Born to protect: leveraging BDNF against cognitive deficit in Alzheimer's disease

Lucia Caffino, Francesca Mottarlini and Fabio Fumagalli*

Department of Pharmacological and Biomolecular Sciences, Università degli Studi di Milano, Via Balzaretti 9, 20133 Milano, Italy.

*Corresponding author: Fabio Fumagalli, Department of Pharmacological and Biomolecular Sciences, Università degli Studi di Milano, Via Balzaretti 9, 20133 Milano, Italy Phone 39-2-50318298; Fax: 39-2-50318278; E-mail: Fabio.Fumagalli@unimi.it

Running title: The role of BDNF in Alzheimer's disease

Declaration of Interest

None

Abstract

Alzheimer's disease (AD) is a chronic, neurodegenerative and devastating disorder affecting a high percentage of the population over 65 years of age and causing a relevant emotional, social and economic burden. Clinically, it is characterized by a prominent cognitive deficit associated with language and behavioral impairments. The molecular pathogenesis of AD is multifaceted and involves changes in neurotransmitter levels together with alterations of inflammatory, oxidative, hormonal and synaptic pathways, which may represent a druggable target for both prevention and treatment; however, an effective treatment for AD still represents an unmet goal.

Since neurotrophic factors participate in the modulation of the above-mentioned pathways, they have been pointed out as critical contributors of AD etiology, whose modulation might be beneficial for AD. We here focused on the neurotrophin Brain-Derived Neurotrophic Factor (BDNF) providing several lines of evidence pointing to BDNF as a plausible endophenotype of cognitive deficit in AD, illustrating some among the most recent possibilities to modulate the expression of this neurotrophin in the brain in an attempt to ameliorate cognition and delay the progression of AD.

This review shows that otherwise disparate pharmacologic or non-pharmacologic approaches converge on BDNF providing a means whereby apparently unrelated medical approaches may nevertheless produce similar synaptic and cognitive outcomes in AD pathogenesis through its modulation, suggesting that BDNF-based synaptic repair may represent a modifying strategy to ameliorate cognition in AD.

Key points:

1) The neurotrophin Brain-Derived Neurotrophic Factor (BDNF) represents a plausible endophenotype of cognitive deficit in Alzheimer's disease (AD) and a mechanistic underpinning to be targeted to offset the cognitive decline of AD.

2) Otherwise disparate pharmacologic or non-pharmacologic approaches converge on BDNF, influencing synaptic plasticity and ameliorating the cognitive deficit

3) BDNF-based synaptic repair may represent an interesting modifying strategy to improve cognition in AD patients.

1. Alzheimer's disease and BDNF

Alzheimer's disease (AD) is a complex, multifactorial disease that primarily affects the aged population in the world, causing a substantial social and economic burden. Its pathophysiological hallmarks are represented by a plethora of dysfunctions involving the accumulation of specific proteins (Aβ and tau) and tau hyperphosphorylation coupled with altered synaptic functions and mitochondrial alterations, all of which would result into marked impairment of cognitive processes that represent the trademark of this neurodegenerative disorder.

Despite the greater understanding of AD pathogenesis over the last 30 years, there is still no cure for the disease, suggesting that novel approaches are requested. Since the neurotrophin Brain-Derived Neurotrophic Factor (BDNF) is crucially involved in synaptic remodeling during cognitive processes, the possibility exists that interventions aimed at restoring BDNF expression and function might be therapeutically [1].

BDNF belongs to a group of proteins called neurotrophins, which play a pleiotropic role in the central nervous system (CNS). Historically, BDNF has been shown to play a critical role during CNS development by modulating cell growth, cell survival and cell differentiation [2]. More recently, besides its well-established role in regulating cell homeostasis, a more 'plastic' role of BDNF has been demonstrated. In fact, several lines of evidence have shown, in the adult brain, a pivotal role of this neurotrophin in neuroprotection and activity-dependent structural remodeling [3]. Also, it is well established that BDNF is critical for the neuroplastic changes subserving cognitive processes [4], thus providing a reasonable ground for therapeutic interventions aimed at restoring cognitive functions in neurodegenerative disorders such as AD.

The organization of the Bdnf gene is complex with several 5' non-coding exons, each characterized by a separate promoter region that drives the transcription of a common 3' exon and encoding for the same protein [5]. These multiple transcripts are differently regulated, although their function is still elusive, it is clear that it provides heterogeneity in expression in different brain regions. We know that specific exons may undergo different intracellular targeting: for instance, exon IIa and VI are targeted to dendrites [6] suggesting that treatments aimed at potentiating the synaptic pool of BDNF may indeed represent a mechanism for the consolidation and strengthening of synapses, thus influencing the cognitive process. BDNF synthesis occurs in the endoplasmic reticulum leading to a precursor form (proBDNF, 32 kDa) that, after being sorted in the Golgi and cleaved at both intracellular and extracellular level, gives rise to the mature form of the neurotrophin (mBDNF, 14 kDa), which is anterogradely transported to its target neurons [7]. Generally, proBDNF and mBDNF are dynamically balanced in the CNS; however, it has to be taken into account that proBDNF, before the cleavage to mBDNF, has opposite functions compared to its mature form in terms of neuron survival suggesting that such proteolytic process of the neurotrophin is a very delicate, sensitive and potentially druggable target to promote BDNF

maturation. Once released, BDNF binds to its high-affinity receptor trkB (tropomyosin receptor kinase B) and, after dimerization and autophosphorylation, trkB is activated [8] and it stimulates three major downstream intracellular pathways, namely phosphoinositide 3-kinase (PI3-K), phospholipase C-γ (PLC-γ) and mitogen-activated protein kinase (MAPK) pathways. Thereafter, the signal is conveyed into the nucleus where it triggers the activation of related transcription factors [such as cyclic AMP response element binding protein (CREB)], which modifies gene expression [9].

Several lines of evidence point to BDNF as critical for AD. The neurotrophin has been associated with a reduction of Aβ aggregation, Aβ-induced neurotoxicity, and synaptic dysfunction [10]. The expression of BDNF is decreased early in the course of disease in transgenic preclinical models of AD [11] and the removal of its high-affinity BDNF receptor, trkB, in transgenic mice precipitates and exacerbates the phenotype [12]. Interestingly, BDNF-devoid neurons contained neurofibrillary tangles, a feature of AD, which were, instead, absent in densely BDNF-labeled neurons [13]. Arancibia and colleagues (2008) showed that BDNF is protective effects against Aβ peptide neurotoxicity in vivo and in vitro [14]. However, we cannot disregard relevant studies contradicting the role of neurotrophins in AD. To this end, Burbach and associates (2004) have shown induction of BDNF in plaque-associated glial cells of aged APP23 transgenic mice that significantly correlated with the β-amyloid load, pointing to the neurotrophin as a critical regulator of inflammatory processes [15]. Interestingly, in the same transgenic mice, a cortical increase of BDNF was observed that tightly correlated with β -amyloid load [16]. Of note, a similar discrepancy is observed in humans as a decrease in the neurotrophin levels has been observed in the brain [17-19], serum [20-22] as well as in the CSF of AD patients [23-25]. In contrast, Durany and coworkers (2000) found a significant increase in BDNF protein in the hippocampus and the parietal cortex of AD patients [26]. Taking these preclinical and clinical data together, the levels of the neurotrophin appear to be variable, presumably depending upon the severity of the degenerative state.

Of note, familial caregivers of AD patients, who are in charge of taking care of their relatives with AD, experience themselves robust emotional burden and display cognitive impairment, suggesting that being a familial caregiver of an AD patient is a risk factor. Notably, Corrêa and associates (2019) have analyzed the serum of caregivers and found lower BDNF levels associated with a functional deficit of prefrontal cortex and hippocampus [27]. Of note, such deficit was associated with contextual memory impairment that was reversible suggesting that caregivers exhibit a cognitive reserve, a sort of plasticity, that can be used in case of demand to reduce the deleterious effects of stress [27] in order to adjust the negative emotional state induced by the family environment.

While we could add a plethora of evidence to further dissect the role of BDNF in AD, the take-home message is that reduction of BDNF levels in experimental animal models as well as in humans points to a multifaceted role of this neurotrophin that could be considered a flexible hub for synaptic plasticity and cognition functioning as prognostic, diagnostic but also a therapeutic factor in AD (Fig 1).

1.1 BDNF polymorphisms

The neurotrophin BDNF is indeed a valuable candidate for disorders involving memory loss, because of its role in hippocampal-mediated long-term neuroplasticity, which is impaired in AD. It has also been widely shown that the BDNF gene suffers from a functional, naturally occurring single nucleotide polymorphism (SNP) in the 5' proregion of the human Bdnf gene at codon 196. Such SNP results in a Valine (Val) to Methionine (Met) amino acid substitution at codon 66 (Val66Met). The joint production of Val-BDNF and Met-BDNF in neurons leads to heterodimers that impair the neurotrophin trafficking and its secretion, causing memory deficit [28]. Along this line of reasoning, Lim and associates found that elevated levels of Aβ in human Met carriers are indicative of a faster cognitive deficit and hippocampal degeneration in an early stage of AD [29]. The role of the BDNF Val66Met polymorphism is reinforced by recent evidence showing that human Met carriers are more prone to gray matter damage [30]. In another recent clinical study, the effect of BDNF Val66Met on cognitive trajectories was investigated, including several cognitive domains. In this study, Met carriers exhibited a steeper decline in episodic memory and executive functions, suggesting that these individuals may show an accelerated cognitive impairment, further substantiating its potential role in the cognitive decline of subjects at risk of AD [31]. In another clinical study, the BDNF Val66Met polymorphism worsened episodic memory deficits in autosomal dominant AD and was associated with increased tau, hippocampal dysfunction, and memory impairment [32]. Furthermore, in the same study, it was shown that carrying the Met66 allele seems to be correlated with a more severe manifestation of AD, primarily in subjects carrying mutations in other genes such as APP, PSEN1 or PSEN2 [32]. Thus, the issue of BDNF polymorphisms appears to be critical in AD; the effect of Val66Met polymorphism on the severity of endophenotypes is well documented, although other Bdnf gene variants do exist such as the rs56164415 that have been shown to be associated with increased of late onset AD in humans [33]. However, we still need to learn more on these polymorphisms and their effects on AD as, for instance, Met carriers seem to better perform, compared to Val/Val homozygotes, at older age [34] suggesting that the role of the neurotrophin on cognition may change over years and Met carriers could even be protected later in life. Taken all together, these findings point to the importance of BDNF polymorphisms for AD pathology. In particular, the proBDNF Val66Met variation impairs the conversion of the preform of BDNF into its mature form resulting in higher levels of proBDNF [35]: the lack of such proteolytic cleavage may be detrimental for AD pathogenesis.

1.2 proBDNF

We have above mentioned that the precursor form of BDNF, proBDNF, undergoes proteolytic processing, ultimately leading to the cleaved mBDNF. Clinical evidence exists showing that proBDNF levels are enhanced over mBDNF levels in the brain of AD patients, suggesting a potential critical role of proBDNF in AD pathogenesis [36]. Besides, reduced levels of proBDNF have been found in the nucleus basalis of Meynert of AD patients [37], preceding the diminution of acetylcholinesterase activity, a marker of AD [36]. It has been hypothesized that the accumulation of proBDNF may activate the p75 pathway causing amyloidogenesis [38]. Along this line of reasoning, Gerenu and colleagues (2017) have elegantly shown that soluble Aβ interferes with the proteolytic cleavage of the neurotrophin, suggesting that impaired BDNF maturation may contribute to degeneration and cognitive deficit in both AD patients and animal models of AD [39]. This evidence has been further corroborated by the work of other groups. Chen and associates (2017) have shown that reduced extracellular conversion of pro-BDNF to mBDNF, with consequent proBDNF accumulation, exacerbates the formation of Aβ deposits promoting the formation of senile plaques, thus accelerating learning and memory deficits in a transgenic mouse model and possibly contributing to AD pathology [40]. The neurotoxic functions of proBDNF in AD are further strengthened by Fleitas and coworkers (2018), who showed that proBDNF levels are increased in the brain and CSF of AD patients [41]. Intriguingly, these authors found that the toxicity of proBDNF can be worsened by common mutations found in familial forms of AD, that interfere with the proteolytic cleavage, a synergistic interaction caused by the potentiation of p75-mediated signaling, further pointing to the proBDNF/p75 pathway as pivotal for AD pathogenesis. These findings suggest that promoting the conversion of proBDNF into mBDNF, thus reducing proBDNF levels at a preclinical stage, may contribute to disease prevention, opening the fascinating possibility that novel neuroprotective strategies for AD might target this specific process. To this end, it would be interesting to carefully monitor the levels of proBDNF/mBDNF during the evolution of AD in order to get crucial information inherent to the mechanisms regulating such proteolytic cleavage for the development of AD pathology.

2. Administration of exogenous BDNF

Although the evidence that reduction of BDNF levels can be considered a hallmark of AD suggesting that its replenishing may be beneficial, however, its exogenous administration faces multiple technical challenges and drawbacks that can result in deleterious secondary effects [42]. In particular, the neurotrophin does not readily cross the blood-brain barrier (BBB), and due to pharmacokinetic issues, its half-life is short in the bloodstream [43-45]. A potential solution could be the intraventricular injection of BDNF; however, since this approach is highly invasive and cannot be used for prolonged treatments, it has been so far pursued in preclinical models of the disease only. For instance, Xu and co-workers (2019)

used this modality of BDNF administration in the okadaic acid rat model of AD [46]. The neurotrophin, delivered via intra-hippocampal injection, mitigated okadaic acid-induced tau hyperphosphorylation, which is known to reduce BDNF secretion and levels in cortical neurons [47]; in addition, BDNF delivered through this way also improved cognition by potentiating PP2A activity through the activation of BDNF downstream pathway PI3K/GSK-3β/Akt [46].

Due to these technical problems, the administration of small molecules, with easy access through the BBB into the brain parenchyma, with the function of mimicking BDNF and its intracellular actions, is suitable as it allows to control the modulation of BDNF-induced activities [45, 48]. To this end, small peptide mimetics exist that can enhance transcription of BDNF through modulation of Trk receptor, thus rescuing BDNF deficient situations in experimental models [49]. BDNF mimetic compounds may be designed to bind BDNF receptors with an affinity similar to the full-length protein with the hope to ameliorate the pharmacokinetic features of BDNF; alternatively, these small peptides can allosterically improve the functional efficacy of BDNF receptor, or they could influence the activation or inhibition of BDNF intracellular signaling [48]. Interestingly, small CNTF-based peptidergic compounds also exist that can enhance transcription of BDNF in rodents rescuing cognitive impairment representing a novel, potential therapeutic approaches [50-53].

Alternatively, BDNF can also be delivered via microspheres, which are minimally invasive. To this end, Bertram and associates (2010) have synthesized polymers based on with Poly Lactic-co-Glycolic Acid (PLGA) micro-particle, which can lead to the delivery of bioactive BDNF lasting for more than 60 days [54]. This approach has been implemented by an innovative method that allows bringing BDNF in the brain by transplantation of exogenous stem cells that can express BDNF, through a complex system using positively charged polyprodrug amphiphiles. In this way, it has been shown that it is possible to control exogenous neural stem cells that may represent a source of BDNF for AD therapy [55]: such way of delivery of BDNF resulted in a significant improvement of cognitive abilities in a transgenic mouse model of AD [55].

The progress of science and increased knowledge has allowed hypothesizing alternative ways of providing BDNF support. Recently, BDNF was conditionally and locally delivered to rescue several deficits observed in an amyloid mouse model of AD [56]. Since astrogliosis is indeed a hallmark of AD [57], these authors engineered astrocytes to deliver BDNF under the GFAP promoter to provide neurotrophic support when needed. In this preclinical model of AD, hippocampal BDNF loss was totally rescued together with BDNF-dependent signaling leading to improvements in cognition as well as structural and functional synaptic plasticity [56].

A very recent possibility to interfere with BDNF expression relies on epigenetic therapy, i.e. the possibility to manipulate chromatin remodeling, histone acetylation/deacetylation and methylation to elevate BDNF expression, which represents novel epigenomic therapeutic targets [58]. Interesting improvements in several markers of AD, including amyloid-β

protein levels and tau phosphorylation as well as improved spatial learning and memory together with increased BDNF expression have been found following treatment with RGFP-966, a brain-penetrant, and selective HDAC3 inhibitor, in vitro and in rodents [59].

Similar to epigenetic therapy, the possibility exists to target specific microRNAs, i.e. small non-coding RNAs that regulate gene expression post-transcriptionally by interfering with the translation of their target mRNAs, to enhance BDNF availability. In fact, Li and colleagues (2016) have shown that targeting of micro-613 may represent a therapeutic intervention to oppose to a BDNF reduction in patients and animal models [60]. Notably, mesenchymal stem cells engineered to over-express antisense of miRNA-937 were transplanted into a murine model of AD leading to reduced deposition of Aβ, improving recognition and short memory as well as learning deficits, at least in part through BDNF elevation [61].

Notably, Eremenko and colleagues (2019) have conceived a T cell-based system to deliver BDNF into the brain parenchyma [62]. These authors genetically engineered Aβ-specific CD4 T cells to express BDNF and then injected these cells intracerebroventricularly in a murine model of AD. These cells augmented the levels of the neurotrophin as well as of other synaptic proteins reducing the amyloidogenic process revealing the therapeutic ability of T cells as a promising strategy to fight AD [62].

In sum, the very recent improvements in knowledge regarding the possibility to convey BDNF in the brain coming from preclinical studies must be taken into account when developing BDNF-based therapies for AD, to overcome the problems related to the exogenous administration of the neurotrophin (i.e. flooding of the neurotrophin in brain regions other than those affected by AD), in an attempt to improve the therapeutic effect and to reduce potential side effects.

3. Modulation of endogenous BDNF

3.1 Pharmacologic modulation

In 2006, we had provided a comprehensive overview of the drugs that, back then, were mainly used for AD, and that shared the peculiarity to modulate the expression of the neurotrophin BDNF in brain regions that are specifically involved in the pathophysiology of the disease [1]. These lines of evidence have been recently corroborated. In fact, recent evidence shows that drugs commonly used to treat AD promote, at least partially, the activation of the BDNF pathway. Donepezil, a cholinergic agonist, has been shown to improve cognitive deficit in a tree shrew model of AD via activation of the BDNF/TrkB signal pathway [63]. Interestingly, recent evidence regarding another approved drug for AD, memantine, indicated that the NMDA inhibition provided by memantine prevents the negative effect of Aβ on BDNF functions in rodents, thus allowing the neurotrophin to positively influence brain plasticity [64].

Although no disease-modifying drugs have recently been developed since then and, on the market, only symptomatic drugs (i.e. drugs that alleviate the clinical manifestations of AD) are available, novel drugs have been shown to improve cognitive deterioration in experimental models of AD, via BDNF-mediated mechanisms. Recent emphasis has been put on the natural compound, 7,8-dihydroxyflavone (7,8-DHF). 7,8-DHF is a prodrug that binds the extracellular domain of the high-affinity BDNF receptor, trkB, acting as a selective agonist and thereby mimicking the physiological actions of the neurotrophin. The properties of 7,8-DHF have also been demonstrated in different independent studies employing animal models of various brain disorders. With respect to AD, 7,8-DHF has been shown to ameliorate spatial memory together with the repression of BACE1 expression and a reduction of Aβ deposits in a murine model of AD characterized by neuronal loss [65]. 7,8-DHF also reduced Aβ deposition in transgenic mice that co-express five familial Alzheimer's disease mutations (5XFAD mice), also inhibiting the hippocampal synapses loss, thus preventing memory deterioration [66]. In addition, Chen and colleagues (2014) showed that 7,8-DHF reverses Aβ deposition, oxidative stress, synaptic dysfunction, and learning impairments caused by the cholinergic antagonist, scopolamine [67]. Recently, Chen and associates (2018) have developed several 7,8-DHF derivatives by inducing several modifications on the catechol ring in the parent compound [68]. Following detailed pharmacokinetic *in vitro* and *in vivo* studies, a single compound, namely R13, was chosen that is characterized by a better absorption, longer half-life, rapid hydrolyzation in liver microsomes, and improved oral bioavailability. The repeated oral administration of R13 to 5XFAD mice reduced Aβ deposit and hippocampal loss of synapses improving memory impairments [68]. Interestingly, the activation of trkB has been shown to indirectly activate glutamate transmission, namely AMPA receptor-dependent transmission, in a transgenic mouse model of AD, ameliorating memory, and learning deficits [69]. Altogether, these findings point to 7,8-DHF as a novel oral bioactive therapeutic agent for the treatment of AD, which acts by activating the BDNF-mediated pathway.

Several causative compensatory mechanisms may contribute to AD, in particular to altered cognition, such as, for instance, anxiety and hyperactivity. Accordingly, drugs that specifically ameliorate such symptoms could also be used for AD, and intriguingly, some of them share the property of interfering with BDNF expression. Accordingly, evidence exists that drugs used for psychiatric disorders may provide benefit to AD patients, through the modulation of BDNF levels. To this end, recent evidence has shown that lithium, the drug of choice for bipolar disorder, may be used for agitation in AD [70]. Notably, chronic micro-doses of lithium prevented memory loss and neuro-histopathological changes in a transgenic murine model of AD through BDNF up-regulation, an effect that was associated with a less anxious state [71]. Such an effect on anxiety in AD also characterizes a second-generation antipsychotic, quetiapine, which prevents memory deficit in a murine model of AD, at least in part through elevation of BDNF expression [72].

Interestingly, a recent report has shown that quetiapine prevents Aβ-induced cell death in cultured neurons via increased release of the neurotrophin from astrocytes, further pointing to astrocytes as critical for the action of drugs that interfere with mechanisms that contribute to AD [73]. Another second-generation antipsychotic shown to interfere with AD mechanisms is clozapine, whose treatment has been shown to improve cognitive decline by reducing Aβ deposits and plaque deposition in a transgenic mouse model of AD, effects that appear to be mediated by BDNF up-regulation [74]. Along with this line of reasoning, another second-generation antipsychotic, aripiprazole, improves Aβ1-42-induced decreased neurite outgrowth and viability in neuronal cells, suggesting that it might be effective against Aβ-induced neurotoxicity in AD-associated psychosis [75].

Mood stabilizers are also employed in AD treatment as AD patients show a higher incidence of epileptic seizures [76], and hyperexcitability appears to be a feature of several murine models of AD [77]. Evidence exists that the antiepileptic drug levetiracetam can rescue the impaired cognition observed in human APP transgenic mice [78]. Interestingly, repeated treatment with the antiepileptic drug lamotrigine mitigates the impairments in synaptic plasticity and cognition observed in a transgenic mouse model of AD [79].

Another class of drugs that may be effective in AD is represented by antidepressants [80]. Previous preclinical and clinical studies had demonstrated ameliorative effects of this class of drugs on cognition in AD [81, 82]. Recently, the selective serotonin reuptake inhibitor (SSRI) escitalopram has been shown to ameliorate the AD-like features, and cognitive deficit caused by ovariectomy and subsequent D-galactose treatment, an accepted experimental model of AD: of note, such improvement occurs, at least partially, through the enhancement of hippocampal BDNF levels [83]. That is in line with previous data showing that escitalopram mitigates forskolin-induced tau hyperphosphorylation and memory deficit in rats [84]. To further sustain the beneficial role of increased serotonergic transmission for AD, Cirrito and coworkers (2011) investigated the effect of serotonin in the accumulation of Aβ plaques in humans. They found that an active serotonin signaling is associated with reduced Aβ accumulation in cognitively normal individuals [85]. In line with the effectiveness of antidepressant drugs in AD, Chadwick and colleagues (2011) have shown that amitriptyline, a tricyclic antidepressant, promotes hippocampal neurogenesis, at least in part via increased expression of hippocampal BDNF, in a transgenic model of AD [86]. The widely used SSRI fluoxetine has also been shown to long-lastingly ameliorate cognitive deterioration in AD transgenic mice harboring three different mutations (3 x TgAD mice) [87]. Of note, a more recent study showed that fluoxetine, when administered during adolescence, can prevent the accumulation of Aβ levels and the development of memory deficit typical of 3 x TgAD mice, through a mechanism that involves the activation of the CREB-BDNF pathway, an effect that lasts, at least for four months [88]. Thus, both antipsychotics and antidepressants may be used in the treatment of AD, leveraging the neurotrophin BDNF as a common denominator. The

added value of using commercially available antipsychotics or antidepressants relies on the evidence that these drugs have been widely studied and approved and, therefore, their unwanted effects are known.

In line with the inflammatory theory of AD, it has been recently found that treatment with the antitumor necrosis factor-alpha (TNF-α) monoclonal antibody adalimumab is able to improve memory deficit in rodents via different mechanisms that include, among the others, mitigation of Aβ-induced BDNF reductions [89]. Of note, another drug, etanercept, known to ameliorate cognition in AD patients, which acts by neutralizing TNFα, improves cognitive performance in preclinical models, at least partially via increased BDNF expression [90, 91]. Similarly, another anti-TNF- α drug, infliximab, has proven effective in the Aβ-induced animal model of AD [92]: interestingly, infliximab is able to modulate hippocampal BDNF levels, preventing cognitive decline [93]. These data lastly suggest that these drugs, via an anti-TNF-α activity, not only improve the inflammatory state but may also rescue BDNF expression, contributing to the amelioration of memory performance, thus providing a potential rationale for their use in AD.

Among other BDNF-modulating compounds, naturally occurring approaches can be counted. The cell membrane components gangliosides, which are widely present in the CNS, represent an attractive option for neurodegenerative disorders due to their neuroprotective and restorative features [94]. However, their role in AD is still elusive as evidence exists, showing both a favoring or a protective role for ganglioside [94]. Evidence exists that, in both animal and human brains, primary ganglioside composition is altered [95, 96]. In particular, the levels of ganglioside GQ1b are reduced in both experimental models and AD patients [96, 97]. It is interesting to note that ganglioside GQ1b is able to ameliorate cognitive deficit typical of experimental models of AD, also reducing amyloid-β protein precursor (AβPP) and tau hyperphosphorylation, an effect that occurs together with the restoration of BDNF levels, which were diminished in 3xTg-AD mice [98]. Thus, from these data, it could be speculated that inhibition of Aβ and tau activation by GQ1b-induced BDNF upregulation might be a remarkable approach for the treatment of AD.

Another potential, naturally occurring approach, relies on the notion that sphingolipids contribute to regulating the function of AβPP and Aβ protein metabolism [99]. Considering that sphingolipids cross-talk with transcription factors to modulate neuronal cell death, Fingolimod, a structural sphingosine analog, and sphingosine 1 receptor modulator, currently in use for the treatment of relapsing-remitting multiple sclerosis, has been proposed as a promising drug to fight AD. Interestingly, Fingolimod has been shown to reduce Aβ secretion and deposition and restore memory deficit in preclinical models through the up-regulation of BDNF levels [100, 101].

Other naturally occurring molecules with a potential role in AD are indeed bile acids [102], although their neuroprotective mechanism is still obscure. Notably, low levels of bile acids have been observed in AD patients but also

healthy elderly subjects [103, 104]. Recently, it has been shown that chenodeoxycholic acid, a bile acid and a potent activator of farnesoid X receptors, i.e., nuclear bile acid receptors regulating cholesterol homeostasis, was able to attenuate cognitive deficit in a mouse model of the disease, by up-regulating various proteins, including the hippocampal levels of the neurotrophin BDNF [105].

Another critical player in AD pathogenesis appears to be protein kinase C epsilon (PKCε). Hongpaisan and colleagues (2011) have first shown that administration of bryostatin-1, a potent activator of PKCε, prevents Aβ accumulation and learning deficit in transgenic animal models of AD. Notably, treatment with bryostatin-1 inhibits the suppression of BDNF in transgenic mice that was associated with elevation of Aβ and synaptic loss, thus suggesting that this drug improves learning deficits, at least partially, via the modulation of the neurotrophin [106]. This is confirmed by Sen and associates (2018), who showed that loss of PKCε results in BDNF down-regulation, an effect that was restored by activating PKCε in transgenic mice[107]. In addition, PKCε was recently found to be reduced in AD autopsy samples [108], further pointing to the role of this BDNF-modulating kinase in AD pathogenesis. To substantiate the importance of PKCε, based on these preliminary lines of evidence, bryostatin-1 has been employed in a randomized, double-blind, placebo-controlled, Phase IIa clinical trial for AD assessing safety, tolerability, and efficacy of bryostatin in the treatment of moderately severe to severe AD [109].

Evidence exists that Rho activity, hypothesized to participate in AD pathogenesis [110], is upregulated in the brain of a mouse model of AD [111]. This evidence would suggest that the inhibition of Rho activity might be beneficial as AD treatment. Yu and coworkers (2017) found that Fasudil, a selective Rho kinase (ROCK) inhibitor, ameliorates disease severity in a transgenic mouse model of AD [112]. However, due to a narrow safety window as well as poor oral availability, Fasudil cannot be employed for long-term exposure. Accordingly, Gu and colleagues (2018) have selected a novel ROCK inhibitor, FSD-C10, which improved the cognitive deficit observed in a transgenic mouse model of AD and reduced Aβ deposition as well as tau hyperphosphorylation [113]. Notably, such improvements were paralleled by the increase of several synaptic proteins, including the neurotrophin BDNF.

It is known that type 2 diabetes has been identified as a risk factor for AD [114]; interestingly, insulin signaling in the hippocampus and cerebral cortex is critical for cognition and synaptic plasticity [115]. Hanyu and colleagues have shown that chronic pioglitazone treatment ameliorates cognition in AD patients and in subjects with type 2 diabetes mellitus [116]. Dong and associates have employed sitagliptin a dipeptidyl peptidase 4 inhibitor used for the treatment of type 2 diabetes mellitus that significantly improved cognition in type 2 diabetic patients with or without AD [117] for a treatment of a transgenic mouse AD model [118]. These researchers showed that sitagliptin effectively improved cognition in the AD mouse model via activation of the BDNF-trKB pathway. It is interesting to note that another drug

approved for type 2 diabetes named liraglutide, a glucagon-like peptide-1 (GLP-1) analog, was able to reverse several hallmarks of AD in a transgenic mouse model [119, 120]. Similar to sitagliptin, liraglutide displays BDNF upregulating features in both mice and cultured hippocampal neurons [121, 122], a characteristic shown also by another GLP-1 analog, exenatide, which delays the cognitive decline in a preclinical model of mid-life brain aging, an effect that appears to occur, at least partially, through the activation of the BDNF-TrkB neurotrophic axis [123]. These data suggest that regulation of insulin secretion and insulin-dependent signaling may represent a valuable treatment for the cognitive deficit observed in AD. This is strengthened by a recent work showing that intranasal insulin can be effective in ameliorating cognitive impairments in AD [124]; notably, intranasal insulin appears to increase BDNF in aged mice, potentially revealing a mechanism of action of its effect in AD [125] and adding this way as a promising, BDNF-dependent method to ameliorate AD symptoms. Also, this finding would be indeed interesting as the intranasal way permits to overcome the obstacles caused by systemic delivery of parenteral or oral drug routes.

3.2 Non pharmacologic modulation

BDNF may be modulated in AD experimental models also by non-pharmacologic approaches. To this end, transcranial magnetic stimulation (TMS) has received much attention recently. TMS is a non-invasive and painless method that uses electromagnetic induction to excite neuronal cells in a manner that can be regulated to high or low frequency. This technique has been used for different disorders of the central nervous system such as depression [126], drug addiction [127], and eating disorders [128], revealing itself as a possible approach of clinical efficacy. Of note, repetitive TMS has been shown to induce the expression of hippocampal BDNF in preclinical models, with neuroprotective and pro-cognitive results [129].

Recent data indicate that this option might be suitable also for AD and, interestingly, that the therapeutic effect could be mediated, at least partially, by BDNF. In fact, Tan and colleagues (2013) showed that repetitive TMS at low frequency ameliorates Aβ-induced toxicity in a rodent model of AD, via hippocampal BDNF up-regulation, which enhances hippocampal LTP improving memory impairments [130]. Chen and associates (2019) caused AD-like symptoms by intracranial injection of Aβ1-42 in mice and found that repetitive TMS ameliorated cognition, reduced apoptosis in mice and improved neuronal viability in mice, at least in part, through BDNF up-regulation [131]. Thus, repetitive TMS appears to promote the up-regulation of BDNF levels as a contributing mechanism for its anti-AD functions, suggesting that this non-pharmacologic option may, perhaps, be useful for AD patients.

Another non-pharmacologic approach that shares a contribution of BDNF modulation for the treatment of AD is represented by acupuncture. Acupuncture, widely used in oriental medicine, provides a somatosensory mechanical stimulation of peripheral nerves, and it has been shown to enhance BDNF expression, perhaps via glutamate-mediated mechanisms [132]. It has been shown that electroacupuncture ameliorates memory deficits in a murine model of AD, reducing Aβ accumulation and promoting neurogenesis through a mechanism that involves BDNF up-regulation [133], a result that was confirmed to be BDNF-mediated in the same transgenic mouse model [134].

An interesting recent option has been recently suggested by Oh and colleagues (2019), who used nasal cavity administration of melanin-concentrating hormone (MCH) to ameliorate cognition in transgenic mouse models of AD [135]. This recent manuscript points to the activation of the BDNF-trkB pathway as a potential mechanism for reduced Aβ toxicity and cognitive enhancement. Notably, MCH has been previously shown to improve cognitive performance in AD patients [136].

Among the non-pharmacologic approaches for AD, we cannot avoid mentioning the role of the environment. The environment plays a role in everyday life and may influence the onset or development of several disorders, neurodegenerative or psychiatric. For instance, it has been demonstrated that animals exposed to an enriched environment showed reduced amyloid-β deposits when compared to animals living in standard conditions [137]. However, the word 'environment' can be declined in various ways, and accumulating evidence has shown a positive role of physical exercise in preventing and/or ameliorating AD symptoms in humans and preclinical models [138]. Epidemiologic data in humans have shown that inactive patients are at higher risk of developing cognitive impairments [139] and that physical exercise protects against cognitive deterioration [140].

The memory-enhancing function of exercise in rodents has been widely demonstrated; notably, in several cases, it appears to be mediated by changes in BDNF levels. Dao and colleagues (2013) showed that treadmill exercise was able to prevent learning and memory deficit following intracerebroventricular injection of Aβ, at least in part through increased neurogenesis as well as BDNF and trkB levels [141]. A recent elegant manuscript showed that the effect of exercise in experimental models of AD is independent on whether it is voluntary, involuntary or forced. Notably, the restorative effect of exercise was linked to increased expression of hippocampal BDNF [142]. It is important to note that Brown and colleagues (2014) found that physical activity, in humans, has a different impact on Met carriers when compared to Val/Val homozygotes: in fact, Met carriers exhibited reduced volume of the temporal lobe, whose volume was instead larger in Val/Val homozygotes [143]. These results suggest that the effects of exercise are largely affected by the BDNF

Val66Met polymorphism, suggesting that the benefit deriving from physical activity is genotype-specific. This finding is of great importance since, if genetics influences the effects of exercise, then the physical activity should be personalized to each subject's genetics.

Among non-conventional treatments for AD, an extremely innovative approach that has collected a compelling interest is represented by the so-called green therapy, consisting primarily of gardening activities for AD patients. Previous data had shown that horticultural therapy, including common gardening tasks, significantly ameliorated cognition in senior individuals who have dementia [144-146]. Thus, green therapy can improve psychological, social, and emotional well-being, perhaps influencing the clinical outcome. Notably, the benefits of gardening activities for cognitive functions appear to be related to increased levels of BDNF in the blood [147] further pointing to BDNF as a dynamic gatekeeper of synaptic plasticity and a functional pro-cognitive stimulus.

4. Botanicals

The use of herbal remedies in neurodegenerative disorders raises a new exciting perspective. However, given to the remarkably huge number of published manuscripts, it is not possible to discuss all of them in this review. To this end, this chapter will only provide a flavor of the potential applications of herbal drugs that act, at least partially, via BDNF modulation, discussing the potential advantages of using these natural products.

To date, we can state that a therapeutic potential exists for herbal medicines in AD [148]. Indeed, herbal compounds may represent an alternative approach to the conventional, still symptomatic treatments nowadays available for AD and could be considered as preventive agents or useful adjuvants, offering some complementary cognitive benefits to classically used drugs. This turns out to be extremely appealing, primarily in view of a poly-therapeutic approach of AD. However, it has to be taken into account that the effectiveness of botanicals tightly depends upon an adequate standardization of the active ingredients as well as on the proper use of the plant, avoiding the presence of toxic bioactive principles. A recent elegant manuscript has reviewed botanicals as modulators of neuroplasticity, providing several lines of evidence that point to herbal drugs as useful candidates to modulate BDNF *in vivo* [149]. Notably, Dey and colleagues (2017) have published a comprehensive review in which they quote several herbal products, including Chinese medicinal plants, and show that some of them ameliorate cognition in experimental models of AD, some of them by up-regulating BDNF expression [150].

When dealing with herbal remedies, several issues must be critically considered, as they include herbal compounds per sè, plant extracts, fractions, and traditional herbal formulations. A limitation may derive from the fact that the standardization of the extract is a critical prerequisite for its efficacy. For instance, the activity of Panax ginseng C.A.

Meyer in an experimental model of AD is amenable to ginsenosides [151], whereas the pharmacological actions of other active herbal drugs are not yet clear. Of note, it has been shown that the ginsenoside Rg1 ameliorates hippocampal long-term potentiation and memory in a transgenic AD model, up-regulating BDNF expression [152].

Another interesting point is that, due to the numerous active ingredients of medicinal plants, they may allow a multi-targeting approach that could be more successful over monotherapy to combat such a complex disease. Thus, herbal preparations containing several phytoconstituents may represent an adding value against the multifaceted nature of AD.

Indeed, herbal remedies are versatile compounds; in fact, they can also act as a mold for the synthesis of compounds with higher bioavailability and potency: to this end, for instance, synthetic curcumin derivatives have been synthesized as inhibitors of amyloid-β aggregation [153] and analogs of phenylpropanoids, a family of natural products with antiaging effects, have been designed [154]. Of note, repeated curcumin exposure improves cognition following Aβ injection by enhancing BDNF-ERK signaling in the hippocampus [155] whereas phenylpropanoids contained, for instance, in the Viscum album L., increase serum BDNF levels in an experimental model of AD [156].

The versatility of natural plants is further confirmed by the evidence that a plant can produce secondary metabolites that allow the plant to better cope with a given environment. The list of these secondary metabolites is indeed long as it includes different active principles that are responsible for the biological activity of the extracts, such as alkaloids, monoterpenoids, diterpenoids, phenolic acids, flavonoids [157]: among their other functions, these compounds act against Aβ deposition, tau protein hyperphosphorylation as well as antioxidant and anti-inflammatory mechanisms in experimental models. For instance, to this end, Dinda and colleagues (2019) have nicely reviewed the properties of plant iridoids in AD. These monoterpenes metabolites appear to delay the degenerative progress and reduce the cognitive deficit through complex synaptic mechanisms involving, among the others, up-regulation of the neurotrophin BDNF [158]. This evidence suggests that, indeed, nature represents a practically inextinguishable source of active principles. While herbal remedies fall into the category of natural products, other natural products do exist, although their handling goes beyond the focus of this review. However, to give a hint of the growing possibilities for neurodegenerative disorders including AD, a novel class of natural compounds deriving from marine sources, such as, for instance, the sea cucumber, a traditional Asian seafood containing cerebrosides, has been shown to ameliorate cognitive deficiency in an Aβ-induced model of AD, at least partially via the modulation of BDNF levels [159].

In conclusion, bioactive compounds from plants do indeed represent a novel possibility of finding new therapeutic avenues to fight AD, although clear-cut evidence of their efficacy in the clinic is still lacking. One exception is represented by Bacopa monnieri that has been used in clinical trials in elderly individuals or subjects with mild cognitive

deficit [160] these trials showed a general positive cognitive effect: notably, evidence exists that Bacopa monnieri (L.) Pennell ameliorated scopolamine-induced cognitive impairments by up-regulating the expression of the neurotrophin BDNF in experimental models of AD [161]. Although there is still a long way to go before obtaining essential results in the clinic, however, the use of compounds of natural origin undoubtedly represents a fascinating possibility for the treatment of AD in the future.

5. Conclusions and future directions

There is no doubt that the treatment of a complex disease such as AD is likely mediated by the subtle modulation of multiple, synergistic processes. Thus, the effect of drugs aimed at ameliorating the disease symptomatology must necessarily involve a coordinated action on several systems. Indeed, BDNF impairments do not represent the main cause of AD but, rather, an important covariable interacting with other cell components. We are also aware that we cannot set a safety threshold of BDNF production below which the disease becomes manifest. However, based on the existing literature, it appears that reduced levels of this neurotrophin may indeed represent a plausible endophenotype of AD pathology. To this end, the evidence that BDNF can be regulated at different levels (i.e., at the level of transcription, translation, processing, and release) makes it a versatile target for potential therapy. Equally notable, it has to be taken into account that the effectiveness of a therapy tightly depends upon the timing of exposure to the therapy itself, which is critical in determining the future set-point for the responsiveness of the cell and, then, the outcome of a given therapy. To this end, if BDNF-modulating drugs are used too late when the neurodegenerative process is at an advanced phase and synaptic activity is highly deficient, they may neither rescue dying neurons nor improve cognition whereas the application of the same drugs when BDNF changes are still subtle may be cognitively beneficial. While the unique regulatory mechanisms of the neurotrophin provide the necessary adjustments under physiological conditions, the above-mentioned drugs rather than simply restoring basal levels of the neurotrophin need to modulate BDNF-dependent responses under dynamic situations. Notably, Fukuchi and associates (2019) have recently set up a method to screen inducers of BDNF neuronal gene transcription from BDNF-luciferase transgenic mice: such a high-throughput screening method might help to identify novel BDNF-related candidate agents useful for AD therapy, fighting the cognitive decline [162].

The collection of data on the modulation of endogenous BDNF expression herein shown indicates that mechanistically unrelated drugs share the characteristic feature of modulating BDNF expression culminating in similar synaptic and cognitive outcomes. These findings suggest that BDNF may be considered a bridge connecting different players that contribute to synaptic maintenance and, consequently, to functional cognition, thus contributing to the development of AD-modifying strategies (Fig 2). Perhaps more interesting than drug-induced modulation of BDNF, the

exogenous administration of the neurotrophin is supported by a plethora of preclinical findings; however, so far, the exogenous conveyance of BDNF has led to disappointing results, because of poor delivery and short-half life. In addition, knowledge should also be provided on the long-term safety of recombinant BDNF. However, it is reasonable to think that, in the future, the continuous technical improvements will likely make available reliable methods that may guarantee the specific regional targeting of BDNF biodelivery, with limited undesired effects, thus offering a real possibility to improve the AD clinical picture.

The evidence that reduced BDNF levels do not represent a unique attribute of AD as they have been observed in other CNS disorders (depression, Parkinson's disease) rule out the possibility that low levels of BDNF in the blood or a deficit of its synthesis in the brain can be considered a reliable marker of AD. However, taking into account that also non-pharmacological approaches are of considerable importance to improve brain health through up-regulation of BDNF, it is tempted to speculate that a combined therapy involving BDNF modulating compounds or exogenous delivery of the neurotrophin together with appropriate lifestyles may provide an option to prevent/retard AD onset. In conclusion, the collection of these disparate, but otherwise related, evidence points to the neurotrophin BDNF as a mechanistic underpinning that could be targeted to offset the cognitive decline of AD.

Source		Clinical relevance	Reference
Leyhe et al., 2008	Increase of BDNF serum concentration during donepezil treatment of patients with early Alzheimer's disease.	A treatment with the AChE-inhibitor donepezil result in an increase of BDNF serum concentration in AD patients reaching the level of healthy controls. BDNF serum concentration (19.2 +/- 3.7 ng/ml) prior Donezepil treatment compared to healthy controls (23.2 +/- 6.0 ng/ml, P = 0.015). BDNF serum concentration increased significantly in the AD patients following 15 months of Donezepil treatment (23.6 +/- 7.0 ng/ml, P = 0.001), showing no more difference to the healthy controls (P = 0.882).	[21]
Laske et al., 2007	BDNF serum and CSF concentrations in Alzheimer's disease, normal pressure hydrocephalus and healthy controls.	Reduced levels of BDNF serum concentration in AD as compared to healthy controls (21.3ng/ml; p=0.041/p=0.017). The decrease of BDNF serum levels in AD may reflect a lack of trophic support and thus contribute to progressive degeneration in both diseases.	[23]
Peng et al., 2005	Precursor form of brain-derived neurotrophic factor and mature brain-derived neurotrophic factor are decreased in the pre-clinical stages of Alzheimer's disease.	proBDNF levels were decreased in MCI (mild cognitive impairment) and AD groups, respectively, as compared with NCI (no cognitive impairment). Also, mature BDNF was reduced in MCI and AD groups, respectively.	[36]
Fahnestock et al., 2002	Neurotrophic factors and Alzheimer's disease: are we focusing on the wrong molecule?	BDNF mRNA levels are decreased in the nucleus basalis of AD patients compared to controls. Human CNS tissue contains both proBDNF and mature BDNF protein. In the parietal cortex of AD patients there is a significant deficit in proBDNF protein compared to controls.	[37]
Fleitas et al., 2018	proBDNF is modified by advanced glycation end products in Alzheimer's disease and causes neuronal apoptosis by inducing p75 neurotrophin receptor processing.	AD patients show a significative increase of proBDNF and Sortilin expression and a significative increase of the ratio proBDNF/BDNF in their cerebrospinal fluid compared to controls. The proBDNF of AD patients is modified by ROS-derived advanced glycation end products. The cerebrospinal fluid from AD patients, but not from controls, induces apoptosis in differentiated hippocampal neurons mainly by the action of AGE-modified proBDNF present in the cerebrospinal fluid of the patients.	[41]
Li et al., 2016	MicroRNA-613 regulates the expression of brain-derived neurotrophic factor in Alzheimer's disease.	A significant decrease of BDNF mRNA and protein expression was observed in serum and CSF of patients and hippocampus in APP/PS1 mice compared with the corresponding controls. miR-613, which is predicted to target the 3'-UTR of BDNF, was also detected in patients and the mouse model. Opposite to the alteration of BDNF, miR-613 expression in serum, CSF and hippocampus were obviously increased compared to the controls.	[60]

Table 1. Clinical evidence of altered BDNF levels in AD patients

ha formattato: Evidenziato

References

1. Fumagalli F, Racagni G, Riva MA. The expanding role of BDNF: a therapeutic target for Alzheimer's disease? Pharmacogenomics J. 2006 Jan-Feb;6(1):8-15.
2. Poo MM. Neurotrophins as synaptic modulators. Nat Rev Neurosci. 2001 Jan;2(1):24-32.
3. Bramham CR, Messaoudi E. BDNF function in adult synaptic plasticity: the synaptic consolidation hypothesis. Prog Neurobiol. 2005 Jun;76(2):99-125.
4. Miranda M, Morici JF, Zanoni MB, Bekinschtein P. Brain-Derived Neurotrophic Factor: A Key Molecule for Memory in the Healthy and the Pathological Brain. Front Cell Neurosci. 2019;13:363.
5. Aid T, Kazantseva A, Piirsoo M, Palm K, Timmusk T. Mouse and rat BDNF gene structure and expression revisited. J Neurosci Res. 2007 Feb 15;85(3):525-35.
6. Chiaruttini C, Sonego M, Baj G, Simonato M, Tongiorgi E. BDNF mRNA splice variants display activity-dependent targeting to distinct hippocampal laminae. Mol Cell Neurosci. 2008 Jan;37(1):11-9.
7. Lessmann V, Gottmann K, Malcangio M. Neurotrophin secretion: current facts and future prospects. Progress in Neurobiology. 2003;69(5):341-74.
8. Lu B, Pang PT, Woo NH. The yin and yang of neurotrophin action. Nat Rev Neurosci. 2005 Aug;6(8):603-14.
9. Huang EJ, Reichardt LF. Neurotrophins: roles in neuronal development and function. Annu Rev Neurosci. 2001;24:677-736.
10. Jiao SS, Shen LL, Zhu C, Bu XL, Liu YH, Liu CH, Yao XQ, Zhang LL, Zhou HD, Walker DG, Tan J, Gotz J, Zhou XF, Wang YJ. Brain-derived neurotrophic factor protects against tau-related neurodegeneration of Alzheimer's disease. Transl Psychiatry. 2016 Oct 4;6(10):e907.
11. Kaminari A, Giannakas N, Tzinia A, Tsilibary EC. Overexpression of matrix metalloproteinase-9 (MMP-9) rescues insulin-mediated impairment in the 5XFAD model of Alzheimer's disease. Sci Rep. 2017 Apr 6;7(1):683.
12. Devi L, Ohno M. TrkB reduction exacerbates Alzheimer's disease-like signaling aberrations and memory deficits without affecting beta-amyloidosis in 5XFAD mice. Transl Psychiatry. 2015 May 5;5:e562.
13. Murer MG, Boissiere F, Yan Q, Hunot S, Villares J, Faucheux B, Agid Y, Hirsch E, Raisman-Vozari R. An immunohistochemical study of the distribution of brain-derived neurotrophic factor in the adult human brain, with particular reference to Alzheimer's disease. Neuroscience. 1999;88(4):1015-32.
14. Tapia-Arancibia L, Aliaga E, Silhol M, Arancibia S. New insights into brain BDNF function in normal aging and Alzheimer disease. Brain Res Rev. 2008 Nov;59(1):201-20.
15. Burbach GJ, Hellweg R, Haas CA, Del Turco D, Deicke U, Abramowski D, Jucker M, Staufenbiel M, Deller T. Induction of brain-derived neurotrophic factor in plaque-associated glial cells of aged APP23 transgenic mice. J Neurosci. 2004 Mar 10;24(10):2421-30.
16. Schulte-Herbruggen O, Eckart S, Deicke U, Kuhl A, Otten U, Danker-Hopfe H, Abramowski D, Staufenbiel M, Hellweg R. Age-dependent time course of cerebral brain-derived neurotrophic factor, nerve growth factor, and neurotrophin-3 in APP23 transgenic mice. J Neurosci Res. 2008 Sep;86(12):2774-83.
17. Phillips HS, Hains JM, Armanini M, Laramee GR, Johnson SA, Winslow JW. BDNF mRNA is decreased in the hippocampus of individuals with Alzheimer's disease. Neuron. 1991 Nov;7(5):695-702.
18. Murray KD, Gall CM, Jones EG, Isackson PJ. Differential regulation of brain-derived neurotrophic factor and type II calcium/calmodulin-dependent protein kinase messenger RNA expression in Alzheimer's disease. Neuroscience. 1994 May;60(1):37-48.

19. Ferrer I, Marin C, Rey MJ, Ribalta T, Goutan E, Blanco R, Tolosa E, Marti E. BDNF and full-length and truncated TrkB expression in Alzheimer disease. Implications in therapeutic strategies. J Neuropathol Exp Neurol. 1999 Jul;58(7):729-39.
20. Ventriglia M, Zanardini R, Bonomini C, Zanetti O, Volpe D, Pasqualetti P, Gennarelli M, Bocchio-Chiavetto L. Serum brain-derived neurotrophic factor levels in different neurological diseases. Biomed Res Int. 2013;2013:901082.
21. Leyhe T, Stransky E, Eschweiler GW, Buchkremer G, Laske C. Increase of BDNF serum concentration during donepezil treatment of patients with early Alzheimer's disease. Eur Arch Psychiatry Clin Neurosci. 2008 Mar;258(2):124-8.
22. Platenik J, Fisar Z, Buchal R, Jirak R, Kitzlerova E, Zverova M, Raboch J. GSK3beta, CREB, and BDNF in peripheral blood of patients with Alzheimer's disease and depression. Prog Neuropsychopharmacol Biol Psychiatry. 2014 Apr 3;50:83-93.
23. Laske C, Stransky E, Leyhe T, Eschweiler GW, Maetzler W, Wittorf A, Soekadar S, Richartz E, Koehler N, Bartels M, Buchkremer G, Schott K. BDNF serum and CSF concentrations in Alzheimer's disease, normal pressure hydrocephalus and healthy controls. J Psychiatr Res. 2007 Aug;41(5):387-94.
24. Zhang J, Sokal I, Peskind ER, Quinn JF, Jankovic J, Kenney C, Chung KA, Millard SP, Nutt JG, Montine TJ. CSF multianalyte profile distinguishes Alzheimer and Parkinson diseases. Am J Clin Pathol. 2008 Apr;129(4):526-9.
25. Diniz BS, Teixeira AL. Brain-derived neurotrophic factor and Alzheimer's disease: physiopathology and beyond. Neuromolecular Med. 2011 Dec;13(4):217-22.
26. Durany N, Michel T, Kurt J, Cruz-Sanchez FF, Cervas-Navarro J, Riederer P. Brain-derived neurotrophic factor and neurotrophin-3 levels in Alzheimer's disease brains. Int J Dev Neurosci. 2000 Dec;18(8):807-13.
27. Correa MS, de Lima DB, Giacobbo BL, Vedovelli K, Argimon IIL, Bromberg E. Mental health in familial caregivers of Alzheimer's disease patients: are the effects of chronic stress on cognition inevitable? Stress. 2019 Jan;22(1):83-92.
28. Egan MF, Kojima M, Callicott JH, Goldberg TE, Kolachana BS, Bertolino A, Zaitsev E, Gold B, Goldman D, Dean M, Lu B, Weinberger DR. The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. Cell. 2003 Jan 24;112(2):257-69.
29. Lim YY, Villemagne VL, Laws SM, Ames D, Pietrzak RH, Ellis KA, Harrington KD, Bourgeat P, Salvado O, Darby D, Snyder PJ, Bush AI, Martins RN, Masters CL, Rowe CC, Nathan PJ, Maruff P, Australian Imaging B, Lifestyle Research G. BDNF Val66Met, Abeta amyloid, and cognitive decline in preclinical Alzheimer's disease. Neurobiol Aging. 2013 Nov;34(11):2457-64.
30. Park CH, Kim J, Namgung E, Lee DW, Kim GH, Kim M, Kim N, Kim TD, Kim S, Lyoo IK, Yoon S. The BDNF Val66Met Polymorphism Affects the Vulnerability of the Brain Structural Network. Front Hum Neurosci. 2017;11:400.
31. Boots EA, Schultz SA, Clark LR, Racine AM, Darst BF, Koscik RL, Carlsson CM, Gallagher CL, Hogan KJ, Bendlin BB, Asthana S, Sager MA, Hermann BP, Christian BT, Dubal DB, Engelman CD, Johnson SC, Okonkwo OC. BDNF Val66Met predicts cognitive decline in the Wisconsin Registry for Alzheimer's Prevention. Neurology. 2017 May 30;88(22):2098-106.
32. Lim YY, Hassenstab J, Cruchaga C, Goate A, Fagan AM, Benzinger TL, Maruff P, Snyder PJ, Masters CL, Allegri R, Chhatwal J, Farlow MR, Graff-Radford NR, Laske C, Levin J, McDade E, Ringman JM, Rossor M, Salloway S, Schofield PR, Holtzman DM, Morris JC, Bateman RJ, Dominantly Inherited Alzheimer N. BDNF Val66Met moderates memory impairment, hippocampal function and tau in preclinical autosomal dominant Alzheimer's disease. Brain. 2016 Oct;139(Pt 10):2766-77.
33. Olin D, MacMurray J, Comings DE. Risk of late-onset Alzheimer's disease associated with BDNF C270T polymorphism. Neurosci Lett. 2005 Jun 24;381(3):275-8.

34. Harris SE, Fox H, Wright AF, Hayward C, Starr JM, Whalley LJ, Deary IJ. The brain-derived neurotrophic factor Val66Met polymorphism is associated with age-related change in reasoning skills. Mol Psychiatry. 2006 May;11(5):505-13.
35. Anastasia A, Deinhardt K, Chao MV, Will NE, Irmady K, Lee FS, Hempstead BL, Bracken C. Val66Met polymorphism of BDNF alters prodomain structure to induce neuronal growth cone retraction. Nat Commun. 2013;4:2490.
36. Peng S, Wuu J, Mufson EJ, Fahnestock M. Precursor form of brain-derived neurotrophic factor and mature brain-derived neurotrophic factor are decreased in the pre-clinical stages of Alzheimer's disease. J Neurochem. 2005 Jun;93(6):1412-21.
37. Fahnestock M, Garzon D, Holsinger RM, Michalski B. Neurotrophic factors and Alzheimer's disease: are we focusing on the wrong molecule? J Neural Transm Suppl. 2002(62):241-52.
38. Costantini C, Weindruch R, Della Valle G, Puglielli L. A TrkA-to-p75NTR molecular switch activates amyloid beta-peptide generation during aging. Biochem J. 2005 Oct 1;391(Pt 1):59-67.
39. Gerenu G, Martisova E, Ferrero H, Carracedo M, Rantamaki T, Ramirez MJ, Gil-Bea FJ. Modulation of BDNF cleavage by plasminogen-activator inhibitor-1 contributes to Alzheimer's neuropathology and cognitive deficits. Biochim Biophys Acta Mol Basis Dis. 2017 Apr;1863(4):991-1001.
40. Chen J, Zhang T, Jiao S, Zhou X, Zhong J, Wang Y, Liu J, Deng J, Wang S, Xu Z. proBDNF Accelerates Brain Amyloid-beta Deposition and Learning and Memory Impairment in APPswePS1dE9 Transgenic Mice. J Alzheimers Dis. 2017;59(3):941-9.
41. Fleitas C, Pinol-Ripoll G, Marfull P, Rocandio D, Ferrer I, Rampon C, Egea J, Espinet C. proBDNF is modified by advanced glycation end products in Alzheimer's disease and causes neuronal apoptosis by inducing p75 neurotrophin receptor processing. Mol Brain. 2018 Nov 14;11(1):68.
42. Lindvall O, Kokaia Z, Martinez-Serrano A. Stem cell therapy for human neurodegenerative disorders-how to make it work. Nat Med. 2004 Jul;10 Suppl:S42-50.
43. Poduslo JF, Curran GL. Permeability at the blood-brain and blood-nerve barriers of the neurotrophic factors: NGF, CNTF, NT-3, BDNF. Brain Res Mol Brain Res. 1996 Mar;36(2):280-6.
44. Thorne RG, Frey WH, 2nd. Delivery of neurotrophic factors to the central nervous system: pharmacokinetic considerations. Clin Pharmacokinet. 2001;40(12):907-46.
45. Price RD, Milne SA, Sharkey J, Matsuoka N. Advances in small molecules promoting neurotrophic function. Pharmacol Ther. 2007 Aug;115(2):292-306.
46. Xu LZ, Li BQ, Jia JP. DAPK1: a Novel Pathology and Treatment Target for Alzheimer's Disease. Mol Neurobiol. 2019 Apr;56(4):2838-44.
47. Atasoy IL, Dursun E, Gezen-Ak D, Metin-Armagan D, Ozturk M, Yilmazer S. Both secreted and the cellular levels of BDNF attenuated due to tau hyperphosphorylation in primary cultures of cortical neurons. J Chem Neuroanat. 2017 Mar;80:19-26.
48. Skaper SD. Peptide mimetics of neurotrophins and their receptors. Curr Pharm Des. 2011;17(25):2704-18.
49. Cardenas-Aguayo Mdel C, Kazim SF, Grundke-Iqbal I, Iqbal K. Neurogenic and neurotrophic effects of BDNF peptides in mouse hippocampal primary neuronal cell cultures. PLoS One. 2013;8(1):e53596.
50. Bolognin S, Blanchard J, Wang X, Basurto-Islas G, Tung YC, Kohlbrenner E, Grundke-Iqbal I, Iqbal K. An experimental rat model of sporadic Alzheimer's disease and rescue of cognitive impairment with a neurotrophic peptide. Acta Neuropathol. 2012 Jan;123(1):133-51.
51. Bolognin S, Buffelli M, Puolivali J, Iqbal K. Rescue of cognitive-aging by administration of a neurogenic and/or neurotrophic compound. Neurobiol Aging. 2014 Sep;35(9):2134-46.

52. Kazim SF, Blanchard J, Dai CL, Tung YC, LaFerla FM, Iqbal IG, Iqbal K. Disease modifying effect of chronic oral treatment with a neurotrophic peptidergic compound in a triple transgenic mouse model of Alzheimer's disease. Neurobiol Dis. 2014 Nov;71:110-30.
53. Kazim SF, Blanchard J, Bianchi R, Iqbal K. Early neurotrophic pharmacotherapy rescues developmental delay and Alzheimer's-like memory deficits in the Ts65Dn mouse model of Down syndrome. Sci Rep. 2017 Apr 3;7:45561.
54. Bertram JP, Rauch MF, Chang K, Lavik EB. Using polymer chemistry to modulate the delivery of neurotrophic factors from degradable microspheres: delivery of BDNF. Pharm Res. 2010 Jan;27(1):82-91.
55. Li Y, Li Y, Ji W, Lu Z, Liu L, Shi Y, Ma G, Zhang X. Positively Charged Polyprodrug Amphiphiles with Enhanced Drug Loading and Reactive Oxygen Species-Responsive Release Ability for Traceable Synergistic Therapy. J Am Chem Soc. 2018 Mar 21;140(11):4164-71.
56. de Pins B, Cifuentes-Diaz C, Farah AT, Lopez-Molina L, Montalban E, Sancho-Balsells A, Lopez A, Gines S, Delgado-Garcia JM, Alberch J, Gruart A, Girault JA, Giralt A. Conditional BDNF Delivery from Astrocytes Rescues Memory Deficits, Spine Density, and Synaptic Properties in the 5xFAD Mouse Model of Alzheimer Disease. J Neurosci. 2019 Mar 27;39(13):2441-58.
57. Oakley H, Cole SL, Logan S, Maus E, Shao P, Craft J, Guillozet-Bongaarts A, Ohno M, Disterhoft J, Van Eldik L, Berry R, Vassar R. Intraneuronal beta-amyloid aggregates, neurodegeneration, and neuron loss in transgenic mice with five familial Alzheimer's disease mutations: potential factors in amyloid plaque formation. J Neurosci. 2006 Oct 4;26(40):10129-40.
58. Esposito M, Sherr GL. Epigenetic Modifications in Alzheimer's Neuropathology and Therapeutics. Front Neurosci. 2019;13:476.
59. Janczura KJ, Volmar CH, Sartor GC, Rao SJ, Ricciardi NR, Lambert G, Brothers SP, Wahlestedt C. Inhibition of HDAC3 reverses Alzheimer's disease-related pathologies in vitro and in the 3xTg-AD mouse model. Proc Natl Acad Sci U S A. 2018 Nov 20;115(47):E11148-E57.
60. Li W, Li X, Xin X, Kan PC, Yan Y. MicroRNA-613 regulates the expression of brain-derived neurotrophic factor in Alzheimer's disease. Biosci Trends. 2016 Nov 15;10(5):372-7.
61. Liu Z, Wang C, Wang X, Xu S. Therapeutic Effects of Transplantation of As-MiR-937-Expressing Mesenchymal Stem Cells in Murine Model of Alzheimer's Disease. Cell Physiol Biochem. 2015;37(1):321-30.
62. Eremenko E, Mittal K, Berner O, Kamenetsky N, Nemirovsky A, Elyahu Y, Monsonego A. BDNF-producing, amyloid beta-specific CD4 T cells as targeted drug-delivery vehicles in Alzheimer's disease. EBioMedicine. 2019 May;43:424-34.
63. Zheng H, Niu S, Zhao H, Li S, Jiao J. Donepezil improves the cognitive impairment in a tree shrew model of Alzheimer's disease induced by amyloid-beta1-40 via activating the BDNF/TrkB signal pathway. Metab Brain Dis. 2018 Dec;33(6):1961-74.
64. Tanqueiro SR, Ramalho RM, Rodrigues TM, Lopes LV, Sebastiao AM, Diogenes MJ. Inhibition of NMDA Receptors Prevents the Loss of BDNF Function Induced by Amyloid beta. Front Pharmacol. 2018;9:237.
65. Devi L, Ohno M. 7,8-dihydroxyflavone, a small-molecule TrkB agonist, reverses memory deficits and BACE1 elevation in a mouse model of Alzheimer's disease. Neuropsychopharmacology. 2012 Jan;37(2):434-44.
66. Zhang Z, Liu X, Schroeder JP, Chan CB, Song M, Yu SP, Weinshenker D, Ye K. 7,8-dihydroxyflavone prevents synaptic loss and memory deficits in a mouse model of Alzheimer's disease. Neuropsychopharmacology. 2014 Feb;39(3):638-50.
67. Chen C, Li XH, Zhang S, Tu Y, Wang YM, Sun HT. 7,8-dihydroxyflavone ameliorates scopolamine-induced Alzheimer-like pathologic dysfunction. Rejuvenation Res. 2014 Jun;17(3):249-54.

68. Chen C, Wang Z, Zhang Z, Liu X, Kang SS, Zhang Y, Ye K. The prodrug of 7,8-dihydroxyflavone development and therapeutic efficacy for treating Alzheimer's disease. Proc Natl Acad Sci U S A. 2018 Jan 16;115(3):578-83.
69. Gao L, Tian M, Zhao HY, Xu QQ, Huang YM, Si QC, Tian Q, Wu QM, Hu XM, Sun LB, McClintock SM, Zeng Y. TrkB activation by 7, 8-dihydroxyflavone increases synapse AMPA subunits and ameliorates spatial memory deficits in a mouse model of Alzheimer's disease. J Neurochem. 2016 Feb;136(3):620-36.
70. Devanand DP, Strickler JG, Huey ED, Crocco E, Forester BP, Husain MM, Vahia IV, Andrews H, Wall MM, Pelton GH. Lithium Treatment for Agitation in Alzheimer's disease (Lit-AD): Clinical rationale and study design. Contemp Clin Trials. 2018 Aug;71:33-9.
71. Nunes MA, Schowe NM, Monteiro-Silva KC, Baraldi-Tornisielo T, Souza SI, Balthazar J, Albuquerque MS, Caetano AL, Viel TA, Buck HS. Chronic Microdose Lithium Treatment Prevented Memory Loss and Neurohistopathological Changes in a Transgenic Mouse Model of Alzheimer's Disease. PLoS One. 2015;10(11):e0142267.
72. Tempier A, He J, Zhu S, Zhang R, Kong L, Tan Q, Luo H, Kong J, Li XM. Quetiapine modulates conditioned anxiety and alternation behavior in Alzheimer's transgenic mice. Curr Alzheimer Res. 2013 Feb;10(2):199-206.
73. Luo G, Huang Y, Jia B, Zhang X, Mo D, Ma N, Gao F, Song L, Wang B, Miao Z. Quetiapine prevents Abeta25-35-induced cell death in cultured neuron by enhancing brain-derived neurotrophic factor release from astrocyte. Neuroreport. 2018 Jan 17;29(2):92-8.
74. Choi Y, Jeong HJ, Liu QF, Oh ST, Koo BS, Kim Y, Chung IW, Kim YS, Jeon S. Clozapine Improves Memory Impairment and Reduces Abeta Level in the Tg-APPswe/PS1dE9 Mouse Model of Alzheimer's Disease. Mol Neurobiol. 2017 Jan;54(1):450-60.
75. Park SY, Shin HK, Lee WS, Bae SS, Kim K, Hong KW, Kim CD. Neuroprotection by aripiprazole against beta-amyloid-induced toxicity by P-CK2alpha activation via inhibition of GSK-3beta. Oncotarget. 2017 Dec 15;8(66):110380-91.
76. Palop JJ, Mucke L. Epilepsy and cognitive impairments in Alzheimer disease. Arch Neurol. 2009 Apr;66(4):435-40.
77. Ziyatdinova S, Gurevicius K, Kutchiashvili N, Bolkvadze T, Nissinen J, Tanila H, Pitkanen A. Spontaneous epileptiform discharges in a mouse model of Alzheimer's disease are suppressed by antiepileptic drugs that block sodium channels. Epilepsy Res. 2011 Mar;94(1-2):75-85.
78. Sanchez PE, Zhu L, Verret L, Vossel KA, Orr AG, Cirrito JR, Devidze N, Ho K, Yu GQ, Palop JJ, Mucke L. Levetiracetam suppresses neuronal network dysfunction and reverses synaptic and cognitive deficits in an Alzheimer's disease model. Proc Natl Acad Sci U S A. 2012 Oct 16;109(42):E2895-903.
79. Zhang MY, Zheng CY, Zou MM, Zhu JW, Zhang Y, Wang J, Liu CF, Li QF, Xiao ZC, Li S, Ma QH, Xu RX. Lamotrigine attenuates deficits in synaptic plasticity and accumulation of amyloid plaques in APP/PS1 transgenic mice. Neurobiol Aging. 2014 Dec;35(12):2713-25.
80. Aboukhatwa M, Dosanjh L, Luo Y. Antidepressants are a rational complementary therapy for the treatment of Alzheimer's disease. Mol Neurodegener. 2010 Mar 12;5:10.
81. Mowla A, Mosavinasab M, Haghshenas H, Borhani Haghighi A. Does serotonin augmentation have any effect on cognition and activities of daily living in Alzheimer's dementia? A double-blind, placebo-controlled clinical trial. J Clin Psychopharmacol. 2007 Oct;27(5):484-7.
82. Ren QG, Wang YJ, Gong WG, Xu L, Zhang ZJ. Escitalopram Ameliorates Tau Hyperphosphorylation and Spatial Memory Deficits Induced by Protein Kinase A Activation in Sprague Dawley Rats. J Alzheimers Dis. 2015;47(1):61-71.
83. Ibrahim WW, Abdelkader NF, Ismail HM, Khattab MM. Escitalopram Ameliorates Cognitive Impairment in D-Galactose-Injected Ovariectomized Rats: Modulation of JNK, GSK-3beta, and ERK Signalling Pathways. Sci Rep. 2019 Jul 11;9(1):10056.

84. Ren QG, Wang YJ, Gong WG, Zhou QD, Xu L, Zhang ZJ. Escitalopram Ameliorates Forskolin-Induced Tau Hyperphosphorylation in HEK239/tau441 Cells. J Mol Neurosci. 2015 Jun;56(2):500-8.
85. Cirrito JR, Disabato BM, Restivo JL, Verges DK, Goebel WD, Sathyan A, Hayreh D, D'Angelo G, Benzinger T, Yoon H, Kim J, Morris JC, Mintun MA, Sheline YI. Serotonin signaling is associated with lower amyloid-beta levels and plaques in transgenic mice and humans. Proc Natl Acad Sci U S A. 2011 Sep 6;108(36):14968-73.
86. Chadwick W, Mitchell N, Caroll J, Zhou Y, Park SS, Wang L, Becker KG, Zhang Y, Lehrmann E, Wood WH, 3rd, Martin B, Maudsley S. Amitriptyline-mediated cognitive enhancement in aged 3xTg Alzheimer's disease mice is associated with neurogenesis and neurotrophic activity. PLoS One. 2011;6(6):e21660.
87. Jin L, Gao LF, Sun DS, Wu H, Wang Q, Ke D, Lei H, Wang JZ, Liu GP. Long-term Ameliorative Effects of the Antidepressant Fluoxetine Exposure on Cognitive Deficits in 3 x TgAD Mice. Mol Neurobiol. 2017 Aug;54(6):4160-71.
88. Sun DS, Gao LF, Jin L, Wu H, Wang Q, Zhou Y, Fan S, Jiang X, Ke D, Lei H, Wang JZ, Liu GP. Fluoxetine administration during adolescence attenuates cognitive and synaptic deficits in adult 3xTgAD mice. Neuropharmacology. 2017 Nov;126:200-12.
89. Park J, Lee SY, Shon J, Kim K, Lee HJ, Kim KA, Lee BY, Oh SH, Kim NK, Kim OJ. Adalimumab improves cognitive impairment, exerts neuroprotective effects and attenuates neuroinflammation in an Abeta1-40-injected mouse model of Alzheimer's disease. Cytotherapy. 2019 Jun;21(6):671-82.
90. Utkan T, Yazir Y, Karson A, Bayramgurler D. Etanercept improves cognitive performance and increases eNOS and BDNF expression during experimental vascular dementia in streptozotocin-induced diabetes. Curr Neurovasc Res. 2015;12(2):135-46.
91. Tobinick EL, Gross H. Rapid cognitive improvement in Alzheimer's disease following perispinal etanercept administration. J Neuroinflammation. 2008 Jan 9;5:2.
92. Kim DH, Choi SM, Jho J, Park MS, Kang J, Park SJ, Ryu JH, Jo J, Kim HH, Kim BC. Infliximab ameliorates AD-associated object recognition memory impairment. Behav Brain Res. 2016 Sep 15;311:384-91.
93. Sahin TD, Karson A, Balci F, Yazir Y, Bayramgurler D, Utkan T. TNF-alpha inhibition prevents cognitive decline and maintains hippocampal BDNF levels in the unpredictable chronic mild stress rat model of depression. Behav Brain Res. 2015 Oct 1;292:233-40.
94. Magistretti PJ, Geisler FH, Schneider JS, Li PA, Fiumelli H, Sipione S. Gangliosides: Treatment Avenues in Neurodegenerative Disease. Front Neurol. 2019;10:859.
95. Kracun I, Kalanj S, Talan-Hranilovic J, Cosovic C. Cortical distribution of gangliosides in Alzheimer's disease. Neurochem Int. 1992 Apr;20(3):433-8.
96. Barrier L, Ingrand S, Damjanac M, Rioux Bilan A, Hugon J, Page G. Genotype-related changes of ganglioside composition in brain regions of transgenic mouse models of Alzheimer's disease. Neurobiol Aging. 2007 Dec;28(12):1863-72.
97. Brooksbank BW, McGovern J. Gangliosides in the brain in adult Down's syndrome and Alzheimer's disease. Mol Chem Neuropathol. 1989 Dec;11(3):143-56.
98. Shin MK, Choi MS, Chae HJ, Kim JW, Kim HG, Kim KL. Ganglioside GQ1b ameliorates cognitive impairments in an Alzheimer's disease mouse model, and causes reduction of amyloid precursor protein. Sci Rep. 2019 Jun 11;9(1):8512.
99. Olsen ASB, Faergeman NJ. Sphingolipids: membrane microdomains in brain development, function and neurological diseases. Open Biol. 2017 May;7(5).
100. Fukumoto K, Mizoguchi H, Takeuchi H, Horiuchi H, Kawanokuchi J, Jin S, Mizuno T, Suzumura A. Fingolimod increases brain-derived neurotrophic factor levels and ameliorates amyloid beta-induced memory impairment. Behav Brain Res. 2014 Jul 15;268:88-93.

101. Doi Y, Takeuchi H, Horiuchi H, Hanyu T, Kawanokuchi J, Jin S, Parajuli B, Sonobe Y, Mizuno T, Suzumura A. Fingolimod phosphate attenuates oligomeric amyloid beta-induced neurotoxicity via increased brain-derived neurotrophic factor expression in neurons. PLoS One. 2013;8(4):e61988.
102. Ackerman HD, Gerhard GS. Bile Acids in Neurodegenerative Disorders. Front Aging Neurosci. 2016;8:263.
103. Frommherz L, Bub A, Hummel E, Rist MJ, Roth A, Watzl B, Kulling SE. Age-Related Changes of Plasma Bile Acid Concentrations in Healthy Adults--Results from the Cross-Sectional KarMeN Study. PLoS One. 2016;11(4):e0153959.
104. MahmoudianDehkordi S, Arnold M, Nho K, Ahmad S, Jia W, Xie G, Louie G, Kueider-Paisley A, Moseley MA, Thompson JW, St John Williams L, Tenenbaum JD, Blach C, Baillie R, Han X, Bhattacharyya S, Toledo JB, Schafferer S, Klein S, Koal T, Risacher SL, Kling MA, Motsinger-Reif A, Rotroff DM, Jack J, Hankemeier T, Bennett DA, De Jager PL, Trojanowski JQ, Shaw LM, Weiner MW, Doraiswamy PM, van Duijn CM, Saykin AJ, Kastenmuller G, Kaddurah-Daouk R, Alzheimer's Disease Neuroimaging I, the Alzheimer Disease Metabolomics C. Altered bile acid profile associates with cognitive impairment in Alzheimer's disease-An emerging role for gut microbiome. Alzheimers Dement. 2019 Jan;15(1):76-92.
105. Bazzari FH, Abdallah DM, El-Abhar HS. Chenodeoxycholic Acid Ameliorates AlCl3-Induced Alzheimer's Disease Neurotoxicity and Cognitive Deterioration via Enhanced Insulin Signaling in Rats. Molecules. 2019 May 24;24(10).
106. Hongpaisan J, Sun MK, Alkon DL. PKC epsilon activation prevents synaptic loss, Abeta elevation, and cognitive deficits in Alzheimer's disease transgenic mice. J Neurosci. 2011 Jan 12;31(2):630-43.
107. Sen A, Nelson TJ, Alkon DL, Hongpaisan J. Loss in PKC Epsilon Causes Downregulation of MnSOD and BDNF Expression in Neurons of Alzheimer's Disease Hippocampus. J Alzheimers Dis. 2018;63(3):1173-89.
108. Khan TK, Sen A, Hongpaisan J, Lim CS, Nelson TJ, Alkon DL. PKCepsilon deficits in Alzheimer's disease brains and skin fibroblasts. J Alzheimers Dis. 2015;43(2):491-509.
109. Farlow MR, Thompson RE, Wei LJ, Tuchman AJ, Grenier E, Crockford D, Wilke S, Benison J, Alkon DL. A Randomized, Double-Blind, Placebo-Controlled, Phase II Study Assessing Safety, Tolerability, and Efficacy of Bryostatin in the Treatment of Moderately Severe to Severe Alzheimer's Disease. J Alzheimers Dis. 2019;67(2):555-70.
110. Mueller BK, Mack H, Teusch N. Rho kinase, a promising drug target for neurological disorders. Nat Rev Drug Discov. 2005 May;4(5):387-98.
111. Petratos S, Li QX, George AJ, Hou X, Kerr ML, Unabia SE, Hatzinisiriou I, Maksel D, Aguilar MI, Small DH. The beta-amyloid protein of Alzheimer's disease increases neuronal CRMP-2 phosphorylation by a Rho-GTP mechanism. Brain. 2008 Jan;131(Pt 1):90-108.
112. Yu J, Gu Q, Yan Y, Yu H, Guo M, Liu C, Song G, Chai Z, Wang Q, Xiao B, Zhang H, Jiang Y, Ma C. [Fasudil improves cognition of APP/PS1 transgenic mice via inhibiting the activation of microglia and shifting microglia phenotypes from M1 to M2]. Xi Bao Yu Fen Zi Mian Yi Xue Za Zhi. 2017 Dec;33(12):1585-93.
113. Gu QF, Yu JZ, Wu H, Li YH, Liu CY, Feng L, Zhang GX, Xiao BG, Ma CG. Therapeutic effect of Rho kinase inhibitor FSD-C10 in a mouse model of Alzheimer's disease. Exp Ther Med. 2018 Nov;16(5):3929-38.
114. Schrijvers EM, Witteman JC, Sijbrands EJ, Hofman A, Koudstaal PJ, Breteler MM. Insulin metabolism and the risk of Alzheimer disease: the Rotterdam Study. Neurology. 2010 Nov 30;75(22):1982-7.
115. Muller AP, Gnoatto J, Moreira JD, Zimmer ER, Haas CB, Lulhier F, Perry ML, Souza DO, Torres-Aleman I, Portela LV. Exercise increases insulin signaling in the hippocampus:

physiological effects and pharmacological impact of intracerebroventricular insulin administration in mice. Hippocampus. 2011 Oct;21(10):1082-92.
116. Hanyu H, Sato T, Kiuchi A, Sakurai H, Iwamoto T. Pioglitazone improved cognition in a pilot study on patients with Alzheimer's disease and mild cognitive impairment with diabetes mellitus. J Am Geriatr Soc. 2009 Jan;57(1):177-9.
117. Isik AT, Soysal P, Yay A, Usarel C. The effects of sitagliptin, a DPP-4 inhibitor, on cognitive functions in elderly diabetic patients with or without Alzheimer's disease. Diabetes Res Clin Pract. 2017 Jan;123:192-8.
118. Dong Q, Teng SW, Wang Y, Qin F, Li Y, Ai LL, Yu H. Sitagliptin protects the cognition function of the Alzheimer's disease mice through activating glucagon-like peptide-1 and BDNF-TrkB signalings. Neurosci Lett. 2019 Mar 23;696:184-90.
119. Townsend M, Mehta T, Selkoe DJ. Soluble Abeta inhibits specific signal transduction cascades common to the insulin receptor pathway. J Biol Chem. 2007 Nov 16;282(46):33305-12.
120. McClean PL, Parthsarathy V, Faivre E, Holscher C. The diabetes drug liraglutide prevents degenerative processes in a mouse model of Alzheimer's disease. J Neurosci. 2011 Apr 27;31(17):6587-94.
121. de Souza AG, Chaves Filho AJM, Souza Oliveira JV, de Souza DAA, Lopes IS, de Carvalho MAJ, de Lima KA, Florenco Sousa FC, Mendes Vasconcelos SM, Macedo D, de Franca Fonteles MM. Prevention of pentylenetetrazole-induced kindling and behavioral comorbidities in mice by levetiracetam combined with the GLP-1 agonist liraglutide: Involvement of brain antioxidant and BDNF upregulating properties. Biomed Pharmacother. 2019 Jan;109:429-39.
122. Park SW, Mansur RB, Lee Y, Lee JH, Seo MK, Choi AJ, McIntyre RS, Lee JG. Liraglutide Activates mTORC1 Signaling and AMPA Receptors in Rat Hippocampal Neurons Under Toxic Conditions. Front Neurosci. 2018;12:756.
123. Bomba M, Granzotto A, Castelli V, Massetti N, Silvestri E, Canzoniero LMT, Cimini A, Sensi SL. Exenatide exerts cognitive effects by modulating the BDNF-TrkB neurotrophic axis in adult mice. Neurobiol Aging. 2018 Apr;64:33-43.
124. Avgerinos KI, Kalaitzidis G, Malli A, Kalaitzoglou D, Myserlis PG, Lioutas VA. Intranasal insulin in Alzheimer's dementia or mild cognitive impairment: a systematic review. J Neurol. 2018 Jul;265(7):1497-510.
125. Yu Q, Dai CL, Zhang Y, Chen Y, Wu Z, Iqbal K, Liu F, Gong CX. Intranasal Insulin Increases Synaptic Protein Expression and Prevents Anesthesia-Induced Cognitive Deficits Through mTOR-eEF2 Pathway. J Alzheimers Dis. 2019;70(3):925-36.
126. Sonmez AI, Camsari DD, Nandakumar AL, Voort JLV, Kung S, Lewis CP, Croarkin PE. Accelerated TMS for Depression: A systematic review and meta-analysis. Psychiatry Res. 2019 Mar;273:770-81.
127. Zhang JJQ, Fong KNK, Ouyang RG, Siu AMH, Kranz GS. Effects of repetitive transcranial magnetic stimulation (rTMS) on craving and substance consumption in patients with substance dependence: a systematic review and meta-analysis. Addiction. 2019 Dec;114(12):2137-49.
128. Jauregui-Lobera I, Martinez-Quinones JV. Neuromodulation in eating disorders and obesity: a promising way of treatment? Neuropsychiatr Dis Treat. 2018;14:2817-35.
129. Yulug B, Hanoglu L, Khanmammadov E, Duz OA, Polat B, Hanoglu T, Gunal MY, Kilic E. Beyond The Therapeutic Effect of rTMS in Alzheimer's Disease: A Possible Neuroprotective Role of Hippocampal BDNF? : A Minireview. Mini Rev Med Chem. 2018;18(17):1479-85.
130. Tan T, Xie J, Liu T, Chen X, Zheng X, Tong Z, Tian X. Low-frequency (1 Hz) repetitive transcranial magnetic stimulation (rTMS) reverses Abeta(1-42)-mediated memory deficits in rats. Exp Gerontol. 2013 Aug;48(8):786-94.
131. Chen X, Chen S, Liang W, Ba F. Administration of Repetitive Transcranial Magnetic Stimulation Attenuates Abeta 1-42-Induced Alzheimer's Disease in Mice by Activating beta-Catenin Signaling. Biomed Res Int. 2019;2019:1431760.

132. Shin HK, Lee SW, Choi BT. Modulation of neurogenesis via neurotrophic factors in acupuncture treatments for neurological diseases. Biochem Pharmacol. 2017 Oct 1;141:132-42.
133. Li X, Guo F, Zhang Q, Huo T, Liu L, Wei H, Xiong L, Wang Q. Electroacupuncture decreases cognitive impairment and promotes neurogenesis in the APP/PS1 transgenic mice. BMC Complement Altern Med. 2014 Jan 22;14:37.
134. Lin R, Li L, Zhang Y, Huang S, Chen S, Shi J, Zhuo P, Jin H, Li Z, Liu W, Wang Z, Chen L, Tao J. Electroacupuncture ameliorate learning and memory by improving N-acetylaspartate and glutamate metabolism in APP/PS1 mice. Biol Res. 2018 Jul 6;51(1):21.
135. Oh ST, Liu QF, Jeong HJ, Lee S, Samidurai M, Jo J, Pak SC, Park HJ, Kim J, Jeon S. Nasal Cavity Administration of Melanin-Concentrating Hormone Improves Memory Impairment in Memory-Impaired and Alzheimer's Disease Mouse Models. Mol Neurobiol. 2019 Dec;56(12):8076-86.
136. Schmidt FM, Kratzsch J, Gertz HJ, Tittmann M, Jahn I, Pietsch UC, Kaisers UX, Thiery J, Hegerl U, Schonknecht P. Cerebrospinal fluid melanin-concentrating hormone (MCH) and hypocretin-1 (HCRT-1, orexin-A) in Alzheimer's disease. PLoS One. 2013;8(5):e63136.
137. Lazarov O, Robinson J, Tang YP, Hairston IS, Korade-Mirnics Z, Lee VM, Hersh LB, Sapolsky RM, Mirnics K, Sisodia SS. Environmental enrichment reduces Abeta levels and amyloid deposition in transgenic mice. Cell. 2005 Mar 11;120(5):701-13.
138. Jahangiri Z, Gholamnezhad Z, Hosseini M. Neuroprotective effects of exercise in rodent models of memory deficit and Alzheimer's. Metab Brain Dis. 2019 Feb;34(1):21-37.
139. Friedland RP, Fritsch T, Smyth KA, Koss E, Lerner AJ, Chen CH, Petot GJ, Debanne SM. Patients with Alzheimer's disease have reduced activities in midlife compared with healthy control-group members. Proc Natl Acad Sci U S A. 2001 Mar 13;98(6):3440-5.
140. Laurin D, Verreault R, Lindsay J, MacPherson K, Rockwood K. Physical activity and risk of cognitive impairment and dementia in elderly persons. Arch Neurol. 2001 Mar;58(3):498-504.
141. Dao AT, Zagaar MA, Levine AT, Salim S, Eriksen JL, Alkadhi KA. Treadmill exercise prevents learning and memory impairment in Alzheimer's disease-like pathology. Curr Alzheimer Res. 2013 Jun;10(5):507-15.
142. Belviranli M, Okudan N. Voluntary, involuntary and forced exercises almost equally reverse behavioral impairment by regulating hippocampal neurotrophic factors and oxidative stress in experimental Alzheimer's disease model. Behav Brain Res. 2019 May 17;364:245-55.
143. Brown BM, Bourgeat P, Peiffer JJ, Burnham S, Laws SM, Rainey-Smith SR, Bartres-Faz D, Villemagne VL, Taddei K, Rembach A, Bush A, Ellis KA, Macaulay SL, Rowe CC, Ames D, Masters CL, Maruff P, Martins RN, Group AR. Influence of BDNF Val66Met on the relationship between physical activity and brain volume. Neurology. 2014 Oct 7;83(15):1345-52.
144. Goto S, Shen X, Sun M, Hamano Y, Herrup K. The Positive Effects of Viewing Gardens for Persons with Dementia. J Alzheimers Dis. 2018;66(4):1705-20.
145. Uwajeh PC, Iyendo TO, Polay M. Therapeutic gardens as a design approach for optimising the healing environment of patients with Alzheimer's disease and other dementias: A narrative review. Explore (NY). 2019 Sep - Oct;15(5):352-62.
146. Pedrinolla A, Tamburin S, Brasioli A, Sollima A, Fonte C, Muti E, Smania N, Schena F, Venturelli M. An Indoor Therapeutic Garden for Behavioral Symptoms in Alzheimer's Disease: A Randomized Controlled Trial. J Alzheimers Dis. 2019;71(3):813-23.
147. Park SA, Lee AY, Park HG, Lee WL. Benefits of Gardening Activities for Cognitive Function According to Measurement of Brain Nerve Growth Factor Levels. Int J Environ Res Public Health. 2019 Mar 2;16(5).
148. Kumar K, Kumar A, Keegan RM, Deshmukh R. Recent advances in the neurobiology and neuropharmacology of Alzheimer's disease. Biomed Pharmacother. 2018 Feb;98:297-307.
149. Sangiovanni E, Brivio P, Dell'Agli M, Calabrese F. Botanicals as Modulators of Neuroplasticity: Focus on BDNF. Neural Plast. 2017;2017:5965371.

150. Dey A, Bhattacharya R, Mukherjee A, Pandey DK. Natural products against Alzheimer's disease: Pharmaco-therapeutics and biotechnological interventions. Biotechnol Adv. 2017 Mar - Apr;35(2):178-216.
151. Kim KH, Lee D, Lee HL, Kim CE, Jung K, Kang KS. Beneficial effects of Panax ginseng for the treatment and prevention of neurodegenerative diseases: past findings and future directions. J Ginseng Res. 2018 Jul;42(3):239-47.
152. Li F, Wu X, Li J, Niu Q. Ginsenoside Rg1 ameliorates hippocampal long-term potentiation and memory in an Alzheimer's disease model. Mol Med Rep. 2016 Jun;13(6):4904-10.
153. Bukhari SN, Jantan I. Synthetic Curcumin Analogs as Inhibitors of beta -Amyloid Peptide Aggregation: Potential Therapeutic and Diagnostic Agents for Alzheimer's Disease. Mini Rev Med Chem. 2015;15(13):1110-21.
154. Huang S, Cao X, Zhou Y, Shi F, Xin S, He S, An Y, Gao L, Yang Y, Yu B, Pei G. An analog derived from phenylpropanoids ameliorates Alzheimer's disease-like pathology and protects mitochondrial function. Neurobiol Aging. 2019 Aug;80:187-95.
155. Zhang L, Fang Y, Xu Y, Lian Y, Xie N, Wu T, Zhang H, Sun L, Zhang R, Wang Z. Curcumin Improves Amyloid beta-Peptide (1-42) Induced Spatial Memory Deficits through BDNF-ERK Signaling Pathway. PLoS One. 2015;10(6):e0131525.
156. Szurpnicka A, Zjawiony JK, Szterk A. Therapeutic potential of mistletoe in CNS-related neurological disorders and the chemical composition of Viscum species. J Ethnopharmacol. 2019 Mar 1;231:241-52.
157. Habtemariam S. Natural Products in Alzheimer's Disease Therapy: Would Old Therapeutic Approaches Fix the Broken Promise of Modern Medicines? Molecules. 2019 Apr 17;24(8).
158. Dinda B, Dinda M, Kulsi G, Chakraborty A, Dinda S. Therapeutic potentials of plant iridoids in Alzheimer's and Parkinson's diseases: A review. Eur J Med Chem. 2019 May 1;169:185-99.
159. Li Q, Che HX, Wang CC, Zhang LY, Ding L, Xue CH, Zhang TT, Wang YM. Cerebrosides from Sea Cucumber Improved Abeta1-42 -Induced Cognitive Deficiency in a Rat Model of Alzheimer's Disease. Mol Nutr Food Res. 2019 Mar;63(5):e1800707.
160. Abdul Manap AS, Vijayabalan S, Madhavan P, Chia YY, Arya A, Wong EH, Rizwan F, Bindal U, Koshy S. Bacopa monnieri, a Neuroprotective Lead in Alzheimer Disease: A Review on Its Properties, Mechanisms of Action, and Preclinical and Clinical Studies. Drug Target Insights. 2019;13:1177392819866412.
161. Pandareesh MD, Anand T. Neuromodulatory propensity of Bacopa monniera against scopolamine-induced cytotoxicity in PC12 cells via down-regulation of AChE and up-regulation of BDNF and muscarnic-1 receptor expression. Cell Mol Neurobiol. 2013 Oct;33(7):875-84.
162. Fukuchi M, Okuno Y, Nakayama H, Nakano A, Mori H, Mitazaki S, Nakano Y, Toume K, Jo M, Takasaki I, Watanabe K, Shibahara N, Komatsu K, Tabuchi A, Tsuda M. Screening inducers of neuronal BDNF gene transcription using primary cortical cell cultures from BDNF-luciferase transgenic mice. Sci Rep. 2019 Aug 14;9(1):11833.

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Declaration of Interest

None

Figure legends

Fig 1

Schematic illustration of a working model of the BDNF pathway in AD.

Reduced expression of BDNF observed both in experimental animal models as well as in humans appears to be critical for cognitive impairment typical of AD. The figure shows the regulation of the neurotrophin BDNF at presynaptic (transcription, translation, processing, and release) and post-synaptic sites (BDNF signaling cascade) that represent a putative site of actions of BDNF-based synaptic repair strategies. It is speculated that engaging such BDNF pathway may play a role in ameliorating cognitive deficit in AD, promoting the survival of neurons and formation of new synaptic contacts.

Fig 2

Summary of the most recent developments in terms of modulation of BDNF expression.

The figure shows the different approaches that share the common property of stimulating the BDNF pathway. In the figure, conventional pharmacological therapies (antipsychotic drugs, antidepressant drugs, mood stabilizers, memantine, cholinergic agonists) are included together with non-pharmacological approaches (acupuncture, lifestyle, gardening), biotechnological approaches (epigenetics, microRNAs), monoclonal antibodies (infliximab and adalimumab), botanicals and a plethora of single molecules that, through their own peculiar mechanism of action, all converge on the modulation of BDNF levels in the brain.

List of Abbreviations

BDNF (Brain-derived neurotrophic factor); proBDNF (pro-Brain-derived neurotrophic factor); TrkB receptor (Tropomyosin receptor kinase B); AD (Alzheimer's disease); Aβ (Amyloid-β); BBB (blood brain barrier);CNS (Central nervous system); CSF (cerebrospinal fluid); PI3-K (phosphoinositide 3-kinase); PLC-γ (phospholipase C-γ); MAPK (mitogen-activated protein kinase); CREB (cyclic AMP response element binding protein); GSK-3β (Glycogen synthase kinase-3 beta); AKT (protein kinase B); SNP (single nucleotide polymorphism); Val (Valine); Met (Methionine); PLGA (Poly Lactic-co-Glycolic Acid); 7,8-DHF (7,8-dihydroxyflavone); PKCε (protein kinase C epsilon); GLP-1 (glucagon-like peptide).