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Review

Features and outcomes of drugs for combination therapy as multi-targets strategy to combat Alzheimer's disease

Atish Kumar Sahoo[a,*], Jagnehswar Dandapat[b], Umesh Chandra Dash[a], Satish Kanhar[a]

[a] Phytotherapy Research Lab., Medicinal & Aromatic Plant Division, Regional Plant Resource Centre, Forest & Environment Department, Govt. of Odisha, Nayapalli, Bhubaneswar 751015, India

[b] Department of Biotechnology, Utkal University, Vani Vihar, Bhubaneswar 751004, India

ARTICLE INFO

Chemical compounds studied:
Physostigmine (PubChem CID: 5983)
Galanthamine (PubChem CID: 9651)
Curcumin (PubChem CID: 969516)
Huperzine A (PubChem CID: 1253)
Resveratrol (PubChem CID: 445154)
Berberine (PubChem CID: 2353)
Ginsenoside Rg1 (PubChem CID: 441923)
Puerarin (PubChem CID: 5281807)
Silibinin (PubChem CID: 31553)
Crocin (PubChem CID: 5281233)
Sinapic acid (PubChem CID: 637775)
Arecoline (PubChem CID: 2230)
Tanshinones (PubChem CID: 164676)
Rutaecarpine (PubChem CID: 65752)
Withanolide A (PubChem CID: 11294368)
Sitoindoside IX (PubChem CID: 189586)
Sitoindoside X (PubChem CID: 189702)
Withaferin A (PubChem CID: 265237)
Honokiol (PubChem CID: 72303)
Magnolol (PubChem CID: 72300)
Nicotine (PubChem CID: 89594)
Lobeline (PubChem CID: 3945)
Cytisine (PubChem CID: 10235)
Tacrine (PubChem CID: 1935)
Donepezil (PubChem CID: 3152)
Rivastigmine (PubChem CID: 77991)
Metrifonate (PubChem CID: 5853)
Ganstigmine (PubChem CID: 89594)
Phenserine (PubChem CID: 192706)
Eptastigmine (PubChem CID: 65872)
Velnacrine maleate (PubChem CID: 5702293)
Memantine (PubChem CID: 4054)

ABSTRACT

Ethnopharmacological relevance: Alzheimer's disease (AD), a deleterious neurodegenerative disorder that impairs memory, cognitive functions and may lead to dementia in late stage of life. The pathogenic cause of AD remains incompletely understood and FDA approved drugs are partial inhibitors rather than curative. Most of drugs are synthetic or natural products as galanthamine is an alkaloid obtained from Galanthus spp. Huperzine A, an alkaloid found in Huperzia spp., gingkolides a diterpenoids from *Gingko biloba* and many ethnobotanicals like *Withania somnifera* (L.) Dunal., *Physostigma venenosum* Balf., *Bacopa monnieri* (L.) Wettst., *Centella asiatica* (L.) Urb. have been used by traditional Indian, Chinese, and European system of medicines in AD. Clinical significance opioid alkaloid in *Papaver somniferum* has shown another dimension to this study. Over exploitation of medicinal plants with limited bioactive principles has provided templates to design synthetic drugs in AD *e.g.* rivastigmine, phenserine, eptastigmine based on chemical structure of physostigmine of *Physostigma venenosum* Balf. Even ZT-1 a prodrug of Hup A and memogain a prodrug of galantamine has achieved new direction in drug development in AD. All these first-line cholinesterase-inhibitors are used as symptomatic treatments in AD. Single modality of "One-molecule-one-target" strategy for treating AD has failed and so future therapies on "Combination-drugs-multi-targets" strategy (CDMT) will need to address multiple aspects to block the progression of pathogenesis of AD. Besides, cholinergic and amyloid drugs, in this article we summarize proteinopathy-based drugs as AD therapeutics from a variety of biological sources. In this review, an attempt has been made to elucidate the molecular mode of action of various plant products, and synthetic drugs investigated in various preclinical and clinical tests in AD. It also discusses current attempts to formulate a comprehensive CDMT strategy to counter complex pathogenesis in AD.

Materials and methods: Information were collected from classical books on medicinal plants, pharmacopoeias and scientific databases like PubMed, Scopus, GoogleScholar, Web of Science and electronic searches were performed using Cochrane Library, Medline and EMBASE. Also published scientific literatures from Elsevier, Taylor and Francis, Springer, ACS, Wiley publishers and reports by government bodies and documentations were assessed.

Results: 60 no. of natural and synthetic drugs have been studied with their significant bioactivities. A decision matrix designed for evaluation of drugs for considering to the hypothetic "CDMT" strategy in AD. We have introduced the scoring pattern of individual drugs and based on scoring pattern, drugs that fall within the scoring range of 18–25 are considered in the proposed CDMT. It also highlights the importance of available natural products and in future those drugs may be considered in CDMT along with the qualified synthetic drugs.

Conclusion: A successful validation of the CDMT strategy may open up a debate on health care reform to explore

Abbreviations: AD, Alzheimer's disease; Aβ, β-amyloid peptide; NFTs, neurofibrillary tangles; EOAD, early-onset AD; LOAD, late-onset AD; OMOT, One-molecule-one-target; ROS, reactive oxygen species; CDMT, Combination-drugs-multi-targets; BBB, blood brain barrier; DDT, Dichlorodiphenyltrichloroethane; DDE, Dichlorodiphenyldichloroethylene; APOE, Apolipoprotein E; ACh, Acetylcholine; AChE, Acetylcholinesterase; AChEI, Acetylcholinesterase inhibitor; APP, Amyloid precursor protein; sAPPα, secreted amyloid precursor protein-α; PSEN, presenilin proteins; MAPT, microtubule-associated protein tau; GSK-3, Glycogen synthase kinase 3; NMDA, N-methyl-D-aspartate; MDA, malondialdehyde; AGE, advanced glycation end products; BChE, butyrylcholinesterase; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; HEK293, human embryonic kidney 293 cells; MCP-1, monocyte chemoattractant protein-1; ERK, extracellular signal-regulated kinases; nAChR, nicotinic acetylcholine receptor; p38 MAPK, p38 mitogen-activated protein kinase; TNF, tumor necrosis factor; IL, Interleukin; DDVP, 2,2-dimethyl dichlorovinyl phosphate; ThT, Thioflavin T; ADAS, Alzheimer's Disease Assessment Scale; WHO, World Health Organization; MAO, monoamine oxidase; BDNF, brain-derived neurotrophic factor; TCM, Traditional Chinese Medicine; ISM, Indian System of Medicine; GAP, growth-associated protein; 5'-APP-UTR, APP 5'-untranslated region; TUNEL, Terminal deoxynucleotidyl transferase dUTP nick end labeling; ASM, Ayurvedic system of medicine; TCM, Traditional Chinese medicine; ISM, Indian system of medicine; AFM, atomic force microscopy

* Corresponding author.
E-mail address: atish_kumar1976@yahoo.co.in (A.K. Sahoo).

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Neramexane (PubChem CID: 6433106)
Nicergoline (PubChem CID: 34040)
Propentofylline (PubChem CID: 4938)
Idebenone (PubChem CID: 3686)
Nimodipine (PubChem CID: 4497)
Zanapezil (PubChem CID: 198752)
E2020 (PubChem CID: 3152)
Xanomeline (PubChem CID: 60809)
Desferrioxamine (PubChem CID: 2973)
ZT-1 (PubChem CID: 101344572)
Talsaclidine (PubChem CID: 6918244)
Minocycline (PubChem CID: 54675783)
LY450139 dihydrate (PubChem CID: 9843750)
Lu 25–109 (PubChem CID: 178030)
Imatinib (PubChem CID: 5291)
Paclitaxel (PubChem CID: 36314)
Thalidomide (PubChem CID: 5426)
Bexarotene (PubChem CID: 82146)
Azithromycin (PubChem CID: 447043)
Tetracycline (PubChem CID: 54675776)
Clioquinol (PubChem CID: 2788)
Rifampin (PubChem CID: 6913622)
Amphotericin B (PubChem CID: 5280965)
Metformin (PubChem CID: 4091)
Nilvadipine (PubChem CID: 4494)
Ladostigil (PubChem CID: 208907)
Quetiapine (PubChem CID: 4494)

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Acetyl cholinesterase

other possibilities of combination therapy. In doing so, it should focus on clinical and molecular relationships between AD and CDMT. A better understanding of these relationships could inform and impact future development of AD-directed treatment strategies. This strategy also involves in reducing costs in treatment phases which will be affordable to a common man suffering from AD.

1. Introduction

Alzheimer's disease (AD) is a progressive, unrepairable neurodegenerative disease and found mostly in the form of dementia in elders. Other etiological features that are prominent in AD are cerebral atrophy, cerebral senile plaques due to the deposition of β-amyloid peptide (Aβ), neurofibrillary tangles (NFTs). Both Aβ-plaques and NFTs are responsible for hyperphosphorylated τ-protein, leading to neuronal cell loss and death (Amatsubo et al., 2010). Based on the age affected by AD is of 2 subtypes as early-onset AD (EOAD) affected people are of 30–60 or 65 years whereas in late-onset AD (LOAD), the affected people are elders of 60–65 years. Approximately 1–6% of EOAD case is reported in which 60% cases found the hereditary link or family history which carries to affect at least 3 upcoming generations (Wang et al., 2010).

In this review, we have discussed the supporting mechanisms of AD pathogenesis and progression. It also highlights the synthetic/semi-synthetic and natural drugs used in AD. Current therapeutic approach of "One-molecule-one-target" (OMOT) strategy which has been prescribed in AD over the years, fails to address the issues in a given time because of multiple pathological features such as cholinergic deficiency, Aβ-plaques and hyperphosphorylated τ-protein, generation of reactive oxygen species (ROS), mitochondrial dysfunction that appears frequently in the transist stages in AD (Bird, 2008). We have introduced here a "Combination-drugs-multi-targets" (CDMT) strategy, which may be a synergistic approach in future for targeting multiple pathological stages or events in AD. We have introduced here the scoring pattern of individual drugs by designing a decision matrix for evaluating the drugs to be considered in combination therapy (Table 1). By referring to the earlier published decision metrix, a major modification has been made here for evaluating different parameters such as "Mode of inhibition", "Supporting evidences", "Pharmacodynamic study", "Use of biomarkers in non-clinical and/or clinical trial", "Experimental gaps of any existing in non-clinical studies", "Effective brain penetration BBB", "Pharmacokinetics (relevant tissue distribution, halflife, % bioavailability, *etc.)*", "Safety/Toxicity", "Drug-drug interactions", "Clinical trials under taken" (Table 2). Most of the drugs available for AD are evaluated based on the above parameters.

Based on the scoring pattern and drugs that are qualified in the decision metrix by following the above parameters are considered in combination therapy. Out of 24 drugs, most of the natural drugs are suitable candidates and considered here in combination therapy along with other qualified synthetic drugs (Table 2). The detail information about the selection criteria of drugs in combination therapy is ellustrated in the discussion section (Table 2). This study has proposed the combinations of drugs that may help in future to develop a synergistic formulatory product that may have the potential to modifying or alter or countering the disease. The proposed hypothesis CDMT needs to be validated further for safe use in future (Figs. 1–4).

2. The pathophysiology of AD

As described by Alois Alzheimer, the pathological features of AD are characterized by generation of Aβ plaques and NFTs in cerebral cortex of brain and resulted in cerebral arteriosclerosis in cerebral nerve cells responsible for loss in memory (Van et al., 2007). In progressive stage of AD, these amyloid fibers will cluster around blood vessels, and as a result the blood serum leaking into the cerebral space causing intercerebral hemorrhage, brain stroke and death. There are different hypotheses, concepts and theories of AD are summarized and still the pathphysiology of AD is yet being recognized completely.

2.1. Theories of AD

There are five fundamental theories are the over precipitating cause of AD.