chloro-9-ethyl)	Tacrine – huperizine A hybrids	Muscarinic M_1 and M_2 receptors agonist	[401] [402]
Bis(12)hupyridone	Huperizine A dimer	α7 nicotinic receptor modulator	[403]
Ro-46-5934	Neostigmine derivative	Muscarinic M_2 receptor antagonist	[404]
Dual Acetylcholinesterase inhibitors and histamine H_3 receptor antagonists			
FUB833	Tacrine-piperidine hybrids	Histamine N-methyltransferase inhibitor (HNMT)	[405] [406]

Table 2. contd….

Compound	Merged Pharmacophores	Additional Activities	References
Dual Acetylcholinesterase inhibitors and histamine H_3 receptor antagonists			
Quinoxaline derivatives	Quinoxaline-piperidine hybrids	BACE1 inhibitor	[396]
Tacrine – piperidine hybrids			[406]
Dual Acetylcholinesterase inhibitors and N-methyl-D-aspartic acid (NMDA) receptor channel blockers			
Carbacrine	Tacrine – carvedilol hybrid	β-amyloid inhibitor Antioxidant	[407]
Bis(7)-tacrine	Tacrine homodimers	BACE1 inhibitor	[408] [392] [353] [393] [354]
Bivalent β-carbolines	β-carboline homodimers		[409]
Dual Acetylcholinesterase inhibitors and serotonin 5-HT_6 antagonists			
Latrepirdine (dimebon)		IMAO-B NMDA receptor inhibitor	[410, 411, 412, 413]
Dual Acetylcholinesterase inhibitors and serotonin 5-HT_3 receptor antagonists			
Tacrine – Arylpiperazine hybrids			[414]
Dual Acetylcholinesterase inhibitors and cannabinoid receptor antagonists			
Diaryl-pyrazolines and diaryl-imidazolines	Tacrine – CB_1 antagonist scaffolds		[415]
Arylbenzofuran-based derivatives			[372]
Dual Acetylcholinesterase and serotonin transporter inhibitors			
RS-1259 (BCG-20-1259)	Rivastigmine – fluoxetine hybrid		[174]
Dual Acetylcholinesterase and σ 1 receptor inhibitors			
SP-04			[416]
Dual Acetylcholinesterase inhibitors and calcium channel blockers			
Bis(7)-tacrine	Tacrine homodimers	BACE1 inhibitor NMDA channel blocker	[392, 353, 393, 408, 354]
Tacripyrines: ITH-4012	Tacrine – dihydropyridine hybrid		[417]
Tacripyrines: ITH-12118	Tacrine – dihydropyridine hybrid		[418, 419, 420]
Tacripyrines			[421]
Dihydropyrimidoquinolinediones			[422]
Dual Acetylcholinesterase inhibitors and platelet activating factor (PAF) antagonists			
PMS-777			[423]
PMS-1339			[424]
Dual monoaminooxidase B (MAOB) inhibitors and iron-chelating agents			
VAR 10200 (HLA-20A)	8-hydroxyquinoline – propargylamino pharmacophore hybrid		[387, 388]
VAR 10300 (M-30D)	8-hydroxyquinoline – propargylamino pharmacophore hybrid		[425, 426, 427, 398]

Table 2. contd….

Compound	Merged Pharmacophores	Additional Activities	References
Dual monoaminooxidase B (MAOB) inhibitors and adenosine A_2 receptor antagonists			
Istradefylline (KW-6002)	Caffeine derivative		[428, 429, 430]
Dual monoaminooxidase B (MAOB) inhibitors and peroxisome proliferator-activated receptor gamma ($PPAR_\gamma$) modulators			
Pioglitazone, Rosiglitazone			[431, 432, 433]
Dual histamine H_3 receptor and presynaptic acetylcholine muscarinic M_2 receptor antagonists			
4,4'-bispiperidines			[434]
Dual NMDA receptor channel and L-type calcium channel blockers			
NGP1-01 (polycyclic cage amines)		Neuroprotective Reduces endothelial iron accumulation	[435, 436, 437]
Dual NMDA receptor channel blocker and serotonin 5-HT_3 antagonist			
Memantine		Tau protein phosphorylation inhibition	[438, 439]
Dual phosphodiesterase-4 inhibitor and α-secretase activator			
Etazolate		$GABA_A$ receptor modulator	[440]
Dual β-secretase (BACE1) inhibitor and metal chelator			
1,3-Diphenylurea derivatives			[441]
Tryptoline and tryptamine triazole derivatives		Anti-amyloid aggregation	[442, 443]
Dual γ-secretase and peroxisome proliferator-activated receptor gamma ($PPAR_\gamma$) modulators			
2-(bis(phenethoxy)pyrimidine-2-ylthio)hexanoic acid and derivatives			[176, 444]
Dual glycogen synthase kinase-3β (GSK-3) and phosphodiesterase-7 (PDE7) inhibitor			
VP1.15 (2,3-diphenyl-1,2,4-thiadiazole derivative)			[445]
Dual protein kinase C (PCK) activators and histone deacetylase (HDAC) inhibitors			
Hexahydrobenzo[e]1,4diazocin-3-ones			[446]
Dual β amyloid oligomerization inhibitors and free radical scavengers			
Phenolic bis-styrylbenzenes			[447]
Curcumin - cholesterol bivalent ligands			[448]
Metal chelators which also target β amyloid			
EDTA-2-phenylbenzothiazol-derivatives			[449]
Benzimidazol-derivatives			[450]
Dual metal chelators and antioxidants			
Deferiprone – BHT hybrids			[451]
Glucopyranosyl conjugates of deferiprone and of tetrahydrosalen	Pro-drugs		[452, 453]

that cannabidiol exerts an inhibitory effect on τ phosphorylation [155]. Recently it has been described that CB1 activation could rescue rat Hippocampal CA1 Pyramidal Neurons from Aβ deleterious action [156].

In this context neuroprotective effects have been described for: HU-211, acting in neurons under neurotoxic environment of glutamate [157]; palmytoyletanolamide, an endocannabinoid that increases survival of cerebellum granular neuron [158]; WIN 55212-2 exerts a protector effect on hippocampus neurons [159]; Δ^9-THC protects spinal medulla neurons against excitotoxicity mediated by CB1 receptor [160]. In addition, several *in vivo* studies reveal that cannabinoids, as Δ^9-THC and anandamide, protect neonatal rat brain [161, 162]. Also, Iuovone *et al*. reported neuroprotective, anti-oxidative and anti-apoptotic effects of cannabidiol against the neurotoxic action of βA [163].

Docking and *in vitro* studies have shown, that Δ^9-THC might bind to AChE with a similar or even higher affinity than reported PAS binders [149], being the AChE inhibitory effect of Δ^9-THC and other synthetic cannabinoids as modest as referred for other PAS binders [149]. To this end the Sánchez-Montero group follows a new strategy trying to bind together the described neuroprotective properties of cannabinoids with enhanced AChE inhibition in a single molecule that could pave a new way in the treatment of AD and other neurodegenerative diseases [133, 164]. Blocking both, CAS and PAS of AChE, might not only alleviate the cognitive deficit of AD patients by elevating acetylcholine (ACh) levels through their AChEI activity, but might also act as disease modifying agents *via* the inhibition of Aβ aggregation. Successful attempts in this sense are reported in the examples of bis-nor-meptazinol derivatives [165] and benzylidene-hydrazono-dihydropyridines, [166], where the dual behavior as AChEI and Aβ fibril formation inhibitors, among others, is observed. In both cases docking studies illustrate the interaction of these compounds with amino acids of the PAS. In the same way, and following a similar methodology, molecular docking of Δ^9-THC (white) shows a similar fit with both sites, CAS and PAS, where the interaction with Tyr 121 is noteworthy, (Fig. **2**) [164]. It has to be remarked that the fitting of Δ^9-THC and donepezil (black) with the amino acids of the PAS, shown in the figure, are very similar [167, 168].

3. AD THERAPEUTIC TARGETS

Targeting the AD appears to be very elusive, although some general pathways –not exclusive to AD- are recognized in different pathogenic cascades, each of them has conducted various "hypothesis" of AD. Researchers are following different approaches to find the optimal molecules. Strategies that according to Grill and Cummings can be classified into two groups, depending on where is the focus for the drug targets is that is, symptomatic therapies, and disease-modifying therapies [169].

3.1. Symptomatic Targets

This strategy is involved in targeting neurotransmission either on neurotransmitters and receptors as ACh [170], GABA and opioid receptors [171], opioid receptor ligands [172], glutamate and NMDA [173], 5-HT (or the serotonin transporter, SERT) [174], H_3 (histamine) [175], peroxisome proliferator-activated receptor γ (PPARγ) [176]; or on the enzymes involved in their metabolism. Whereas disease-modifying targets strategy is related to Aβ, τ protein and different aspects of neuroprotection. However, the molecules obtained do not fall exclusively into one or another group, and it has been found that compounds targeting neurotransmission also are involved in many other aspects. As an example of the situation targeting synaptic dysfunction [177, 178] will pertain to both targeting neuro-transmission and to disease-modifying targets, as Aβ oligomers induce synaptic dysfunction [24]. Thus, multi-targeting surpasses the classifying capacity of the initial two-group classification.

3.1.1. Targeting Cholinergic System and Glutamatergic Neurotransmission

Among the drugs for the treatment of AD symptoms, currently they target either cholinergic or glutamatergic neurotransmission, and the first group constitutes the majority of the approved drugs. Memantine, is up to date the only approved drug that antagonizes NMDA-type glutamate receptors, thus preventing excitotoxicity by an excess of aberrant neuronal stimulation [42]. On the other hand, according to cholinergic hypothesis, AChE hydrolyze ACh, leading to decreased levels of the neurotransmitter, then inhibiting CAS on the enzyme will raise ACh levels, recovering the loss of cholinergic transmission and synaptic density in AD patients. This was for a long time the premise that led to optimize the search for molecules that could inhibit AChE with fewer side effects [179]. Recently, it has been pointed out that H_3 antagonists can also elevate ACh levels in some cerebral areas, enhancing memory preclinical models; it is thought that there are multiple biochemical pathways involved in the mechanisms [180]. On the other hand, Inestrosa *et al*. [61] reported that AChE is also implicated in AD pathology by accelerating Aβ aggregation, due to the activity of enzyme PAS, therefore AChE became an enzyme that could be targeted by two means. AChE also has some non-catalytic trophic functions whose relevance as a valuable therapeutic target –if any- is not yet defined [181, 182].

Cholinergic brain receptors are another target that has been researched [183]; both muscarinic and nicotinic acetylcholine receptors are implicated in the pathophysiology of AD, although the relevance of the different subtypes in the disease is not yet clear [20, 57]. Activation of M_1 muscarinic receptor was reported by Nitsch *et al*. [184] as a stimulator of the non-amyloidogenic processing of the APP preventing the formation of AB, *via* PKC activation and MAPK dependent pathways, and decrease τ hyper-phosphorylation *via* GSK-3β inhibition [185]. More recently, Fisher argues that cholinergic hypofunction could be expected to be restored to normal, specifically *via* selective activation of M1 muscarinic receptors, and then alter the onset or progression of AD [57].

Finally, targeting butyrylcholinesterase (BChE), a serine hydrolase related to acetylcholinesterase that also catalyzes the hydrolysis of acetylcholine, has been considered relevant

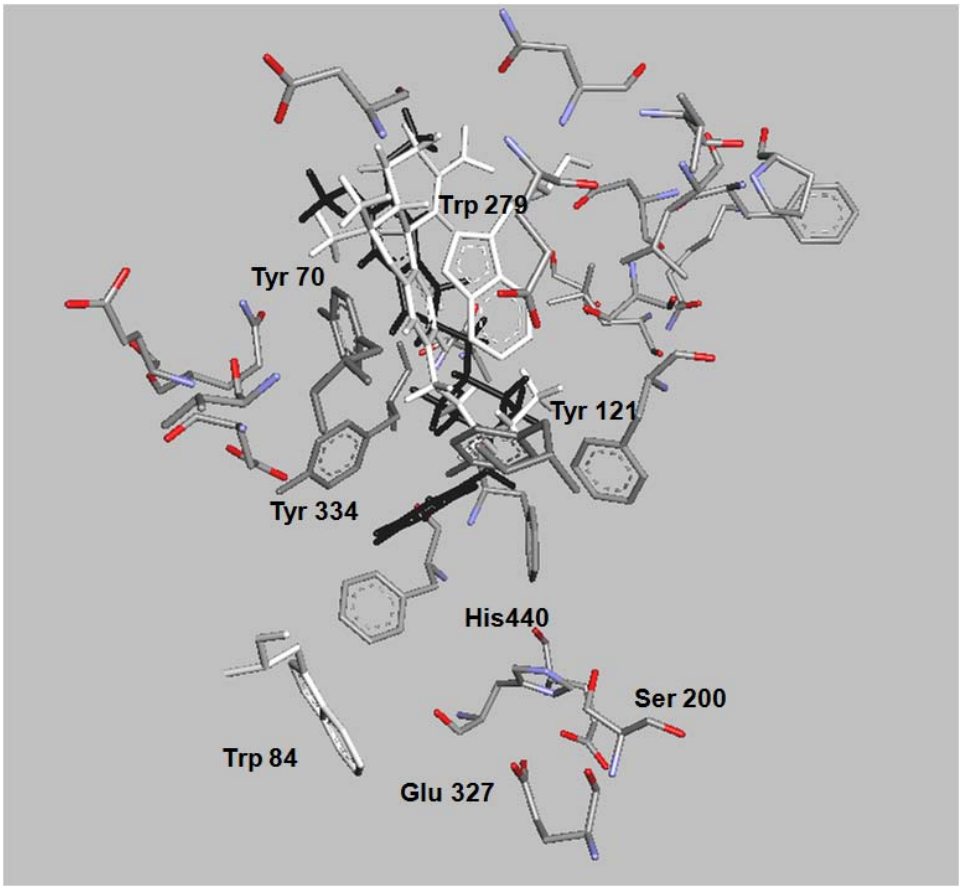

Fig. (2). The binding pattern of dronabinol (Δ9-THC; (tetrahydrocannabinol) (white) and donepezil (black) to acetylcholinesterase is shown. The represented amino acids showed in the binding site are part of PAS, CAS and the active catalytic site of the enzyme.

because of its implication in the pathogenesis of AD [186] and is considered a possible responsible of the inefficacy of AChE selective inhibitors [69].

3.2. Disease Modifying Targets

The other targeting strategy, namely disease-modifying tries to intervene in the different pathologic processes developed in AD; taking them as targets: defective proteins, ApoE4, oxidative/nitrosative stress, mitochondrial damage, altered apoptosis, autophagy impairment, neuroinflammation and activation of immune system, Ca^{2+} and metal dyshomeostasis, and prostacyclin and endocannabinoid system signaling. In addition to these targets, recently it is been proposed the possibility to modulate epigenetic modifications what could be preventive and also curative target.

3.2.1. Targeting Defective Protein: Aβ and τ

Aberrant accumulation of misfolded proteins is double targeted, Aβ [187] and τ protein aggregation [188], although there are many confluences and overlapping characteristics between the two targets.

In the endoplasm reticulum (ER) modulation of the stress pathways and their interactions with mitochondria are being investigated as feasible targets of Aβ production, as ER is not only the main organelle for the synthesis and processing of proteins as Aβ peptides -but also the main cellular source of Ca^{2+}- [189]. Also, targeting retromers -proteins that modulate the endosomal residency time of secretases- can be modulated through the production of Aβ peptides, by mediating the retrieval of transmembrane proteins from endosomes to the trans-Golgi network [190].

Another crucial step in peptides processing path is molecular recognition and self-assembly events targeted by using hybrid molecules such as α-aminoisobutyric acid plus an aromatic moiety, that could inhibit amyloid fibrils and oligomers formation [191].

There are also attempts to disrupt aberrant APP processing, by targeting β- or γ-secretase either by inhibiting their activities [192] or -more effectively- modulating its activity. In this way, it has been found that some non-steroidal anti-inflammatory drugs (NSAID) reduce oligomer formation by modulating γ-secretase activity indirectly [193], as inhibiting secretases directly is somehow dangerous given the importance of other crucial substrates that could be affected [24, 194]; thus, the search for more selective compounds is continued [195]. Inhibiting secretase compounds are found in natural origin as stilbenoids, from the ethyl acetate soluble fraction of *Smilax china* L., and show an intense BACE1-inhibiting activity [196]. Chemically related compound stilbenes (compounds related to resveratrol) have

been suggested as neuroprotective agents against AD; however, the mechanism for this remains unclear [197]. In the other way around, targeting α-secretase is also under scrutiny as its activity generates sAPPα that, as described previously, has neuroprotective effects [198]. Regarding this effect sirtuins –a family of histone deacetylases involved in numerous cellular signaling pathways- and more specifically SIRT1, has been shown to direct APP processing by activating expression of the α-secretase gene *ADAM10*; upregulation of SIRT1 can also induce the Notch pathway which has the capacity to repair neuronal damage [199] and also inhibit mTOR (mammalian target of rapamycin, see 3.2.3) signaling [200].

Other ways to eliminate pathologic Aβ peptides could be by means of immunotherapy either vaccinating with Aβ active-peptide or passive infusion of anti-Aβ monoclonal antibodies but the failures with vaccination -mentioned earlier- has imposed more cautious procedures as in the trial where 6% of treated patients developed autoimmune meningoencephalitis [114]. Another approach to eliminate oligomers could be the stimulation of its selective degradation by proteases as plasmin or cathepsin B [24]; resveratrol would also enhance the clearance of Aβ peptides [201], although some authors showed concern on the capacity of resveratrol to prevent oligomer formation [202]. Perhaps, the most promising way of removing Aβ up to date is by modulating *APOE* expression (see below targeting ApoE4).

Regarding targeting τ protein, τ kinases, including CDK5, GSK-3β, MARK, MAPK, are considered reliable targets for AD therapy as modulators of τ phosphorylation, although there are serious concerns about the safety of their use, and it is thought that it would be better to reduce τ protein levels than τ phosphorylation [3]. Adding a touch of overlapping, GSK-3β has also been related with presenilins and with Aβ [203, 204]. Methylene blue, whose mechanism of action was first believed to be an inhibition of τ-τ interactions, later has been shown to possess other actions as reducing soluble τ protein and also other activities [205]. Recently the relationship among Aβ, τ protein and mTOR has been pointed out [206]. Also, misfolded τ protein of neurofibrillary tangles constitutes a primary target struggled by geldanamycin through the inhibition of heat shock protein 90 (HSp90), a molecular chaperone with important roles in regulating protein folding related to pathogenic transformation [207]. Thus, geldanamycin would activate proteasome resulting in an accelerated degradation of misfolded τ protein [208].

Another protein that can be targeted is TAR-DNA-binding protein-43 (TDP-43), which is a predominantly nuclear protein identified as a regulator of crucial transcriptional events in the central nervous system and is strongly associated with neurodegeneration [209]. Aggregates of TDP-43 in patients with ALS and frontotemporal dementia, and also a correlation with τ protein accumulation has been found [30].

3.2.2. Targeting ApoE4

Targeting ApoE4 has been studied from its dependent and independent effects on Aβ. The anti-aggregation and clearance action of ApoE4 on Aβ has led to the search ways of reducing its expression. ApoE expression is transcriptionally regulated by the ligand-activated nuclear receptor PPARγ that acts with liver X receptor, and both form heterodimers with retinoid X receptors (RXRs), leading to microglial activation and suppressing the inflammatory status of the brain [118]. It has been shown that chronic administration of agonists of both receptors reduces Aβ levels and also improves cognitive function in mouse models of AD. Although PPARγ agonists phase III clinical trial outcome was negative [118] hopes have not decreased and bexarotene, a blood-barrier permeant RXR agonist, is the new promising compound which has displayed its efficacy in preclinical models of AD [210, 211]. Another approach to target ApoE4 is by means of identifying the so called "small-molecule structure correctors" that are capable of disrupting ApoE4 domain interaction (altered protein conformation) that makes it highly susceptible to proteolytic cleavage and the generation of neurotoxic fragments [101, 102].

3.2.3. Other Disease Modifying Targets

Classic AD hallmarks are closely accompanied by other pathologic processes: increased oxidative/nitrosative stress, neuroinflammation, microglia accumulation, mitochondrial damage, autophagy impairment, increased apoptosis, altered integrity and function of BBB, aberrant cholesterol metabolism, and Ca^{2+} and metal dyshomeostasis. In addition, very recently it has been shown that prostaglandins and endocannabinoid signaling are impaired in AD [212]. These events are under scrutiny for research that can be both directly or indirectly targeted. Despite the fact that these processes are considered secondary and less relevant, they are guiding the search for new MTDLs and also incorporating specific moieties with capacity to cope each of them. In the following paragraphs their relevance to AD therapy and the way they can interact with each other and with other targets will be shown.

Oxidative/nitrosative stress is one of the central pathologic processes present in AD, albeit previous, consequence or simultaneous to the disease, some researchers have put their efforts to target them by using antioxidants [213], and to actively incorporate them to MTDL for e.g. with retinoids [214], or lipoic acid [215]. The relationship between oxidative stress and immune function and its relevance for searching targets has been studied by some authors [216, 217]. Another recent field of research of new MTDL is of PLA_2 inhibitors, which has been discussed in 1.2.6. $cPLA_2$ is involved in oxidative/nitrosative aberrant signaling pathways that are linked to excessive NMDA activation and to NADPH oxidase activity, and also seems to play important roles in the pathophysiology of neurodegenerative diseases such as AD [218-221]. However, it should be determined whether to activate [222] or to inhibit [223, 224] PLA_2. To this respect botanical phenolics are considered as valuable substances within these novel therapeutic strategies for AD [23, 225].

Another pathological process present in AD patients is neuroinflammation that raised some interest as a possible target. In this regard NSAIDs were proposed as therapeutic preventing compounds [226] (see 3.2.1). Neuroinflammation is related to an increased microglia accumulation that has

been observed nearby amyloid plaques, but interestingly increasing Aβ clearance, has led to a novel therapeutic strategy [227].

Mitochondria play a crucial role in cell survival and death through multiple functions; mitochondrial dysfunction and altered dynamics are present early in AD and are crucial in its pathogenesis [228]. Among the mitochondrial dysfunctions, results of induction of oxidative damage are crucial in AD pathology [229], Ca^{2+} homeostasis and neuro-inflammation [152]. In addition, it has been shown that ER is linked to mitochondria both physically and biochemically, *via* a specialized subcompartment of ER named mitochondria-associated ER membranes (MAM), where APP would be processed, as MAM reveals PS1, PS2 and γ-secretase activity [230]. Recently, specific mitochondria therapeutic drugs as mitochondria-directed antioxidants and Szeto–Schiller peptides has been proposed, whereas small cell permeable peptide antioxidants target mitochondria in a potential-independent manner [231, 232]. Methylene blue which has been discussed above due to its inhibiting activity of τ protein also appeared to protect mitochondrial function in addition to enhance brain metabolism and hemodynamics [233].

Autophagy is a crucial mechanism for eliminating defective cellular products, and whenever this function is defective or insufficient will lead to cellular dysfunctions as neurodegeneration that is found in AD and other diseases as PD or ALS. On the contrary, an increase of autophagy function will conduce to the clearance of those products and subsequently to the cellular recovery, if not too late. Thus, there has been put in a lot of efforts to obtain compounds with the ability to enhance this cellular function; Sarkar *et al*. in their review show an exhaustive list of 30 autophagy enhancers [234]. The authors differentiate among autophagy enhancers that are mTOR dependent and those that are not. mTOR is an evolutionarily conserved Ser/Thr protein kinase that plays a crucial role in several biological processes as regulation of cell growth and survival. Recently, mTOR has been proposed as a valuable target in obtaining compounds for AD and other neurodegenerative diseases [235]. Synaptic plasticity is another process under mTOR influence as there is a correlation of its impairment with the inhibition of mTOR signaling [236]. On the contrary, inhibition of mTOR reduces Aβ *in vivo* [237], and increases autophagy through the control of autophagy-lysosome protein degradation [238]. Also changes in mTOR levels in lymphocytes are related to AD [239]. Small molecule enhancers of rapamycin (SMERs) related to mTOR, also induced autophagy, improved cell viability and neurodegenerative proteins clearance in cellular models [240].

Apoptosis, a characteristic event of the neuro-degenerative diseases [241], has not been properly investigated as a target; however, Kobayashi *et al*. proposed increased astrocyte apoptosis as a new histological hallmark of white matter degeneration in AD [242]. Dyshomeostasis of both Ca^{2+} and metals have been lately used in MTDL research [4, 6, 243], in order to obtain anti-oxidative and anti-apoptotic activities among others.

Recently in AD, the event of the breakdown of BBB, and a deficient clearance of Aβ through it have been discovered. One of the disease modifying targets that has been proposed is RAGE (receptors for advanced glycation end products), which interacts with BBB and lead to oxidative stress, inflammation response and reduced cerebral blood flow. RAGE also interacts with circulating Aβ and mediates its transport across BBB into the brain [244]. Deane discusses the structure-function relation of RAGE-ligand interaction and suggests that is a potential target for the research of new molecules for treatment of AD [244]. In addition, Kook *et al*. identified a potential molecular pathway that underlies Aβ-RAGE interaction-induced breakdown of BBB [245]. Gelsolin is a molecule that could be inversely related to Aβ deposition in BBB, which is putatively produced in choroid plexus, although it is also expressed in a wide variety of organs. It has been found that gelsolin levels in brain are decreased in AD [246], and its administration could control the accumulation of Aβ in brain vessels walls, which eventually controls CAA progression [247]. In this way, a novel therapeutic target is tissue transglutaminase that is a Ca^{2+}-dependent enzyme which presents covalent extracellular matrix protein cross-linking activity associated with CAA pathology. Thus, inhibiting this activity could also prevent CAA [32]. Megalin receptor has been also implicated in Aβ clearance from CNS across the choroid plexus epithelium, thus increasing its expression is an interesting target in the struggle against AD [248].

Another recently defined target for AD is monoacylglycerol lipase (MAGL), an enzyme of the serine hydrolase superfamily which is known for metabolizing lipids, but its relevancy as a target in AD therapy comes from its role of hydrolyzing the endocannabinoid molecule 2-arachidonoylglycerol (2-AG). 2-AG has many functions as retrograde messenger, such as modulating synaptic transmission and plasticity [249], and as neuroprotective. Consequently, MAGL inhibition has been shown to suppress Aβ production and accumulation, as well as to reduce BACE1 expression, and prevents neuroinflammation and neurodegeneration in AD *in vivo* models [250].

There are more targets under study such as those related to latrepirdine and its relationship with protein catabolism pathway [251], P53 and its functional cross-talk linking presenilins and Pen-2 [252], inhibition of the *de novo* synthesis of cholesterol by statins, that might decrease the risk of developing AD [253], toll-like receptors signaling in plasticity, neurogenesis and disease [254], MTDL based on iron chelating compounds with the ability to regulate the transcriptional activator hypoxia-inducible factor 1 (HIF-1), that could compensate for oxidative stress [144], or compounds that inhibit primary amine oxidase (PrAO) such as phenelzine, an enzyme which has been found to be implicated in the etiology of AD [131]. In addition, there are therapies related to nutritional supplements [255], such as proprietary diets that contain both polyphenols and polyunsaturated fatty acids [256]. Hormonal therapy, namely estrogen or testosterone treatments, is proposed to struggle against AD and may also reduce the risk or delay the onset of dementia [257, 258].

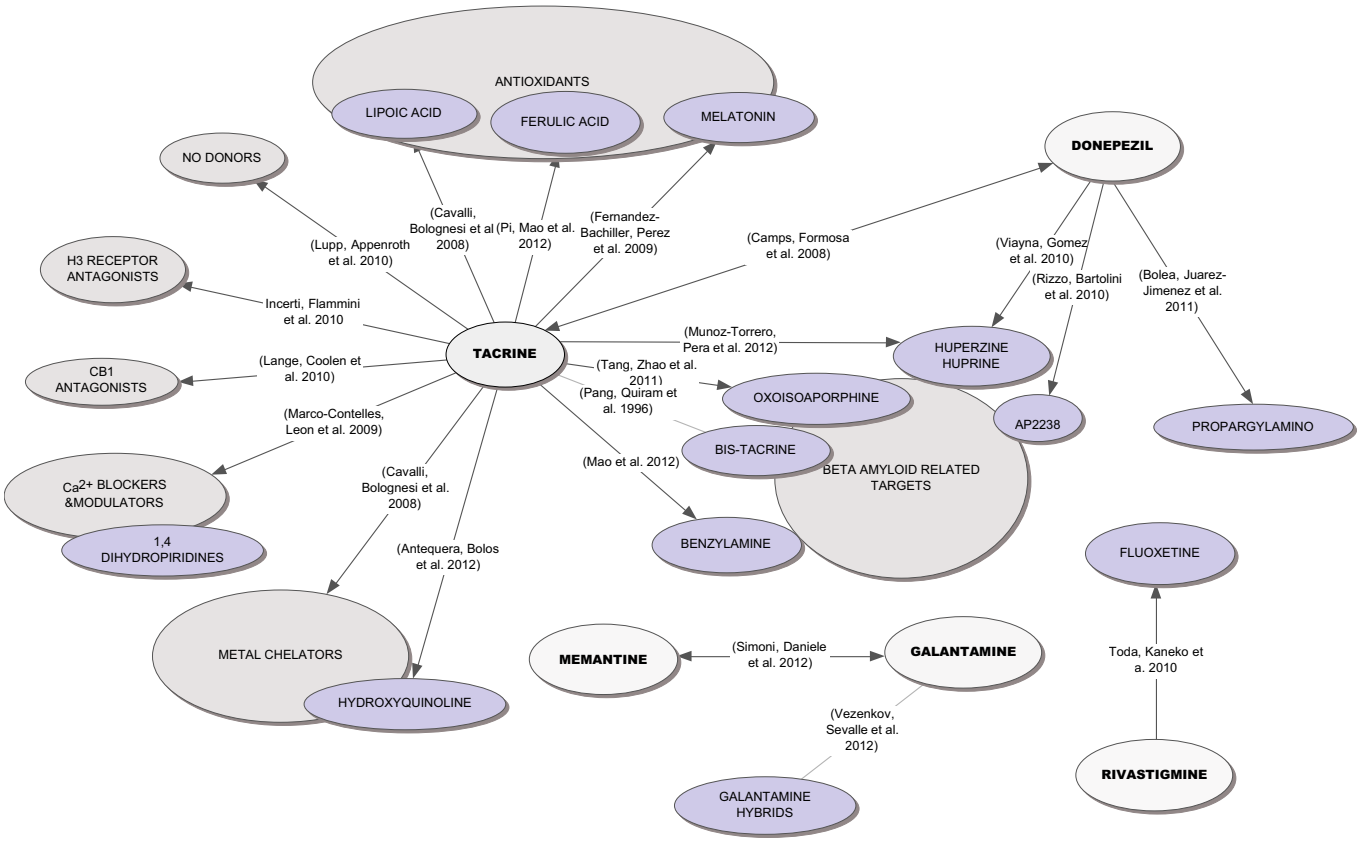

Fig. (3). Conceptual map showing main trends in constructing hybrid molecules from approved molecules and well known pharmacophores, to obtain new multi-target-directed ligands.

3.2.4. Epigenetics as a Possible Preventive and/or Therapeutic Target

In spite of the specificity of gene repression by epigenetic mechanisms it has been shown that the treatment with unspecific inhibitors could lead to good clinical outcomes. One of the modifiers of gene are histone deacetylases (HDACs) that induce decreasing or silenced gene transcription by transferring acetyl groups from acetylated histone protein back to CoA. Substances that show HDAC inhibiting activity (HDAC-I) have demonstrated their capacity to revert previous gene repression and reinstate, for instance, learning behavior in animal models, and to decrease Aβ [259]. Valproic acid, with HADC-I activity, seems to have the Aβ reducing capacity [260] but phenyl butyrate, another compound with HADC-I activity, did not act on the Aβ levels albeit normalized phosphorylated τ protein was present in hippocampus [261].

DNA methylation is another mechanism by which some genes are silenced or repressed in the living cell. To this respect, some nutrients namely folate, vitamin B12, vitamin B6, riboflavin, methionine, choline and betaine, are related to the epigenetic mechanism of DNA methylation [262], by acting on the levels of the universal methyl donor S-adenosylmethionine and methyltransferase inhibitor S-adenosylhomocysteine. Thus, folate/methionine/homocysteine metabolism has been proved to be highly relevant in this epigenetic mechanism. Folate deficiency results in a reversible hypomethylation in both animal models and humans, but alterations in the methionine/homocysteine are also related to the Aβ deposition [263].

In spite of the promising results obtained by the cited compounds, it is difficult to assume that new drugs developed to specifically modulate epigenetic changes could act without side effects [264]. On the other hand, this amplitude gives a framework for the diverse genetic and environmental factors interacting in the development of AD.

3.3. Targets and Lead Moieties

The multifactorial etiology of AD put forward the aptitude of the new therapy strategy of MTDL. However, the best way to follow is a maze, not only there are a multitude of mechanisms implied but also the selection of a lead molecule is not clearly seen, be it from natural or synthetic origin. The amount of hybrid molecules resulting from randomly joined moieties is out of capacity nowadays, and the number of possible candidates is large enough even for joining two different chemical groups, so the possible combinations using three or more moieties make the effort almost unfeasible.

The "tangled web of targets" [38] makes it difficult to show an organized taxonomy of the candidate molecules. One of the ways to classify them could be by grouping different chemical compounds within a target. Each group of molecules within the same target could further be grouped

into a chemical lead, and then incorporated into different molecules or moieties that bring the additional properties of the original molecule. The amount of candidate molecules from natural origin suggests that they should be presented separately from the synthetic ones. Table **1** shows those natural origin compounds and some of their properties that could be useful in designing new molecules. In Table **2** are presented some useful non-natural origin compounds that are also good candidates to be considered in designing new MTDL. Fig. (**3**), materializes the concept that hybrid molecules will form a web of relationships among them, representing a conceptual map with hybrid molecules constructed from approved therapeutic drugs that are being investigated to maximize the benefits of two or more moieties grouped in a molecule.

Published reviews on MTDL classify the new molecules based on one chemical lead and then list the modifications or moieties addition that could be done on the scaffold to maximize the pharmacological parameters measured in it [5, 8, 69, 123, 124].

CONCLUSIONS

The question arises as to whether the search to cure AD is a kind of a search for a pot of gold. Every announcement with the final solution on it is followed by the news about its failure in one or another of its development steps. From years' perspective this behavior seems to be the rule till date, thus the problem has remain unresolved and is most likely to remain unresolved through traditional approaches. It is a point of concern whether the reviewed targets lead towards the final solution. May be, but in spite of the enormous and crucial advancements in the knowledge of the mechanisms and implications in AD, multifactoriality of the disease perhaps would need a multifactorial answer. Multi-Target-Directed Ligands are believed to be precisely the right answer to the conundrum; or perhaps because it is probably that idiosyncrasy that people carry in their lives that would need to design more acutely the solutions, depending not only on the genetics, but also on the epigenetics and environment differences.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflict of interest.

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