Review

ADAM10 in Alzheimer's disease: Pharmacological modulation by natural compounds and its role as a peripheral marker

Patricia Regina Manzine[a,b,*], Miren Ettcheto[b,c,d,e], Amanda Cano[c,f,g], Oriol Busquets[b,c,d,e], Elena Marcello[h], Silvia Pelucchi[h,i], Monica Di Luca[h], Kristina Endres[j], Jordi Olloquequi[k], Antoni Camins[b,c,d], Márcia Regina Cominetti[a]

[a] Department of Gerontology, Federal University of São Carlos, São Carlos, Brazil
[b] Departament de Farmacologia, Toxicologia i Química Terapèutica, Facultat de Farmàcia i Ciències del'Alimentació, Universitat de Barcelona, Barcelona, Spain
[c] Biomedical Research Networking Centre in Neurodegenerative Diseases (CIBERNED), 28031 Madrid, Spain
[d] Institut de Neurociències, Universitat de Barcelona, Barcelona, Spain
[e] Unitats de Bioquímica i Farmacologia, Facultat de Medicina i Ciències de la Salut, Universitat Rovira i Virgili, Reus, Tarragona, Spain
[f] Department of Pharmacy, Pharmaceutical Technology and Physical Chemistry, Faculty of Pharmacy and Food Sciences, University of Barcelona, Barcelona, Spain
[g] Institute of Nanoscience and Nanotechnology (IN2UB), Barcelona, Spain
[h] Department of Pharmacological and Biomolecular Sciences, Università degli Studi di Milano, Milano, Italy
[i] Department of Neurosciences, Psychology, Drug Research, and Child Health, University of Florence, Florence, Italy
[j] Department of Psychiatry and Psychotherapy, University Medical Center Johannes Gutenberg-University Mainz, Mainz, Germany
[k] Instituto de Ciencias Biomédicas, Facultad de Ciencias de la Salud, Universidad Autónoma de Chile, Talca, Chile

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ABSTRACT

Alzheimer's disease (AD) represents a global burden in the economics of healthcare systems. Amyloid-β (Aβ) peptides are formed by amyloid-β precursor protein (AβPP) cleavage, which can be processed by two pathways. The cleavage by the α-secretase *A D*isintegrin *A*nd *M*etalloprotease 10 (ADAM10) releases the soluble portion (sAβPPα) and prevents senile plaques. This pathway remains largely unknown and ignored, mainly regarding pharmacological approaches that may act via different signaling cascades and thus stimulate non-amyloidogenic cleavage through ADAM10. This review emphasizes the effects of natural compounds on ADAM10 modulation, which eventuates in a neuroprotective mechanism. Moreover, ADAM10 as an AD biomarker is revised. New treatments and preventive interventions targeting ADAM10 regulation for AD are necessary, considering the wide variety of ADAM10 substrates.

1. Introduction

The amyloid-β precursor protein (AβPP) is a transmembrane protein found in mostly all cell types. In pathological conditions, as Alzheimer's disease (AD), AβPP is mainly processed by β- and γ-secretases, resulting in the production of amyloid-β (Aβ) peptides, the main players for the generation of senile plaques [1]. In physiological conditions, AβPP is mainly cleaved in the middle of the Aβ region by an α-secretase, identified as *A D*isintegrin *A*nd *M*etalloproteinase 10 (ADAM10), releasing a soluble fragment (sAβPPα) in a non-amyloidogenic and neuroprotective pathway [2]. Therefore, reduction of Aβ formation and sAβPPα production by stimulating the non-amyloidogenic pathway seem promising strategies for the AD treatment [3]. In addition, the non-amyloidogenic cleavage of AβPP remains largely unknown, mainly regarding pharmacological approaches that may affect different

signaling pathways and improve the ADAM10 activity. This bibliographical review analyzes articles published in different levels of scientific evidence. Studies from Medline/PubMed databases (1990–2018) were included. These databases were chosen due to the great number of scientific articles with international availability focused on health follow-up, besides being provided with the most qualified forms of online search. For this, the search descriptors were defined according to the Medical Subject Headings (Mesh), using the vocabulary structured with the terms "ADAM10 protein", "Alzheimer disease", "alpha secretase" and "natural products". According to this specific search, about 70 studies were found within this theme, of which compounds of plant or animal origin were included for analysis.

This review emphasizes natural compounds that can directly or indirectly stimulate the neuroprotective mechanism achieved by ADAM10 induction, besides highlighting the challenges of this protein
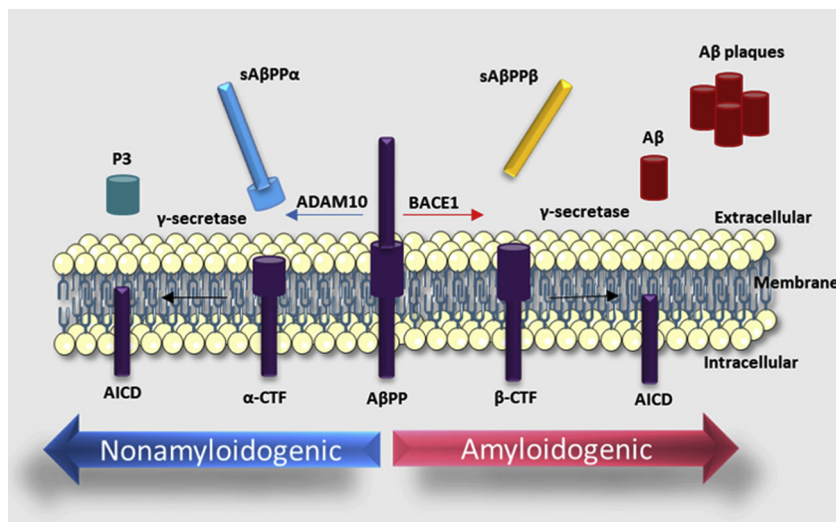
Fig. 1. Non-amyloidogenic and amyloidogenic pathways in AD through consecutive cleavages of AβPP protein in the membrane by ADAM10 and BACE-1, respectively.

as a biomarker for AD therapy.

2. ADAM10 and Alzheimer's disease

ADAM10 belongs to the ADAMs family of proteins, which comprises transmembrane, as well as secreted metalloproteinases with functions in cell adhesion and proteolytic processing of diverse cell surface receptors ectodomains and signaling molecules [4]. ADAM10 substrates comprise more than 40 molecules, including adhesion molecules (e.g., cadherins), chemokines (e.g., CX3CL1), growth factors (e.g., EGF and Tumor Necrosis Factor - α), signaling receptors, ligands (e.g., Notch receptor and Fas ligand) and AβPP [5–7].

ADAM10 is a multimodular transmembrane protein constitutively expressed in neurons, vascular cells, leukocytes and tumor cells [8]. It is synthesized in the endoplasmic reticulum (ER) as an inactive zymogen containing C-terminal, transmembrane, cysteine-rich, disintegrin and zinc-binding metalloprotease domains. There is also a pro-domain, which maintains the protease in a latent inactive form, via a cysteine switch mechanism, where a cysteine residue in the pro-domain coordinates the zinc ion in the catalytic site, preventing proteolytic activity [9]. During transport to the plasma membrane, ADAM10 is N-glycosylated at four positions and undergoes maturation through pro-domain removal by proprotein convertases [10]. Pro-ADAM10 has a molecular weight of ∼90kDa and after pro-domain removal, the full-length active ADAM10 has ∼65kDa [10,11].

Ectodomain shedding of ADAM10 leaves a ∼10kDa membrane-anchored C-terminal fragment and releases a ∼55kDa soluble ADAM10. Therefore, apart from its role in protein shedding and the initiation of regulated intramembrane proteolysis of several substrates, ADAM10 itself is subject to a similar proteolytic cascade by other ADAMs, such as ADAM9 and 15 and by γ-secretase. The γ-secretase presenilin releases ADAM10 intracellular domain, which then translocates to the nucleus and localizes to nuclear speckles, thought to be involved in gene regulation. This suggests that ADAM10, in addition to its important function as a membrane-tethered sheddase, also has the potential to be a signal transducing protein [12].

ADAM10 can be differentially regulated from transcriptional to translational and post-translational levels [7,13]. In neuronal cells, ADAM10 is localized at the synapses, at the presynaptic vesicles and at the postsynaptic side [14,15]. ADAM10 shedding activity at the synapse is under the control of trafficking mechanisms. SAP97 mediates ADAM10 trafficking from dendritic Golgi outposts to the synapse upon protein kinase C (PKC) activation [14,16], while AP2 interaction

triggers ADAM10 endocytosis [17]. Notably, ADAM10 is a relevant enzyme in the synapses because its activity participates in the remodeling of the spines [18]. Indeed, its activity is finely regulated by activity-dependent synaptic plasticity [17].

The results of ADAM10 regulation, as well as its action as a shedding molecule, are related to different physiological and pathological conditions, such as cancer and AD. For instance, the synaptic levels of ADAM10 are significantly reduced in AD patients hippocampi compared to age-matched healthy control subjects [19]. Since the seminal paper from Lammich and co-workers (1999), demonstrating that ADAM10 has α-secretase activity and is responsible for the proteolytic processing of AβPP within the Aβ stretch, this metalloproteinase has been increasingly studied [20]. The argument that captivates and attracts interest from researchers is the strategy of increasing its activity in order to decrease Aβ production and hence, preventing or avoiding AD appearance or progression.

AβPP is a type I transmembrane glycoprotein constitutively expressed in many types of mammalian cells, including neurons. It serves as the precursor of Aβ, whose sequence includes 28 amino acids of the extracellular and 12–15 residues of the membrane-spanning region of AβPP. The sequential AβPP cleavage by β and γ secretases is the basis of the amyloid cascade hypothesis, first proposed by Hardy and Higgins in 1992 [21]. Although it has been criticized over the years alternatively raised hypothesis were not able to fully explain the disease mechanisms.

According to the amyloid hypothesis, AβPP ectodomain is detached from the neuronal membrane through sequential proteolytic cleavages that involve α, β and γ-secretases [22]. The main β-secretase involved in AβPP cleavage at β-site is the cleaving enzyme β-secretase (BACE-1) [23]. The action of α-secretases, instead of β-, drives the pathway to a non-amyloidogenic cleavage, avoiding Aβ production. In the non-amyloidogenic pathway, AβPP is cleaved mainly by ADAM10, between Lys-16 and Leu-17 in the middle of the Aβ region, thus, releasing sAβPPα - a structure with neurotrophic and neuroprotective functions, retaining a 83-amino acid membrane-bound fraction (α-CTF or C83) residue in the membrane. The subsequent cleavage of α-CTF by γ-secretases liberates P3, which is supposedly beneficial and not found in amyloid plaques [24] (Fig. 1).

Easily available, low invasive, cost-effective and early-stage disease detection biomarkers are urgently needed in AD clinical practice. Perhaps the massive failure faced so far in clinical trials for AD is due to the fact that the drugs were tested in patients with established dementia and a few in patients with mild cognitive impairment (MCI), but not

early in the disease process - in prodromal or preclinical stages. Peripheral blood is a good source to investigate AD biomarkers, despite all difficulties regarding assay standardizations and replicability of results [25]. Among the peripheral tissues, platelets present the highest AβPP expression levels [26]. They store and liberate neurotransmitters and carry appropriate transporters and receptors, normally expressed by neuronal cells [27]. In addition, platelets can produce all AβPP fragments found in neurons, thus indicating that they have α, β and γ-secretases activities and that, as well as neurons, can process AβPP through the amyloidogenic and the non-amyloidogenic pathway. Finding the same products from the secretases in platelets and in neurons, it is acknowledged that the formers are easily accessible and potentially useful as a clinical tool to monitor the effects of new therapies based on β and γ-secretases inhibition and/or α-secretases activation [28]. In healthy individuals, the cleavage by α-secretase seems to be the dominant way used by platelets since the detected levels of sAβPPα are much higher than the levels of sAβPPβ [28].

Two studies have demonstrated that ADAM10 is the primordial α-secretase in neurons, which are the most affected cells in AD [29,30]. In addition, its beneficial role in alleviating the Aβ burden in AD has been demonstrated both *in vivo* and *in vitro* [31,32]. Furthermore, in addition to the four established AD susceptibility genes, AβPP, Presenilin-1, Presenilin-2 [33] and Apolipoprotein E [34], increasing evidence indicates that *ADAM10* is a candidate for AD susceptibility gene [35,36]. As a consequence of the several roles of ADAM10 in the brain, it not only would act as a major α-secretase, but also can affect tau pathology, synaptic functions, hippocampal neurogenesis, and gliogenesis by interacting with its substrates [2].

3. ADAM10 modulation by natural compounds

Based on the Aβ hypothesis, compounds that lower Aβ peptide brain levels, either by inhibiting its production or increasing its clearance and those that prevent Aβ aggregation represent disease-modifying therapeutic agents, which should alter its course. If we assume that the amyloidogenic hypothesis is important, one of the therapeutic strategies for AD prevention will be the inhibition of $Aβ_{42}$ formation, misfolding and aggregation until substantial neurodegeneration is developed and the cognitive decline appears as the main symptom of this progressing disease [37–39] .

The non-amyloidogenic pathway and the specific role of ADAM10 in AD neuropathology have been described above. The administration of drugs directed to increase ADAM10 activity is an interesting and future therapeutic option for AD treatment. The main feature of the α-secretase activation pathway is the increase in the generation of sAβPPα, which has neurotrophic, neuroprotective properties and is involved in the maintenance of dendritic integrity in the hippocampus. Hick and colleagues reported that acute application of exogenous recombinant sAβPPα to mouse models of AD improves synaptic strength and enhance memory performance, while sAβPPβ was ineffective [40]. In addition, the α7-nAChRs has been recently identified as a crucial physiological receptor specific for sAβPPα, but not for sAβPPβ [41].

Therefore, this preclinical data reinforce the hypothesis that enhancing brain sAβPPα levels is a potential strategy to improve AD-related symptoms and attenuate synaptic deficits. It has been demonstrated that a virus-mediated intracranial expression of sAβPPα can mitigate the Aβ-related synaptic deficits of APP/PS1 mice *in vivo* [42]. sAβPPα has synaptotrophic effects in an Aβ-independent pathology [41].The functional synaptic plasticity was also modulated by sAβPPα in the hippocampus, including long-term potentiation (LTP) and long-term depression (LTD) of synaptic transmission, through the activation of the *N*-methyl-ᴅ-aspartate subtype of glutamate receptors (NMDAR) [40]. Furthermore, the beneficial effects of sAβPPα could be explained by the inhibition of BACE-1 activity. Peters-Libeu and colleagues reported that sAβPPα can directly inhibit BACE-1, suggesting that it could be an endogenous ligand of this enzyme [43]. In addition, Tan and

colleagues reported that direct administration of sAβPPα into the hippocampus has a potential therapeutic impact by increasing the process of neurogenesis [44]. Therefore, the stimulation of the non-amyloidogenic pathway could significantly reduce Aβ release and sAβPPβ levels, being a suitable therapeutic strategy in AD. Furthermore, both enzymes, ADAM10 and BACE-1 compete for the AβPP cleavage, therefore potentiating ADAM10 activity might inhibit the neurotoxic amyloid generation. Moreover, sAβPPα can prevent the activation of the JNK stress kinase-signaling pathway and has an anti-apoptotic effect [45]. Therefore, a drug able to promote ADAM10 activity in the brain can provide a multi-target therapy for AD to reduce Aβ generation and limit its toxic synaptic signaling, increasing Aβ clearance and favoring neurogenesis.

In this framework, in order to increase therapy effectiveness and to reduce the occurrence of potential side effects, the challenge is directly targeting the drug to the brain, attempting to tackle a brain and disease-specific mechanism able to regulate ADAM10 activity. Undesirable effects obtained by non-specific ADAM10-targeting might be found in cancer proliferation [46], cell adhesion [47–49], promotion of T cell/NK-cell precursor [50], inflammation [51,52] and others, since several *in vitro* studies have shown a wide variety of ADAM10 substrates [53]. A potential strategy could be the use of natural compounds for therapeutic approaches to treat AD, as in the recent years they have been shown to increase ADAM10 expression. Therefore, it seems more appropriate to promote the long-term intake of natural origin products that are being used for a long time in indigenous cultures, and mainly through the consumption of such compounds by diet. In this context, it recently emerged that some natural compounds such as the plant extracts *Ginkgo biloba* and green tea–epigallocatechin-3-gallate can specifically activate the α-secretase cleavage of AβPP, as will be shown below (Fig. 2).

In AD, ADAM10 activators could be disease-modifying therapies since they could increase the cognitive process and lead to slow neuronal loss and functional memory decline. Moreover, disease-modifying therapies should be introduced early in the course of a disease to achieve maximum benefit for patients. In addition to AD, ADAM10 is a suitable therapeutic target for other cognitive loss diseases such as Fragile X Syndrome (FXS) and autism spectrum disorder [54,55]. Further research is required to understand the molecular mechanisms of these agents involved in ADAM10 activation and their beneficial and adverse effects in patients with AD and other diseases.

3.1. Natural α-secretase inducers as potential disease modifiers

Three of membrane-anchored zinc-dependent metalloproteinases, ADAM10, ADAM17 and ADAM9 display alpha-secretase activity [56,57]. However, since the individual knock-out of these proteinases in neither case completely prevented alpha-secretase processing of AβPP, it is likely that different ADAMs are compensating mutually, and under different conditions may contribute to alpha-secretase cleavage of AβPP.

3.1.1. Retinoids

Several biological processes are regulated by Vitamin A (all-*trans*-retinol), like embryonic development, growth, differentiation and cellular apoptosis, as well as brain functions [58]. Derivate from pro-vitamin A carotenoids, these can be obtained from colorful fruits and vegetables or from animal sources such as dairy, liver and egg yolk [59] which are converted into retinal and subsequently to retinoids [60]. Retinoids play important roles in the regulation of adult brain functions such as neuronal differentiation, neurite growth, neurotransmitter release and LTP [61].

Currently, the etiology of late-onset AD remains unclear, however, previous studies reported that retinoic acid (RA) signaling is essential for normal brain maintenance [62]. Retinoid signaling is mediated by two classes of receptors, namely, retinoic acid receptors (RARα, β, and
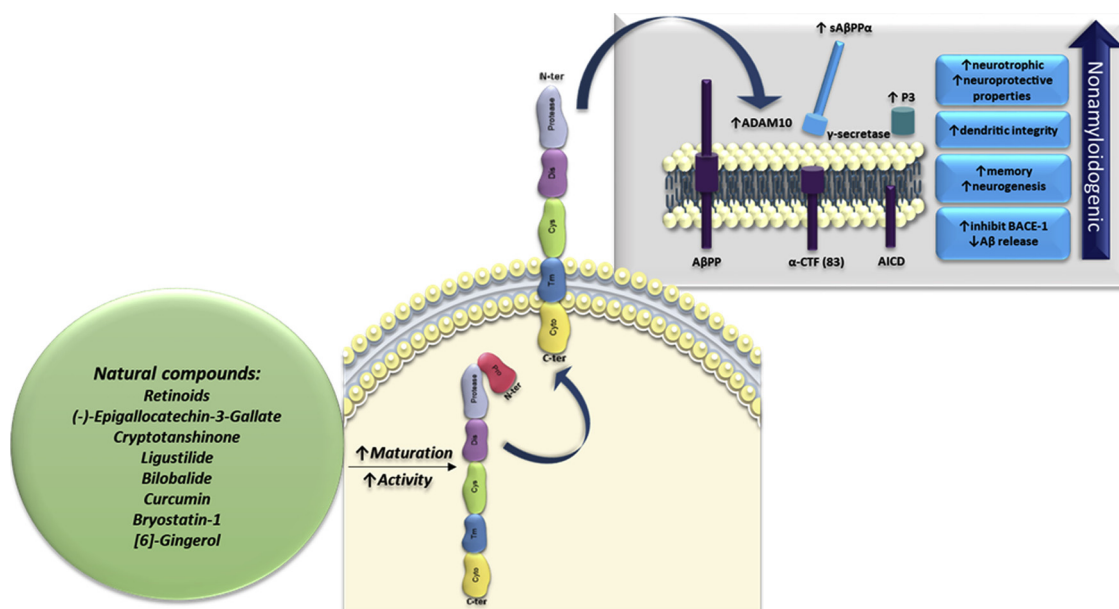
Fig. 2. Natural compounds can stimulate ADAM10 maturation and/or activation. The increased activity of ADAM10 in the membrane promotes the greater release of sAβPPα, a neuroprotective cleavage product of AβPP.

γ) and retinoid X receptors (RXRα, β, and γ). Both receptor types are widely distributed in the brain, being RARα and RXRα the main subtypes of receptors found in the hippocampus playing an important role in neuronal plasticity. Furthermore, Chiang and colleagues described that RARβ is also essential in hippocampal CA1 LTP, spatial learning and memory [63].

The research study of Corcoran and colleagues was the first demonstrating that a loss of brain retinoic acid function leads to Aβ deposition in the brain of adult rats [64]. They suggest the decrease of cholinergic function and in acetylcholinesterase expression due to a lack of RA before Aβ deposition. In a preclinical study, Tippmann and colleagues evaluated the effects of acitretin, a synthetic retinoid effective for the treatment of psoriasis. This drug stimulated ADAM10 promoter activity increasing mature ADAM10 as well as α-secretase activity. The authors suggested that acitretin activates the RAR/RXR-heterodimers bound to the ADAM10 promoter, through the major vitamin A metabolite all-trans retinoic acid, and thereby upregulates ADAM10 transcription [65]. Furthermore, acitretin regulates some genes linked to the AD neuropathology, such as choline acetyltransferase (ChAT) [66].

In the preclinical Tg2576 mouse AD model, Jarvis and colleagues reported that the administration of RARα agonist significantly decreased brain Aβ production and that these effects were receptor specific because neither RARβ nor γ-agonists affected Aβ production [67]. Moreover, in neuronal cortical cultures, RARα agonists were demonstrated to be neuroprotective, as they prevented Aβ-induced neuronal cell death. Therefore, RARα agonists induce ADAM10 expression and have multiple effects apart of AβPP processing. In the non-amyloidogenic pathway, they decrease intracellular Aβ production and are neuroprotective, indicating that RARα agonists have therapeutic potential for the treatment of late-onset AD [67].

Using the same AD preclinical model, Gonçalves and coworkers evaluated the efficacy of several retinoid receptor agonists including AM 580, CD2019 and CD437, which are selective RARα, RARβ and RARγ agonists, respectively. They specifically demonstrated that activation of RARα receptor signaling pathway favors Aβ clearance by upregulating the enzymes NEP and IDE and modulating the release of proinflammatory cytokine TNF-α by glial cells [68].

Likewise, in patients with mild to moderate AD, a key study performed by Endres and coworkers demonstrated that acitretin treatment significantly increased CSF sAβPPα levels. Therefore, this research confirms preclinical data and was the first human evidence of an increase in ADAM10 activity by this drug in AD patients. In addition, this study gives support to the potential use of retinoid agonists as potential disease-modifying therapy drugs for AD treatment [69].

Similarly, Fukasawa and co-workers observed that Tamibarotene, a retinoid receptor agonist, lowered the insoluble $A\beta_{40}$ and $A\beta_{42}$ levels in AβPP23 transgenic mice by upregulating α-secretase expression [70]. Furthermore, in association with HX630, an RXR agonist, Tamibarotene significantly enhanced the cognitive process in the preclinical mouse model as observed by the Morris water maze test [71]. In addition, Tamibarotene has been also administered to 13-month-old SAMP8 mice and improved memory/learning. Likewise, this cognitive improvement could be due to RA activation and increased hippocampal ADAM10 mRNA expression and protein production, leading to the release of the soluble neuroprotective fragment sAβPPα [72].

In APP/PS1 transgenic mice, Ding and colleagues administrated all-trans retinoic acid (atRA) 20 mg/kg, intraperitoneally for 8 weeks [73]. This treatment improved spatial learning and memory compared with the vehicle-treated animals, assessed by the Morris water maze test. Furthermore, atRA inhibited Aβ formation, tau hyperphosphorylation, glial activation, and prevented loss of presynaptic terminals. Authors suggest that neuroprotective effects of atRA in AD could be also associated with an increase in the ChAT levels. However, potential adverse side effects of higher atRA concentrations could restrict its potential clinical applications in AD therapeutics.

Bexarotene is a highly specific RXR receptor agonist, which has a suitable safety profile in humans. In a clinical trial study, Cummings and colleagues (registered in ClinicalTrials.gov under the identifier NCT01782742) conducted a double-blind, randomized, placebo-controlled, parallel group study of a single dose (300 mg/day) of bexarotene. This study also included groups of AD patients, carriers and non-carriers of APOE allele. Patients were treated for 4 weeks and an improvement was observed in the APOE non-carriers treated group, showing a significant reduction in brain Aβ levels compared with the APOE4 carrier group [74].

In a recent clinical research, Ghosal and coworkers evaluated the effects of Bexarotene on the alteration of Aβ metabolism in cognitively healthy individuals (NCT02061878) and reported a problem with Bexarotene due to its poor CNS penetration in cognitively healthy

subjects [75].

It is important to emphasize that studies using natural products as a source of retinoids are needed and were not found in this literature search, so that only assays induced by retinoic acid, modulation of their receptors or of synthetic origin were analyzed.

3.1.2. (-)-Epigallocatechin-3-Gallate

(-)-Epigallocatechin-3-gallate (EGCG) is the major polyphenol of the *Camellia sinensis* leaf, from which green tea is produced. EGCG has antioxidant properties that might be useful since oxidative stress bears significance in AD development. It has been reported that this natural polyphenol shows neuroprotective properties in hippocampal neurons and neuronal-like cultures, inhibiting $A\beta$ oligomer toxicity [76–78]. Apart of its potential antioxidant activity, neuroprotective EGCG properties could be explained through the modulation of several signaling pathways, among them the protein kinase C (PKC)/α-secretase/sAβPPα pathway, leading to increasing the α-secretase activity.

A report by Obregon and coworkers was the first research suggesting that EGCG was able to induce ADAM10 maturation and in addition to favoring AβPP non-amyloidogenic α-secretase processing in neuronal cells. They also describe the molecular mechanism involved in EGCG modulation of ADAM10 activity through estrogen receptor [79,80]. Additionally, preclinical research studies confirm that EGCG induced non-amyloidogenic sAβPPα release and inhibited the generation of Aβ peptide via a PKC-dependent α-secretase activation. In AD preclinical models, such as APP/PS1 mice, the administration of EGCG induced cognitive improvement associated with the activation of brain insulin receptor [81]. In addition, there was Akt activation and inhibition of GSK3β signaling with a significant decrease in the hippocampal $A\beta_{42}$ levels, and an inhibition of JNK/TNFα pathway (anti-inflammatory). In the SAMP8 mice model of AD and aging, EGCG significantly prevented $A\beta_{42}$ accumulation through the overexpression of NEP [82]. Likewise, in the same mouse model, Guo and coworkers reported that EGCG improved memory function evaluated by the Morris water maze through the decrease of $A\beta_{42}$ and BACE-1 levels. Likewise, the administration of EGCG (3 mg/kg for 1 week) in a mouse model of AD was able to prevent $A\beta_{42}$-induced memory loss. The improvement in memory function was related to a decrease of $A\beta_{42}$ levels and a decrease in β-secretase levels [83].

Furthermore, additional targets involved in EGCG neuroprotection have been suggested, such as modulation of tyrosine-phosphorylation-regulated kinase 1 A (DYRK1 A) that could be important in Down's syndrome neuropathology. Recent studies give support to the use of EGCG as a cognitive enhancer in Down's syndrome patients. Torre and coworkers (NCT01699711) reported that patients with Down's syndrome treated with EGCG (9 mg/kg per day) during 12 months in parallel with cognitive training presented beneficial effects on memory compared to placebo-treated patients or the placebo plus cognitive training group in cognitive tests [84]. Despite the fact that this clinical trial has so far only been performed in Down's syndrome patients evaluating the effects of EGCG on DYRK1 A and AβPP and its role improving cognitive performance, its action in AD should also be considered.

In addition, a clinical trial completed in 2015 (NCT00951834) studied the effect of an EGCG formulation called Sunphenon in early-stage AD cases, however, the results about the potential disease-modifying effects of the drug were not yet reported.

3.1.3. Cryptotanshinone

The dried root of *Salvia miltiorrhiza* BUNGE (Labiatae), called 'Danshen' in China, is a very popular traditional Chinese medicine. Preclinical studies have shown that this plant possesses multiple pharmacological activities and has been used for the treatment of various diseases such as cardiovascular, blood circulation disorders, angina pectoris, hyperlipidemia, insomnia, and inflammation [85]. Analysis of the chemical constituents of *S. miltiorrhiza* root revealed the presence of

two classes of secondary metabolites. Among them, a family of lipid-soluble, hydrophobic diterpene pigments known as tanshinones and water-soluble, hydrophilic, polyphenolic compounds mainly consisting of caffeic acid monomers, dimers, trimers or tetramers in the form of salvianolic acids.

Preclinical evidence suggests that cryptotanshinone has neuroprotective effects and provides potential therapeutic benefit against neurodegenerative disorders such as AD. Interestingly, tanshinone derivatives cryptotanshinone and 15, 16-dihydrotanshinone I improve cognitive function and learning in scopolamine-treated rats through the inhibition of acetylcholinesterase activity in a dose-dependent manner [86]. Likewise, it was reported that cryptotanshinone shows anti-apoptotic effects in rat cortical cultures against glutamate-induced apoptosis through Bcl-2 activation, which is a downstream signaling target of PI3K/Akt pathway and mediated the neuroprotective effect [87]. In addition, the activation of this PI3K pathway in cortical neurons enhances α-secretase activity [88]. Cryptotanshinone prevents $A\beta_{42}$-induced apoptosis and cytotoxicity in SH-SY5Y [89]. Moreover, in N2a mouse neuroblastoma cells it reduced Aβ production and facilitated activation and translocation of ADAM10 and PKC-α to the cell membrane [90]. The increase of ADAM10 activity and secretion of sAβPPα could be attributed to a mechanism involving PKC activation.

In the APP/PS1AD transgenic mouse model 4 months of daily oral cryptotanshinone administration beginning at 3 months of age, significantly improved learning and spatial navigation with a reduction of amyloid plaque deposition. Due to the ability to cross BBB, its peripheral administration was able to stimulate ADAM10-mediated AβPP cleavage, increase sAβPPα production, and reduce the amounts of $A\beta_{42}$ peptides in CNS [91].

3.1.4. Ligustilide

Ligustilide is a natural lipophilic compound present in the Umbelliferae family of medicinal plants. Some preclinical studies suggest that this natural compound might be a promising therapeutic candidate for the treatment of age-related neurodegenerative diseases, such as AD. A recent preclinical study in APP/PS1 mice demonstrated that intragastrically administered ligustilide (30 mg/kg) for 14 weeks, starting at 8.5 months of age, significantly improved the neurobehavioral deficits of transgenic compared with control wild-type mice. Authors suggested that ligustilide-evoked cognitive effects were mediated by an increase in non-amyloidogenic pathway, specifically by increasing ADAM10 expression and enzymatic activity [92]. Logically, this effect on ADAM10 decreased soluble and insoluble $A\beta_{42}$ levels and plaque deposition in the brains of APP/PS1 mice.

Kuang and colleagues reported that oral administration of 40 mg/kg ligustilide exerted a neuroprotective effect against Aβ neurotoxicity when administered intracerebroventricularly [93]. In addition, the compound improved the cognitive deficits and authors suggested that the effects could be explained by the inhibitory effect of glial cells and TNF-α-signaling pathway. Recently, in a 7-month-old APP/PS1 mice assay, Xu and co-authors [94] verified that 8 weeks of daily intragastric administration of ligustilide alleviate mitochondrial dysfunction and morphology issues, exert an antioxidation effect by reducing the levels of malondialdehyde (MDA) and reactive oxygen species (ROS), reduces Aβ levels, provided synaptic protection and ameliorates memory deficit. Furthermore, it has been reported that the positive effect of ligustilide on cognitive process can be inhibited by scopolamine - an inhibitor of acetylcholinesterase activity - and thus act via enhancing cholinergic function and memory processes [95].

Interestingly, chronic administration of ligustilide prevented the development of AD-like neuropathologies and memory impairment in SAMP8 mice. One potential neuroprotective mechanism proposed is through Klotho upregulation, which is an aging-suppressor gene that causes systemic anti-aging and increases longevity. The increase in brain Klotho levels inhibited the IGF-1 pathway and decreased oxidative stress in the brain [96].
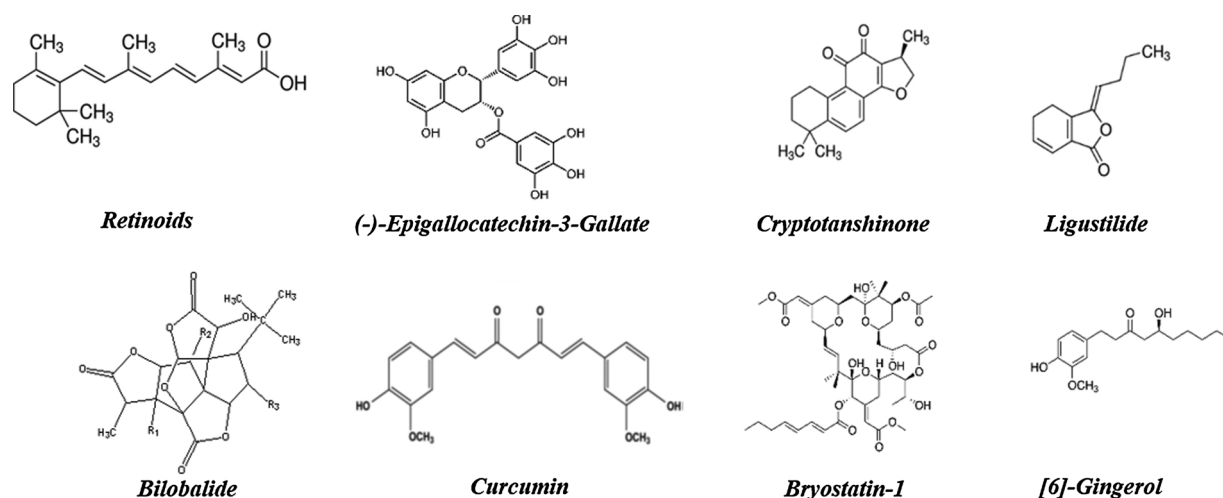
Fig. 3. Chemical structure of natural compounds involved in ADAM10 modulation.

3.1.5. Bilobalide - Ginkgo biloba extract

The seeds and leaves of *Ginkgo biloba* (Ginkgoaceae) have been used in traditional Chinese medicine. Although the extracts of the *Ginkgo biloba* leaves contain flavonoids, bilobalide and ginkgolides that can cross the BBB and also produce pharmacological effects in the CNS, a recent study published by Vellas and colleagues reported the *Ginkgo biloba* extract was ineffective in lowering the risk of AD [97]. It has been reported that the *Ginkgo biloba* extract presented an antioxidant effect on mitochondrial oxidative stress and prevented Aβ-induced neuronal apoptosis in neuronal cell cultures. However, although the total extract may not be effective in the prevention of AD, it has been reported that bilobalide, a sesquiterpenoid extracted from *Ginkgo biloba* leaves, presented neuroprotective effects against Aβ$_{42}$ [98]. Furthermore, Shi and colleagues reported that bilobalide increased sAβPPα secretion in SH-SY5Y cells, while decreased Aβ production [99]. Moreover, bilobalide up-regulated the ADAM10 expression through an up-regulation of PI3K activity without increasing PKC activity [100]. Accordingly, Yin and coworkers reported that bilobalide prevented Aβ$_{25-35}$ induced cognitive loss in Morris water maze test. The authors suggested that bilobalide beneficial effects are mediated by the inhibition of oxidative stress and the prevention of neuronal apoptosis in the brain of treated rats [101].

3.1.6. Curcumin

Curcumin is the major constituent of the Asian spice, turmeric, isolated from the rhizome of *Curcuma longa*. This natural product, due to its size, can easily penetrate the BBB, and it was suggested as a promising AD therapy [102]. In an excellent review, Reddy and colleagues described in detail the mechanisms involved in the neuroprotective effects of curcumin in AD preclinical models [103]. Among them, curcumin demonstrated antioxidant, anti-inflammatory, autophagic effects in APP/PS1 mice, decreasing Aβ levels and BACE-1 activity, among other beneficial effects. Narasingapa and coworkers developed curcumin amino acid conjugates that showed a potent α-secretase stimulatory activity [104]. The mechanisms underlying these effects are still unclear, however, it seems that curcumin can activate SIRT1 expression [105], transcriptionally increasing ADAM10 levels [106].

In addition, some clinical trials evaluated the efficacy of this drug in AD. The clinical trial NCT00164749 investigated the potential effectivity of curcumin and *Ginkgo biloba* on AD progression, but the results showed that the combination failed to reduce Aβ levels in the blood of AD patients or to improve their cognition.

The clinical trial NCT00099710 examined the safety and tolerability of curcumin and determined its effect on patients with mild to moderate AD. Ringman and colleagues published the results of this study, demonstrating no beneficial effects of curcumin in decreasing CSF Aβ levels. They suggested that problems with bioavailability could be responsible for the observed inefficacy of this drug [107].

3.1.7. Bryostatin-1

This drug is responsible for the stimulation of α-secretase activity through activation of PKC and subsequent promotion of sAβPPα secretion [108]. Interestingly, this a typical compound of animal origin that is able, at nanomolar concentrations, to promote an increase in PKC activity, increase sAβPPα levels and decrease brain Aβ levels without inducing pro-tumor activity [109].

It was demonstrated that administration of Bryostatin-1 in the APP/PS1 model of familial AD improved cognitive deficits compared to control mice [110]. Some clinical trials evaluated the efficacy of this drug in AD patients. The clinical trial NCT02221947 is a single center, randomized, double-blind, placebo-controlled, parallel group's trial in AD patients. The patients received a single intravenous dose of placebo or 25 µg/m^2 bryostatin-1 and safety, efficacy, pharmacokinetics, and pharmacodynamics of drug were investigated. The bryostatin was able to increase the Mini-Mental State Examination (MMSE) score, was well tolerated in AD patients and no drug-related adverse events were reported [108].

The clinical trial NCT02431468 evaluated the effects of bryostatin-1 (two doses with 20 and 40 µg administered i.v.) in the treatment of moderately severe to severe AD. No clinical data from the study has been currently reported.

3.1.8. [6]-Gingerol

Gingerol (Zingiberaceae family) is a dietary compound that can be found in a number of plants. Its major phenolic component is the [6]-gingerol, which has antitumor, antimutagenic, antioxidant, anti-apoptotic, anti-inflammatory, cardio- and hepatoprotective properties [111]. [6]-Gingerol has neuroprotective effects by suppressing the GSK-3β activation and increasing Akt activity [112]. In addition [6],-gingerol was able to restore Aβ$_{25-35}$-depleted endogenous antioxidant glutathione and affected Aβ$_{25-35}$-induced intracellular ROS accumulation by upregulating heme oxygenase-1 (HO-1) and γ-glutamylcysteine ligase (GCL) in SH-SY5Y cells mediated by NF-E2-related factor 2 (Nrf2). Therefore [6]-gingerol can be a potential drug for AD prevention and/or treatment through its antioxidant capacity [113] Fig. 3.

3.2. Other compounds that activate α-secretase pathway

Besides to the natural compounds that can modulate the ADAM10 described earlier (Figs. 2 and 3), it was reported that Myricetin, a

quercetin isomer, induced α-secretase and decreased Aβ levels regulating also BACE-1 activity [114]. Genistein is an isoflavonoid of the Leguminosae family that can activate PKC signaling and thus α-secretase activity increasing sAβPPα levels [115]. In addition, it can decrease Aβ levels through the BACE-1 inhibition and improve cognition via inhibiting acetylcholinesterase activity. Interestingly, Avramovich and co-workers reported that non-steroidal drugs such as nimesulide, ibuprofen and indomethacin, can increase α-secretase activity, thereby reducing the Aβ formation and thus, as we have proposed in previous studies, it is a suitable cofactor strategy for AD prevention [116].

Shuck and co-authors analyzed 313 extracts of medicinal plants indigenous to Korea for ADAM10 gene in SH-SY5Y cells. The extract of *Caragana sinica* (Buc'hoz) Rehder was identified as the best candidate for ADAM10 gene enhancers in peripheral tissue, without side effects. By fractionating *Caragana sinica* extract, alpha-viniferin was identified as one of the biologically active components that can achieve BBB penetrance and might be used as novel therapeutic options for treating AD by increasing ADAM10 gene expression [117].

Resveratrol (RSV) also is a natural polyphenolic flavonoid, which can be found in grapes and red wine, and exerts neuroprotective and antioxidant properties [118]. RSV decreased total cholesterol concentration in hypercholesterolemic rats [119]. The direct and positive effects of RSV on AD pathology are related to the activation of nuclear retinoic acid receptors, which may activate ADAM10 gene transcription [65], as discussed earlier in this review. RSV treatment under experimental conditions in Chinese hamster ovary (CHO) cells expressing human AβPP$_{695}$ containing a Swedish mutation showed a significant increase in ADAM10 expression, especially its mature form and maybe the reason for the increase of the AβPP α-CTF fragment after RSV treatment [120].

Acetyl-L-carnitine (ALC) is a compound that helps to maintain mitochondrial bioenergetics and decreases the oxidative stress associated with aging [121]. ALC is present at high concentrations in the brain and contains portions of carnitine and acetyl, both with neurobiological properties. Carnitine is important in the β-oxidation of fatty acids and the acetyl portion can be used to maintain acetyl-CoA levels. Other reported neurobiological effects of ALC include brain energetic modulation and phospholipid metabolism, synaptic morphology and synaptic transmission via multiple neurotransmitters [122]. ALC is active in cholinergic neurons, where it is involved in acetylcholine production. ALC treatment has been shown to stimulate α-secretase activity and, consequently, to reduce the β-secretase-mediated pathway [123]. It is known that ALC pre-treatment of cortical neurons in culture significantly reduced Aβ-induced cytotoxicity, protein oxidation and lipid peroxidation in a concentration-dependent manner [121]. In hippocampal neurons, treatment with ALC caused an increase in ADAM10 levels in the post-synaptic compartment [124–126]. Another study showed that ALC can influence the non-amyloidogenic metabolism of AβPP, without affecting total AβPP and ADAM10 levels. The data suggest that ALC did not alter ADAM10 protein levels, but rather influenced the delivery of ADAM10 to the post-synaptic compartment, and consequently positively modulated its enzymatic activity towards AβPP in neuronal cells [123].

4. Future perspective

4.1. Challenges of ADAM10 as a predictor of therapy outcome for Alzheimer's disease

ADAM10 expression and/or activity dysregulation are involved in a number of human pathologies [127], ranging from those affecting the brain [32,128], liver [129], epithelium [130,131], immune system [132–134] to cancer [135–137]. In this way, ADAM10 activation or inhibition therapies will differ according to the pathology (see the review from Wetzel and co-authors) [127]. However, experimental trials verify better tolerance in its moderate upregulation than in its

inhibition [127]. ADAM10 overexpression in adult mice can cause changes in the expression of more than 300 genes, however, effects were mild and age-dependent as in the case of Notch signaling, one of ADAM10's main substrates [138]. Another important point to consider is the great functional similarity of ADAM10 and ADAM17, so that they could be co-affected and, in some cases, develop undesirable situations, such as inflammation and impaired tissue regeneration [139].

New natural treatments and preventive interventions on ADAM10 regulation for AD patients are necessary, however, they have to be carefully investigated in animal models and later in clinical trials, considering the wide variety of ADAM10 substrates, with e.g. more than 90 just in the brain [140]. In addition, most studies have used *in vitro* approaches to identify substrates for ADAM10. Thus, besides the urgent need to confirm these candidates *in vivo*, also attention is required for new substrates that may limit ADAM10 activation, due to toxic effects. Despite its possible benefit when activated for patients with AD, it can be highly detrimental in other situations, such as cancer, tumor progression, metastasis, FXS, inflammation and others [53,55]. In this way, for future perspectives, it will be necessary to develop focused drugs on tissue-substrate-specific ADAM10 interaction as these approaches could reduce unwanted systemic effects. Moreover, since AD is currently seen as a multifactorial disease, multi-drug therapies should be considered that besides ADAM10 target other molecules or pathways, for example, neurogenesis.

Taken together, all the information about ADAM10 clearly indicates that more studies must be performed in order to definitely demonstrate its role in the underlying AD mechanisms. A deep investigation of ADAM10 functions would offer new understandings of its biological mechanisms of action, as well as provide novel possibilities for the development of AD treatments or predicting therapeutic outcomes. Finally, the possibility of measuring ADAM10 alterations in peripheral cells of AD patients can be exploited to monitor the response of the patients to therapeutic strategies targeting ADAM10 activity.

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