The Research Progress of the Application of Bioinformatics in the Diagnosis and Treatment of Alzheimer's Disease

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Abstract

Alzheimer's disease (AD) is characterized by a complex pathogenesis, limited diagnostic methods, and a lack of effective therapeutic drugs in clinical settings, posing significant challenges in modern medical research. Bioinformatics offers new perspectives for identifying key pathological biomarkers of AD, analyzing differentially expressed genes in AD, screening for effective drug targets against AD, studying the mechanisms of AD pathogenesis, and discovering novel anti-AD drugs. However, data preprocessing and statistical analysis methods in bioinformatics research can significantly impact results, and there is a lack of consistency and coordination in analysis methods across platforms and laboratories in practical studies, making it difficult to compare data between studies. Therefore, it is crucial to establish standardized operating procedures and quality control protocols, improve the reproducibility of methods across platforms, and promote data comparison between studies.

Keywords
- Alzheimer's disease
- bioinformatics
- Chinese herbs
- Chinese herbal compound
- biomarkers
- therapeutic targets

Introduction

Alzheimer's disease (AD) is a degenerative disease of the central nervous system, primarily characterized by memory, cognitive, and language impairments, as well as behavioral changes, accounting for about 60% of all cases of dementia. Its pathological features mainly include the deposition of β-amyloid protein, neurofibrillary tangles, synaptic damage, and neuronal loss.[1] According to statistics, there are currently over 50 million people with dementia worldwide, and this number is expected to reach 152 million by 2050, with medical care and other related expenditures surpassing 1.1 trillion US dollars.[2] The pathogenesis of AD is not entirely clear, involving hypotheses related to oxidative stress, mitochondrial dysfunction, neuroinflammation, vascular changes, and abnormalities in metabolic pathways.[1] Moreover, no drugs with significant efficacy have been developed yet, making AD a focus and challenge in modern medical research.

Bioinformatics primarily focuses on biological data related to nucleic acids, proteins, analyzing and mining these data for applications in studying the origins of life, biological evolution, disease occurrence, and development patterns.[3] In recent years, the application of bioinformatics in researching the mechanisms, potential therapeutic targets, and drug design of AD has become increasingly widespread and important.[4] This article provides an overview of the

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applications of bioinformatics in the diagnosis, identification of potential targets, and drug development of AD.

The Application of Bioinformatics in the Diagnosis of Alzheimer's Disease

Currently, the diagnosis of AD in clinical settings is mainly through the collection of medical history, psychological assessments, and various imaging tests.[5] However, these indicators largely depend on the experience of physicians and carry a certain degree of subjectivity. Biomarkers can diagnose AD more rapidly, objectively, and accurately and are also crucial for monitoring the progression of AD and evaluating the effectiveness of treatments. Commonly used biomarkers for AD mainly include amyloid-β (Aβ), total microtubule-associated protein tau (t-tau), and phospho-tau (p-tau) proteins in cerebrospinal fluid (CSF).[6] The pathogenesis of AD is complex, and identifying new and effective biomarkers can not only improve the accuracy of AD diagnosis and understand its pathological mechanisms but also aid in drug development. The rapidly developing bioinformatics technologies provide a convenient and effective means for identifying biomarkers, and the combined use of various bioinformatics methods can uncover new biomarkers for AD and reveal the biological processes of the disease.

AD generally cannot be diagnosed through biopsies to obtain tissue samples, and postmortem tissue samples cannot reflect the early pathology of the disease. Therefore, body fluids are an ideal source for detecting AD biomarkers. CSF is located in the subarachnoid space and ventricular system of the brain and spinal cord. It carries the brain's interstitial fluid through the ventricular membranes, and the changes in proteins in the CSF can directly reflect the neuropathology of the brain. Therefore, CSF biomarkers are a fundamental neuropathological indicator, widely used in the diagnosis of neurodegenerative diseases.[7] In recent years, many proteins in the CSF have been identified as potential biomarkers for AD, such as neuroflament light (NFL)-related to neuronal damage, neurogranin and synaptosome associated protein 25 (SNAP-25) reflecting synaptic dysfunction unsoluble triggering receptor expressed on myeloid cells 2 (sTrem2) and chitinase-3-like protein (YKL-40) for neuroinflammation, etc.[8] In a proteomics study on AD CSF biomarkers, Bader et al[9] developed a highly reproducible mass spectrometry proteomics workflow called the "rectangular strategy," which allows for deep analysis with minimal volumes of CSF. This study not only identified known AD biomarkers, such as tau protein, but also screened 40 new potential biomarkers, including Parkinson protein 7 (PARK7) and superoxide dismutase 1 (SOD1) related to neurodegeneration, tyrosine 3-monooxygenase (YWHAZ) related to AD genetics, chitinase 3 like 1 (CHI3L1) reflecting astrocyte activation, and many proteins related to glucose metabolism. Li et al[10] identified 29 significantly differentially expressed proteins by analyzing the differential protein expression in the CSF of AD patients compared to healthy individuals. Through functional enrichment analysis, they found that these proteins were mostly concentrated in metabolic-related pathways. To further identify central proteins in the CSF of AD patients, the team used the Least Absolute Shrinkage and Selection Operator regression and random forest feature selection algorithms for further data processing, screening out six central proteins: YWHAZ, SPARC-related modular calcium binding 1 (SMOC1), CH3L1, aldolase A (ALDOA), secreted phosphoprotein 1 (SPP1), and pyruvate kinase M (PKM). Among them, SMOC1, ALDOA, and PKM were specifically upregulated in AD patients and highly correlated with Aβ and tau protein pathology, making them potential biomarkers for diagnosing AD.

At the same time, blood also contains a large number of disease-related proteins and can be obtained noninvasively, with simple sampling, high efficiency and low cost. Yao et al[11] combined computational prediction with experimental validation for the first time to identify blood protein biomarkers for AD. They first collected tissue transcriptome data from AD patients and healthy control groups from the Gene Expression Omnibus database, identifying 2,754 differentially expressed genes. Then, they used a blood secretion protein prediction program to predict these genes, finding 296 genes encoding AD-related blood secretory proteins. Based on the expression levels of these proteins' corresponding genes, their functions, and their relevance to AD, they selected 10 proteins as potential biomarkers for AD. Finally, they collected blood samples from AD patients and healthy controls and conducted experimental validation through the enzyme-linked immunosorbent assay, where gelsolin, brain-derived neurotrophic factor, tissue inhibitor of metalloproteinases 1 (TIMP1), very low-density lipoprotein receptor (VLDLR), and amyloid beta precursor like protein 2 were consistent with the prediction results. Receiver operating characteristic curve analysis found that TIMP1 and VLDLR had the strongest ability to differentiate AD patients from healthy controls, which was also confirmed by subsequent western blot experiments. TIMP1 is a cytokine with neuroprotective effects, capable of improving cognitive dysfunction in AD by clearing Aβ protein deposits and maintaining synaptic integrity.[12] VLDLR is an aolipoprotein E (ApoE) receptor related to the risk factors for AD, distributed in synaptic regions. It participates in neuronal synaptic plasticity and affects learning and memory abilities by regulating the renin-angiotensin system (Ras) signaling pathway associated with neurodegenerative changes such as AD, altering the formation of presynaptic and postsynaptic dendritic spines.[13] In the blood of AD patients, TIMP1 significantly increases and VLDLR significantly decreases,[11] suggesting that TIMP1 and VLDLR could potentially become new blood biomarkers for AD. The abovementioned research provides an effective method for finding AD-related biomarkers in blood. However, a limitation is that gene expression changes do not accurately reflect protein expression changes. Therefore, the proteins predicted by this method need further validation in large-scale blood samples.

In addition, body fluids such as saliva and urine can also be used as noninvasive samples for the diagnosis of AD. For example, Guo et al[14] used sequencing technology to detect saliva and gingival crevicular fluid of subjects. β diversity

analysis showed a significant difference in the periodontal microbiota between AD patients and control group, and the main species of the microbiota changed with the severity of AD.

Although many body fluids are easily obtainable, different sample collection procedures, such as serum and plasma, quantitative platforms, etc., can have a certain impact on research results. Ideal biomarkers should meet conditions such as disease specificity, result reproducibility, and translatability from the laboratory to clinical settings. Therefore, large-scale prospective multicenter studies are needed for these identified potential AD biomarkers. Compared to traditional research methods, bioinformatics technology has the advantages of high throughput and big data and can achieve automated analysis and processing of data through computer programs and algorithms, effectively avoiding human intervention. It has now become an important approach for further exploration of the pathogenesis of AD and diagnosis based on biomarkers.

The Application of Bioinformatics in Exploring Therapeutic Targets for Alzheimer's Disease

Due to the complex pathological process of AD, identifying effective therapeutic targets is particularly challenging. As mentioned above, there are multiple pathogenic hypotheses in the occurrence and progression of AD, each of which provides a possible strategy for treating AD.

Bioinformatics has become an important tool for identifying therapeutic targets for AD. Some transcriptomic studies on AD have reported that stress and immune responses are closely related to the pathogenesis of AD,[15–17] which could serve as potential therapeutic targets for AD. However, these studies have analyzed small sample sizes and only assessed differential expression at the single gene level, which has certain limitations. Park et al[18] first used two independent cohorts, Alzheimer's disease neuroimaging initiative (ADNI) and AddNeuroMed, to conduct weighted gene coexpression network analysis based on blood samples from AD patients. They identified AD-related modules, determined the biological pathways enriched in AD-related modules through enrichment analysis, and conducted correlation analysis with known AD biomarkers such as $A\beta_{42}$ and p-tau. Studies have found significant dysregulation of the Fc gamma (Fcγ) receptor-mediated phagocytosis pathway, osteoclast differentiation pathway, and tuberculosis pathway in ADNI and AddNeuroMed. Key genes ankyrin repeat and PH domain 1 (ASAP1) and protein kinase C delta (PRKCD) in the Fcγreceptor-mediated phagocytosis pathway show abnormal expression, and PRKCD is strongly correlated with cognitive function, $A\beta_{42}$, and p-tau. This suggests that blocking the Fcγ receptor and its pathway may alleviate AD pathology. Phitthayaphong et al[19] provided experimental evidence for this viewpoint through in vitro experiments.

In recent years, emerging single-cell sequencing technology has become an effective approach to deeply understand the molecular mechanisms and to identify therapeutic targets in the pathophysiological process of AD. Some single-cell sequencing studies on AD brain tissue have identified a series of brain cell clusters related to AD,[20,21] but these studies have mainly focused on clustering and differential analysis, without fully utilizing the single-cell sequencing data. Lau et al[22] conducted single-nucleus transcriptome analysis on 169,496 nuclei from cortical samples of AD patients and normal control group, identifying 43 specific cell clusters. Differential analysis showed that cell type-specific transcriptional changes in AD were associated with disruptions in biological processes such as angiogenesis, immune activation, synaptic signaling, and myelination. Subcluster analysis indicated that AD brains contain fewer neuroprotective astrocytes and oligodendrocytes compared to normal brains and induced a subpopulation of angiogenic endothelial cells.

These angiogenic endothelial cells exhibit increased expression of angiogenic growth factor and its receptors EGF-like domain multiple 7 (EGFL7), Fms-related receptor tyrosine kinase 1, von willebrand factor, and antigen presentation mechanism beta-2-microglobulin and major histocompatibility complex, indicating that the pathogenesis of AD may be related to dysregulation of angiogenesis and antigen presentation in endothelial cells. These studies have revealed previously unknown pathological molecular changes and cell targets, providing an important theoretical basis for the treatment or improvement of AD pathological progress.

Bioinformatics technology has provided some new ideas for exploring the treatment of AD, but how to reasonably and accurately analyze a large amount of research data, explore key signaling targets, and promote clinical translation remains a research hotspot in the fields of bioinformatics and neuroscience.

The Application of Bioinformatics in Drug Research for Alzheimer's Disease Treatment

Current Status of Drugs for Alzheimer's Disease Treatment

The treatment methods for AD so far mainly fall into two directions: (1) Preventing or delaying the onset and progression of AD to reduce or even repair neuronal damage; (2) Symptomatic treatment aimed at improving cognitive impairment and controlling psychiatric symptoms. Currently, the AD treatment drugs approved by the Food and Drug Administration (FDA) mainly focus on symptomatic treatment, including acetylcholinesterase inhibitors (donepezil, galantamine, rivastigmine, and huperzine A), and N-methyl-D-aspartic acid receptor antagonists (memantine hydrochloride). These drugs can only alleviate patient symptoms, have a single therapeutic effect and limited duration, unable to produce significant disease improvement effects.[23,24] The Aβ-targeting monoclonal antibody Aducanumab, which was newly approved for marketing in 2021, also failed to prevent or delay the progression of AD, and its efficacy has been controversial.[25] Therefore, there is an urgent need for new treatment methods that can prevent or delay clinical

symptoms of AD, slow down or even terminate the pathological progression of AD.

The Application of Bioinformatics in the Research on Chinese Herbs in Treating Alzheimer's Disease

Compared to FDA-approved Western medicine, Chinese herbs have the characteristics of multiple components and targets, as well as unique advantages such as overall regulation, reliable efficacy, and minimal adverse reactions. Bioinformatics plays an important role in the research and development of new Chinese herbs in treating AD. By utilizing bioinformatics technology, rich information related to drugs can be effectively managed, such as the molecular targets of drugs, the association between targets and diseases, and the interactions of targets in cellular network environments. Based on the analysis of these data, the biological activity and pharmacokinetic characteristics of Chinese herbs can be predicted, thereby identifying potential drugs for AD. So far, many research works have proven that Chinese herbs have significant anti-AD effects.

The Application of Bioinformatics in the Research on Single Chinese Herb in Treating Alzheimer's Disease

Many databases provide the basis for bioinformatics research on Chinese herbs in treating AD. Sun et al[26] conducted large-scale literature data mining on PubMed and clinical trial databases (www.Clinicaltrials.gov), proving that various Chinese herbs and their active ingredients, such as Yinxingye (Ginkgo Folium), Shishan (Huperzia), and Danshen (Salviae Miltiorrhizae Radix et Rhizoma), can exert anti-AD effects by inhibiting AD-related pathways, such as down-regulating intracellular Ca^{2+} homeostasis and inhibiting inflammatory cytokines. Ginsenoside Rd is an active ingredient with broad pharmacological effects in Renshen (Ginseng Radix et Rhizoma). Chen et al[27] conducted literature searches on major scientific databases such as China national knowledge infrastructure, Elsevier, ScienceDirect, and PubMed and found that ginsenoside Rd is a neuroprotective agent with anti-inflammatory, antioxidative, antiapoptotic, and mitochondrial protective effects. It can inhibit neurotoxicity and regulate nerve growth factors to promote nerve regeneration through these pathways, making it a multifunctional lead compound for the treatment of AD and even neurodegenerative diseases.

In recent years, network pharmacology has become one of the hot topics in the field of traditional Chinese medicine (TCM) research. Wang et al[28] used a combination of network pharmacology and comparative metabolomics to study the main active ingredients of the Chinese herb Huangjing (Polygonati Rhizoma) and its anti-AD target effects. They further used molecular docking to identify the binding ability of these active ingredients with the AD-related target AChE. Finally, they verified the actual therapeutic effects of several key active ingredients in Huangjing (Polygonati Rhizoma) on AD through in vivo and in vitro experiments. The results indicated that the active ingredients in Huangjing (Polygonati Rhizoma), such as cafestol, rutin, and isorhamnetin, can significantly inhibit AChE activity, increase neuronal cell vitality, exhibit anti-inflammatory properties, and reduce oxidative stress damage, thereby demonstrating a multilayered anti-AD effects.

In addition, various molecular simulation methods have been widely used in AD drug development. Shinzato et al[29] conducted studies on the binding characteristics of some curcumin derivatives with Aβ using protein-ligand docking simulations and fragment molecular orbital methods. They found that when the COH_3 group in the aromatic ring of curcumin-Ib was substituted with OH, it can strongly bind to Aβ and effectively inhibit Aβ aggregation, thus playing a therapeutic role in AD treatment.

The Application of Bioinformatics in the Study of Chinese Herbal Compound Treatment for Alzheimer's Disease

Chinese herbal compound refers to a prescription composed of two or more Chinese medicinal ingredients. It has complex chemical compositions and exerts pharmacological effects on multiple components and targets. The synergistic effects among various drugs often result in better therapeutic outcomes compared to single herbal medicine. Traditional pharmacology, molecular biology, and other experimental methods have limitations in fully elucidating the characteristics of drug effects. Therefore, the application of bioinformatics techniques in the study of Chinese herbal compound is more advantageous for the development of therapeutic drugs.

Research has shown that Liuwei Dihuang Pill, a classic Chinese herbal formula, has the effects of regulating immune cell infiltration to alleviate neuroinflammation, reducing Aβ aggregation, and delaying cognitive impairment.[30] However, the specific molecular mechanisms of its action have not been fully understood. Zhao et al[31] used bioinformatics methods to explore the molecular immune mechanism of Liuwei Dihuang Pill in the treatment of AD by studying the infiltration patterns of different types of immune cells in AD. The study found that in hippocampal tissue samples from AD patients, the infiltration levels of M2 macrophages and quiescent CD4+ memory T cells were higher compared to healthy individuals, and there were significant differences in the infiltration levels of M1 macrophages as well. Protein–protein interaction (PPI) network analysis revealed that Liuwei Dihuang pill could regulate two core immune targets in AD, nuclear factor kappa B inhibitor alpha, and protein kinase C beta (PRKCB), which were involved in multiple biological signaling pathways. Among them, PRKCB showed the best molecular docking effect with quercetin, a key active component of the herbal formula. Therefore, through bioinformatics, the study discovered and confirmed that Liuwei Dihuang Pill can regulate immune cell infiltration through multiple components, targets, and pathways, providing a new research direction for the immune therapy of AD.

Li et al[32] developed a new Chinese medicine formula called Nao Tan Qing based on the theory of resolving phlegm and opening orifices in TCM. The formula is composed of Dannanxing (Arisaema cum Bile), Huangqin (Scutellariae Radix), Huanglian (Coptidis Rhizoma), Banxia (Pinelliae Rhizoma), Tianma (Gastrodiae Rhizoma), Ganjiang (Zingiberis Rhizoma), Shichangpu (Acori Tatarinowii Rhizoma), and Gancao (Glycyrrhizae Radix et Rhizoma). This study used network pharmacology

and omics analysis to discover that Nao Tan Qing can inhibit neuroinflammation in AD mice by regulating the NF-κB and Toll-like receptor pathways while also regulating their glucose and lipid metabolism. The study demonstrated that Nao Tan Qing may improve AD by modulating signal pathways associated with neuroinflammation and metabolism and is a potential drug for the treatment of AD.

Shen et al[33] applied network pharmacology to explore the action targets, pathways, and mechanisms of Chuanxiong Renshen Decoction (CRD) in the treatment of AD. The study first identified the main effective components of CRD using mass spectrometry analysis, retrieved potential targets of CRD components from the SwissTargetPrediction database, and screened AD-related targets from the Disgenet and Genacards databases. By taking the intersection of these two sets of targets, they obtained 65 potential key target genes for CRD in the treatment of AD. PPI network analysis identified the core targets for the treatment of AD as caspase 3, epidermal growth factor receptor, amyloid beta precursor protein, cannabinoid receptor 1, prostaglandin-endoperoxide synthase 2, and glutamate metabotropic receptor 5. Molecular docking results showed good binding of each component with potential core targets. Gene Ontology and Kyoto Encyclopedia of Genes and Genomes enrichment analysis indicated a concentration on the tumor necrosis factor (TNF) signaling pathway, and mitogen-activated protein kinase 1 (MAPK) signaling pathway.

The Application of Bioinformatics in the Research on Combined Chinese Medicine and Western Medicine Treatment for Alzheimer's Disease

Research has confirmed that the combined use of Chinese medicine and Western medicine showed a stronger anti-AD effect compared to using them individually.[34] Wang et al[35] conducted a network meta-analysis on the effect of Kidney-tonifying Decoction combined with donepezil in the treatment of AD. A total of 56 related studies were retrieved, and 30 randomized clinical trials were eventually included. The analysis revealed that the total effective rate of the treatment of AD with Kidney-tonifying Decoction and donepezil in combination was the highest at 88%, followed by Kidney-tonifying Decoction alone at 58.5% and donepezil alone at 3.5%. Compared to single-drug therapy, combination therapy can significantly improve clinical symptoms of AD such as memory decline and motor dysfunction, resulting in better clinical efficacy. However, the specific action mechanisms still require further investigation.

The pure bioinformatics prediction research on Chinese herbs and compound formulas for treating AD is still somewhat limited (see ►**Table 1**). In future research, a combination of bioinformatics and experimental verification can be used to more deeply explore the mechanism of action and pharmacological substance basis of Chinese herbs and compound formulas, and better serve clinical practice.

Table 1 The application of bioinformatics in the treatment of AD with Chinese herbs

Chinese herbs	Research method	Action mechanism
Yinxingye (Ginkgo Folium), Shishan (Huperzia), and Danshen (Salviae Miltiorrhizae Radix et Rhizoma)	Data mining	Downregulation of intracellular Ca^{2+} homeostasis, inhibition of inflammatory cytokines, and inhibition of AD-related pathways[26]
Ginsenoside Rd	Data mining	Inhibition of neurotoxicity, regulation of nerve growth factor to promote nerve regeneration[27]
Huangjing (polygonati rhizoma)	Network pharmacology combined with metabolomics	Inhibition of AChE activity, enhancement of neuronal cell vitality, anti-inflammatory effects, and reduction of oxidative stress damage[28]
Curcumin-Ib	Protein-ligand docking simulation and fragment molecular orbital	Effective inhibition of Aβ aggregation[29]
Liuwei Dihuang Pill	Data mining combined with molecular docking	Multifaceted regulation of immune cell infiltration[31]
Nao Tan Qing	Network pharmacology combined with metabolomics	Inhibition of neuroinflammation through the NF-κB and Toll-like receptor pathways, while also regulating glucose and lipid metabolism[32]
Chuanxiong Renshen Decoction	Network pharmacology combined with molecular docking	Regulation of the TNF signal pathway and MAPK signal pathway[33]
Kidney-tonifying Decoction combined with donepezil	Meta-analysis	Improvement of clinical symptoms of AD such as memory decline and motor dysfunction[35]

Abbreviations: Aβ, amyloid-β; AChE, acetylcholinesterase; AD, Alzheimer's disease; MAPK, mitogen-activated protein kinase 1; TNF, tumor necrosis factor.

Conclusion

The pathological process of AD is complex, and the pathogenesis is not yet clear. Currently, there is a lack of simple and effective diagnostic methods in clinical practice, and it also faces many challenges of anti-AD drugs. The emergence of bioinformatics provides new ideas for screening key pathological biomarkers of AD, analyzing differentially expressed genes in AD, exploring new targets, and discovering new anti-AD drugs. It is worth noting that in bioinformatics research, data preprocessing (such as detection of abnormal values, data normalization, etc.) and statistical analysis methods will have a significant impact on the results. In actual research, the lack of consistent coordination in analysis methods across platforms and laboratories makes it difficult to compare data.[36] Therefore, it is crucial to establish standard operating procedures and quality control protocols, improve the repeatability of methods across platforms, and promote data comparison between studies. In addition, there are certain limitations in bioinformatics prediction research. Experimental validation at the biological level and in-depth interdisciplinary research should be conducted based on this foundation to determine the role of Chinese herbs and Chinese herbal compound in the complex mechanism of AD. Furthermore, these predictions must undergo clinical validation before they can further provide new theoretical basis for the comprehensive diagnosis and treatment of AD with Chinese medicine.

CRediT Authorship Contribution Statement

Zhiyang Yu: Conceptualization, data curation, software, and writing original draft. Wenpan Wang: Visualization, and formal analysis. Qiong Qiao: Data curation, and writing-review and editing. Yiran Sun: Software and methodology. Zhishen Xie and Junying Song: Project administration, writing-review and editing. Zhenqiang Zhang and Huifen Ma: Funding acquisition, supervision, writing-review and editing.

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Conflict of Interest

The authors declare no conflict of interest.

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