Natural Products from Plants and Algae

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Neurodegenerative disorders including Parkinson's disease (PD), Huntington's disease (HD) and the most frequent, Alzheimer's disease (AD), represent one of the most urgent medical needs worldwide. Despite a significantly developed understanding of disease development and pathology, treatments that stop AD progression are not yet available. The approval of sodium oligomannate (GV-971) for AD treatment in China emphasized the potential value of natural products for the treatment of neurodegenerative disorders. Many current clinical studies include the administration of a natural compound as a single and combination treatment. The most prominent mechanisms of action are anti-inflammatory and anti-oxidative activities, thus preserving cellular survival.

Keywords: Alzheimer's disease ; neurodegeneration ; drug development ; clinical studies

1. Introduction

Neurodegenerative diseases are a group of disorders in which neuronal function and survival are seriously affected. Many of these diseases, including Parkinson's, Huntington's and Alzheimer's Disease (AD), are caused by structural changes and the deposition of proteins; therefore, they are also assigned to the group of protein misfolding diseases or amyloidoses [1][2][3]. AD is by far the most common cause of neurodegeneration and dementia. It is estimated that AD currently affects 55 million people worldwide (World-Alzheimer-Report-2021. Available online: https://www.alzint.org/u/World-Alzheimer-Report-2021.pdf, accessed on 4 February 2022). Characteristic symptoms of the disease are progressive memory loss, impaired cognitive function and paranoia. The histopathological hallmarks of AD, extracellular amyloid deposits ("amyloid plaques"), which mainly consist of the peptide Aβ, and intraneuronal neurofibrillary tangles of the hyperphosphorylated protein tau, mainly affect the cerebral cortex and the hippocampus [4][5]. Numerous studies suggest that the disease is initiated by the deposition of Aβ, which starts presumably years or decades before the first symptomatic changes [6]. The slow Aβ deposition triggers a downstream cascade (the amyloid cascade), which involves pathologic tau formation and hyperphosphorylation, widespread neuroinflammation and, finally, neuronal death [7][8]. Although the intense research during the last decades enabled a much better understanding of the crucial events in AD pathogenesis, a curative therapy that halts the progression of the disease is not yet available. Most of the so-called disease-modifying experimental drugs are targeting events of the amyloid cascade such as the generation and aggregation of Aβ and the phosphorylation of tau or the cellular metabolism and energy homeostasis [9]. The drug development in AD is faced with several challenges which has resulted in numerous setbacks in recent years [10]. For instance, the enzymes responsible for Aβ formation also have physiological substrates and functions. This complicates the suppression of amyloid peptide formation without interfering with other proteolytical degradation processes. Prominent examples are the γ-secretase complex and the β-secretase BACE1, which play a role in the formation of Aβ peptides [11][12][13]. Moreover, several reports suggest that Aβ1–40/42 and tau also have physiological functions, which leads one to question whether these represent druggable targets [14][15][16][17]. Also, many of the amyloidogenic proteins are localized in the cell nucleus or cytosol, which makes an effective suppression of the aggregation or the breakdown of the conglomerates, e.g., by antibodies, even more difficult [18]. Third, the efficient passage of the blood-brain barrier is needed and thus the pharmaceuticals are required to meet various physicochemical parameters [19][20]. Hence, methods are currently being examined (e.g., focused ultrasound) to make the blood-brain barrier more permeable [21].

Finally, major factors hampering the development and testing of new drugs are based on the clinical presentation of dementia and the currently available diagnostic biomarkers. AD patients frequently also show the presence of Lewy bodies and thus, significant pathological overlap with patients with dementia with Lewy bodies (DLB). As a result, the clinical testing of new active ingredients does not take place in "pure" Alzheimer's patient populations. Accordingly, attempts are being made (using imaging methods and genetic analyses, among others) to conduct clinical studies in narrowly defined patient populations at an early stage of the disease [22][23][24]. Previously, numerous approaches were therefore undertaken in patients with a possibly too advanced a disease stage [23][25]. In addition, the available diagnostic

biomarkers often do not specifically reflect the neurodegenerative disease or provide enough correlation with the clinical status of the patients. These imponderables could be responsible for the failure of different therapeutic approaches in the clinical phase. As mentioned above, alterations in biomarkers precede the symptoms of the disease [6][26], i.e., the measured value of a biomarker cannot be directly correlated with an effect on cognition. An example of this is the antibody bapineuzumab, which caused a significant change in phospho-tau in CSF in phase 2, but missed clinical endpoints [27].

All of these factors finally led to the numerous failures of disease-modifying drugs in AD clinical trials. The very recent accelerated approval of Aducanumab to treat AD may thus represent a first sign of success. However, the complexity also triggered the intense investigations of other fields, such as drugs from natural sources and nutraceuticals (**Table 1**). One potential reason is that food supplements may have the status as being generally regarded as safe (GRAS) and thus can be quickly applied in clinical testing, and eventually in combination with experimental drugs. Most of these substances are addressing protective mechanisms to cells by, e.g., anti-oxidative effects. However, there are also compounds in testing which are dedicated to disease-modification by, for example, their influence on immune cells. A prominent example is represented by oligomannate from red algae, which obtained approval for AD therapy in China and is currently being tested in additional clinical trials. Due to the emerging role in clinical testing, this entry focuses on the current treatment strategies which are based on natural products.

Table 1. Natural agents in Clinical trials of Alzheimer's disease drug development (US National Library of Medicine. Available online: https://clinicaltrials.gov, accessed from September 2021 to November 2021.

Agent	Mechanism of Action	Therapeutic Purpose	Trial Identifier and Status	Phase
Huperzine A	AChE inhibitor, inhibition of Aβ	improve memory	Not yet recruiting NCT02931136	IV
Sodium oligomannate (GV-971)	neuroinflammation modulators, microbiome modulators, amyloid beta-protein inhibitors; reconditioning the dysbiosis of gut microbiota, preventing peripheral immune cells from invading the brain, inhibiting the inflammatory response in the brain targeting protein folding errors in the brain tissue	improve the cognitive function of patients with mild to moderate AD	Recruiting NCT05058040	IV
Sodium oligomannte capsules (GV-971)	neuroinflammation modulators, microbiome modulators, amyloid beta-protein inhibitors; reconditioning the dysbiosis of gut microbiota, preventing peripheral immune cells from invading the brain, inhibiting the inflammatory response in the brain targeting protein folding errors in the brain tissue	improve the cognitive function of patients with mild to moderate AD	Recruiting NCT05181475	IV
Ginkgo biloba	metabolism and bioenergetics; plant extract with antioxidant properties	Improve brain blood flow and mitochondrial function (cognitive enhancer)	Recruiting NCT03090516	III
Sodium oligomannate (GV-971)	reconditioning the dysbiosis of gut microbiota, preventing peripheral immune cells from invading the brain, inhibiting the inflammatory response in the brain targeting protein folding errors in the brain tissue	improve the cognitive function of patients with mild to moderate AD; evaluate safety, tolerability and efficacy of GV-971	Recruiting NCT04520412	III
Curcumin + aerobic yoga	herb with antioxidant and anti-inflammatory properties	decrease inflammation and oxidation related neurotoxicity	active, not recruiting NCT01811381	II
Elderberry Juice	rich in anthocyanins, has anti-inflammatory and antioxidant activity	improve mitochondrial function	completed NCT02414607	II
Grape powder	antioxidant, anti-inflammatory and anticarcinogenic	improves cognitive performance preservation of metabolism in brain regions important to cognitive function	recruiting NCT03361410	II
Icosapent ethyl (IPE)	synaptic plasticity, neuroprotection; purified from of the omega-3 fatty acid EPA	improve synaptic function; reduce inflammation	recruiting NCT02719327	II

Agent	Mechanism of Action	Therapeutic Purpose	Trial Identifier and Status	Phase
Meganatrual-Az Grapeseed Extract	polyphenolic extract with antioxidant properties	anti-oligomerization agent; prevents aggregation of amyloid and tau	recruiting NCT02033941	II
Omega-3 PUFA	fish oil concentrate standardized to long chain in n-3 PUFA content	reduces inflammation and glial activation; enhances amyloid removal; protect small blood vessels	active, not recruiting NCT01953705	II
Rapamycin	anti-inflammatory, antineoplastic; macrolide compound from *Streptomyces hygroscopicus*	selectively blocks the transcriptional activation of cytokines	recruiting NCT04629495	II
Rifaximin	inflammation, infection and immunity; antibiotic	reduce proinflammatory cytokines secreted by harmful gut bacteria	completed NCT03856359	II
Tacrolimus	tau proteins; macrolide from culture broth of a strain of *Streptomyces tsukubaensis*	reduce pathological changes of tau proteins	withdrawn NCT04263519	II
THC-free CBD Oil	anti-oxidant and anti-inflammatory; cannabinoids	behavioural and psychological symptoms of dementia (BPSD) decrease with use of cannabinoids	recruiting NCT04436081	II
VGH-AD1	undisclosed; traditional Chinese herbal medicine	undisclosed (cognitive enhancer)	not yet recruiting NCT04249869	II
Yangxue Qingnao pills	blood circulation; traditional Chinese medicine, composed of Angelicae Sinensis Radix, Chuanxiong Rhizoma, Paeoniae Radix Alba, Rhemannia glutinosa, Uncaria macrophylla Wall, Caulis spatholobi, Spica Prunellae, Catsia tora Linn, Mater Margarita, Corydalis ambigua and Asarum sieboldii	improve cerebral blood flow and brain nourishment	not yet recruiting NCT04780399	II
BDPP (bioactive dietary polyphenol preparation)	metabolism and bioenergetics, amyloid; combination of grape seed polyphenolic extract and resveratrol	prevents amyloid and tau aggregation	recruiting NCT02502253	I
Pomace olive oil	prevent inflammation; lipophilic minor components	consumption of olive oil reduces activation of microglia by TRL (triglyceride-rich lipoproteins)	completed NCT04559828	not applicable
Extra virgin olive oil “Coratina”	anti-amyloid; biophenol	improve cerebral performance	not yet recruiting NCT04229186	not applicable

2. Natural Products from Non-Algal Sources

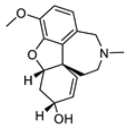
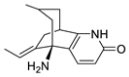
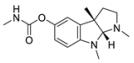
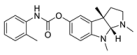
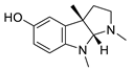
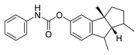
2.1. Esterase Inhibitors

Galantamine. The advanced stage of AD is characterized by a widespread loss of cholinergic basal forebrain neurons [28]. The inhibition of the cholinesterases acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) leads to an increased acetylcholine level in the brain [29][30].

Galantamine [(4aS,6R,8aS)-5,6,9,10,11,12-Hexahydro-3-methoxy-11-methyl-4aH-[1] benzofuro [3a,3,2-ef] [2]benzazepine-6-ol] (**Table 2**) was first isolated in 1947 from the common snowdrop *Galanthus nivalis* [31][32]. Later, it was also isolated from *Galanthus woronowii* and the red spider lily, *Lycoris radiata* [32][33][34]. In 1960, it was found that galantamine is an inhibitor of cholinesterase [35]. Due to its activity toward muscle AChE, it was used to treat myopathies, post polio paralytic conditions and neuromuscular blockades after anesthesia [36][37]. In 1977 it was reported that galantamine can reverse the acute anticholinergic syndrome induced by scopolamine [38]. The chemical synthesis of galantamine was upscaled and optimized so that quantities of up to 100 kg could be produced under GMP-conditions in the 1990s [39]. Since 2000, Galantamine has been approved in the USA and Europe for the treatment of the symptoms of

AD (for example as Reminyl®). It is a reversible, competitive AChE inhibitor and an allosteric modulator of the nicotinic acetylcholine receptors (nAChRs) [40] modulating the α4β2 and α7 nicotinic receptors [41][42][43]. In Phase III studies, it showed side effects like nausea or vomiting with mild severity, mostly during the dose-escalation phase [44].

Table 2. Chemical structures and characteristics of esterase inhibitors.

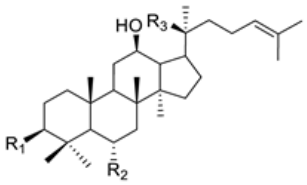
Name	Structure	Source	Characteristics	Ref.
galantamine		***Galanthus nivalis***	**reversible, competitive AChE inhibitor, allosteric modulator of nicotinic acetylcholine receptors, modulates α4β2 and α7 nicotinic receptors**	**[40][41][42][43]**
huperzine A		***Huperzia serrata***	**specific and reversible AChE inhibitor, protects cells against hydrogen peroxide, β-amyloid toxicity, glutamate, ischemia and staurosporine-induced cytotoxicity and apoptosis**	**[45][46][47][48][49]**
physostigmine		***Physostigma venenosum, Streptomyces pseudogriseolus***	**AChE inhibitor**	**[50]**
tolserine		**Physostigmine derivative**	**AChE inhibitor**	**[51]**
eseroline		**Physostigmine derivative**	**AChE inhibitor**	**[51]**
phenserine		**Physostigmine derivative**	**AChE inhibitor**	**[51]**

Huperzine A. Huperzine A, which is isolated from the Chinese club moss *Huperzia serrata,* is a specific and reversible AChE inhibitor [45]. It binds more tightly and specifically to AChE compared to other inhibitors such as physostigmine, galantamine, donepezil and tacrine [46][47][48]. The dissociation rate from the enzyme is very low [52][53]. The (+)-huperzine A enantiomer and the (−)-huperzine A enantiomer have similar neuroprotective properties, but the (+)-huperzine A enantiomer is 50-fold less potent in inhibiting AChE in an amyloid-β peptide model of toxicity [49]. In another study, the (+)-huperzine A and (−)-huperzine A showed similar results in protecting cells against Aβ toxicity [54]. The neuroprotective effects of huperzine A are created by its potential to protect cells against hydrogen peroxide, β-amyloid toxicity, glutamate, ischemia and staurosporine-induced cytotoxicity and apoptosis [46][47][48][54]. Toxicological studies in different animal species and clinical trials in China have shown that huperzine A has less cholinergic side effects than other AChE inhibitors [47][55][56][57][58]. The most common side effect of huperzine A is nausea [58]. Also, huperzine A improved the memory of aged subjects and patients with AD [56][58]. It is available as a dietary supplement.

2.2. Plant Natural Products with Antioxidant and Anti-Inflammatory Efficacy

Ginseng. Extracts of the rhizome of the plant *Panax ginseng* have been used in Asia for thousands of years to treat different diseases including neurological disorders [59].The extract of the plant has several active compounds, ginsenosides, ginseng polysaccharides, volatile oils, peptides and amino acids [60][61]. There are several ginsenosides identified as useful in the treatment of neurodegenerative disease such as AD, PD and HD. The ginsenoside Rb1, Rg1, Rg2, Rg3, Re and Rh2 and Gintonin showed a beneficial effect on AD symptomatology; Rg1, Re and Rd in PD and Ginseng total saponins and Ginsenosides in HD [62][63][64]. The ginsenosides are classified in two groups: the 20(*S*)-protopanaxadiol (PPD) group and the 20(*S*)-protopanaxtriol (PPT) group. Rb1, Rc, Rb2, Rd and Rg3 belong to the 20(*S*)-protopanaxadiol group, while Rg1, Re, Rg2 and Rh1 belong to the 20(*S*)-protopanaxtriol group [65]. The chemical structure of the ginsenosides is shown in **Table 3**. Ginsenosides prevent neuroinflammation and oxidative stress. They also have a positive influence on the brain function by apparently diverse mechanisms [66][67][68][69].

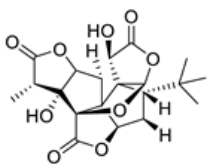
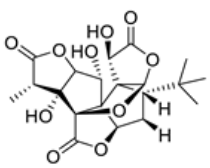
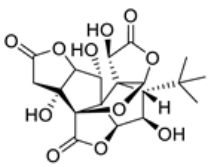
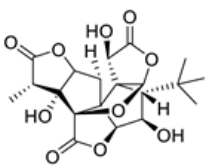
Table 3. Chemical structures of ginsenosides [70].

Structure	Ginsenoside		R1	R2	R3
	PPD-type	Rb1	-O-Glc-Glc	-H	-O-Glc-Glc
		Rb2	-O-Glc-Glc	-H	-O-Glc-Ara(p)
		Rc	-O-Glc-Glc	-H	-O-Glc-Ara(f)
		Rd	-O-Glc-Glc	-H	-O-Glc
		Rg3	-O-Glc-Glc	-H	-OH
		F2	-O-Glc	-H	-O-Glc
		Rh2	-O-Glc	-H	-OH
		Compound K	-OH	-H	-O-Glc
		PPD	-OH	-H	-OH
	PPT-type	Re	-OH	-O-Glc-Rha	-O-Glc
		Rf	-OH	-O-Glc-Glc	-OH
		Rg1	-OH	-O-Glc	-O-Glc
		Rg2	-OH	-O-Glc-Rha	-OH
		Rh1	-OH	-O-Glc	-OH
		F1	-OH	-OH	-O-Glc
		PPT	-OH	-OH	-OH

For instance, the ginsenoside Rb1 and Rg1 protects spinal cord neurons from oxidative stress induced by H_2O_2 and excitotoxicity induced by glutamate and kainic acid with an optimal dose of 20–40 µM [59]. In an AD mouse model, Rg1 showed neuroprotective effects through improved cognition and amyloid pathology, modulation of the amyloid precursor protein process and activation of the hippocampal-dependent protein kinase/hippocampal-respond element-binding protein (PKA/CREB) signalling [71]. The ginsenoside Rb1 has several neuroprotective effects. It promotes neural growth, the expression of growth-promoting kinases and helps prevent their levels from decreasing and has played the role of an antiapoptotic agent after Aβ-induced apoptosis in an AD cell model [72][73]. Furthermore, Rb1 seemed to protect the brain from Aluminium-induced toxicity. It reversed the glycogen synthase kinase 3β and the protein phosphates level and thereby reduced tau phosphorylation [74].

Ginkgo biloba. Ginkgo biloba is the oldest living tree species in the world. The standardized Ginkgo biloba extract (GBE) from the dried leaves has neuroprotective effects and is used for the treatment of memory impairment and dementia [75][76]. GBE contains 6% terpenoids, 24% flavonoid glycosides and 5–10% organic acids [77]. The terpenoids include the ginkgolides A, B, C and J (**Table 4**). Flavonoids and terpenoids are considered to be the pharmacologically active compounds of GBE [78][79]. GBE was shown to reduce the expression of transgenic human amyloid precursor protein expression in mouse brain [80] and to compensate for changes in brain glucose metabolism induced by streptozotocin treatment in rat brain [81].

Table 4. Chemical structures of ginkgolides [78][79] from GBE extracts. GBE has been described to reduce APP expression and to improve cognitive function [80][82][83][84][85].

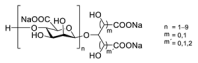
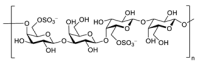
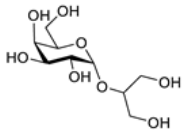
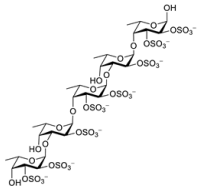
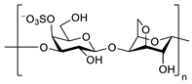
Name	Structure	Name	Structure
ginkgolide A		ginkgolide B	
ginkgolide C		ginkgolide J	

3. Neuroprotective Algal Metabolites

3.1. Carbohydrates

Sodium oligomannate is a mixture of oligosaccharides obtained by the depolymerization of alginate from marine brown algae, followed by its oxidation to oligosaccharides [86][87] (**Table 5**). In November 2019, it was conditionally approved for the treatment of mild to moderate AD in China [88]. The patients treated with sodium oligomannate showed significant improvement in ADAS-cog12 score compared to the placebo group in a phase II study, whereby the treated group did not show significantly more adverse reactions than the placebo group [89]. The mechanism of action is not completely understood. Studies in mice suggest that oligomannate might act via decreasing neuroinflammation by remodeling gut microbiota and balancing the amino acid metabolism, especially phenylalanine and isoleucine [87].

Table 5. Chemical structures and neuroprotective characteristics of carbohydrates from algae.

Name	Structure	Source	Characteristics	Ref.
GV971 (Sodium oligomannate)		**marine brown algae**	**might act via decreasing neuroinflammation by remodeling gut microbiota and balancing the amino acid metabolism, especially phenylalanine and isoleucine**	**[87]**
porphyran		***Porphyra yezoensis***	**superoxide anion and hydroxyl radical scavenging activity**	**[90]**
floridoside		***Laurencia undulata***	**anti-inflammatory activity, inhibits the production of NO and ROS, downregulates iNOS and COX-2**	**[91]**
fucoidan		***Ascophyllum nodosum***	**inhibits ROS and TNF-α release, reduces NO, PGE2, COX-2, iNOS, MCP-1, TNF-α and IL-1β**	**[92] [93]**
κ-carrageenan			**inhibits TNF-α secretion**	**[94]**

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