MEDDOCS

Open Access Publisher

ALZHEIMER'S DISEASE

AND TREATMENT

Targeting Alzheimer's Disease Through Pharmacoinformatics: New Challenges in Drug Design

David Ramírez[1]*; Lily Arrue[1]; Miguel Reyes-Parada[2,3]

[1]Instituto de Ciencias Biomédicas, Facultad de Ciencias de la Salud, Universidad Autónoma de Chile, El Llano Subercaseaux 2801 - Piso 6, Santiago, Chile.

[2]Centro de Investigación Biomédica y Aplicada (CIBAP), Escuela de Medicina, Facultad de Ciencias Médicas, Universidad de Santiago de Chile, Av. Libertador Bernardo O'Higgins 3677, Santiago, Chile.

[3]Facultad de Ciencias de la Salud, Universidad Autónoma de Chile, Talca, Chile.

Corresponding Author: David Ramírez

Instituto de Ciencias Biomédicas, Facultad de Ciencias de la Salud, Universidad Autónoma de Chile, El Llano Subercaseaux 2801 - Piso 6, 8900000 Santiago, Chile.
Tel: +56-9-223036667;
Email: david.ramirez@uautonoma.cl

Published Online: May 10, 2021

eBook: Alzheimer's Disease & Treatment

Publisher: MedDocs Publishers LLC

Online edition: http://meddocsonline.org/

Keywords: Alzheimer disease; Pharmacoinformatics; Polypharmacology; Drug design; Bioinformatic tools.

Abstract

Neurodegenerative diseases associated with dementia are highly prevalent, and it is estimated that about 35 million people worldwide suffer some type of dementia, with Alzheimer's Disease (AD) being the most frequent condition. Three hypotheses have been postulated in the pathophysiology of AD: cholinergic, amyloid and neurofibrillary tangles. Despite having different characteristics and mechanisms, all three converge on the hypothesis of disruption in synaptic transmission, leading to difficulties in cognitive processes such as memory loss. The few drugs currently FDA approved (donepezil, tacrine, rivastigmine, galantamine, and memantine) for AD treatment are palliative in nature, aimed at improving the quality of life of patients, but not to cure this multifactorial, complex disease. Thus, great challenges arise in the research of new therapeutic alternatives against AD.

Pharmacoinformatics emerged from the use of integrative methods from biology, chemistry, pharmacology and informatics, thereby facilitating the design of new strategies to identify key targets in AD. It allows to study how these targets interact with each other, thus forming a complex Protein-Protein Interaction network (PPI). Pharmacoinformatics could be used then to make predictions of bioactive molecules that can potentially modulate two or more targets in the PPI (multi-target drugs), thus having a positive therapeutic effect at the systemic level, allowing to have an impact on the potentiation of the cholinergic synapse, or in the reduction of amyloid plaque as well as neurofibrillary tangles.

Introduction

Neurodegenerative diseases associated with dementia are some of the most challenging and complicated diseases in terms of the patient's quality of life [1]. They are generally attributed to multiple genetic factors and, thus, are genetically heterogeneous. It is estimated that about 35 million people around the globe suffer from some type of dementia. Among neurodegenerative diseases, Alzheimer's Disease (AD) is the most frequent condition affecting older adults. Despite that the advances in medicine have led to a decrease in mortality as a consequence of this disease, and to an improvement in the quality of life of older adults, AD is still the most common and devastating neurodegenerative pathology in this age group. The typical clinical signs are an impairment of the cognitive functions of short-term memory and attention, followed by a deterioration of the cogni-

Citation: Ramírez D, Arrue L, Reyes-Parada M, (2021). Targeting Alzheimer's disease through Pharmacoinformatics: New Challenges in Drug Design. Alzheimer's Disease and Treatment, MedDocs Publishers. Vol. 4, Chapter 1, pp. 1-5.

tive functions of memory and attention as well as impairment of language skills and abstract thinking, among others. One of the main difficulties in the treatment of this disease is that an effective way to diagnose it in the early stages of the patient's life has not yet been determined; on the contrary, it is only possible to confirm the development of the disease post mortem, by detecting some of the pathophysiological characteristics of AD in the brains of patients [2].

From a pharmacological perspective, there are currently only two groups of drugs for the treatment of AD, acetylcholinesterase inhibitors and NMDA receptor antagonists, aimed at increasing cognitive functions, but they do not act to ameliorate the pathological causes of AD [3]. Therefore, active multidisciplinary research to find new therapeutic alternatives is a primary need for the treatment of AD. When it comes to designing new drugs or modifying existing molecules, traditional approaches have shown very little success, so computational approaches have proven to be very useful, helping to explore a large chemical space, saving valuable resources in the process, especially time and money.

In recent years, researchers around the globe have made extensive use of structural bioinformatics tools such as virtual screening and modeling. These methods have boosted the search for many promising compounds [4,5]. Additionally new technologies derived from data science and artificial intelligence such as machine and deep learning have been integrated into drug discovery programs against AD and other complex diseases, yielding promising results in the identification of new targets and the prediction of bioactive compounds. Thanks to the continuous efforts to study AD in depth, researchers have focused on some well-known targets, such as cholinergic receptors (muscarinic/nicotinic), tau kinases and phosphatases, and amyloid precursor protein-cleaving enzymes [4]. At the same time, different new and promising targets have been identified, orienting drug design processes towards these new targets [4]. In addition to the exploration and synthesis of chemical compounds, natural products have been tested for AD. Compounds such as flavonoids, alkaloids and terpenoids have been shown to be bioactive against various targets [6]. Thus, thanks to the help of pharmacoinformatics framed by the use of computational biology, biophysics, and cheminformatics tools, in close coupling with medicinal chemistry, molecular biology and pharmacology, there are several promising molecules on the horizon, and many lead candidates are in different phases of clinical trials that provide a hopeful light for the future.

Pathophysiology of alzheimer's disease

From the pathophysiological point of view, AD is multifactorial in nature, where several mechanisms converge in a phenotype strongly marked by deterioration of the cognitive functions of memory and attention as well as impairment of language skills and abstract thinking. Among these mechanisms we find the accumulation of amyloid plaque, neurofibrillary tangles, disorder of energy metabolism (glucose), decreased cholinergic synapses, altered free radical metabolism, premature neuronal death due to genetic programming, disorders in neuronal calcium regulation, where its accumulation inside the neuron acts as a toxic agent, and neuroinflammation. Any of the proposed mechanisms could have a central role in the onset of this disease, while other mechanisms would act through their effects, that is, they would be secondary to the initial problem. In general, the research has focused on three main features i) diffuse neuronal loss, ii) appearance of senile plaques due to deposition and aggregation of amyloid proteins, and iii) formation of neurofibrillary tangles [7]. These characteristics coincide with the three hypotheses proposed for the study of this disease:

1. Cholinergic hypothesis: Describes the reduction in brain production of the neurotransmitter acetylcholine, which is responsible for carrying out processes related to memory and learning. As a consequence of its decrease, cholinergic processes are affected causing the characteristic symptoms of this disease [8].

2. Amyloid hypothesis: Describes the accumulation of aggregates of amyloid peptides (amyloid plaques), understood as conglomerates of amino acids that are located in the neuronal environment, preventing the correct development of the synapse [9]. As a consequence of this plaque accumulation, microglia releases a cocktail of cytokines that trigger the neuroinflammation.

3. Neurofibrillary tangles hypothesis: Describes the formation of neurofibrillary tangles in the neuronal environment, due to an alteration in the activity of the TAU protein, which is responsible for the structure and function of the microtubules of the neuronal cytoskeleton. As a result of this alteration, neuronal mobility and structure is severely compromised, and difficulties in nutrient and information transport arises [10].

Both the formation of amyloid peptide and neurofibrillary tangles can have consequences not only in information processing, but also in the neurodegenerative process, since the neuron, not being able to exert its functions correctly and in the presence of oxidative stress, triggers mechanisms of cell survival and/or death, generating atrophy mainly in the cerebral gyri, sulci and ventricles. It is believed that there are two types of development in AD, one of late onset, where symptoms increase with age, comprising between 90-95% of cases, due to the appearance of a specific allele, where its development could be related to lifestyle and environmental conditions, and another of early onset, considered hereditary, which consists of the mutation of an gene that incorrectly decodes the function of the protein responsible for the modulation of the amyloid peptide [11].

Pharmacoinformatics methods for anti-alzheimer agents

The use of computational methods to study biological systems is becoming more and more common, especially when it comes to designing new bioactive molecules for a specific pathology. This is known as pharmacoinformatics, where several sciences converge (data science, artificial intelligence, bioinformatics, chemoinformatics, biophysics, etc.) with the aim of expanding the chemical space and exploring new therapeutic alternatives for diseases. Pharmacoinformatics is very useful for studying complex diseases such as Alzheimer's disease (Figure 1), where the central focus is on the pathology, the therapeutic targets involved in the disease, and the drugs that can modulate these targets.

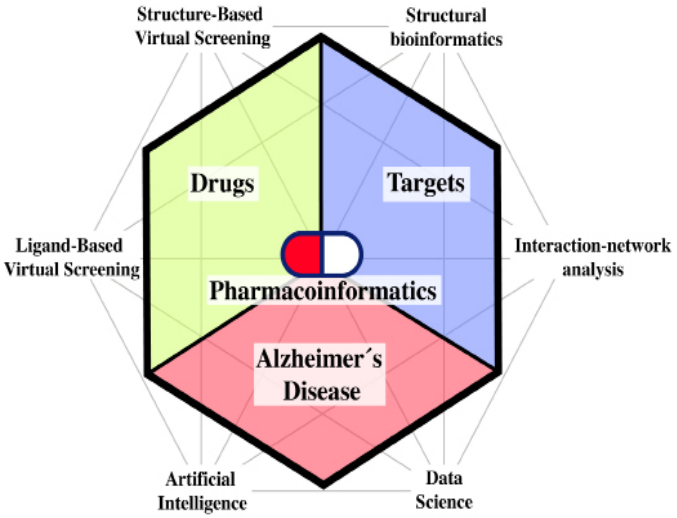


Figure 1: Integration of pharmacoinformatics drug design methods for anti-Alzheimer agents. The integration of different pharmacoinformatics methods and computational approaches will contribute to the understanding and prediction of the complex interplay between drugs, targets, and the AD.

The use of pharmacoinformatics methods in the drug discovery process could reduce time and efforts in two preclinical stages of the process, i.e. boosting the key-target identification through the establishment of protein-protein interaction networks by using data science and artificial intelligence algorithms [12-14], and/or reducing the number of molecules to test in the wet-lab from hundreds of thousands to a few tens by using Ligand-Based (LBVS) [15] and/or Structure-Based Virtual Screening (SBVS) [16].

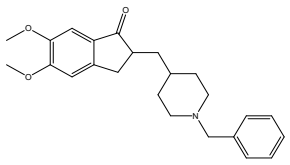
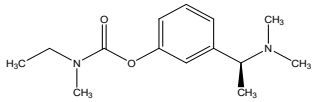
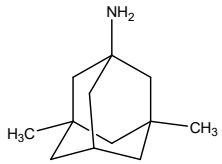
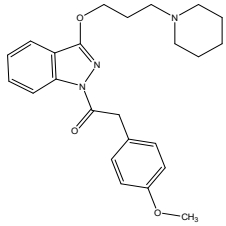
Computational predictions followed by experimental assessment have been successfully used to identify new bioactive compounds against key-targets in AD [17]. Each computational method has its own field of application, limitations and pitfalls. The scope of each method must be well understood, always being aware that none of them alone will be able to reveal (or even model) the complex interaction between drugs, targets and multifactorial diseases such as AD. For this reason, integrative work focused on pharmacoinformatics should be done, thus enhancing the likelihood of success in medicinal chemistry campaigns to find new bioactive chemical entities.

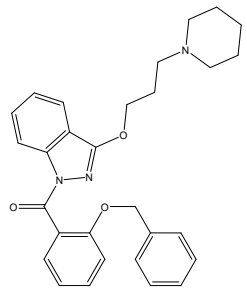
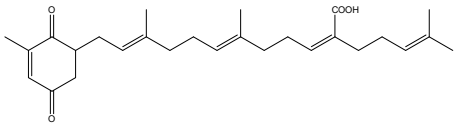
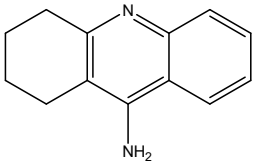
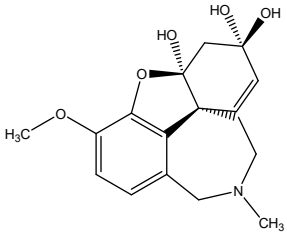
Multi-target anti-alzheimer agents

Given the need for effective drugs with fewer side effects and, as a trend in pharmacology, following the intention to intervene in more than one of the targets involved in certain pathologies, especially in multifactorial diseases such as AD, several authors have devoted their efforts to the pharmacoinformatic and experimental design of multi-target compounds against AD (Table 1). Thus, by simultaneously modulating more than one key target involved in the pathophysiology of AD, the biological effect of a given drug could be enhanced, and thus its therapeutic profile, while reducing the potential toxicity and adverse effects associated with a combined drug therapy.

For an effective multitarget drug design, the different types of molecular targets involved in the pathophysiology of the disease must be known. In this sense, for AD, there are several key targets [18], mainly involved in cholinergic, amyloid and neurofibrillary tangles hypotheses. In addition, there are other targets that have secondary actions such as those that regulate wakefulness, related to the modulation of acetylcholine as well as other neurotransmitters. These include the Muscarinic Acetylcholine Receptors (mAchR), dopamine 2 receptor, γ-aminobutyric acid A receptor, γ-glutamate metabotropic receptor, serotonin 5-HT6 receptor, Monoamine Oxidase B (MAO-B), nicotinic acetylcholine receptors (nAChR), angiotensin receptor, Amyloid Precursor Protein (APP), among others. Some FDA approved drugs and compounds in preclinical stages, with polypharmacological activity against two or more key targets are described in Table 1 [19-24].

Table 1: Multi-target drugs described in Alzheimer´s disease.

Compound	Structure	IC_{50} (μM)	Ref
Donepezil		AChE: 0,023 BACE1: 0,17	[19]
Rivastigmine		AChE: 3.03 BuChE: 0.03	[20]
Memantine		NMDA receptor: 1,04	[21]
NP137		BuChE: 42% (>10) BACE1: 60% (10 μM) CB2: Agonist	[22]

NP148		BuChE: 0.0025 BACE1: 38.35% (10 µM) CB2: Agonist	[22]
3		AChE: 69.3 BuChE: 10.5 BACE1: 12.1	[23]
Tacrine		AChE: 0.424 BuChE: 0.045	[24]
Galantamine		AChE: 1.59 BuChE: 10.93	[25]

Conclusions and future perspectives

AD is multifactorial in nature, so the search for therapeutic alternatives is not an easy task. In order to face this challenge, experimental and theoretical work must be combined very well, allowing us to reduce costs and time, thus enhancing the efforts implemented in the drug discovery process. The pharmacoinformatics perspective offers us the possibility of using multiple computational approaches to "navigate" through the large amount of information available (mostly in scientific databases), thus finding "clues" that are sufficiently solid to develop hypotheses that allow us to delimit an experimental investigation. The choice of the most appropriate computational approach (es) will depend on the nature of the pathology under study, and in the case of neurodegenerative diseases, the use of several integrative methodologies is recommended (Figure 1). Future efforts should be directed in more detail to unravel the nodes and edges of the network linking AD to drugs and therapeutic targets. Efficiently integrating the huge and heterogeneous amount of available information (biochemical, pharmacological, clinical data, etc.) into a workflow is not a simple task, so employing different pharmacoinformatics methods will provide valuable opportunities to broaden the domain of applicability of each method and further exploit information from different sources, thus improving the integration of multidisciplinary work. An approach based on protein-protein and protein-drug interaction networks will provide new pathways to surf through all potential links between drugs and neurodegenerative diseases, thus creating new opportunities for anti-Alzheimer's drug discovery.

Acknowledgment

The authors would like to thank the CONICYT-PCI grant Nº REDES190074 and Proyecto Dicyt Asociativo 022101MB_DAS.

References

1. Carrera I, Cacabelos R. Current Drugs and Potential Future Neuroprotective Compounds for Parkinson's Disease. Curr Neuropharmacol. 2018; 17: 295-306.
2. Kaur S, DasGupta G, Singh S. Altered Neurochemistry in Alzheimer's Disease: Targeting Neurotransmitter Receptor Mechanisms and Therapeutic Strategy. Neurophysiology. 2019; 51: 293-309.
3. Mount C, Downton C. Alzheimer disease: progress or profit? Nat Med. 2006; 12: 780-784.
4. Lahiri DK, Farlow MR, Sambamurti K, Greig NH, Giacobini E, Schneider LS. A critical analysis of new molecular targets and strategies for drug developments in Alzheimer's disease. Curr Drug Targets. 2003; 4: 97-112.
5. Zeng H, Wu X. Alzheimer's disease drug development based on Computer-Aided Drug Design. Eur J Med Chem. 2016; 121: 851-863.
6. Williams P, Sorribas A, Howes M-JR. Natural products as a source of Alzheimer's drug leads. Nat Prod Rep. 2011; 28: 48-77.
7. Rosini M, Simoni E, Minarini A, Melchiorre C. Multi-target Design Strategies in the Context of Alzheimer's Disease: Acetylcholinesterase Inhibition and NMDA Receptor Antagonism as the Driving Forces. Neurochem Res. 2014; 39: 1914-1923.
8. Son M, Park C, Rampogu S, Zeb A, Lee KW. Discovery of novel acetylcholinesterase inhibitors as potential candidates for the treatment of alzheimer's disease. Int J Mol Sci. 2019; 20: 1-15.
9. Chaudhary A, Maurya PK, Yadav BS, Singh S, Mani A. Current Therapeutic Targets for Alzheimer's Disease. J Biomed Biotechnol. 2018; 3: 74-84.
10. Hooper C, Killick R, Lovestone S. The GSK3 hypothesis of Alzheimer's disease. J Neurochem. 2008; 104: 1433-1439.

11. Herrera Rivero M, Hernández Aguilar ME, Manzo Denes J, Aranda Abreu GE. Enfermedad de Alzheimer: inmunidad y diagnóstico. Revista de Neurología. 2010; 51: 153.

12. Caberlotto L, Nguyen T-P. A systems biology investigation of neurodegenerative dementia reveals a pivotal role of autophagy. BMC Syst Biol. 2014; 8: 65.

13. Nguyen TP, Priami C, Caberlotto L. Novel drug target identification for the treatment of dementia using multi-relational association mining. Sci Rep. 2015; 5: 1-13.

14. Lavecchia A. Machine-learning approaches in drug discovery: Methods and applications. Drug Discov Today. 2015; 20: 318-331.

15. Afantitis A, Melagraki G, Koutentis PA, Sarimveis H, Kollias G. Ligand-based virtual screening procedure for the prediction and the identification of novel β-amyloid aggregation inhibitors using Kohonen maps and Counterpropagation Artificial Neural Networks. Eur J Med Chem. 2011; 46: 497-508.

16. Ghosh S, Nie A, An J, Huang Z. Structure-based virtual screening of chemical libraries for drug discovery. Curr Opin Chem Biol. 2006; 10: 194-202.

17. Gu L, Lu J, Li Q, Wu N, Zhang L, Li H, et al. A network-based analysis of key pharmacological pathways of Andrographis paniculata acting on Alzheimer's disease and experimental validation. J Ethnopharmacol. 2020; 251: 112488.

18. Gong C-X, Liu F, Iqbal K. Multifactorial Hypothesis and Multi-Targets for Alzheimer's Disease. J Alzheimers Dis. 2018; 64: S107-S117.

19. Muñoz-Torrero D. Acetylcholinesterase Inhibitors as Disease-Modifying Therapies for Alzheimer's Disease. Frontiers in Medicinal Chemistry. 2008; 34-86.

20. Bolognesi ML, Banzi R, Bartolini M, Cavalli A, Tarozzi A, et al. Novel Class of Quinone-Bearing Polyamines as Multi-Target-Directed Ligands to Combat Alzheimer's Disease. J Med Chem. 2007; 50: 4882–4897.

21. Parsons CG. Comparative patch-clamp studies with freshly dissociated rat hippocampal and striatal neurons on the NMDA receptor antagonistic effects of amantadine and memantine. Eur J Neurosci. 1996; 8: 446-454.

22. Nuñez-Borque E, González-Naranjo P, Bartolomé F, Alquézar C, Reinares-Sebastián A, Pérez C, et al. Targeting Cannabinoid Receptor Activation and BACE-1 Activity Counteracts TgAPP Mice Memory Impairment and Alzheimer's Disease Lymphoblast Alterations. Mol Neurobiol. 2020.

23. Seong SH, Ali MY, Kim HR, Jung HA, Choi JS. BACE1 inhibitory activity and molecular docking analysis of meroterpenoids from Sargassum serratifolium. Bioorganic and Medicinal Chemistry. 2017; 25: 3964-3970.

24. Zha X, Lamba D, Zhang L, Lou Y, Xu C, Kang D, et al. Novel Tacrine-Benzofuran Hybrids as Potent Multitarget-Directed Ligands for the Treatment of Alzheimers Disease: Design, Synthesis, Biological Evaluation, and X-ray Crystallography. J Med Chem. 2016; 59: 114-131.

25. Lee S, Youn K, Lim GT, Lee J, Jun M. In silico docking and in vitro approaches towards BACE1 and cholinesterases inhibitory effect of citrus flavanones. Molecules. 2018; 23: 1-12.