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Review paper

Nose to brain strategy coupled to nano vesicular system for natural products delivery: Focus on synaptic plasticity in Alzheimer's disease

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ABSTRACT

A wide number of natural molecules demonstrated neuroprotective effects on synaptic plasticity defects induced by amyloid-β (Aβ) in *ex vivo* and *in vivo* Alzheimer's disease (AD) models, suggesting a possible use in the treatment of this neurodegenerative disorder. However, several compounds, administered parenterally and orally, are unable to reach the brain due to the presence of the blood-brain barrier (BBB) which prevents the passage of external substances, such as proteins, peptides, or phytocompounds, representing a limit to the development of treatment for neurodegenerative diseases, such as AD. The combination of nano vesicular systems, as colloidal systems, and nose to brain (NtB) delivery depicts a new nanotechnological strategy to overtake this limit and to develop new treatment approaches for brain diseases, including the use of natural molecules in combination therapy for AD. Herein, we will provide an updated overview, examining the literature of the last 20 years and using specific keywords that provide evidence on natural products with the ability to restore synaptic plasticity alterations in AD models, and the possible application using safe and non-invasive strategies focusing on nano vesicular systems for NtB delivery.

1. Introduction

Currently, phytotherapy and the use of natural compounds as esteemed resources for the development of more effective therapeutic agents have a significant role in neuropharmacology [1].

A large number of natural compounds have been shown to have various biological activities, including antioxidant and anti-inflammatory properties [2] which were confirmed by *in vitro* and *in vivo* investigations conducted in several preclinical models of neurodegenerative disorders [3]. In this light, phytoconstituents may help forestall neurodegeneration and ameliorate memory and cognitive abilities, improving the decline characteristic of Alzheimer's disease (AD) [4].

Natural-derived medications constitute a most hopeful field for the development of treatments for neurodegenerative diseases, including AD. Indeed, due to pleiotropic action and a wide variety of activities associated with the reduction of amyloid-β (Aβ) plaque formation, neuroprotection against synaptic loss, and deterioration correlated to cognitive improvement, they represent a promising source for new treatments. Nevertheless, a strong limitation for natural compounds is represented by their reduced bioavailability due to high sensitivity to chemical and physical degradation, rapid metabolism, and inability to pass the blood-brain barrier (BBB), resulting in poor enrichment of the brain. For useful treatment in neurodegenerative disease, the ability to cross the BBB is crucial, and in this way, new nanotechnology, such as colloidal systems, has a key role in this challenge.

The focus of the present review is on the promising natural compounds that have demonstrated effectiveness on synaptic plasticity alterations correlated with AD, discussing their bioavailability limits with particular emphasis on recent advances in brain delivery systems.

Consequently, the retrieved literature was consulted from 1993 to 2024 using the PubMed, Google Scholar, and Web of Science databases, and considering the following keywords: synaptic plasticity, AD, natural substances in AD, ascorbic acid (AA), curcumin, ellagic acid (EA), galantamine, ginkgolic acid (GA), psalmotoxin 1 (PcTx1), resveratrol, rosmarinic acid (RA), quercetin, BBB, drug delivery systems, and nanovescicular systems. Hundreds of articles were obtained by this research. We summarized the natural

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products showing protective properties on synaptic plasticity deficits present in AD, and characterized by pharmacokinetic limits to provide a reference for follow-up studies on the development of nano vesicular systems for natural product delivery as a potential new strategy of co-treatment in AD.

2. Nano vesicular system coupled to nose to brain (NtB) delivery: a strategy to overcome BBB for the treatment of neurodegenerative disease

The BBB, due to its complex structure, plays a crucial role in protecting the central nervous system (CNS) from potential neurotoxic substances representing an obstacle to the treatment of brain disease since approximately 98% of all small molecules and almost all large molecules are unable to cross it [5,6].

Structurally, the BBB is a semi-permeable barrier that separates the brain from the blood compartments, and it exerts maximum control over the microenvironment of brain cells playing numerous roles. 1) It provides the brain with essential nutrients and mediates the outflow of many waste products. 2) It limits ions and fluid movements between the blood and the brain, allowing specific ions transporters and channels with the regulation of ions trafficking to produce a brain interstitial fluid that provides an optimal medium for neuronal function [7,8].

In this context, BBB can adapt accordingly to the CNS requirements due to its communication with other cells of the CNS, forming the neurovascular unit [9–11] (Fig. 1).

The neurovascular unit is constituted by several periendothelial structures, such as astrocytes and pericytes, which are separated from a basement membrane by an extracellular collagen matrix guaranteeing further compactness to this anatomical-functional structure [11].

The complex structure of BBB is also characterized by the presence of two immune cell types of microglia and perivascular macrophages, both of which can be activated by systemic inflammation, trauma, and other pathological states, appropriately defending the CNS.

The main cause of the inability of many drugs to cross the BBB is the presence of tight junctions (TJs) [11], which form a tight and continuous seal that surrounds each endothelial and epithelial cell at the apical border and have the purpose of strictly regulating the movement of molecules through the paracellular route. Consequentially, TJs make the brain capillary endothelial cell monolayer a nearly impermeable barrier to systemically administered drugs [10]. Nevertheless, brain selectivity is also caused by the presence of transporters and ion channels, selective only for certain molecules useful for the physiological maintenance of the brain, as well as by the presence of efflux proteins, which have the task for recognizing substrate molecules and expelling them outside the CNS. One well-known example is P-glycoprotein (P-gp), which contributes to the inefficiency and drug resistance observed with many medications targeting the CNS [12–14].

Consequentially, to overcome these issues, it is increasingly necessary to identify new non-invasive therapeutic strategies, better than invasive strategies in terms of patient safety and well-being, for treatments of neurodegenerative disease.

Particularly, various non-invasive therapeutic techniques have been developed to optimize the BBB crossing without lasting damage, and for targeted drug delivery in the CNS, such as the use of transcranial magnetic stimulation [15], or focused ultrasound, which could be assisted by other techniques, such as the magnetic resonance imaging (MRI) [16]. However, the long-term side effects of most of them are unknown, and their higher purchase and maintenance costs are not always sustainable. In this regard,

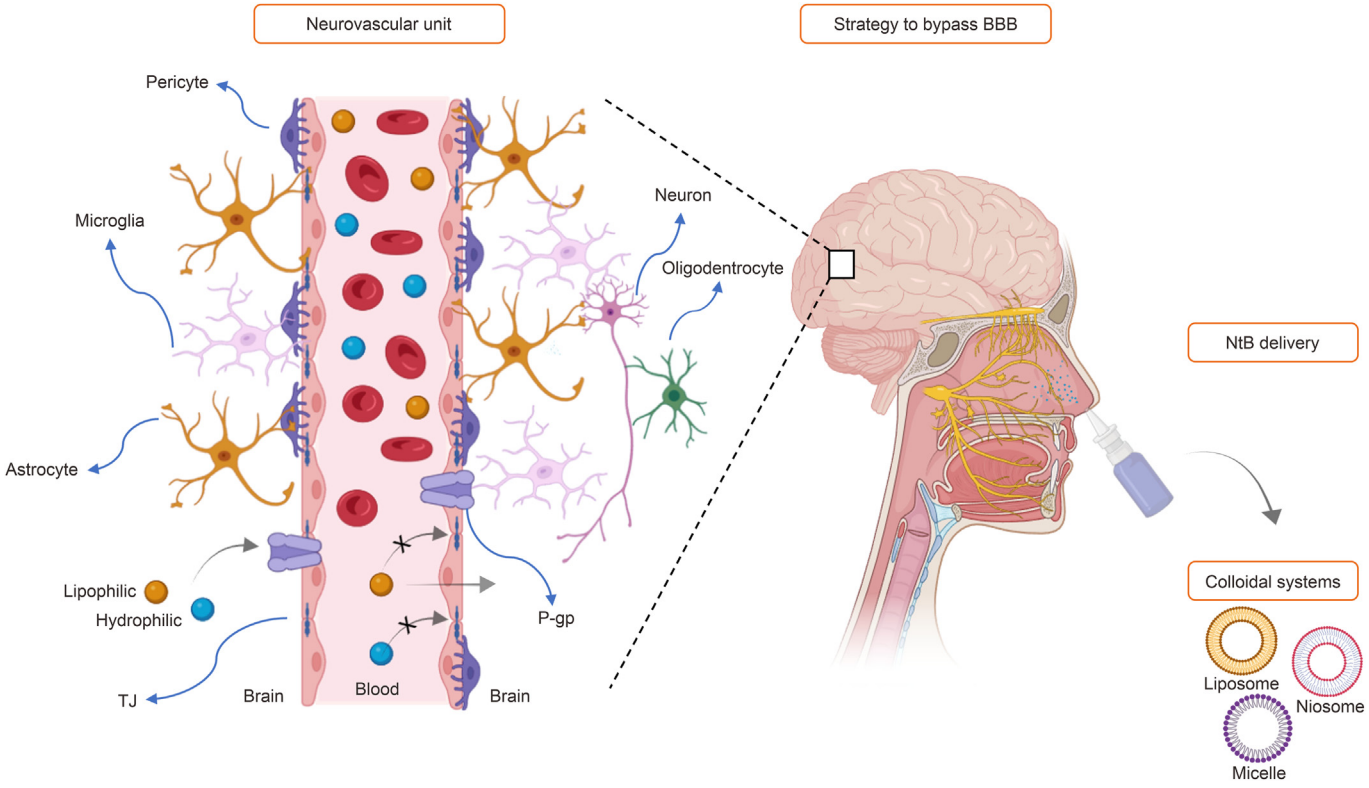


Fig. 1. Nanotechnology for brain delivery, a strategy to bypass the blood-brain barrier (BBB) and a schematic representation of the neurovascular unit on the left. TJ: tight junction; P-gp: P-glycoprotein; NtB: nose to brain. (Created in BioRender.com).

nowadays much research focuses on the development of current AD treatments using nano vesicular system formulations, such as colloidal systems, applied to NtB delivery [17,18], a valid and safe approach for brain delivery increasing permeation across the nasal cavity and promoting drug accumulation into the CNS (Fig. 1).

Colloidal systems delivered by the NtB route could be a valid approach since several studies suggest that NtB delivery may be favorable as a treatment approach for many CNS illnesses, including AD disease [19–21] (Fig. 1). In the present scenario, broad studies at preclinical and clinical levels of various drugs are undergoing to be approved for the treatment of several brain damages using NtB delivery, including peptide, hormones, immunomodulators, and well-known medicines loaded in different type of nanocarriers [22].

In particular, different preclinical studies using animal models of AD highlighted the precious potential use of this administration route as demonstrated by amelioration in cognitive and memory behavioral tasks induced by various drugs including donepezil, curcumin, galantamine, memantine, and quercetin, and also by peptides such as nerve growth factor (NGF) and vasoactive intestinal peptide (VIP), since they showed an increased drug brain availability when administered intranasally and formulated in colloidal systems drug load compared to conventional formulations [23,24].

In this context, the development of colloidal systems in the field of nanotechnology represents a valid strategy to overcome problems related to the presence of BBB as well as the problems related to NtB delivery due to their ability to protect drugs from nasal enzymatic degradation [25] and to avoid the mucociliary clearance increasing the mucoadhesion in the nasal cavity. The main strategy used is coating the nanocarriers' surface with several mucoadhesive polymers, such as chitosan which can interact with mucin, the main component of the nasal mucus layer, and it acts to prolong the contact time between the drug and mucosa itself [26,27]. A novel strategy combines colloidal systems with in situ nasal-gelling formulations, utilizing mucoadhesive and thermosensitive polymers such as the Pluronics family. This approach creates a controlled and sustained release system that facilitates the nasal absorption of various compounds [28,29].

Furthermore, colloidal systems can also increase the access to CNS of substances that otherwise couldn't reach the brain independently, even with NtB delivery. Such limitations are often observed with some biomolecules due to their high molecular weight and hydrophilic nature, as well as with other potential drugs that exhibit low solubility or limited permeation through biological membranes [30].

Specifically, in the field of colloidal systems, the main ones used are liposomes and niosomes since they are biocompatible, and could increase drug diffusion through biological membranes and/or protect drugs against enzyme inactivation [31].

In this regard, liposomes, nanovesicles similar to biological membranes that are produced from cholesterol and phospholipids [32,33] (Fig. 2), facilitate the permeation of drugs across various biological membranes due to the phospholipids bilayer and, at the same time, they offer the possibility of surface modification or coating with various active agents or ligands to target specific sites and facilitate site-specific delivery as described above [34–38]. Although liposomes offer significant advantages, their high cost and limited stability pose challenges. The instability arises from the susceptibility of phospholipids to oxidation and hydrolysis, which shortens the shelf life of liposomal formulations.

On the other side niosomes, similar in structure to liposomes, consist of an aqueous core and a non-ionic surfactant bilayer (Fig. 2), a family of Span or Tween, so they have a greater stability, and easier storage stability than liposomes, resulting in more promising use. Furthermore, niosomes, like liposomes, could also target specific brain sites and cross BBB, using the specific surfactants or by coating with specific polymers according to NtB delivery, such as Tween 80 or poloxamer 407, whose increase cell permeability through nasal mucosa to the brain [39,40].

Notwithstanding the several advantages of intranasal delivery, including 1) the easier drug administration resulting in improved compliance, 2) direct absorption into the brain due to the highly vascularized nasal mucosa, and 3) reduced dose requirements by avoiding first-pass metabolism and pharmacokinetic variations associated with oral administration, it presents numerous limitations. These limitations include 1) restricted volume of administration, 2) limited residence time in the nasal cavity, and 3) relative mucociliary clearance, all constraints that reduce the time for drug absorption [41]. On the other hand, the formulation's characteristics, such as pH and viscosity, may be irritant to the nasal mucosa [42]. All these chemical and biological boundaries, with the local tissue limitations due to the damage fostered by chronic treatment administration as in neurodegenerative diseases, feature a significant challenge in the development of successful NtB delivery formulations [43], in which the combination with nano vesicular systems represents an alternative approach [17,18].

3. AD as template of synaptic plasticity defeat to study new therapeutics

AD is a major neurodegenerative disorder clinically characterized by a progressive decline of memory performance associated with impairment of cognition and language, deterioration of daily living activities, and behavioral disturbances, ultimately leading to dementia [44]. It is caused by damage to neurons, with the first population affected are responsible for memory, language, and thinking processes. Indeed, the initial symptoms of AD typically involve memory loss and deterioration of cognitive function. However, brain changes begin approximately 20 years before the onset of noticeable symptoms [45].

The hippocampus, a brain area essential for memory, represents the first region in which impaired synaptic functions occur as early

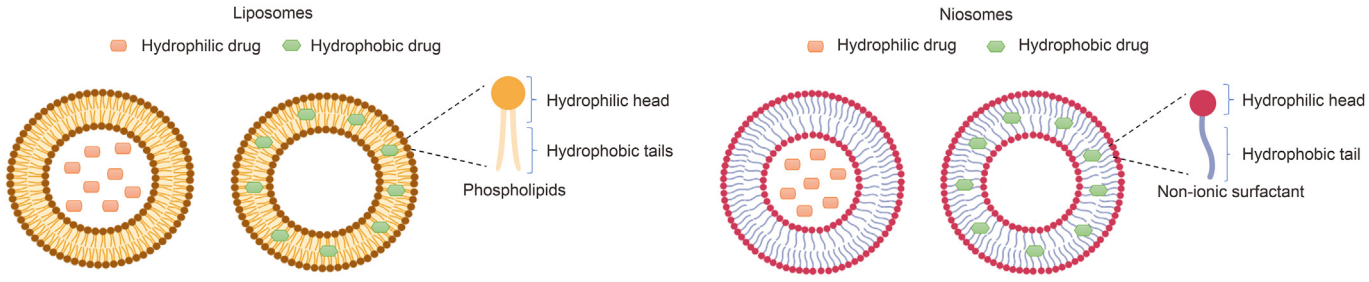


Fig. 2. Schematic representation of nano vesicular systems: liposome and niosomes in comparison. (Created in Biorender.com).

events leading to defective hippocampal-dependent memory, manifesting long before the buildup of characteristics hallmarks of pathology, such as senile plaques and intracellular neurofibrillary tangle (NFT) [46]. Today, the "amyloid cascade hypothesis" represents the major accredited theory, postulating that neurodegeneration in AD arises from the abnormal accumulation and aggregation of amyloid beta plaques in several brain areas [47]. Due to their toxicity, Aβ protofibrils and plaques cause downstream reactions resulting in chronic neuroinflammation, loss of synaptic and neuronal function, neuronal death, and increased tau phosphorylation with consequent buildup of NFT [48]. The increased toxicity of Aβ has therefore been related to its great propensity to form aggregates and justifies its potent effect on inducing a direct depressant effect on synaptic transmission [49].

However, the presence of this protein in a physiological state is essential for a variety of physiological functions, such as neural growth and survival, protection against oxidative stress, toxins, and pathogens, modulation of neurotransmission, and the execution of synaptic plasticity [50].

Synaptic plasticity refers to the ability of experience to modify neural circuits, influencing many patterns involved in thinking, feeling, and behavior. It plays a main role in the development of the nervous system by modifying the architecture of connections and in the capability to learn and remember new information as well as to adapt to environmental changes [51]. Therefore, plastic changes in the CNS, which underlie the phenomena of learning and memory, involve alteration in the efficiency of signal transmission between cells. These changes may include an increase or decrease in synaptic surface area or modification in the number of synaptic contacts, or adjustments in membrane receptors density [52].

In agreement with several studies, memory and learning deficiency are linked with alterations in the synaptic plasticity process [53]. As observed in AD patients, Aβ accumulation fosters changes at synaptic levels, which correlated with impairment in synaptic function and plasticity [54], and consequently, AD has been hinted to be a template of synaptic plasticity defeat [55] (Fig. 3).

Particularly, synaptic plasticity represents a peculiar feature of the brain, playing a key role in the establishment of learning and memory processes [56], which are typically affected in AD. Indeed, a large body of evidence has demonstrated that synaptic loss, rather than accumulation of AD hallmarks, such as Aβ plaques and NFTs, represents the best pathological correlate of cognitive damage [55,57]. Additionally, weakened hippocampal synaptic plasticity occurs as an early event primary to defective memory processing long before the formation of amyloid plaque lesions and neuronal death [58]. Given the crucial role that synaptic plasticity plays in learning and memory proceedings, a broad number of studies using the electrophysiological approach have described the hippocampal role in information storage [59]. Furthermore, given that many AD patients exhibit memory and cognitive impairments in the early stages of the disease, it has been suggested that these symptoms arise from early structural and functional alterations in hippocampal synapses [46]. This brain area is largely implicated in long-term potentiation (LTP) and long-term depression (LTD) represent models of the information storage by the hippocampal region. Investigating changes in neuronal ability to modify synaptic strength following damage suggests that extensive synaptic changes in the hippocampus may be responsible for the memory impairments predominant in the early stages of AD.

Much of the information known about the implication of the hippocampus in the pathophysiology of AD results from histological studies in post-mortem AD patients' brains and from animal models [48], where a strong positive correlation between dementia severity, Aβ plaque deposition, and disruption of synaptic markers has been found [46]. In a transgenic mouse model of AD (amyloid precursor protein (APP) mouse), deposition of Aβ-containing fragments was associated with altered hippocampal LTP of excitatory glutamatergic synaptic transmission and hippocampus-dependent learning [60]. Most studies have reported that Aβ at nanomolar concentrations had acute effects on synaptic plasticity, mediating inhibition of LTP or reduction in excitatory neurotransmission and neurotransmitter release probability in animal and *ex vivo* models [61]. Furthermore, Aβ in the *ex vivo* model affects the form of LTD synaptic plasticity, suggesting a broad range of effects mediated by Aβ at the synaptic level underlying synaptic plasticity deficits [62].

In this light, several works investigated the ability of different drugs to improve the synaptic plasticity deficits Aβ-mediated. In certain studies, the molecules tested are a selective blocker for a

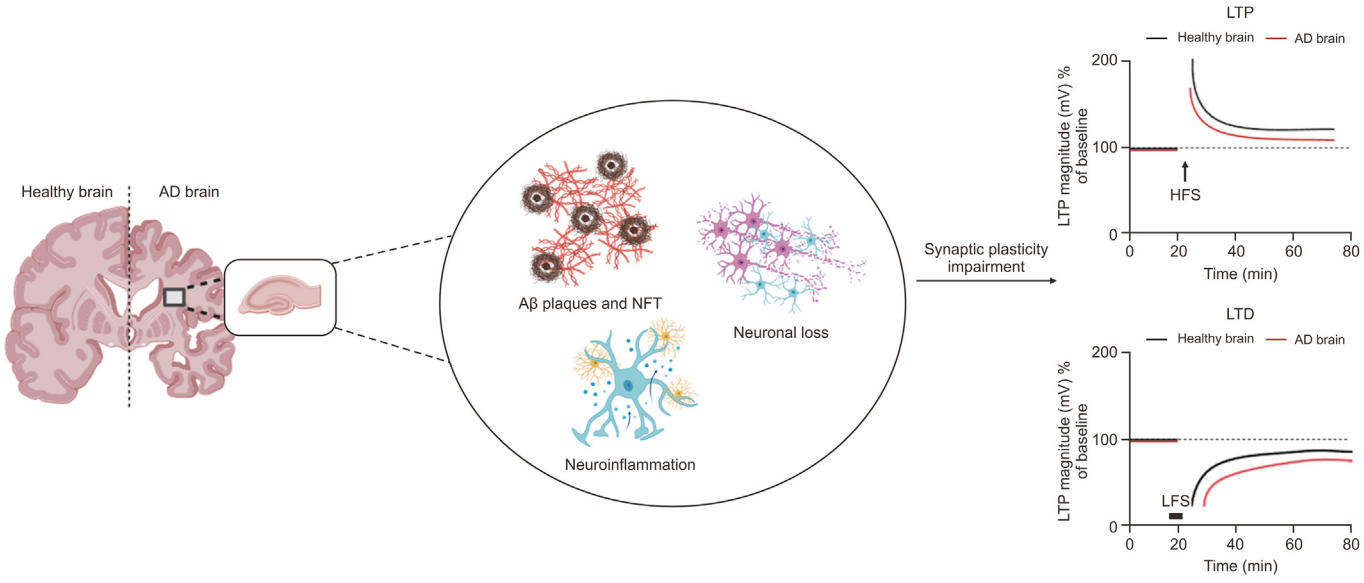


Fig. 3. Schematic representation of histopathological features and synaptic plasticity alterations in Alzheimer's disease (AD) brain. In the graph on the right, the black and red lines represent a healthy brain and an AD brain's long-term plasticity response, respectively. Aβ: amyloid-β; NFT: neurofibillary tangles; LTP: long-term potentation; HFS: high-frequency stimulation; LTD: long-term depression; LFS: low-frequency stimulation. (Created in BioRender.com).

specific receptor or they can act on specific mechanisms, such as for insulin, for which much evidence suggests a causal role of insulin resistance in AD development and progression. Insulin induces α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs) internalization [63] and potentiation of *N*-methyl-D-aspartate receptors (NMDARs) activity and phosphorylation [64,65], modulating the long-term synaptic plasticity. In particular, the case of insulin represents a paradigm of a natural molecule with a positive effect on cognitive function decay characteristic in AD, and the requirement to deliver the molecule in the brain. Indeed, intranasal insulin administration allows the molecule to reach the CNS with the absence of systemic uptake and associated peripheral side effects [66,67]. In other studies, natural phytocomplex have showed the ability, likely due to their pleiotropic activity, to influence synaptic plasticity alterations and restore a magnitude of synaptic plasticity to a level comparable to the control condition.

4. Natural compounds with neuroprotective effect and their bioavailability limitations

In this section, we provide an overview of some natural drugs that have demonstrated the prowess to restore hippocampal synaptic plasticity alteration Aβ-mediated in different models, summarized in Table 1 [68–76] with their bioavailability limitations, potentially overcome with the use of nano vesicular system.

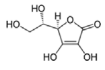
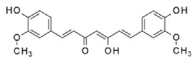
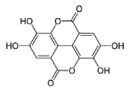
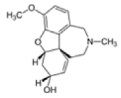
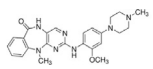
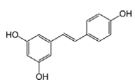
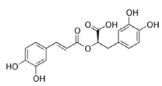
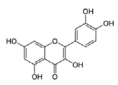
4.1. AA

AA, known as vitamin C, is a hydrosoluble vitamin widely present in biological systems as a naturally occurring free radical scavenger presenting antioxidant activity [77]. Specifically, brain AA levels are under heavy homeostatic regulation which includes a brain regional distribution and a characteristic concentration in neurons and glia [78]. The neuroprotective activity of AA has been shown in *in vitro* and *in vivo* models of several neurological diseases associated with marked oxidative stress, such as AD [79]. Interestingly, vitamin C acts on neurotransmission, with involvement in the synthesis, release, and uptake of monoamines and catecholamines, and it acts as an allosteric modulator on numerous receptors including T-type calcium (Ca^{2+}) channels, NMDARs, dopamine receptors, 5-hydroxytrptamine 3 (5-HT_3) receptors, and gamma-aminobutyric acid (GABA) receptors [80]. Particularly, AA has shown activity directly on synaptic plasticity, restoring LTP alteration in the dentate gyrus of the hippocampus in the AD animal model. Additionally, these data were confirmed by retrieval of learning and memory impairment caused by the intracerebroventricular (ICV) injection of Aβ in the same animals [68], suggesting its potential use in AD. Moreover, clinical data suggest that in AD patients, the relationship between the cerebrospinal fluid and plasma AA ratio represents a predictor of cognitive decline due to the increased consumption of AA to counteract the oxidative stressed brain, compared to healthy patients [81]. Nevertheless, the biggest challenge in the application of vitamin C is its instability when exposed to heating, light, moisture, oxygen, and metal ions, accompanied by color changes [82].

4.2. Curcumin

Curcumin (diferuloylmethane) is a major chemical component of the turmeric plant Curcuma longa [83]. Several studies show its

Table 1
The table summarizes natural compounds relevant data relative to functional rescue in experimental Alzheimer's disease (AD) models.

Name	Molecular structure	Functional rescue	Model	Refs.
AA		Restores LTP and learning and memory impairment	*In-vivo* model (ICV of Aβ)	[68]
Curcumin		Restores LTP, synaptic transmission, and memory	*In-vitro* and *in vivo* models (APP mice)	[69]
EA		Improves learning and memory deficits	*In-vivo* model (ICV of Aβ)	[70]
Galantamine		LTP potentiation, improves cognitive, and learning and memory deficits	*Ex-vivo* and *in-vivo* models (post-operative cognitive and dysfunction mice) and clinical study	[71]
GA		Restores LTP and neurotransmission alterations	*Ex-vivo* model (AD model)	[72]
PcTx1		Restores LTP and ameliorate memory	*Ex-vivo* model (AD model)	[73]
Resveratrol		Restores synaptic functions and cognitive deficits	*In-vivo* model (ICV of Aβ)	[74]
RA		Restores cognitive deficits and improves memory	*In-vivo* model (ICV of Aβ)	[75]
Quercetin		Restores cognitive deficits and improves memory	*In-vivo* models (LPS-induced AD mice, APP, 3xtg, and 5xFAD)	[76]

AA: ascorbic acid; LTP: long-term potentiation; ICV: intracerebroventricular; Aβ: amyloid-β; APP: amyloid precursor protein; EA: ellagic acid; GA: ginkgolic acid; PcTx1: psalmotoxin 1; RA: rosmarinic acid; LPS: lipopolysaccharides; 3xtg: triple-transgenic mouse model of AD; 5xFAD: five-familial AD.

beneficial activity in different pathology conditions, including in neurodegenerative conditions such as AD [84], with neuroprotective activity on hippocampal neurons against excitotoxic and traumatic injury [85,86]. Particularly, curcumin has been reported to rescue Aβ detrimental effects *in vitro* [87,88] and improve memory in animal models of AD, such as in transgenic APPs mice [85]. Interestingly, this molecule can protect and modulate synaptic transmission and plasticity from Aβ insult [69], regulating Aβ-induced decrease in synaptic function via a calcium/calmodulin-dependent protein kinase II (CaMKII)-dependent pathway which is involved in the induction of LTP [69] and leading to the promotion of dendritic spine enlargement and synaptic strength [89,90]. However, its use, as a promising natural compound for the treatment of neurodegenerative disease, is hampered by its poor water solubility and short biological half-life, resulting in low bioavailability in both plasma and tissues, and the use of nanocarriers could face up to this difficulty also increasing brain targeting across BBB [91].

4.3. EA

EA is a polyphenol present in many plant species such as pomegranate plants, grapes, raspberries, blackberries, strawberries, and walnuts [92,93], and it has been shown several pharmacological effects, including anti-bacterial, anti-inflammatory, and antioxidant properties, with a particularly notable neuroprotective effect. It modulates various cell signaling pathways and it exerts free radical scavenging properties, metal chelation, and conserving mitochondrial functions [94–96]. EA can decrease the expression of inflammatory cytokines including interleukin (IL)-1β and IL-6 in rats and shows its anti-inflammatory activity [97], leading to the rescue of LTP [98], since IL-6 affects synaptic plasticity reducing LTP expression [98], while IL-1β influences glutamate release modulation, the function of NMDARs and calcium channel influx affecting the magnitude of LTP, all implicated in AD [98–100]. Additionally, when administrated orally, EA mitigates hippocampal oxidative stress and neuroinflammation by modulating the insulin-like growth factor 1 (IGF-1) pathway [101], which is directly involved in the synaptic plasticity. The involvement of EA in synaptic plasticity suggests its ability to improve memory deficits and learning [102], determining its potential use in the treatment of AD, as evidenced by beneficial effects reported in precursor protein (APP/presenilin 1(PS1)) double-transgenic animal model, where it was reported a reduction of Aβ aggregation and tau-hyperphosphorylation [70]. Despite the benefits of EA, its poor water solubility and extensive first-pass metabolisms and, consequently, low oral bioavailability of EA, have limited its therapeutic potential to mature into clinical trials [103].

4.4. Galantamine

Galantamine from Narcissus plants is a reversible competitive inhibitor of acetylcholinesterase, and it contributes to the improvement of the cognition, learning, and memory of patients with AD via multiple pathways. Particularly, galantamine is involved in the potentiation of LTP by activating CaMKII and prtoein kinase C (PKC) in rat hippocampal CA1 region, and through the activation of a seven-type nicotinic acetylcholine receptors (nAChRs) and NMDARs, it likely mediates improvement of cognitive, learning, and memory deficit in patients with AD [104]. Galantamine is also involved in the regulation of astrocytic Ca^{2+} signaling, LTP, and synaptic transmission, suggesting that Ca^{2+} signaling may be involved in synaptic function, as astrocytes play active roles in synaptic transmission and plasticity [104]. In this case, galantamine presents a relatively good pharmacokinetics but its oral administration can cause some unwanted side effects [105], potentially solvable with the use of a nano vesicular system.

4.5. GA

GA is an active component of *Ginkgo Biloba* extract (GBE), which is widely used and represents a valid phytotherapy to ameliorate the cognitive decline in aging, mild cognitive impairment, and AD [106]. A growing body of investigations has been conducted to delineate the vast number of pharmacological activities including neuroprotection [72]. Particularly, GA significantly prevents LTP impairment Aβ-mediated in the *ex vivo* AD model [61], confirming the positive effect observed in a clinical study. However, the clinical studies suggest that a high dose for a prolonged administration can improve the early stage of AD, but the limited data on the bioavailability of GBE and low brain enrichment, as shown by poor studies, suggest further investigation for this phytocomplex as a possible relevant treatment in cognitive decline [107].

Moreover, GA has a limited bioavailability due to the activity of P-gp and breast cancer-resistant protein, two pumps for xenobiotics present in BBB, for which GA constitutes a substrate [108,109]. These limitations suggest that nano vesicular systems could help avoid low bioavailability.

4.6. PcTx1

PcTx1 is the first isolated venom peptide, particularly from South American tarantula (Psalmopoeus cambridgei), and it consists of 40 amino acid residues with potent and specific inhibitor effects on acid-sensing ion channels 1a (ASIC1a) receptors [110].

ASIC1a represents an acid sensor widely expressed in CNS, and numerous studies have investigated the involvement of these channels in processes involving calcium (Ca^{2+}) and protons (H^{+}), suggesting implications in a variety of physiological and pathological conditions [111]. Several studies highlighted the role of these channels in different synaptic plasticity forms. Particularly, in the hippocampal brain area, ASIC1a was implicated in LTD metabotropic glutamate (mGlu)-dependent amplification observed in AD models. PcTx1 can reestablish the magnitude of LTD at the control level in *ex vivo* models, slices treated with Aβ or obtained from AD mouse model. Based on these data, PcTx1 represents a promising drug; however, the high molecular weight and chemical characteristics, typically of proteins, severely limit its oral bioavailability, as demonstrated by the administration in mice [112].

4.7. Resveratrol

Resveratrol is a polyphenolic compound that belongs to the phytoalexin superfamily, and it presents several activities, especially neuroprotective activity through its inhibitory activity on β-secretase, the generation of the reactive oxygen intermediates, and the aggregation of Aβ peptide [113,114]. Furthermore, resveratrol ameliorates spatial learning memory impairment induced by Aβ in rats [74] highlighted by the rescue of LTP impairment in area CA1. The molecular mechanism speculated to be responsible for its ability to reduce sirtuin 1 (SIRT1) expression and cyclic adenosine monophosphate (cAMP)-response element binding protein (CREB) phosphorylation, typically altered in Aβ treated rats, suggests the possibility of resveratrol's use in AD conditions. However, resveratrol administration could be difficult due to its pharmacokinetic limitations, such as low bioavailability due to its short biological half-life, its rapid metabolism and clearance, chemical instability, high photosensitivity, and poor solubility in water [115,116].

4.8. RA

RA is a polyphenolic ester of caffeic acid, and it exhibits several pharmacological activities as antioxidant, neuroprotective, and antidepressant-like effects [117–119]. It enhances the LTP magnitude since it is involved in the expression of brain-derived neurotrophic factor (BDNF) and glutamate receptor 2 (GluR-2) proteins [120], which are associated with hippocampal LTP induction. Interestingly, RA induces LTP by its activity on NMDARs [120], which are also essential for Aβ impairment of LTP [121]. Since RA has been shown activity to reduce Aβ aggregation by increasing monoamine secretion [122] and alleviating deficits in cognition, synaptic regulation, and adult hippocampal neurogenesis in an Aβ-induced mouse model of AD [75], it could be a good candidate for treating neurodegenerative disease, like AD. Nevertheless, RA shows poor oral bioavailability and permeability in CNS [123].

4.9. Quercetin

Quercetin is a flavonol-type flavonoid commonly present in herbaceous and woody plants [124], and it is characterized by several biological activities, especially antioxidant and anti-inflammatory effects, allowing its potential use in neurodegenerative disorders, such as AD [125]. It has been reported that the neuroprotective effect of quercetin could be related to its inhibition of sodium channels in a dose- and voltage-dependent manners, and it is able to protect against LTP changes in the hippocampus induced by chronic cerebral ischemia [126]. In this light, the effect of quercetin on LTP, a molecular mechanism underlying learning and memory, typically affected in AD, could be useful for AD treatment. Indeed, different studies have investigated the neuroprotective activity of quercetin using several AD mouse models, evaluating its impact on cognitive and memory functions and exploring its involvement in many signaling pathways involved in AD [76,127–133]. Moreover, it has been shown that administration of quercetin in triple-transgenic mouse model of AD (3xTg-AD) mice has shown reversal of Aβ levels due to inhibition of phosphorylation of AT-8 tau in the brain, with a neuroprotective activity induced by modulation of serine/threonine kinase 1 (AKT)/protein kinase B (PKB) and extracellular signal-regulated kinase 1/2 (ERK1/2) signaling pathways involved in synaptic plasticity [130,134]. Additionally, quercetin interacts with mitogen-activated protein kinases (MAPK) proteins contributing to the maintenance of learning, memory, and synaptic plasticity mechanisms including LTP [135].

Nevertheless, poor solubility and the difficulty of quercetin in passing across the BBB restricts effects in CNS [136].

5. NtB delivery: challenge for AD therapy

Considering all data discussed regarding natural compounds with potential therapeutic effects on synaptic dysfunctions in AD (Fig. 4), the advancement of nanocarriers technology represents a

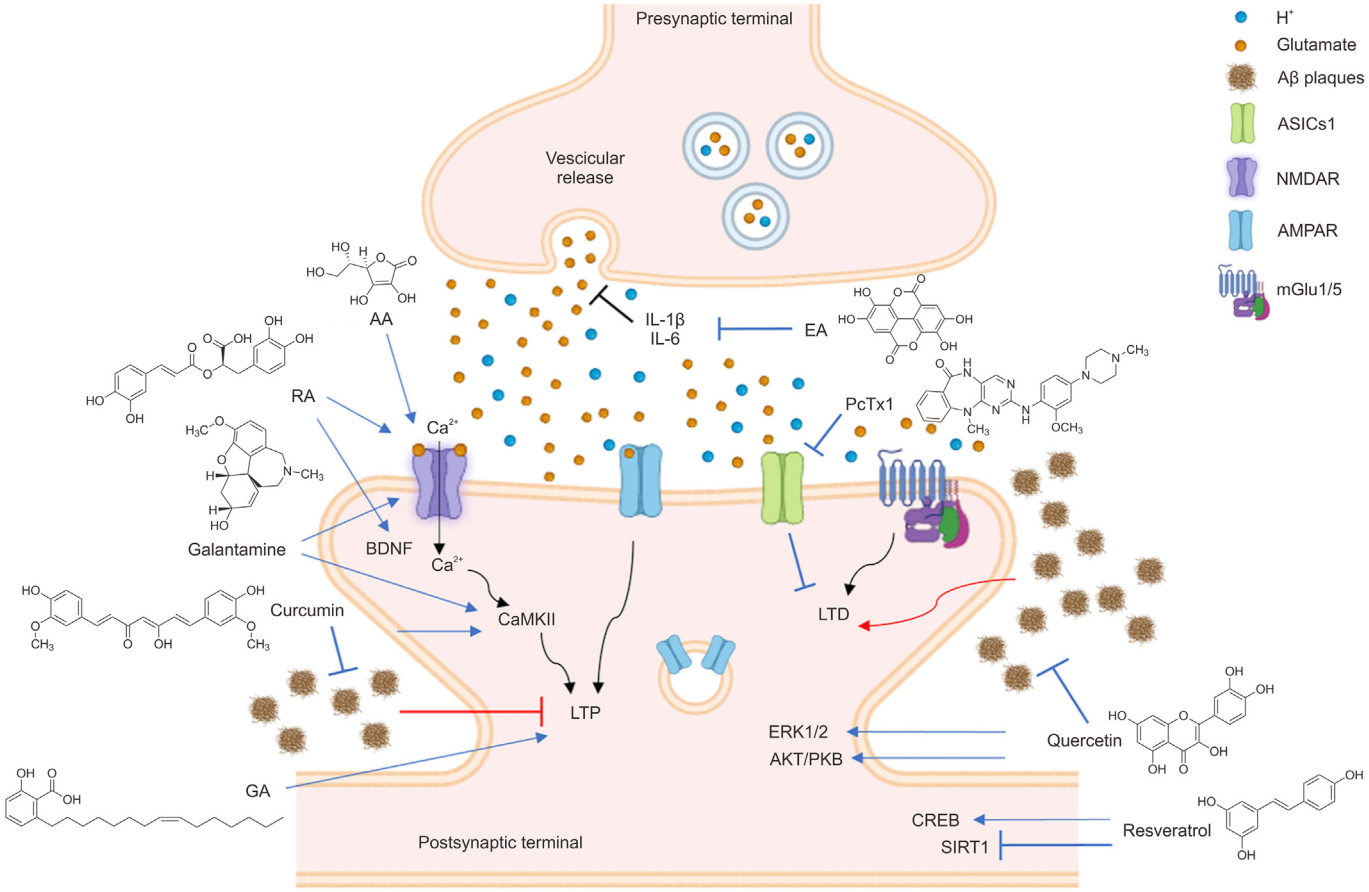


Fig. 4. Natural compounds synaptic targets for plasticity rescue. Aβ: amyloid-β; ASICs1: acid sensing ion channels 1; NMDAR: *N*-methyl-D-aspartate receptor; AMPARs: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; mGlu1/5: ; AA: ascorbic acid; RA: rosmarinic acid; GA: ginkgolic acid; BDNF: brain-derived neurotrophic factor; CaMKII: calcium/calmodulin-dependent protein kinase II; LTP: long-term potentiation; IL: interleukin; EA: ellagic acid; PcTx1: psalmotoxin 1; LTD: long-term depression; ERK1/2: extracellular signal-regulated kinase 1/2; AKT: serine/threonine kinase 1; PKB: protein kinase B; CREB: cyclic adenosine monophosphate (cAMP)-response element binding protein; SIRT1: sirtuin 1. (Created in BioRender.com).

promising strategy. Specifically, when combined with delivery via the NtB route, this approach offers a dual benefit: protecting compounds from degradation and achieving optimal concentrations in the brain while bypassing the limitations of the BBB.

Most drugs, administered parenterally and orally, are unable to reach the brain due to the presence of the BBB, which prevents the passage of many substances, especially large ones such as proteins, peptides, or phytocompounds. In addition to the BBB, pharmacokinetic aspects such as first-pass metabolism, enzymatic degradation, and systemic clearance also greatly reduce the bioavailability of drugs [137]. An alternative to all these complexities, as mentioned above, could be NtB delivery, which can represent a non-invasive valid approach to bypass the BBB and deliver drugs directly to the brain through the nasal cavity using olfactory and trigeminal pathways or via the systemic circulation, since the respiratory region is widely vascularized [137–140]. In addition, NtB is a promising administration route, due to the easy accessibility of the nasal cavity allowing for self-administration and patient compliance and it minimizes systemic exposure reducing peripheral side effects. Particularly, NtB is an alternative approach for peptide or protein delivery, considering that most recent drugs for the treatment of neurodegenerative disease are peptide or protein-based which, as biomolecules, are not able to bypass the BBB and are also characterized by pharmacokinetic limits, especially enzymatic degradation, when delivered parentally or orally [141,142]. Interestingly, several studies have demonstrated that NtB delivery of NGF, IGF-1, or VIP, increased their biodistribution into the brain in comparison when administered intravenously [143–145]. Also, several studies support the conjecture that intranasal insulin enriches the brain, improving functional connectivity and cognitive performances with a decrease of Aβ concentration in AD animal models [146–149] and the plasma of AD patients, encouraging the use of this formulation as a novel therapeutic for AD treatment [150].

However, the NtB route presents several challenges that should be considered, such as mucociliary clearance, enzymatic degradation, and nasal absorption, which cause a low delivery efficiency and retention of drugs [151–153]. Moreover, the NtB formulations must present appropriate viscosity, physiological tonicity, and pH compatible with the nasal mucosa [154].

Today, nanotechnology, as colloidal drug delivery systems, represents a valid approach for drug delivery to the brain, increasing permeation across the nasal cavity and promoting drug accumulation into the CNS, as also described above.

This nanotechnology promises to overcome several limits related to chemical properties as was demonstrated for AA and resveratrol, characterized by high instability to heating, light, and oxygen that showed greater *ex vivo* antioxidant activity when formulated in nanocarriers compared to free forms of the two natural compounds [76,118,119]. This valid strategy is also developed using a specific formulation of curcumin-loaded micelles, which have shown a higher drug distribution in the brain compared to the free form of the curcumin [155] or using surfactants to improve the bioavailability with an increase of cell membrane interaction as tested for resveratrol [156].

Nanotechnology-based delivery systems also allow the mounting of nanoparticles loaded with different compounds and the possibility to administrate two drugs concurrently in the same treatment, as demonstrated for quercetin and curcumin [154]. A recent study has described a new formulation to improve the brain delivery of quercetin using a gel for a nasal route with significant improvement of the substance concentration in the brain [128] and in the same way, a new galantamine formulation was described to overtake the side effects induced by oral administration [105], demonstrating the huge perspective of nanotechnology in the development of neuropharmacology treatment for AD [157,158].

For several compounds, the use of nanocarrier systems has demonstrated an improvement in brain bioavailability [159]. For example, it has been reported by soft nanosystems delivery that the neuroprotective activity is more effective than EA delivered alone [160]. Similar results were reported in the case of RA, which shows poor oral bioavailability and permeability in the CNS that can be bypassed by loading RA into nanocarriers [75,123], while when it is delivered loaded into nanocarriers and by NtB route, it shows an easier administration route and ability to bypass BBB [161].

Furthermore, colloidal systems could also help to overcome side effects induced by compounds, as in the case of a new galantamine formulation delivered through the NtB strategy, which was described to overpass the side effects induced by oral administration, allowing access directly to the CNS too, or as the PcTx1, whose pharmacokinetics limits [157] could be overtaken by including it in a colloidal system for NtB delivery. Furthermore, formulating nanocarriers with surfactant can enhance the solubility and the stability of resveratrol to the light and other degradative processes too [162,163]. In this regard, several studies have been conducted to load resveratrol into nanocarriers, such as liposomes or niosomes [163], to improve its bioavailability by increasing the interaction between surfactants and cell membranes [156].

6. Conclusions and future perspectives

The combination of nano vesicular system and NtB delivery represents a future rising therapeutic strategy for the development of potential neurodegenerative disease treatments, such as AD, exploiting a wide number of natural molecules that have been demonstrated to have effects on synaptic deficits but are characterized by pharmacokinetics limitations that hinder their delivery to the brain. In the last years, there has been a substantial increase in studies investigating intranasal delivery, offering new formulations to improve brain disorders' treatments. This surge is supported by several advantages, including low risk of injury during application, non-invasive self-administration, and consequently increased patient compliance. The versatility of these formulations in delivering different molecules and the possibility of combining multiple active entities for co-treatment make these nanoformulations particularly promising for developing new therapeutics for brain pathologies. Moreover, in complex pathological conditions such as AD, which involve multiple targets, the use of natural products with polypharmacological efficacy holds great potential for the development of new medications.

In the future, research should focus on exploring and testing new treatments at pre-clinical and clinical levels to validate nanocarrier preparation loaded with neuroprotective molecules for NtB delivery. Indeed, NtB represents an alternative route of administration that is particularly promising for overcoming the intrinsic limitations of natural products, which are often characterized by low bioavailability and stability. The use of innovative technologies can pave a novel route to obtain new naturally based therapeutics for brain disorders. Multiple pieces of evidence attest to positive effects on drug stability and brain targeting suggesting a revolutionary overture in the management of neurodegenerative diseases. Notably, some drugs are already being tested using this type of formulation to enrich the brain, including treatments for conditions such as cancer and cognitive impairment. This approach represents a crucial step forward in addressing the challenges of brain drug delivery and offers the potential for enhancing outcomes in neurodegenerative disorders.

In conclusion, the loading of natural molecules with neuroprotective activity into nanocarriers, combined with innovative delivery routes such as NtB, holds immense promise for the future of neurodegenerative disease treatment. Continued research and

development in this area is essential for transforming these rising strategies into effective clinical therapies.

CRediT authorship contribution statement

Nunzia Maisto: Data curation; Formal analysis; Writing – original draft, Writing – review & editing. **Dalila Mango:** Conceptualization; Supervision; Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that there are no conflicts of interest.

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