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Natural Products and its Derived Drugs for the Treatment of Neurodegenerative Disorders: Alzheimer's Disease-A Review

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ABSTRACT

Natural products once served humankind as the source of all drugs, and higher plants provided most of these therapeutic agents. Natural products continue to provide useful drugs in their own right but also provide templates for the development of other compounds. A major advantage of natural products approach to drug delivery is that it is capable of providing complex molecules that is not accessible by other routes. Among CNS disorders, neurodegenerative disorders affects majority of population worldwide. Neurodegenerative disorders such as Parkinson's disease (PD), Alzheimer's disease (AD), Huntington's disease (HD) and amyotrophic lateral sclerosis (ALS) are currently incurable pathologies with huge social and economic impacts closely related to the increasing of life expectancy in modern times. Although the clinical and neuropathological aspects of these debilitating disorders are distinct, they share a pattern of neurodegeneration in anatomically or functionally related regions. The majority of the compounds examined to date with a direct relevance to AD are primarily from plants, from animal, marine and microbial sources. Successful drugs achieved so far are found to act by inhibiting acetyl cholinesterase enzyme. In future, more emphasis should be given in finding new targets for AD therapies. The review focuses on the natural products that might underlie the purported beneficial improvements in memory and cognition, neurovascular function, and in neuroprotection. It may be concluded that natural product chemistry brings tremendous diversity and historical precedent to a huge area of unmet medical need. Cooperative effort from all the technical disciplines related to drug discovery should be continued to make plant-derived natural product research an essential contributor in future.



Introduction

Natural products are the best source for the discovery of new drugs, which were in use even from the Vedic period. It is well established that 80% drug molecules are natural products or natural compound inspired¹. The investigation of natural products as a source of novel human therapeutics reached its peak in the western pharmaceutical industry during 1970-1980, which resulted in a pharmaceutical landscape heavily influenced by non synthetic molecules². The past history of use of plants and other natural product-derived drugs in the treatment of many major afflictions like cancer, cardiovascular diseases and neurological conditions augurs well for their future utilization in this regard. Traditional Indian System of Medicine has a very long term history of usage in a number of disease, disorders, but lacks recorded safety and efficacy data³. Ayurvedic Indian and Chinese systems are great traditional systems that have relatively organized database, and more exhaustive description of botanical material that is available and can be tested using modern scientific methods. Both systems of medicine thus have an important role in bioprospecting of new medicines². Recently, it has been suggested that drug discovery should not always be limited to discovery of a single molecule and the current belief is that rationally designed poly herbal formulation could also be investigated as an alternative in multi-target therapeutics and prophylaxis. Development of standardized, safe and effective herbal formulation with proven scientific evidence can also provide an economical alternative in several disease areas³.

Natural products played a significant role in the management of neuropsychiatric disorders, with the serendipitous discovery of drugs for psychosis, depression and

anxiety in 1950s^{4,5}. Discovery of the plant *Rauwolfia serpentina* by Sen and Bose (1931) was a major break-through in clinical neuropharmacology and psychopharmacology who published the first report on the use of this plant. Important areas of its use include hypertension, depression and Parkinson's diseases (PD)⁶. Important early discovered natural product derived drugs for the treatment of CNS diseases include opium alkaloid from opium poppy, *Papaver somniferum*, ergot from the fungus *Claviceps purpurea*, tropane alkaloids like cocaine from *Erythroxylon coca*, and anti-cholinesterase physostigmine from *Physostigma venenosum*⁷. Among CNS disorders, neurodegenerative disorders affects majority of population worldwide. Alzheimer's disease (AD) is a progressive neurodegenerative disorder leading to most common form of dementia, very particularly in elderly people. This has already affected approximately 36 million people worldwide as of 2010 report⁸.

Although other major causes of death have been decreasing deaths attributable to AD have been rising dramatically. Between 2000 and 2006, cardiovascular mortality decreased to 11.1%, stroke deaths decreased 18.2%, prostate cancer related deaths decreased 8.7% and deaths attributed to AD increased 46.1%⁹. In fact the overall case number in developed countries is estimated to increase by 100% between 2001 and 2040, but by more than 300% in India and China. Recent estimates indicate that nearly 5 million additional new dementia cases are diagnosed per year. Alzheimer's is predicted to affect 1 in 85 people globally by 2050¹⁰. The 2003 World Health Report estimates that dementing diseases contribute a greater overall burden of disability than cardiovascular disease, stroke, and cancer¹¹.

Promising natural products under clinical developments against Alzheimer's disease

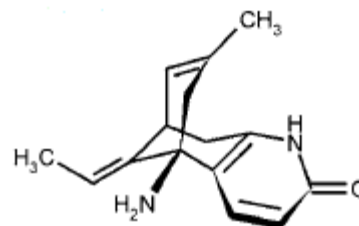
Currently there are five USFDA approved drugs for the symptomatic treatments of AD that may help lessen or stabilize the cognitive symptoms such as memory loss and confusion for a limited time by affecting certain chemicals involved in carrying messages among the brain's nerve cells. Four of these drugs are acetylcholinesterase inhibitors, which include donepezil, galantamine, rivastigmine, and tacrine. Fifth drug is memantine, which is the first anti-Alzheimer drug found to act by modulating N-methyl-D-aspartic acid (NMDA) receptors¹².

Recently discovered natural product derived drugs for the treatment of neurodegenerative disorders like AD, Parkinson's disease (PD) include the following:

1. Huperzine A

Huperzine A is a quinolizidine alkaloid isolated from Club moss *Huperzia serrata* (Thumb) Trevis belonging to Lycopodiaceae family which is used in various formulations in traditional Chinese medicine to alleviate problems of memory loss, promote circulation, and for fever and inflammation¹³. It has been found to inhibit the enzyme acetylcholinesterase reversibly and selectively. It also displayed good pharmacokinetics with rapid absorption and a wide distribution in the body at a low to moderate rate of elimination. The completed phase II clinical studies suggested that Huperzine A is well tolerated at a dose up to 0.4 mg twice daily for 24 weeks with a significant benefit is regarding the existing drug for the treatment of AD, because most patients were unable to tolerate currently marketed acetylcholinesterase inhibitors for a long period of time. Huperzine A is marketed in China for the indications of AD. Currently the drug is in larger well designed

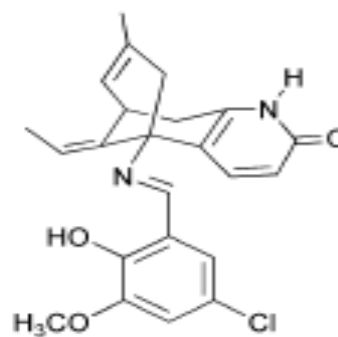
phase III clinical trial in USA which might help to approve it as a standard treatment of AD¹⁴.



Huperzine A

2. ZT-1

A pro-drug of Huperzine, ZT-1 is a new drug derived from a plant extract already used in China for memory disorders, originally synthesized by Zhu and Coworkers at Shanghai Institute of Material Medica¹⁵. It acts by blocking the action of the acetylcholinesterase enzyme and restores adequate levels of acetylcholine. This drug has completed phase-II clinical trials for the treatment of AD and in June 2007 positive results has been announced after the trial against AD^{16,17}.

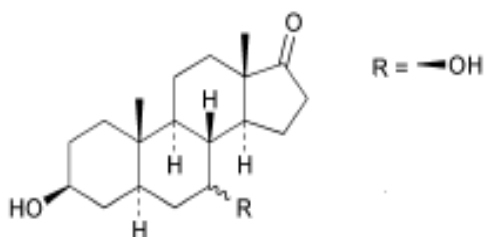


ZT-1

3. HF-0220

Another compound called 7 β -OH epiandrosterone (HF-0220) is now under phase II clinical trial for chronic and acute neurodegenerative diseases. Dehydroepiandrosterone (DHEA) is produced in brain and is hydroxylated into 7 α - and 7 β -derivatives by a cytochrome P450 enzyme that is expressed at high level in brain &

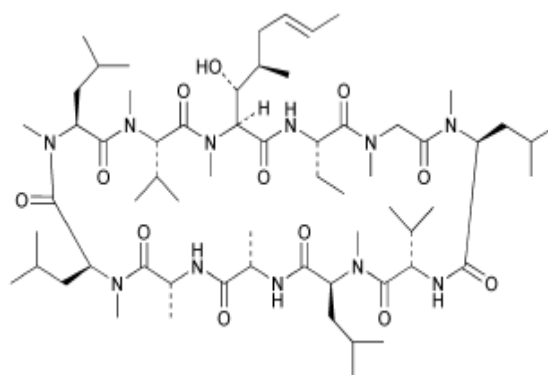
alpha and 7 β derivatives have been found to significantly reduced neurotoxicity at 10 and 100 mM respectively. In addition to neuroprotection, 7 β -OH-epiandrosterone has shown promise in in-vitro pre clinical studies for ischemic stroke and cardio protection models. Surprisingly, 17 α -estradiol has been successfully completed phase I clinical trial for its efficacy in the treatment of AD¹⁸⁻²².



HF-0220

4. Cyclosporin A (CsA)

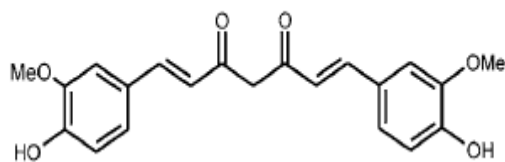
Cyclosporin A is a cyclic non ribosomal peptide of 11 amino acids produced by the fungus *Tolypocladium inflatum*, and is a widely used strong immunosuppressant. CsA binds to the cytosolic protein cyclophilin in T-cells, and the CsA-cyclophilin complex inhibits calcineurin has shown potent neuroprotective properties in stroke trauma and neurodegeneration by prevention or reduction of neuron cell death by inhibition of critical enzymes and free radicals and protecting mitochondria. Preclinical studies showed that cyclosporine A is the most powerful known neuroprotectant in stroke and traumatic brain injury and now this drug in phase II A clinical trials for stroke and brain injury. Cyclosporine is also considered as a promising drug in the treatment of AD, PD and amyotrophic lateral sclerosis (ALS)²³⁻²⁵.



Cyclosporin A (CsA)

5. Curcumin

Curcumin is a well known polyphenolic ingredient obtained from the turmeric plant *Curcuma longa* L. (Zingiberaceae), recently being under investigation in the field of dementia. Many studies have reported that curcumin has various beneficial properties such as antioxidant, anti-inflammatory and antitumour^{26,27}. Recent reports have suggested therapeutic potential of curcumin in AD. In *in vitro* studies on curcumin has been reported to inhibit amyloid- β -(A β) protein aggregation, and A β induced inflammation as well as the activities of β -secretase and acetylcholinesterase. In *in vivo* studies, oral administration of curcumin has resulted in the inhibition of A β deposition, A β oligimerization and tau phosphorylation in the brains of AD animal models and improvements in behavioral impairment in animal models. These findings recommend curcumin as a promising drug in the treatment of AD. Currently, Longvida, a curcumin formulation, is being evaluated in phase II Alzheimer's clinical trial²⁸⁻³³.



Curcumin

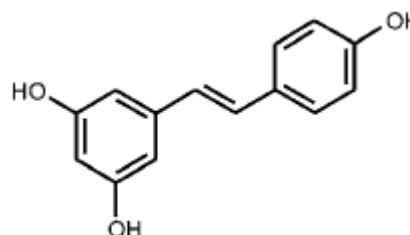
6. Resveratrol (trans-3,4',5 trihydroxy-stilbene)

Resveratrol occurs in various plants belonging to the family Vitaceae (e.g., *Vitis Vinifera* L.) and shows mechanistic effects including antioxidant, relevant for AD treatment. This polyphenol promotes the decomposition and clearance of intracellular A β aggregates by resveratrol enhanced proteosomal degradation of A β . It was also noted that proteasome activity is reduced in an AD brain, supporting a possible novel therapeutic mechanism of resveratrol in AD^{34,35}. A recent study suggest resveratrol disrupts A β hydrogen bonding thus preventing fibril formation and it can destabilize preformed fA β in vitro, but does not prevent oligomerization³⁶. Specifically, it scavenges reactive oxygen species, upregulates cellular antioxidants including glutathione and is neuroprotective against oxidative stress *in vitro* and *in vivo*^{27,37,38}.

Resveratrol protects astrocytes in rat hippocampal slices from hydrogen peroxide induced oxidative stress by increasing glutathione levels in addition to other mechanisms³⁹. It also prevents cognitive impairments and associated oxidative stress *in vivo*^{27,40} and reduces plaque formation in a transgenic model of AD⁴¹. Recent evidence suggests that resveratrol may modulate AD pathology due to antioxidant effects or by various other mechanisms^{27,42}. Resveratrol is currently in phase III clinical trials as a nutritional supplement in combination with glucose and malate. The proposed mechanism underlying this study

involve glucose and malate prime oxidative metabolism and the Kreb's cycle in the brain which aids in regenerating the reduced form of resveratrol under normal brain cell metabolism⁴².

In a recent study, the phenolic compound has been found to be a potent activator of sirtuin1 (SIRT1), genes encoding the human sirtuin family of proteins, through a molecular pathway that mimics the effects of caloric restriction. Caloric restriction normally prepares the body to deal with stress. Sirtuin1 proteins affect the aging process and are also involved in enhancing the function of mitochondria. This study also found that resveratrol was specifically capable of enhancing neuronal survival and preventing neurodegeneration in cell models of AD and amyotrophic lateral sclerosis⁴³.

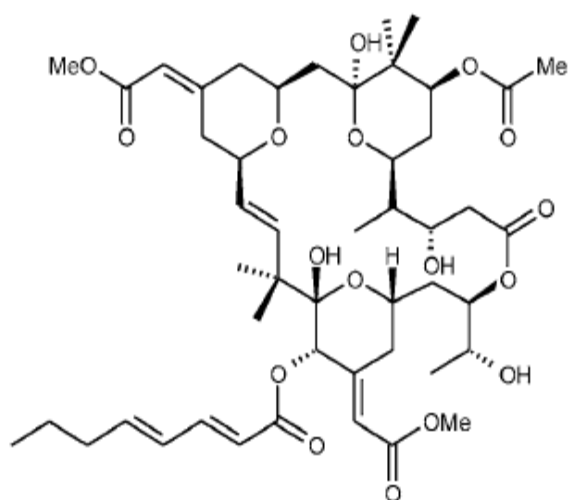


Resveratrol (trans-3,4',5 trihydroxy-stilbene)

7. Bryostatin-1

Bryostatin-1 is a macrolide lactone, first isolated by George Pettit from the bryozoans *Bugula neritina* L (Bugulidae), is currently under investigation as anti cancer agent and as a memory enhancing agent⁴⁴⁻⁴⁶. Bryostatin-1 enhances α -secretase activation in human fibroblast cells, reduces A β levels and reduces mortality of transgenic AD mice⁴⁷. It also reverses A β produced deficits of protein kinase C (PKC) and extracellular signal regulated kinase 1 and 2 phosphorylation in cellular models of AD. This compound appeared to be a very promising drug in enhancing memory of animal models⁴⁸. Also the drug increased rate of learning in rats⁴⁹. Currently

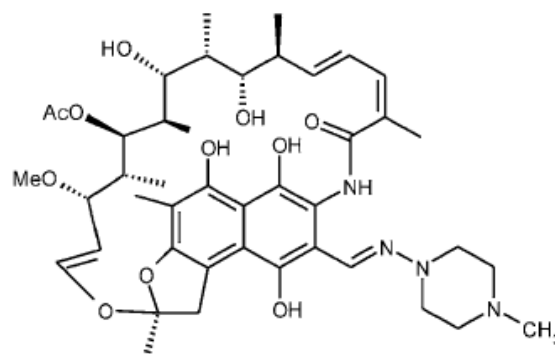
Bryostatin-1 is in clinical trial phase II for the treatment of treatment against AD. This drug has also been found to alleviate brain damage in is chemically brain injured rats, which also makes it a promising drug in future⁵⁰.



Bryostatin-1

8. Rifampicin

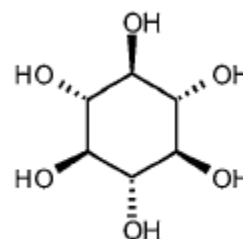
Rifampicin is a semisynthetic polyketide antibiotic originally derived from *Amycolatopsis rifamycinia* Bala (pseudonocardaceae), found to inhibit AB aggregation in *in vitro* studies⁵¹. Recently, a randomized trial to assess the effectiveness of the combination therapy of rifampicin and another semisynthetic antibiotic doxycycline, over a three month period demonstrated a reduction in cognitive decline after six months in patients with mild to moderate AD⁵². Proposed mechanism involved are anti inflammatory and anti aggregation effects. Currently the drug is in phase IIIa clinical trial for evaluating the effect of this combination on AD biomarkers in the cerebrospinal fluid⁴².



Rifampicin

9. ELND- 005

Known generically as scyllo-inositol, is a naturally occurring plant sugar alcohol found in the coconut palm, oak bark, and other plants. The experimental drug is being tested in Phase II clinical trial for mild to moderate AD. It is a part of an emerging class of disease modifying agents that have the potential to both reduce the disease progression and improve symptoms such as cognitive function. It has been found to break down neurotoxic fibrils and block the accumulation of β -amyloid oligomers, allowing amyloid peptides to clear the body rather than form amyloid plaques⁵³.



ELND- 005

10. Bapineuzumab

Bapineuzumab is a humanized monoclonal antibody from mouse that acts on the nervous system and it found to exhibit potential therapeutic value for the treatment of AD^{54,55}. This drug is an antibody to the β -amyloid plaques that are

believed to underlie Alzheimer's neuropathology. Currently this compound is in phase III clinical trial, which is a passive immunotherapy approach in which patients are treated with humanized monoclonal antibodies with specificity to A β peptides. The treatment with antibodies should bind and clear A β with the potential added benefit of a better safety and tolerability profile⁵⁶⁻⁶¹.

11. Solanezumab

Solanezumab is a monoclonal antibody found to act by neutralising β -amyloid plaques, which is now in phase III clinical trial^{62,63}.

12. Crenezumab

Crenezumab is also a monoclonal antibody to the β -amyloid plaques, that are believed to underlie Alzheimer's neuropathology. Currently this compound is in phase II clinical trial^{64,65}.

13. Gantererumab

Gantererumab is an investigational, fully human anti-amyloid β -monoclonal antibody, with a high capacity to bind and remove β -amyloid plaques in the brain. This compound currently undergoing phase II and III clinical trials represents a promising agent with a disease modifying potential in AD⁶⁶.

14. BAN2401

BAN2401 is a humanized immunoglobulin-1 (IgG1) monoclonal antibody that binds selectively to large, soluble A β oligomers, called protofibrils, and neutralizes their damage to brain cells. This compound is currently in Phase II study for evaluating its effectiveness as a possible treatment for people with mild cognitive impairment or mild AD⁶⁷.

15. BIIB 037

BIIB037 is a fully human IgG-1 monoclonal antibody that is being developed as a disease modification treatment for AD. In animal models of Alzheimer's, treatment with BIIB037 was shown to decrease β -amyloid content in animal brains. A single ascending dose study of BIIB037 in people with mild to moderate Alzheimer's is ongoing. This study will be conducted in people with prodromal or mild Alzheimer's to assess the safety, tolerability, pharmacokinetic, and pharmacodynamic profile after multiple doses of BIIB037⁶⁸.

Future Prospects

Currently, there are five USFDA approved drugs for the symptomatic treatments of AD that may help lessen or stabilize the cognitive symptoms such as memory loss and confusion for a limited time by affecting certain chemicals involved in carrying messages among the brain's nerve cells, which include donepezil, galantamine, rivastigmine, tacrine and memantine. Targets for new AD therapies to be emphasized include preventing bioenergetic upstream pathways from β amyloid peptide production, delivering nerve growth factor for neuron survival, boosting immune responses with vaccine treatments, preventing formation and accumulation of β amyloid protein and plaques, inhibiting formation of neurofibrillary tangles containing tau proteins and preventing brain cell dysfunction and death.

The successful track record of natural products from plants, microorganisms and other organisms has demonstrated amply that these small organic molecules represent a highly use full source of molecular diversity in drug discovery⁶⁹⁻⁷¹. Today, natural products (and their derivatives and analogs) still represent over 50% of all drugs in clinical use, with higher plant- derived natural

products representing about 25% of the total⁶⁹. In addition to the natural products which have found direct medicinal application as drug entities, many others can serve as chemical models or templates for the design, synthesis, and semi synthesis of novel substances for treating humankind's diseases. Although there are some new approaches to drug discovery, such as combinatorial chemistry and computer-based molecular modeling design, none of them can replace the important role of natural products in drug discovery and development^{72,73}.

Conclusion

Plant-derived bioactive compounds, in addition of directly being developed as drugs, also serve as prototype drug molecules known as 'lead compounds', and as pharmacological probes to help better understand pharmacological and biochemical mechanisms. Obviously natural products will continue to be extremely important as sources of medicinal agents. The WHO estimates that 80% of people in the developing countries of the world rely on the traditional medicine for their primary health care, and about 85% of traditional medicine involves the use of plant extracts. This means that about 3.5 to 4 billion people in the world rely on plants as sources of drugs⁷⁴.

Due to the insufficiency in understanding the exact pathophysiology of neurodegenerative disorders, they still present a great challenge in finding an appropriate treatment to these devastating diseases. Clinical treatment of neurodegenerative conditions is palliative and relies, in most cases, on improving stimulation at the relevant receptors by either increasing levels of the endogenous neurotransmitter or by the use of substances which have a similar agonist response.

The majority of the compounds examined to date, with a direct relevance to AD, are primarily from plants, from animal,

marine and microbial sources. Natural molecules can also be subjected to chemical derivatisation and synthesis of analogues for better pharmacokinetics and efficacy. Natural products have always been and continue to be the important medical reservoirs with considerable number of modern FDA approved medications having been derived from natural sources. Several conclusions on the possibility of natural product leads have already been supported by the experimental outcomes.

Thus natural products have emerged as promising hope in the drug discovery programmes in AD. Successful drugs achieved so far found to act by inhibiting acetyl cholinesterase enzyme. In future, more emphasis should be given in finding new targets for AD therapies. Targets for new AD therapies to be emphasized include preventing building up of amyloid plaques, preventing building up of paired helical segments and preventing brain cell dysfunction and death.

Authors' Contribution

BKV and RS: have made substantial contributions to conception and design,

VMA and BRA: have been involved in drafting the manuscript or revising it critically for important intellectual content;

MS, TT, GK, SP: made substantive intellectual contributions to a published study.

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