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Alternative Approaches to the Search for Alzheimer's Disease Treatments

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Abstract: Clinical trials of drugs for Alzheimer's disease have called into question the role of amyloid in the disease. The reasons several drugs recently failed clinical trials for Alzheimer's disease are presented. An alternative approach with a traditional plant medicine is discussed. The pharmacology of the phytochemicals found in the plant medicine is provided.

Keywords: Alzheimer's disease; vaccines; secretase inhibitors; receptor for advanced glycation end products (RAGE) inhibitor; immunotherapy

1. Introduction

Alzheimer's disease (AD) is an age-related, chronic disease affecting more and more people as life expectancy continues to increase. There has been some speculation about prevention or slowing down the progression of AD with lifestyle changes [1]. Many pharmaceutical companies have adapted the classical approach in searching for new drugs to treat AD through different phases of clinical trials. In recent years, over a dozen different agents have gone through clinical trials and failed to show positive results or efficacy. The results of these trials and possible explanations for their failures are summarized in Table 1.

2. Major Challenges for Alzheimer's Disease (AD) Treatment

In spite of the long history of association between amyloid formation and the development of AD, it is still not proven whether amyloid formation is the cause or result of the disease. There are cases of seniors with amyloid plaques in the brain who were still free of AD. There are also subjects who phenotypically and clinically appear to have AD, but have virtually no amyloid in the brain, as visualized by Amyloid positron emission tomography (PET) imaging [2]. It is quite possible that biochemical changes leading to AD are similar to but not identical to the changes leading to amyloid formation. It takes longer to develop AD than to accumulate amyloid. Furthermore, vascular contributions to AD demonstrate that there is a very significant overlap between Vascular Cognitive Impairment Dementia (VCID) and Alzheimer's Dementia [3]. In fact, it is becoming more and more common now that patients suffer from a mixed dementia, VCID and AD together. Damage to the blood brain barrier induced by ceramide and visfatin could be an early change in the development of AD [4].

A paper by Masters' group examined 200 participants (145 healthy controls, 36 participants with mild cognitive impairment, and 19 participants with AD). The patients were assessed at enrolment and every 18 months for a mean follow-up of 3.8 years. At follow-up, 163 (82%) of the 200 participants

showed positive rates of β-amyloid accumulation. The importance of the paper is that it showed that β-amyloid deposition leading to AD takes 19.2 years (95%, confidence interval (CI) 16.8–22.5) and accumulates in an almost linear rate [5].

There are many changes at the molecular level which are affected by lifestyle, nutritional intake, and mental and physical stress. Over a long time period, these changes may lead to amyloid formation and/or AD. It is easier to prevent than to reverse these cumulative changes in the central nervous system (CNS). There are also important genetic factors such as apolipoproteinE4 and presinillin 1 genotypes which increase the risk of AD.

3. Alternative Natural Treatment of AD used in Folk Medicine

AD, senile dementia, or vascular dementia was known among California Indians before Europeans came to California [6]. These conditions were commonly treated with a native plant, *Heteromeles arbutifolia* (California holly, also called Toyon). Oral consumption of 5 g of the dried berries slows down the progression of AD and helps patients to have productive lives. We have recently studied the chemistry and safety of the plant [7]. Seven phytochemicals have been isolated and characterized. Their structures and biological activities are summarized in Table 2. Four of these phytochemicals have been found in various traditional medicines previously. Among the seven compounds, three are polyphenols of flavonoid structure and three are pentacyclic triterpenes. Among the reported biological activities, antioxidant and anti-inflammatory activities are the most common.

It may be worthwhile to further study the effects of a standardized extract of *H. arbutifolia* or the dried berries in AD clinical trials. Alternatively, the phytochemicals themselves could be tested in the prevention/treatment of AD. It is becoming more evident now that AD pathophysiology is complex with significant vascular contributions such as decreased blood flow in the CNS, increased blood brain barrier permeability, and decreased cerebrospinal fluid clearance of toxic proteins such as amyloid and tau [8]. It is possible that poly-pharmacy and therapeutic approaches that act to prevent AD also improve vascular health and decrease amyloid protein deposition. In addition, other mechanisms need to be considered together.

Table 1. Some recent clinical trials of different agents and reasons for their failure.

Agents	Possible Causative Factors in Negative Clinical Results
1 Simvastatin 2 Atorvastatin	All hydroxy-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) have serious side effects that make them unsuitable for long-term use, including type 2 diabetes, hemolytic anemia, thrombocytopenia, myopathy, rhabdomyolysis, leukopenia, cataracts, ophthalmoplegia, loss of libido, erectile dysfunction, fulminant hepatic necrosis, hepatoma, and peripheral neuropathy [9,10].
3 Aβ vaccine, AN1792 (Elan, Dublin, Ireland/Wyeth, Philadelphia, PA, USA) 4 Bapineuzumab (Elan; Johnson & Johnson, New Brunswick, NJ, USA; Pfizer, New York, NY, USA) 5 Solanezumab (LY 2062430, Lilly, Indianapolis, IN, USA)	Vaccines and antibodies are foreign proteins. After long-term use, the body makes antibodies against them, nullifying their intended effects [2,11,12].
6 Tarenflurbil (Myriad, Salt Lake City, UT, USA) (R-flurbiprofen) an arylpropionic acid nonsteroidal anti-inflammatory drugs (NSAID)	The R-enantiomer exerts almost no cyclooxygenase (COX) inhibitory activity. Only 1.5% of the R-enantiomer is converted into the S-form (inhibitor of COX) [13,14]. The R-enantiomer reduces the levels of β-amyloid which may not be the main cause of Alzheimer's disease (AD).
7 Semagacestat (LY450139, Lilly)	The agent blocks γ-secretase which, along with β-secretase, is responsible for cleaving β-amyloid from amyloid precursor protein (APP) in rats and is presumed to be a causative agent in AD. The negative clinical finding suggests that the mechanism is not so straight forward in human long-term studies [15].

Table 1. *Cont.*

Agents	Possible Causative Factors in Negative Clinical Results
8 Scyllo-inositol (ELND005, Elan/Transition, Toronto, ON, Canada) hexa-hydroxycyclohexane	A simple organic, low molecular weight compound (180.16 g/mol). High doses (100–200 mg) were effective; unfortunately, severe adverse reactions—including nine deaths—occurred. A higher molecular weight may produce a better central nervous system (CNS) active drug [16].
9 Tramiprosate (Bellus, Laval, QC, Canada) homotaurine	A synthetic homolog of taurine [17], its N-acetyl analog was approved by the food and drug administration (FDA, 2004, acamprosate) to treat alcohol dependence. It was not effective in phase III clinical trials for AD for any primary endpoint. It is a partial γ-Aminobutyric acid type A ($GABA_A$) agonist. Its dipolar (zwitterion) nature may prevent penetration across the blood brain barrier.
10 Rosiglitazone (Avandia, GSK, Brentford, UK)	Antidiabetic agent [18] with a thiazolidinedione group and a tertiary amino group attached to a pyridine ring. It exists mainly as a cation under physiological pH. It has been withdrawn from the market in several European countries. It has been alleged to increase the risk of heart attack and death.
11 Receptor for advanced glycation end products (RAGE) Inhibitor (Pfizer/Transtech, Oulu, Finland)	May cause inhibition of pro-inflammatory gene activation. RAGE is hypothesized to be involved in inflammatory diseases like diabetes, AD, and some tumors. A balance between pro-inflammatory and anti-inflammatory factors is needed for longevity [19].
12 Avagacestat (BMS-708163 (synthetic compound 520.88 g/mol with a heterocycle and two benzene rings attached to a sulfonamide)	A γ-secretase inhibitor, decreases Aβ40 and Aβ42. Phase II trials did not support further development. The amyloid hypothesis of AD remains to be confirmed or refuted [20].
13 IVIG Gammagard (Baxter, Deerfield, IL, USA)	Immunoglobulin therapy is useful in some acute infectious diseases, but may not be suitable for long-term use against chronic diseases like AD [21].

Table 2. Phytochemicals isolated from *Heteromeles arbutifolia*.

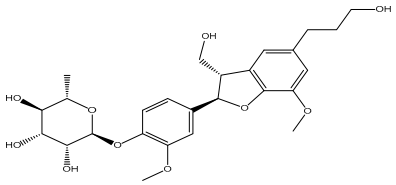
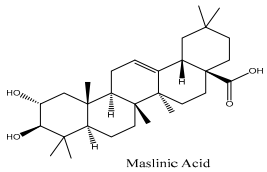
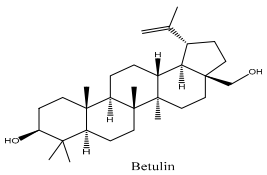
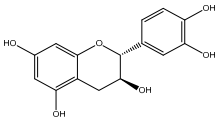
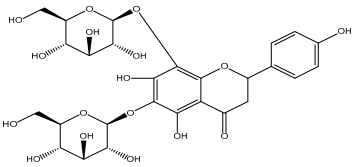
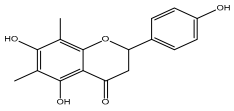
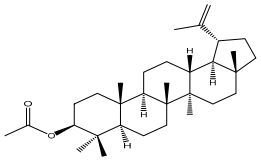
Structure	Category	Biological Activities	References
 Icariside E4	A dihydro-benzofuran lignan	Anti-inflammatory activity due to inhibition of excessive NO production	[22]
 Maslinic Acid	A pentacyclic triterpene	Antitumor, antidiabetic, antioxidant, cardio-protective, neuroprotective, antiparasitic, growth simulating	[23]
 Betulin	A pentacyclic triterpene	Antineoplastic, causes apoptosis in tumor cells, decreases synthesis of cholesterol and fatty acids by inhibition of sterol regulatory element binding proteins, increases insulin sensitivity	[24,25]

Table 2. *Cont.*

Structure	Category	Biological Activities	References
 Catechin	Flavonoid (polyphenol)	Antioxidant, antibacterial, antiestrogenic	[26]
 Vicenin-2	A flavonoid glycoside with functional groups similar to estradiol(polyphenol)	Estrogenic, stimulates egg laying in *Papilio xuthus* on citrus leaves	[24,27]
 Farrerol	Flavonoid (polyphenol)	Antibacterial, antitussive (CNS)	[24]
 Lupeol acetate	A pentacyclic triterpene	Antineoplastic, hypoglycemic, antiarthritic	[24,28]

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Conflicts of Interest: The authors declare no conflict of interest.

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