Candidate Drugs for Alzheimer's Disease

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Alzheimer's disease (AD; progressive neurodegenerative disorder) is associated with cognitive and functional impairment with accompanying neuropsychiatric symptoms. The available pharmacological treatment is of a symptomatic nature and, as such, it does not modify the cause of AD. The currently used drugs to enhance cognition include an N-methyl-d-aspartate receptor antagonist (memantine) and cholinesterase inhibitors. The PUBMED, Medical Subject Heading and Clinical Trials databases were used for searching relevant data. Novel treatments are focused on already approved drugs for other conditions and also searching for innovative drugs encompassing investigational compounds.

Keywords: Alzheimer's disease ; antidepressants ; antidiabetics ; bexarotene ; cognitive ; curcumin ; myricetin ; resveratrol

1. Introduction

Alzheimer's disease (AD) is a neurodegenerative, debilitating, and fatal disease characterized by progressive cognitive impairment, behavioral disorders, and loss of function in daily life. AD is the most common cause of dementia, accounting for 50–70% of dementia cases worldwide [1]. The 2018 World Alzheimer's Disease Report shows that 50 million people worldwide have dementia [2].

AD has several neuropathological hallmarks, including the deposition of β-amyloid (Aβ) peptides in the extracellular matrix between neurons (known as amyloid plaques), the intracellular formation of neurofibrillary tangles arising from the accumulation of hyperphosphorylated tau protein in neurons, neuronal loss, neuroinflammation, and oxidative stress [3][4][5]. It has been reported that amyloid accumulation in brain tissue can be observed up to 10–20 years before the onset of clinical symptoms [6]. Risk factors for AD include age, family history, apolipoprotein E_4 (apoE) genotype, diabetes, hypertension, obesity, hypercholesterolemia, traumatic brain injury, and low education level [7]. Mutations in the genes presenilin 1, presenilin 2, and amyloid precursor protein (*APP*) are associated with early-onset autosomal-dominant AD [7]. At present, only symptomatic but not disease-modifying drug treatments are available.

2. APOE and Alzheimer's Disease

APOE is a gene that encodes apoE, having three different isoforms (E2, E3 and E4). The E3 allele is the most common form in the population and accounts for approximately 80% of allelic variation, while the frequency of E2 and E4 is less than 7% and 15%, respectively. ApoE E4 is a recognized risk factor for AD, in contrast to apoE E2, which has a protective effect and significantly reduces the risk of developing late-onset AD [8][9]. In vivo studies in genetically modified rodent models (have a human APOE knock-in background) have attempted approaches to improve phenotypes characteristic of AD patients. Unfortunately, although a lot of research in this direction has started, much less continues [8].

One of the treatment suggestions was to increase the concentration and lipidation of APOE in the brain. It was observed that deletion of the ABCA1 gene induced poor apoE lipidation and increased Aβ plaque burden. On the other hand, when ABCA1 is overexpressed, a reduction in Aβ accumulation is noted. Stimulation of the retinoid X receptor induces the expression of ABCA1 as well as ABCG1 [10][11].

Bexarotene, a drug used in cancer therapy, is a retinoid X receptor agonist [12]. Recently, the US Food and Drug Administration approved it as a drug for use in patients with cutaneous T-cell lymphoma [8]. More recent published data also revealed the effect of bexarotene on an intensive reduction in Aβ plaques and improvement of cognitive function in three genetically modified mouse models of AD (APPswe/PSEN1dE9—at a dose of 100 mg/kg for 3, 7, 14 or 90 days; APP/PS1-21—at a dose of 100 mg/kg for 20 days; and Tg2576—at a dose of 100 mg/kg for 3 or 7 days). In all three models, the drug was administered orally. The results point to reduced soluble or insoluble Aβ and Aβ plaques, improved memory and increased HDL levels, most likely related to increased ATP-binding cassette transporter (a product of ABCA1 gene), ATP-binding cassette sub-family G member 1 (a protein encoded by the ABCG1 gene) expression and apoE lipidation [11]. Similar results were obtained with a bexarotene dose of 100 mg/kg for 30 days in very old triple transgenic AD mice (3xTg-AD mice). The authors demonstrated improved cognitive function, as well as baseline synaptic transmission and synaptic plasticity, reduced astrogliosis and reactive microglia in both the cortex and hippocampus. In addition, increased expression of APOE was found, but limited to CA1 hippocampal subfield [13].

In contrast, Fitz et al. [14], treating APP/PS1ΔE9 mice, obtained similar effects on the reduction in memory deficits and significant decrease in interstitial fluid Aβ, but no effect on amyloid deposition was found. Similarly, Veeraraghavalu et al. [15] showed only a reduction in soluble Aβ40 levels in mice, but no effect of the drug on the plaque burden that exhibits Aβ amyloidosis.

Clinical trials evaluating the effects of bexarotene have been conducted. Ghosal et al. [16] conducted a randomized double-blind, placebo-controlled trial (proof-of-mechanism trial, phase Ib) involving healthy, young (12 participants, mean age approximately 30–32 years) subjects with the APOE ε3/ε3 genotype. Volunteers received orally for 3 days a placebo or 225 mg of bexarotene twice daily (at 9 a.m. and 7 p.m.). After analysis of the results, the drug was found in plasma at concentrations of 1 to 2 μM, with very low concentrations in cerebrospinal fluid (CSF) (in nM). Furthermore, bexarotene increased apoE concentrations by 25%, and no changes in Aβ peptide metabolism were demonstrated [16]. Among the side effects, increases in triglycerides (three people—over 200 mg/dl) and total cholesterol (one person—over 200 mg/kg) were observed. In addition, thyroid dysfunction and increases in liver enzymes were observed (two people each), as well as isolated cases of nausea, headache or rash. All adverse effects were judged to be non-significant, which spontaneously resolved by the end of the study [16].

Cummings et al. [17] conducted a double-blind, placebo-controlled, proof-of-concept trial in which patients with moderate AD were administered 300 mg of bexarotene or placebo for 4 weeks. The results show no change in amyloid burden in apoE4 carriers, while in apoE4 noncarriers, a significant association was observed between increased serum Aβ1-42 and reductions in brain amyloid. Among side effects, a large increase in triglycerides (more than 200 mg/dL) in most patients and an increase in total cholesterol of more than 300 mg/dL in half of the subjects, representing a high risk of cardiovascular disease, as well as isolated cases of symptoms such as delusions, dizziness, dry cough, and toe blister or diverticulitis, were demonstrated [17].

Another candidate for the treatment of patients with AD is ADCS-6253, a peptide, a C-terminal apoE derivative, which directly activates ABCA1 expression, as demonstrated in vitro. In vivo studies have been performed with young genetically modified mouse models (APOE3 knock-in and APOE4 knock-in) [17]. In APOE4 knock-in mice, an increase in apoE4 lipidation AND ABCA1 expression and "*a reversal of the apoE4-driven Aβ42 accumulation and tau hyperphosphorylation in hippocampal neurons, as well as of the synaptic impairments and cognitive deficits*" were observed. The above changes were not observed in APOE3 knock-in mice [18].

The available data suggest that apoE4 facilitates Aβ deposition, but the exact mechanisms are not known. Hori et al. [19] conducted a study in which injected Aβ protofibrils induced Aβ deposition in the brain of APP transgenic mice, demonstrating a correlation of Aβ protofibrils and Aβ accumulation. In the next step, Aβ protofibrils were injected with apoE3, resulting in a reduction in Aβ deposition. On the other hand, when combined with apoE4, no such effect was observed [19]. In vitro studies indicate that conversion of Aβ protofibrils to fibrils occurs faster in correlation with apoE4 and are more stable than in combination with apoE2 or apoE3 [19]. This explains why 2.7 times lower levels of Aβ oligomers are found in the brains of apoE3 AD patients [20]. An interesting idea then is to impede the interaction of apoE4 and Aβ [8] [21]. Studies have been conducted in mouse models of AD disease in this direction using monoclonal anti-apoE antibodies as well as small molecules that act as Aβ mimetics [19][20].

Liao et al. [22] showed that administration of HJ6.3, a monoclonal antibody against apoE (at a dose of 10 mg/kg/week for 21 weeks) to APPswe/PS1ΔE9 (APP/PS1) mice, decreased soluble and insoluble Aβ and microglia, slightly decreased brain Aβ plaques and increased plasma Aβ. In addition, a slight improvement in spatial learning performance was observed, but no effect of the antibody on total blood cholesterol or cerebral amyloid angiopathy was noted. To evaluate the mechanisms of immunotherapy, HJ6.3 antibodies were applied to the surface of the cerebral cortex. The results of imaging studies (over a period of 2 weeks) show that the antibody prevented the formation of new Aβ deposits, reduced the growth of existing deposits, and even the occasional removal of amyloid plaques was observed [22]. Another antibody was also tested—"*anti-human apoE antibody, anti-human apoE 4 (HAE-4), that specifically recognizes human apoE4 and apoE3 and preferentially binds nonlipidated, aggregated apoE over the lipidated apoE found in circulation*" in APPPS1-21 x APOE4 knock-in mice. HAE-4 (administered centrally or by peripheral injection) reduced the accumulation of Aβ in the brain [23].

Krishnamurthy et al. investigated the effect (over a period of 40 days) of an apoE mimetic CN-105 in APP/PS1/APOETR mice [24]. Analysis of the results indicated that the mimetic reduced soluble Aβ and Aβ plaques as well as improved memory. In addition, the authors provided evidence that better effects were obtained when the mimetic was applied at an early stage of the disease [24]. This compound (at doses of 0.1, 0.5, or 1 mg/kg) will also be tested for its effects in postoperative dementia in a randomized, double-blind, placebo-controlled trial (phase 2) in adults (aged ≥ 60). The study is at the patient recruitment stage (NCT03802396).

Since apoE is undeniably responsible for the accumulation of Aβ in brains, there has been a proposal to reduce apoE levels. In vivo studies have shown that apoE genetic deletion or haploinsufficiency in fact reduced Aβ accumulation [25] and tau-induced neurodegeneration in tauopathy [26]. Another way to decrease Aβ is to increase the expression of apoE

receptors, in that increased expression of low-density lipoprotein receptor (LDLR) results in decreased deposition of amyloid plaques in the brain. This is because LDLR increases the transport of Aβ from the brain into the blood [27]. Another option to lower brain apoE levels is to silence APOE expression with specific antisense oligonucleotides. Studies were performed on mouse models of AD, including APPPS1-21 × APOE3 knock-in mouse and APPPS1-21 × APOE4 knock-in mice. The experiments showed a reduction in soluble apoE concentrations by half with anti-APOE antisense oligonucleotides by approximately 50%. Such a change contributed to a reduction in Aβ concentrations (both soluble and insoluble Aβ forms), Aβ plaques and dystrophic neurites. Similar effects were obtained when the compound was administered intracerebrally at birth as well as early in the course of the disease (approximately 6-week-old mice) [28].

3. Insulin and Other Antidiabetics as a Potential Therapy for Alzheimer's Disease

Patients with Alzheimer's disease often have glucose metabolism abnormalities leading to type 2 diabetes [29].

Thus, another attempt to treat AD is the use of intranasal insulin treatment. Some studies have shown that acute and prolonged intranasal insulin administration alleviates AD neuropathology. Significant improvements were found in memory performance and synaptic plasticity, while increases in regional glucose uptake were also observed [30].

Previous studies have shown a close association between diabetes, insulin resistance and mild cognitive and memory impairment. Additionally, it is noted that patients with impaired brain energy utilization have a significantly higher risk of AD. This is because diabetes attenuates the amyloid precursor protein metabolism, which increases the deposition of β-amyloid (as a consequence of abnormal removal of Aβ plaques), increases tau protein phosphorylation and increases glycogen synthase kinase 3β levels [31][32]. In addition, sustained chronically high peripheral insulin levels interfere with insulin transport across the blood–brain barrier. This in turn alters insulin signaling in the brain, resulting in anti-apoptotic effects [33]

Additionally, in patients with high insulin levels, increased levels of inflammatory factors, oxidative stress and mitochondrial dysfunction were observed. In addition, neuroimaging studies showed damage to cerebral vessels [31][32][33]. The existence of common pathways in the pathomechanism is also important evidence for the coexistence of the relationship between diabetes and AD, including enzymatic degradation of Aβ, forehead box protein O1 (FOXO) signaling or insulin signaling [34].

Vandal et al. [35] performed experiments on a genetic mouse model of 3xTg-AD. This model (animal model of type 2 diabetes) is characterized by hyperinsulinemia and hyperglycemia (hippocampus in particular). In addition, animals were found to have low CSF-insulin levels and low insulin-mediated glucose disposal. The use of a high-fat diet in this mouse model resulted in "*cerebral expression of human AD transgenes led to peripheral glucose intolerance, associated with pancreatic human Aβ accumulation*". In addition, increased glucose intolerance, elevated brain soluble Aβ, as well as memory impairment in rodents were observed. In a further step, it was shown that a single insulin (3.8 units/kg of human insulin) injection reversed the impairment caused by a high-fat diet, which the authors explained is most likely due to changes in Aβ production and/or clearance [35].

Other studies have shown that even systemic administration of exogenous insulin can contribute to the onset of memory impairment and neuronal dysfunction. On the other hand, there are studies indicating that the induced hyperinsulinemia to uphold the euglycemia can improve memory, which has been shown in the healthy brain as well as in AD. In animal studies, it has also been demonstrated that an acute increase in blood glucose levels can improve memory, which is related, among other things, to an increase in cholinergic activity. It should be remembered, however, that in the case of chronic hyperglycemia, as occurs in untreated/poorly treated diabetes, the effects are the opposite and cause cognitive impairment, particularly in older people [36].

The available literature shows that the way in which insulin is delivered to the body is also important for its action in AD patients [37]. Weinstein et al. [38] reported that peripheral insulin use increases the risk of dementia by 50%. These authors attributed this effect to the hypoglycemic action of insulin and the brain dysfunction associated with hypoglycemia [38].

On the other hand, other studies indicated that the use of intranasal insulin reduces cognitive impairment and the risk of developing dementia, as shown by Maimaiti et al. [39]. The authors evaluated the effects of insulin administration in two forms: short-acting insulin lispro (Humalog—the dose received 1–3 h prior to memory testing) or long-acting insulin detemir (Levemir—for 8–11 days) on cognitive function in ageing F344 rats. Additionally, insulin's effects on the Ca^{2+}-dependent hippocampal after hyperpolarization (AHP), a neurophysiological marker that increases in aging animals with memory impairment, were investigated. The results clearly indicate that the use of low-dose insulin (0.0715 IU/day/rat) in both treatment regimens reduced AHP and overall, significant improvements in memory tasks were evident [39].

It has also been reported that the effect of intranasal insulin may depend not only on the treatment regimen (acute vs. subchronic), but even on the sex and age of the patient and the APOE genotype [40].

Reger et al. [41] studied the effect of intranasal insulin in patients with different APOE genotypes—with (epsilon4+) and without (epsilon4-) the APOE- epsilon4 allele. Patients (memory-impaired adults with AD or amnestic mild cognitive impairment vs. control group) were given five intranasal treatment conditions consisting of insulin (10, 20, 40, or 60 IU) or placebo. Behavioral tests were performed after 15 min and blood was drawn after 45 min. The results show improvement in "*verbal memory in memory-impaired epsilon4- adults, with performance generally peaking at 20 IU. In contrast, memory-impaired epsilon4+ subjects demonstrated a relative decline in verbal memory*". Changes in plasma amyloid-beta levels were also observed for memory-impaired subjects and normal controls, effects that again differed by APOE genotype. Intranasal insulin administration had no effect on insulin levels and plasma glucose [41].

Another research group has shown that acute intranasal insulin (40 I.U) improves odor-induced spatial memory. The study was conducted in a double-blind, placebo-controlled, counterbalanced within-subject design in young men. [42].

Data are also available that state no effect of such therapy. In recent months, the first multicenter, randomized, double-blind (phase 2/3) clinical trial evaluating the feasibility, safety and efficacy of intranasal insulin in the treatment of patients (ages 55 to 85) with mild cognitive impairment and dementia in AD was released. Participants received 40 IU of insulin (administered with 2 intranasal delivery devices) or placebo daily for 12 months followed by a 6-month open-label extension phase. However, the results were not as expected. The first device used for 49 patients to administer insulin had inconsistent reliability, so only the second device was used for the remaining 240 participants. In this clinical trial, no cognitive and functional benefits were observed with intranasal insulin treatment over. There were also no changes in CSF biomarker levels. The only difference shown between the study group and placebo was a slight reduction in hippocampal volume, but this change is of unclear clinical significance [43].

Another research group carried out a single-center, randomized, double-blind, placebo-controlled study to evaluate the efficacy of intranasal glulisine—rapid-acting insulin (at a dose of 20 IU twice daily). The study group were subjects with amnestic mild cognitive impairment or mild probable AD. The results show, as in previous studies, that glulisine did not affect plasma insulin or glucose levels. There was also no effect of the drug on patients' cognitive function and memory [44].

Summing up intranasal insuline, its clinical use seems safe but, as suggested by Hallschmid [45], more data from broad clinical trials are required in order to compare responses from female and male patients and optimize delivery devices.

Batista et al. [46] investigated the effects of liraglutide, a glucagon-like peptide-1 analog, in different experimental models of AD (hippocampal cell cultures, mouse model and the infusion of amyloid-β oligomers (AβOs) into the lateral cerebral ventricle of non-human primates (NHPs)). In the mouse model, memory impairment was induced by AβOs (at a dose of 10 pmol) injected into the lateral ventricle. AβOs "*are small, diffusible aggregates of the Aβ peptide that accumulate in AD brains*". The presence of AβOs causes changes similar to those seen in AD, including neuronal tau hyperphosphorylation, increased oxidative stress, and inhibition of synaptic plasticity, and this gives a clinical picture in the form of memory and cognitive dysfunction. Furthermore, impaired insulin signaling induces re-entry into the neuronal cell cycle, resulting in neuronal death [46][47][48][49]. In turn, in the case of NHPs, AβOs induce changes such as brain inflammation, loss of synapses, as well as tau hyperphosphorylation and tangle formation [46][50]. The authors obtained favorable results after liraglutide was administered (i.p) at a dose of 25 nmol/kg for 7 days. In vitro studies (hippocampal neuronal cultures) have shown that liraglutide has neuroprotective effects through activation of the protein kinase A (PKA) signaling pathway. Treatment with liraglutide in a third research model (NHPs) reduced AD-related insulin receptor, synaptic and tau pathologies in specific brain regions [46]. Another drug being investigated is metformin. However, studies to date are quite controversial. Some of the available data indicate a protective effect of the drug (especially with long-term therapy) by slowing the rate of cognitive decline [51]. Other studies show no association between metformin use and cognitive impairment, similar to that of sulfonylurea [38][52]. Another drug from this group, pioglitazone, was reported in three studies to improve cognitive performance in diabetic patients with AD; however, two studies with the use of this drug provided negative data [53].

4. Selective Serotonin Reuptake Inhibitors (SSRI)

There are numerous reports that antidepressants from the SSRI group exhibit neuroprotective effects with a diverse mechanism of action. Preclinical and clinical studies indicate beneficial effects on cognitive function [54][55][56][57][58][59][60][61]. Furthermore, literature data indicate that SSRIs "*increase neurotrophic factors including brain-derived neurotrophic factor, promote neurogenesis in the hippocampus, and reduce levels of toxic Aβ*" [62]. There are also reports of properties to decrease Aβ generation and plaque load. Therefore, due to its interesting properties, the SSRI group of drugs is increasingly becoming the focus of research into the treatment of patients with AD. An additional aspect is the fact that depression itself represents an increased risk of AD, and therefore the applied treatment could significantly delay the progression to AD [60].

4.1. Citalopram

Citalopram is a selective serotonin reuptake inhibitor that, according to scientific reports, may have neuroprotective effects in AD patients. Reddy et al. [54] evaluated the effect of citalopram on mitochondrial dysfunction in immortalized mouse primary hippocampal cells (HT22) expressing APP (SWI/IND) mutations. Exposed cells showed "*reduced levels of the mitochondrial fission genes, increased fusion, biogenesis, autophagy, mitophagy, and synaptic genes*" compared to the control group, which showed increased mRNA levels of mitochondrial fission genes and changes indicative of impaired autophagy and mitophagy. Furthermore, it was shown that cells in the experimental group had an increased number of mitochondria and cell survival rates were increased. These results may suggest a protective role for citalopram against damage associated with Aβ accumulation in AD patients [54]. Clinical trials evaluating the effects of citalopram have also been conducted. The first of these, the Citalopram for Agitation in Alzheimer Disease Study, was a randomized, placebo-controlled, double-blind, parallel group trial in which participants were patients with probable AD and clinically significant agitation. Study participants received citalopram or placebo for 9 weeks. Dosing started at 10 mg/day and was titrated to 30 mg/day over 3 weeks. The results show that the drug reduced patients' agitation, but caused cognitive impairment and cardiovascular side effects, which limits its practical use in patient therapy [55].

Another clinical study evaluated the effect of citalopram on, among other things, cognitive function in patients with moderate AD and clinically significant behavioral and psychological symptoms of dementia. Study participants (study group) received memantine (at the dose of 20 mg/day) plus citalopram (starting at the dose of 10 mg/day to titrated to 30 mg/day over 2 weeks). The control group received memantine (at the dose of 20 mg/day) plus placebo. The whole study lasted for 12 weeks. Analysis of the results showed that the overall neuropsychiatric scores of the patients after treatment were significantly lower compared to the pre-treatment scores in both groups. However, indices assessing symptoms such as apathy, dysphoria and anxiety obtained lower values. Among the adverse effects, as in the previous study, only QTc interval prolongation was found in two patients treated with the combination with citalopram at a dose of 30 mg/day. In conclusion, the drug combination can significantly improve cognitive function as well as reduce behavioral and psychological symptoms in patients with moderate AD, but a dose <30 mg/day is recommended [56].

4.2. Escitalopram

Another drug being considered as a candidate for the treatment of AD is escitalopram, the most specific selective serotonin reuptake inhibitor [57].

The authors evaluated the effect of chronic administration of the drug on brain interstitial fluid Aβ and Aβ plaque size in the amyloid precursor protein (APP)/presenilin 1 mouse model of AD (APP/PS1+/− hemizygous mice to wild-type C3H/B6 mice). Animals received the drug at doses of 2.5 or 5 mg/kg or vehicle (2% DMSO in normal saline), injected intraperitoneally for 28 days or in a single dose. Analysis of the results showed that escitalopram administered in the acute model reduced brain interstitial fluid Aβ by 25% by increasing α-secretase cleavage of APP. Interesting results were also obtained in the chronic model, with a significant reduction in plaque load. At a dose of 2.5 mg/kg, a 28% reduction was achieved, whereas at a dose of 5 mg/kg, the reduction was 34%. Furthermore, the authors found that escitalopram at a dose of 5 mg/kg, although not removing existing plaques, stopped their growth [57].

Sheline et al. [58] recently published the results of a double-blind placebo-controlled clinical trial on escitalopram. The study was conducted in healthy older volunteers who were then allocated to the following groups: placebo, 20 mg escitalopram × 2 weeks, 20 mg escitalopram × 8 weeks, or 30 mg escitalopram × 8 weeks. Both before and after treatment, CSF samples were collected from participants. Analysis of the results showed an overall 9.4% greater reduction in CSF Aβ42, which may suggest an interesting therapeutic option in studies involving AD patients [58].

Among the new data, there are also reports that escitalopram may affect tau hyperphosphorylation. In vitro studies have shown that exposure of human embryonic kidney HEK293/tau441 cells (were pretreated with 4 μM of forskolin for 2 h) to the antidepressant (at concentrations of 0, 5, 10, 20, 40, 80 μM) for 22 h, "*protect tau from hyperphosphorylation induced by pharmacological activation PKA at a dose of 20, 40, and 80 μM in vitro*" [63].

Similar results were obtained by another group [64] who showed that escitalopram inhibited Aβ1-42-induced tau hyperphosphorylation in primary hippocampal neurons [63].

Wang et al. [62] evaluated a possible mechanism of action of this drug in aged P301L mice. Animals were intraperitoneally injected with escitalopram for a period of 4 weeks. In the next stage of the experiments, behavioral tests were performed and brain tissue was collected for analysis. Based on the results of the behavioral tests, no significant improvement in learning and memory processes was observed in the ageing mice. On the other hand, analysis of the brain tissue of the animals showed significantly decreased tau phosphorylation, which may suggest some protective properties of escitalopram [62].

5. Natural Products and Alzheimer's Disease

5.1. Resveratrol (RV)

RV (3,5,4′-trihydroxystilbene) is a compound from the polyphenol family that occurs naturally, mainly in black grapes, but also in blackberries or peanuts. There are many data on the promising properties of RV, including anticancer, antioxidant, cytoprotective, anti-inflammatory (including inhibition of microglial activation and the regulation of neuroinflammation), neuroprotective or anti-aging [65][66][67][68]. Previous studies indicate that RV may be a preventive or therapeutic option for patients with disorders such as insulin resistance, diabetes, lipid disorders and obesity or cardiovascular disease [69][70].

More recent studies indicate that RV has properties that may influence various pathomechanisms of AD. These range from molecular disorders, including processes responsible for the accumulation of abnormal proteins. One of the most important pathways whose disruption affects the development of AD is the ubiquitin-proteasome system, which is the primary proteolytic mechanism to aberrant clearance proteins, including Aβ and p-Tau [71]. Studies on AD models indicate that RV improves proteosome functionality in AD models. The polyphenol has been shown to increase Aβ clearance on the one hand, and to decrease protein production on the other by stimulating proteasomal proteolysis, as demonstrated in cell lines expressing APP695 and an Alzheimer's model of *Caenorhabditis elegans* [72][73][74].

Other studies have shown that RV reduces mitochondrial dysfunction. This compound has been observed to exhibit anti-inflammatory, antioxidant and anti-apoptotic properties [75]. Moreover, it induces autophagy and mitophagy, which was confirmed in an in vivo model [76].

In several in vivo studies, RV has been shown to inhibit ROS formation by suppressing nicotinamide adenine dinucleotide phosphate oxidase [77] and promoting the expression of antioxidant enzymes including superoxide dismutase, catalase, thioredoxin, and glutathione peroxidase [78].

Wang et al. [79] suggested that RV (at a dose of 200 mg/kg/day for 8 weeks) could be an option for AD-adjuvant therapy after human umbilical cord stem cell transplantation. This was due to the fact that RV stimulated factors such as the expression of brain-derived neurotrophic factor precursor, neuronal growth factor, and neurotrophin 3, which physiologically regulate the process of neurogenesis and also affect memory and learning [79]. Another research group, Simão et al. [80], injected RV intraperitoneally (at a dose of 30 mg/kg for 7 days) into rats. Then, the rodents were subjected to 10 min of four-vessel occlusion. Analysis of the results showed that RV prophylaxis reduced astrocyte and microglia activation and suppression of the inflammatory response in the hippocampus [80]. Moussa et al. [81] conducted a study evaluating the effect of RV in patients with mild-moderate AD. The authors showed that RV reduced pro-inflammatory factors and increased activation of microglia/macrophages was observed, which may indicate a neuroprotective effect through induction of long-term adaptive immunity. Again, analysis of the results revealed a significant reduction in brain volume (excluding CSF, brain stem, and cerebellum) and an increase in ventricular volume. The above changes did not correlate with greater cognitive decline. These changes are most likely related to the strong anti-inflammatory effect in the brain of the patients and the reduction in tissue swelling, as no potential neuronal loss was excluded. Furthermore, no significant side effects were found in the study, confirming the safety and good tolerability of the polyphenol [81].

Another group conducted a randomized, double-blind, placebo-controlled phase II study of resveratrol in the treatment of mild to moderate dementia due to AD [82][83]. They evaluated the safety and tolerability of RV and its effects on biomarkers of this neurodegenerative disease. Low nanomolar concentrations were determined in CSF and, by implication, in brain tissue, indicating the low bioavailability of oral RV. The next step was to determine the levels of anti-inflammatory and pro-inflammatory cytokines, chemokines and metalloproteinases in plasma and CSF samples. A significant, approximately 50% decrease in the level of metalloproteinase-9 in CSF was observed. Similar results were also obtained in other in vivo studies (Wistar rats) [84] and in the already mentioned clinical trial [81]. This is a particularly important result because metalloproteinase-9 affects BBB permeability and "*cleaves the vascular basal lamina and tight junctions in the neurovascular bed*" [83][85]. The above data may indicate that RV, by decreasing BBB permeability, may limit infiltration of inflammatory cells and mediators [83][85].

Other studies have shown that RV may modify the composition of the gut microbiota, which, as previously mentioned, may be important for preventive treatment of AD patients. There are few data on this topic, but it has been suggested that RV produce beneficial metabolic effects through interactions with the gut microbiota [86].

RV has been shown to be a potent activator of silent information regulator-1 (SIRT1). Sirtuins are "*deacetylases that link energy balance (NAD^+/NADH) to regulation of gene transcription*" [83]. It has been shown that reduced levels of SIRT1 expression exacerbate, in turn, over-expression of SIRT1 reduces Aβ production [76][87][88]. SIRT1 has also been shown to regulate other processes that may be involved in AD pathogenesis, i.e., cellular homeostasis, mitochondrial biogenesis, glucose metabolism as well as tissue insulin sensitivity, all of which directly or indirectly affect mitochondrial survival [89][90][91]. In addition, RV also increases cerebral blood flow, promotes neurogenesis and prevents hippocampal damage, and by acting on SIRT1, RV improves synaptic pathway plasticity and cognitive function [92].

In conclusion, RV affecting the regulation of so many processes including, but not limited to, antioxidant, anti-inflammatory, neuroprotective or anti-apoptotic effects may represent a promising, safe and well-tolerated therapeutic

option for AD patients.

5.2. Curcumin

Curcumin is the main polyphenol found in the turmeric curry (*Curcuma longa*). This compound has been found to have strong beneficial properties affecting cognitive function or memory, among other things. Furthermore, the polyphenol has been shown to pass through the BBB [93]. This may be related to the fact that the main biosynthetic pathway of turmeric begins with phenylalanine, which in turn is a precursor in the biosynthesis of flavonoids, compounds that have been proven to have therapeutic effects in neurodegenerative disorders [94][95]. In addition, curcumin and its derivatives are among the most bioactive components of saffron, which boasts many properties such as anti-inflammatory, antidiabetic, antiviral, antiproliferative, antioxidant, pro-apoptotic as well as anti-amyloidogenic effects [96][97].

More recent publications indicate that curcumin also affects Aβ plaque aggregation and tau protein hyperphosphorylation [93][98]. Small et al. [98] conducted a double-blind, placebo-controlled 18-month trial in which they evaluated the effects of curcumin (90 mg, twice daily) in adults without dementia. After analyzing the results, the authors found improvements in verbal and visual memory, attention in the study group, while imaging studies found significantly decreased tau accumulation in the amygdala and in brain regions modulating mood and memory [98].

Zheng et al. [99] evaluated the effect of applied curcumin (at doses of 150 or 300 mg/kg/day, intragastrically, for 60 days) in 5×FAD transgenic mice as an AD model. After the experiments, a significant decrease in Aβ production was demonstrated, which is most likely related to a decrease in β-secretase 1 expression [99][100]. Furthermore, a reduction in synaptic degradation, as well as improving spatial learning and memory impairment, was observed [99]. On the other hand, Xiong et al. [101] showed that curcumin affected the protein levels of presenilin-1 and glycogen synthase kinase-3β (GSK-3β). These proteins, together with protein in the γ-secretase complex, are involved in Aβ production. When the authors treated human neuroblastoma SHSY5Y cells with curcumin, a significant decrease in Aβ production was observed, as well as a decrease in PS-1 and GSK-3β proteins [101]. Similar promising results were obtained by another research group that evaluated the effects of curcumin (80mg/kg/day, orally, for 3 months) in a rat model of AD disease. Aβ accumulation in the hippocampus was shown to be reduced, cognitive function improved, and a significant reduction in apoptosis and oxidative stress processes was observed [102].

Another important finding is the demonstration that curcumin inhibits aggregation and promotes disaggregation of fibrillar Aβ, which has been confirmed in both in vivo and in vitro studies [93][103][104].

In addition, other studies have shown that curcumin regulates the insulin signaling pathway and thus affects cognitive dysfunction associated with the already mentioned insulin resistance. Feng et al. [105] tested the mechanism of curcumin action in a transgenic mouse model of AD. Curcumin was administered to the animals for a period of 6 months. After this period, it was shown that "*the hippocampal CA1 tissue expressed lower levels of insulin receptor and IRS-1, while the expression of PI3K, phosphorylated PI3K, Akt, and phosphorylated Akt increased compared to control*". The above data confirmed that curcumin stimulated the PI3K/Akt signaling pathway, resulting in reduced insulin resistance [105]. Other authors additionally showed that curcumin therapy improved memory in a rat model of diabetes [106].

Long-term studies have shown other equally important properties of the compound. The polyphenol lowers cholesterol, binds copper, inhibits neuroprotective effects by reducing the inflammatory activity of microglia, and has also been shown to increase the phagocytic activity of microglia [107]. The great variety of effects as well as the properties of curcumin allow multidirectional action and modification of the disease process [108]. Candidate drugs and compounds for the management of AD are shown in Table 1 and Table 2.

Table 1. Selected drugs and compounds as candidates for the management of Alzheimer's disease.

Compounds/Drugs	Probable Mechanism of Action	Type of Research			Effects	References
		Clinical Trials	Animal Model of Alzheimer's Disease	In Vitro		
Bexarotene	↓ ABCA1, ABCG1 expression ↑ ApoE lipidation		+		↓ Soluble or insoluble Aβ ↓ Aβ plaques Improved memory ↑ HDL levels	[11]
					Improved cognitive function Improved baseline synaptic transmission and synaptic plasticity ↓ Astrogliosis and reactive microglia in both cortex and hippocampus ↑ Expression of APOE (limited to CA1 hippocampal)	[13]
					↓ Memory deficits ↓ Interstitial fluid Aβ level No effect on amyloid deposition	[14]
					↓ Soluble Aβ40 No effect on plaque burden that exhibit Aβ amyloidosis	[15]
					↑ ApoE concentrations by 25% No effect on Aβ peptide metabolism Adverse reactions (non-significant)	[16]
		+			No effect on amyloid burden in apoE4 carriers Significant correlation between ↑ serum Aβ1-42 and ↓ in brain amyloid in apoE4 noncarriers, significant adverse reactions	[17]
ADCS-6253	Directly activates ABCA1 expression		+		APOE4 knock-in only ↑ ApoE4 lipidation ↑ ABCA1 expression ↓ Aβ and phosphorylated tau	[18]
HJ6.3–monoclonal antibody against apoE	Blocking apoE and Aβ interaction		+		↓ Soluble and insoluble Aβ ↓ Microglia ↓ Brain Aβ plaques ↑ Plasma Aβ ↓ Pro-inflammatory cytokines	[22]
HAE-4	Blocking apoE and Aβ interaction		+		↓ accumulation of Aβ in the brain	[23]
CN-105	ApoE mimetic		+		↓ Soluble Aβ ↓ Aβ plaques Improved memory	[24]
Anti-APOE antisense oligonucleotides	Silencing APOE		+		↓ Soluble APOE ↓ Soluble and insoluble Aβ ↓ Aβ plaques ↓ Dystrophic neurites	[28]
Intranasal insulin	Reduced AHP		+		↓ Cognitive impairment, improves memory in	[39]
		+			patients without (epsilon4-,) improves verbal memory	[41]

Compounds/Drugs	Probable Mechanism of Action	Type of Research			Effects	References
		Clinical Trials	Animal Model of Alzheimer's Disease	In Vitro		
Liraglutide	Glucagon-like peptide-1 analog Activation of protein kinase A (PKA) signaling pathway		+		Prevented the "*loss of brain insulin receptors and synapses, and reversed memory impairment*" induced by AβOs ↓ AD-related insulin receptor ↓ Synaptic and tau pathologies in specific brain regions	[46]
Probiotic therapy with the SLAB 51 cocktail	↑ Intestinal metabolites of the short-chain fatty acid type		+		Impede the formation of toxic soluble amyloid aggregates ↑ Cognitive function ↓ Aβ aggregates ↓ Brain injuries Partial restoration of altered neuronal proteolytic pathway	[109]
Dipeptides of tryptophan-tyrosine and tryptophan-methionine	Suppression of the inflammatory response of microglia ↑ Aβ phagocytosis		+		Improve cognitive function ↓ Hippocampal long-term potential deficit ↓ Memory impairment	[110]
Selenium or selenium with probiotic	Anti-inflammatory and antioxidant effects ↑ Total glutathione and the quantitative insulin sensitivity check index (QUICKI)	+			↓ High sensitivity C-reactive protein Improvement of lipidogram results ↑ Cognitive function	[111]
VEGF	Anti-inflammatory effects		+		Improved spatial learning and memory along with ↓ Aβ levels	[112]
				+	↑ cell viability ↓ ROS production Improved mitochondrial structure and function ↑Number of mitochondria ↑ Stimulation of mitochondrial biogenesis	
Kisspeptin	Activates the hypothalamic-pituitary-gonadal axis		+		↓ Memory impairment ↑ Levels of choline acetyltransferase ↓ Aβ accumulation	[113]
				+	Induces mitophagy and autophagy processes	[114]
			+		↑ Number of mitochondria ↑ Complex I activity ↑ ATP levels	
			+		↑ Spatial memory consolidation and retrieval Alleviated Aβ-induced memory impairment	[115]

Compounds/Drugs	Probable Mechanism of Action	Type of Research			Effects	References
		Clinical Trials	Animal Model of Alzheimer's Disease	In Vitro		
Citalopram	Selective serotonin reuptake inhibitor			+	↓ Levels of the mitochondrial fission genes ↑ Fusion, biogenesis, autophagy, mitophagy, and synaptic genes ↑ Number of mitochondria and cell survival rates	[54]
		+			↑ Cognitive impairment Cardiovascular side effects	[55]
Escitalopram	Selective serotonin reuptake inhibitor		+		↓ Aβ level in CSF ↓ Plaque load Inhibition of amyloid plaque growth	[57]
		+			↓ Aβ42 level in CSF	[58]
				+	Inhibition of tau hyperphosphorylation	[63][64]
Resveratrol	Stimulating proteasomal proteolysis Stimulating factors such as expression of brain-derived neurotrophic factor precursor, neuronal growth factor, and neurotrophin 3 Anti-inflammatory, antioxidant and anti-apoptotic action Induces autophagy and mitophagy Activator of silent information regulator-1 (SIRT1)		+		↓ Astrocyte and microglia activation and suppression of the inflammatory response in the hippocampus	[72][73][74][80]
		+			↓ MMP-9 levels in CSF ↓ Aβ40 levels in CSF ↑ Macrophage-derived chemokine, fibroblast growth factor-2 and interleukin (IL)-4 levels ↓ Plasma concentrations of pro-inflammatory mediators, including IL-1r4, IL-12P40, IL-12P70, and TNF-α ↓ Brain volume (excluding CSF, brain stem, and cerebellum) ↑ Ventricular volume	[81]
		+			↓ MMP-9 levels in CSF	[82][83]
Curcumin	Affects Aβ plaque aggregation and tau protein hyperphosphorylation Antioxidant, anti-inflammatory, antidiabetic, antiviral, antiproliferative, antioxidant, pro-apoptotic as well as anti-amyloidogenic action Regulates levels of PS-1 and GSK-3β	+			Improvements in verbal and visual memory ↓ Tau accumulation in the amygdala	[98]
			+		↓ Aβ production ↓ Synaptic degradation Improving spatial learning ↓ Memory impairment	[99]
			+		Improving cognitive function ↓ Apoptosis and oxidative stress processes ↓ Aβ accumulation	[102]
				+	↓ Aβ production	[101]

↓—decrease; ↑—increase; AHP—Ca^{2+}-dependent hippocampal after hyperpolarization; ATP—adenosine triphosphate; VEGF—Vascular endothelial growth factor; GSK-3β—glycogen synthase kinase-3β; PS-1—presenilin-1; MMP-9—matrix metalloproteinase-9.

Table 2. Candidate drugs in selected clinical trials.

Drugs/Substances	Dosage	Time-Dependent Therapy	Route of Administration	Diagnostic Tool/Tests	Patients	Referer
Bexarotene	225 mg or placebo twice daily	For 5 days	Oral	Applied "*stable isotope labeling kinetics (SILK-ApoE and SILK-Aβ) to measure the effect of bexarotene on the turnover rate of apoE and Aβ peptides and stable isotope spike absolute quantitation (SISAQ) to quantitate their concentrations*" in CSF	Healthy volunteers; aged 21 to 49 years (average 32 years old); with APOE ε3/ε3 genotype	[16]
Intranasal insulin	10, 20, 40, or 60 IU or placebo five times a day	Cognition was tested 15 min after treatment and blood was drawn immediately after insulin/placebo administration and 45 min after treatment	Intranasal	Verbal declarative memory measures (Story Recall and Hopkins Verbal Learning Test) A test of selective attention (Stroop Color-Word test) A visual working memory measure (Self-Ordered Pointing Task) A test of psychomotor processing speed (Digit Symbol)	Participants with (epsilon4+or epsilon4-) the APOE-epsilon4 allele with memory-impaired with either probable AD or amnestic MCI or multiple domain MCI with amnestic features (mean age of about 77) and cognitively normal older (epsilon4+or epsilon4-) as control groups (mean age of about 74)	[41]
Selenium or selenium with probiotic	Selenium (200 µg/day) plus probiotic (containing *Lactobacillus acidophilus, Bifidobacterium bifidum, and Bifidobacterium longum*) (2 × 109 CFU/day each), selenium (200 µg/day) or placebo	For 12 weeks	Oral	Cognition was tested using the Mini-Mental State Examination (MMSE) biomarkers of inflammation and oxidative stress, metabolic profiles and plasma glucose	Patients with AD (aged 55 to 100 years)	[111]
Citalopram	Dosing began at 10 mg/day with planned titration to 30 mg/day over 3 weeks based on response and tolerability or placebo	Psychosocial intervention plus either citalopram or placebo for 9 weeks	Oral	Assessment of agitation, hostility/uncooperativeness, and disinhibition—Neurobehavioral Rating Scale agitation subscale (NBRS-A) the modified Alzheimer Disease Cooperative Study-Clinical Global Impression of Change (mADCS-CGIC) Cohen-Mansfield Agitation Inventory (CMAI) Neuropsychiatric Inventory (NPI) Activities of daily living (ADLs) Caregiver distress; cognitive safety (MMSE)	Patients with probable AD and clinically significant agitation	[55]
Escitalopram	20 mg or 30 mg/day or placebo	For 2 or 8 weeks	Oral	Lumbar punctures to sample CSF levels before and after treatment	Cognitively normal older adults (aged 50 to 84 years)	[58]
Resveratrol	up to 1 g by mouth twice daily (500 mg once daily (with a dose escalation by 500-mg increments every 13 weeks, ending with 1000 mg twice daily)	For 52 weeks	Oral	"M*agnetic microspheres internally coded with two fluorescent dyes to measure markers of neurodegeneration (Millipore, Cat#: HNABTMAG-68K)*"	Patients with mild-moderate AD	[81][82]

Drugs/Substances	Dosage	Time-Dependent Therapy	Route of Administration	Diagnostic Tool/Tests	Patients	Referer
Curcumin	**90 mg or placebo twice daily—(180 mg/day)**	**for 18 months**	**Oral**	**Verbal (Buschke Selective Reminding Test [SRT]) Visual (Brief Visual Memory Test-Revised [BVMT-R]) Memory attention (Trail Making A) Assessment of amyloid and tau accumulation in the brain (2-(1-{6-[(2-[F-18]fluoroethyl)(methyl)amino]-2-naphthyl}ethylidene)malononitrile positron emission tomography (FDDNP-PET)**	**Middle-aged and older adults without dementia (age 51 to 84 years)**	[98]

CSF—cerebrospinal fluid; MCI—mild cognitive impairment.

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