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COMPREHENSIVE REVIEW OF MULTI-DRUG TARGETING STRATEGIES FOR ALZHEIMER'S DISEASE FROM A "ONE HEALTH" PERSPECTIVE

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ABSTRACT

Alzheimer's disease (AD) is a leading cause of dementia, characterized by progressive cognitive decline and memory loss, and remains a major public health challenge worldwide. Current therapeutic options primarily address symptoms and offer limited efficacy, necessitating the exploration of innovative treatment strategies. This review focuses on multi-drug targeting approaches, which aim to address the multifactorial nature of AD by intervening at multiple pathogenic pathways simultaneously.

Multi-drug targeting strategies encompass the use of drug combinations, polypharmacology (single molecules with multiple targets), and the integration of pharmacological treatments with biological agents such as monoclonal antibodies. These approaches strive to modify disease progression by reducing amyloid-beta plaques, preventing tau aggregation, mitigating neuroinflammation, and preserving synaptic function.

Incorporating the "One Health" perspective, this review emphasizes the interconnectedness of human, animal, and environmental health in the context of AD. A holistic approach considers environmental factors, lifestyle, and co-morbidities, advocating for comprehensive interventions that include lifestyle modifications, dietary adjustments, and environmental controls alongside pharmacological treatments.

The objectives of this review are to provide a detailed analysis of multi-drug targeting strategies for AD within the "One Health" framework, evaluate their efficacy and safety, and discuss the potential benefits of integrating broader health determinants in therapeutic approaches. The review covers the pathophysiology of AD, current therapeutic limitations, detailed discussion of multi-drug strategies, and how environmental and lifestyle factors can enhance treatment outcomes. Through this

comprehensive analysis, the review aims to propose a more effective and holistic strategy for combating Alzheimer's disease.

Keywords; Alzheimer's Disease, Multi-Drug Targeting, Combination Therapy, Polypharmacology, One Health

1.INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive decline, memory loss, and a host of other cognitive impairments. As one of the leading causes of dementia worldwide, AD poses a significant public health challenge. Despite extensive research, current therapeutic strategies remain largely symptomatic, providing only modest improvements in cognitive function and quality of life. This has driven the search for more effective treatment approaches, including multi-drug targeting strategies.

2.BACKGROUNDS

Alzheimer's Disease (AD) is a complex neurodegenerative disorder with no current disease-modifying treatments available to halt its progression. The multifactorial nature of AD, characterized by amyloid-beta (Aβ) plaques, neurofibrillary tangles (NFTs), synaptic dysfunction, and neuroinflammation, necessitates a shift from the conventional "one-drug, one-target" approach to multi-drug targeting strategies. This comprehensive review synthesizes insights from recent research, advocating for a "One Health" perspective that encompasses a holistic approach to AD therapy[1][2]. Recent advancements in monoclonal antibodies targeting Aβ, such as donanemab and lecanemab, underscore the importance of targeting pathological hallmarks of AD but also highlight the limitations of single-target therapies[3]. The recognition of AD's multifactorial pathogenesis has spurred interest in multi-target strategies, aiming to address various aspects of the disease simultaneously. These strategies include the development of multi-target-directed ligands (MTDLs) that target multiple AD-related pathways, offering a promising avenue for more effective treatments[4][5].

Innovative approaches in drug development have focused on combining pharmacophores from bioactive molecules to target various pathogenic pathways, including oxidative stress, decreased neurotransmission, and neuroinflammation[6]. Hybrid therapeutic compounds, developed from naturally isolated molecules, specifically target and block various AD-associated pathogenic pathways, representing a significant advancement over conventional multitarget drug development methods[7]. Furthermore, the exploration of neuromodulators and their altered functions in AD presents another potential therapeutic avenue. Combining neuromodulator targeting with novel drug delivery methods, such as encapsulated nanoparticle systems, could overcome limitations of current treatments[8]. Additionally, the design of molecules based on pharmacophoric features of known compounds has led to the identification of promising multi-targeted agents, exemplified by compound 4c2, which exhibits significant AChE inhibitory activity and anti-neuroinflammatory potential[9]. The pursuit of effective therapies for AD also involves the identification of novel natural compounds targeting key regulatory

proteins, as demonstrated by the virtual screening and molecular dynamics simulation of natural product-like compounds[10]. This approach aligns with the "One Health" perspective by exploring the potential of nature-derived compounds in addressing the complex pathophysiology of AD. In conclusion, the shift towards multi-drug targeting strategies, encompassing MTDLs, hybrid therapeutic compounds, and nature-derived molecules, offers a promising path forward in the quest for effective AD therapies. This holistic approach, grounded in the "One Health" perspective, acknowledges the intricate interplay of various pathological mechanisms in AD and the need for comprehensive therapeutic strategies.

3. METHODOLOGY

The research adopted a mixed methodology in conducting a systematic review through the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (supplementary table 1) framework [11] Literature was sourced from databases including PubMed, Scopus, and Web of Science, covering publications from the past decade. Inclusion criteria focused on studies detailing biotechnological methods for the surveillance and control of EIDs. Data extraction and analysis were performed to evaluate the efficacy and innovation of the biotechnological approaches discussed.

3.1 Research questions

Based on the guidelines obtained from The University of North Carolina at Chapel Hill Libraries System, the present study developed research questions relevant by the [SPIDER (S-Sample, PI-Phenomenon of Interest, D-Design, E-Evaluation, R-Research Type)] framework, [12], as indicated in Table 1.

3. Quality assessment of included studies

The quality assessment using the Long and Godfrey Individual Assessment Instrument confirmed that most included studies are of high quality, providing robust evidence for the systematic review on multi-drug targeting strategies for Alzheimer's Disease. This rigorous evaluation enhances the reliability of the review's conclusions and supports the integration of qualitative insights into developing comprehensive treatment strategies within a "One Health" framework (see Table2)

4. RESULTS

Alzheimer's disease treatments can be developed using a multi-target strategy, which may effectively treat various pathologies. Namzaric TM has been beneficial in a combination treatment strategy. Clinical studies have shown the effectiveness of multi-target medicines with or without chloroquine (ChEs). Qikprop is used to determine drug-likeness and ADME characteristics. Herbal medicine has shown promise as a multi-target, multi-time treatment. Interdisciplinary biomarkers for cognitive impairment treatment using herbal medicine are being investigated. Current pharmacological therapy for Alzheimer's disease and its pathophysiology are reviewed. Examples of AD medications targeting multiple targets include compound 15 that inhibited four key AD targets without adverse effects,

compound 9 exhibiting PDE4D inhibitory efficacy and antioxidant properties, and compound 4c2 exhibiting strong AChE inhibitory action and Nrf2 activation. Machine learning is used to prioritize genes and medication candidates linked with risk.

4.1. **How effective are combination therapies in improving cognitive function and reducing pathological markers in patients with Alzheimer's Disease?**

Combination therapies have shown promise in improving cognitive function and reducing pathological markers in Alzheimer's Disease (AD) patients (see Table 3). Studies suggest that a combination of cell-based therapies, involving neural stem cells overexpressing ChAT, microglial cells encoding NEP or SRA genes, can synergistically restore learning and memory functions by eliminating Aβ deposits and recovering ACh levels [13]. Additionally, a combination of FDA-approved drugs, Fasudil targeting synaptic formation and Lonafarnib targeting cellular clearance pathways, effectively reduced intraneuronal Aβ and improved cognitive performance in AD mouse models [14]. Furthermore, a combination of metabolic activators led to enhanced cognitive functions and improved clinical parameters in AD patients, indicating the potential of combination therapies in treating AD [15].

4.1.1.the neuroprotective and cognitive effects of polypharmacology approaches in Alzheimer's Disease treatment

Polypharmacology approaches in Alzheimer's Disease (AD) treatment offer neuroprotective and cognitive benefits by targeting multiple pathways simultaneously [23]. These approaches involve compounds that modulate various mechanisms such as neuroinflammation, oxidative stress, and amyloid aggregation, which are crucial in AD pathogenesis. By utilizing multitarget compounds, polypharmacology aims to address the complexity of AD and provide disease-modifying effects, potentially improving memory functions and protecting neurons. For instance, compounds like polydatin have shown promise in counteracting AD-related neuroinflammatory, apoptotic, and oxidative stress pathways, highlighting their neuroprotective potential. Additionally, the development of innovative polypharmacological compounds targeting the endocannabinoid system demonstrates the efficacy of multitarget strategies in addressing neurodegenerative diseases like AD.

4.1.2. Polypharmacology approaches impact neuronal health in Alzheimer's

Polypharmacology approaches play a crucial role in impacting neuronal health in Alzheimer's disease (AD) by targeting multiple pathways simultaneously[24]. Traditional single-target drugs have shown limitations in treating the complex mechanisms of AD, leading to the emergence of polypharmacology as a promising strategy. By utilizing multitarget compounds, such as those affecting the endocannabinoid system, cholinesterases, and various other targets involved in AD pathology, polypharmacology offers a more comprehensive approach to combating neurodegeneration. These multi-target directed ligands can modulate several disease-related pathways, including

neuroinflammation, amyloid aggregation, and neuronal death, ultimately contributing to improved neuronal health and potential disease modification in AD.

4.1.3.the key mechanisms of polypharmacology in Alzheimer's

Polypharmacology in Alzheimer's disease (AD) involves targeting multiple pathways to address the complexity of the disease. Key mechanisms include the use of multi-target directed ligands (MTDLs) to regulate various targets in the AD network, such as cholinesterases, oxidative stress mechanisms, and neuroinflammatory responses [25]. This approach aims to provide disease-modifying effects by acting on different aspects of AD pathology simultaneously. By utilizing pharmaceutical agents that target multiple pathways, polypharmacology offers a promising strategy to combat the multifaceted nature of AD and potentially enhance therapeutic outcomes. Additionally, the exploration of phytochemicals as neuroprotective agents further contributes to the polypharmacological approach in AD treatment [26].

4.1.4. multiple drugs interact in Alzheimer's treatment

Multiple drugs interact in Alzheimer's treatment through the concept of polypharmacology, which involves using pharmaceutical agents that act on multiple targets simultaneously. This approach is crucial due to the complex nature of Alzheimer's disease (AD)[27]. For instance, acetylcholinesterase (AChE) inhibitors like donepezil, rivastigmine, and galantamine, along with N-methyl-D-aspartate (NMDA) receptor antagonist memantine, are FDA-approved drugs for symptomatic AD treatment[5]. Additionally, the development of multi-targeted drugs (MTDs) that can affect various determinants in AD pathophysiology is a promising strategy[28]. Recent research has focused on designing molecules that target AChE inhibition, neuroinflammation, and other pathways simultaneously to provide more effective treatment options for AD[29]. These multi-targeted agents show potential in improving cognitive function, reducing neuroinflammation, and even rescuing memory impairment in AD models.

4.2.What impact do repurposed drugs have on cognitive decline and disease progression in Alzheimer's Disease?

Repurposed drugs show promise in mitigating cognitive decline and disease progression in Alzheimer's Disease (AD). Studies suggest that repurposed drugs like Fasudil and Lonafarnib target AD neuropathologies effectively, reducing amyloid-β and tau pathologies, and improving memory performance [30]. Additionally, the sphingosine-1-phosphate analogue fingolimod demonstrates potential in reversing synaptic deficits and memory dysfunction in AD mouse models, even after disease onset [31]. Furthermore, chronic metformin treatment may enhance attention and inhibitory control in younger mice but lead to impairments in memory retention and discrimination learning at older ages, indicating a complex impact on cognitive functions [32]. These findings highlight the

importance of exploring repurposed drugs as potential therapeutic strategies to address cognitive decline and disease progression in AD.

4.2.1. repurposed drugs affect Alzheimer's cognitive decline

Repurposed drugs show promise in impacting Alzheimer's cognitive decline by targeting various neuropathologies simultaneously[32]. For instance, Fasudil reduces amyloid-β levels and plaques, while Lonafarnib targets tau neuropathology[2]. The combination of these drugs enhances the reduction of amyloid-β and improves contextual memory performance[31]. Regorafenib, a multikinase inhibitor, repurposed from cancer treatment, may inhibit amyloid-β aggregation, offering potential as an Alzheimer's therapeutic[32]. However, caution is advised with metformin, an anti-diabetic drug, as chronic treatment may exacerbate cognitive impairments and AD pathology, highlighting the need for careful reconsideration when repurposing this drug for AD patients[30]. Overall, repurposed drugs present a novel approach to address Alzheimer's cognitive decline by targeting multiple disease pathways simultaneously.

4.2.2. the potential side effects of repurposed Alzheimer's drugs

The potential side effects of repurposed Alzheimer's drugs include cognitive impairments, increased risk of Alzheimer's disease progression, and adverse effects on memory retention and learning[30]. Additionally, medications commonly used in Alzheimer's treatment, such as acetylcholinesterase inhibitors (AChEIs) and memantine, are considered relatively safe but may still have side effects that need to be monitored closely[32] [34]. Drug repurposing strategies have identified compounds like beta-blockers and multi-kinase inhibitors, which show promise in potentially lowering the risk of developing Alzheimer's disease, but their side effect profiles need further evaluation[35]. Therefore, while repurposed drugs may offer new avenues for Alzheimer's treatment, careful consideration of their side effect profiles is crucial for safe and effective use in patients.

4.2.3.repurposed Alzheimer's drugs affect cognitive function

Repurposed Alzheimer's drugs have shown promising effects on cognitive function. Studies have explored drug combinations like acamprosate and baclofen, targeting the excitatory and inhibitory systems to protect neurons and endothelial structures against amyloid-beta oligomers, ultimately alleviating cognitive deficits [32]. Additionally, repurposing drugs approved for other indications has led to clinical trials investigating their effects on Alzheimer's disease. For instance, atomoxetine, a norepinephrine transporter inhibitor, significantly reduced CSF Tau and pTau levels, normalized protein biomarkers linked to synaptic function, and increased brain activity in key temporal lobe circuits, showing potential for slowing disease progression [36]. Furthermore, hormone therapies like tibolone have been studied for their mitochondrial-protective effects, potentially reducing the risk or delaying the onset of Alzheimer's symptoms, particularly in postmenopausal women [37].

4.3.What are the safety and efficacy of gene therapy and RNA-based approaches in the treatment of Alzheimer's Disease?

Gene therapy and RNA-based approaches show promise in Alzheimer's Disease (AD) treatment. Gene therapy targets amyloid pathway intermediates, tau protein, APOE4 downregulation, and neurotrophin expression [38]. RNA-based strategies focus on microRNAs (miRNAs) as potential diagnostic tools and therapeutic targets, regulating gene expression in AD-affected brains [39] . While gene therapy trials have shown some benefits by upregulating nerve growth factor (NGF) in AD patients, challenges like delivery methods and cost hinder widespread application . RNA-based approaches offer insights into disease mechanisms, potential biomarkers, and therapeutic targets, emphasizing the importance of exploring noncoding RNAs for novel AD treatments . Further research is needed to enhance the safety and efficacy of these innovative approaches in combating AD.

4.3.1. gene therapy approaches target Alzheimer's Disease

Gene therapy approaches targeting Alzheimer's Disease (AD) focus on various strategies to combat the neurodegenerative processes associated with the condition. One approach involves the development of small peptide inhibitors to prevent the formation of neurotoxic oligomers linked to AD and Parkinson's Disease [40]. Additionally, genetic therapies aim to target specific pathways and proteins implicated in AD, such as amyloid pathway intermediates, tau protein, APOE variants, and inflammatory cytokines [41]. Another promising avenue is the use of gene therapy to reduce the expression of CD33 on microglial cells, which has shown to decrease amyloid beta accumulation and neuroinflammation in AD models [42]. Furthermore, advancements in nonviral gene therapy methods are being explored to modulate key factors like amyloid beta, BACE1, apolipoprotein E, and neurotrophic factors in the CNS [43].

4.3.2. the latest advancements in gene therapy for Alzheimer's

The latest advancements in gene therapy for Alzheimer's disease (AD) involve targeting key genes and pathways associated with the disease. Nonviral gene therapy methods, such as physical and chemical approaches, aim to modulate the expression of amyloid beta, BACE1, apolipoprotein E, and neurotrophic factors in the central nervous system [44]. Genetic therapies in AD focus on upregulating nerve growth factor (NGF), downregulating tau protein, and altering inflammatory cytokines [42]. Advanced gene delivery techniques, including viral vectors, plasmid transfection, nanoparticles, and CRISPR-based therapeutics, offer promising avenues for treating AD and other neurological disorders [46]. Antisense oligonucleotides (ASO) have emerged as a novel strategy to inhibit the translation of pathological genes involved in AD, potentially reducing the development of toxic protein aggregates. These approaches highlight the potential of nucleic acid-based therapies in addressing the complexities of AD treatment [47].

4.4.How do environmental factors and cross-species studies contribute to our understanding of Alzheimer's Disease etiology and progression?

Environmental factors play a crucial role in understanding Alzheimer's Disease (AD) etiology and progression[48]. Studies highlight the impact of environmental enrichment, such as increased physical activity, in preventing neuronal loss and promoting neurogenesis in AD mouse models[4]. Additionally, investigations into gene-environment interactions in individuals at risk of AD shed light on the complex interplay between genetics, environmental exposures, and AD biomarkers[49]. Cross-species studies, particularly in rhesus monkeys, provide valuable insights into the initiation and progression of AD pathology, emphasizing the role of dysregulated molecular signaling events, tau phosphorylation, and inflammation in aging association cortices. By integrating data from environmental factors and cross-species studies, researchers can enhance their understanding of AD pathogenesis and potentially identify new therapeutic targets.

4.4.1.environmental pollutants impact Alzheimer's Disease development

Environmental pollutants, such as particulate matter (PM), ultrafine particles (UFPs), and polycyclic aromatic hydrocarbons (PAHs), play a significant role in impacting the development of Alzheimer's Disease (AD). These pollutants can lead to neurodegenerative changes in the brain, oxidative stress, neuroinflammation, and cognitive impairment [50]. Specifically, exposure to PM2.5 has been linked to cognitive decline and an increased risk of AD, with constituents like black carbon, organic matter, sulfates, and ammonium significantly associated with the development of dementia and AD [51]. Furthermore, PAHs like Benzo[a]Pyrene have been shown to interact with Aβ42 peptides, accelerating or suppressing their oligomerization kinetics, which is crucial in the progression of AD . Molecular dynamics simulations have also highlighted the inhibitory effect of UFPs on the formation of beta sheets in amyloid beta peptides, further implicating environmental pollutants in AD development [52].

4.4.2. the main sources of environmental pollutants

The main sources of environmental pollutants encompass a wide array of anthropic activities and natural occurrences. These sources include emissions from motor vehicles, industrial operations, volcanic eruptions, toxic emissions, forest fires, deforestation, bush burning, and cosmic dust clouds, contributing to air pollution [1]. Additionally, pollutants such as hydrocarbons, chlorinated compounds, pesticides, explosives, endocrine-disrupting chemicals, polyfluorinated compounds, and pharmaceutically active compounds from various industries and agricultural practices contaminate water bodies, leading to water pollution [2]. Furthermore, toxic pollutants like sewage, particulates from power plants, heavy metals from mining, and chemicals from industries contaminate the air, land, and water, posing immediate health risks to humans and ecosystems [3] [4]. Moreover, toxic metals and metal(loid)s originating from agricultural, domestic, and industrial effluents are persistent pollutants that threaten the environment and human health globally [5].

4.5.How does a "One Health" perspective influence the development and implementation of these strategies?

Multi-drug targeting strategies for Alzheimer's Disease benefit from a "One Health" perspective by emphasizing the interconnectedness of human health with animals, plants, and ecosystems, promoting a holistic approach to healthcare. This perspective encourages the consideration of various factors influencing disease development and treatment, leading to the exploration of multi-target directed ligands (MTDLs) that can address the complex pathophysiological pathways of Alzheimer's Disease effectively [10] [26]. By integrating insights from diverse disciplines and recognizing the interdependencies of health across different domains, such strategies can offer a comprehensive and synergistic approach to combating Alzheimer's Disease, potentially enhancing treatment outcomes and paving the way for more effective therapeutic interventions [2].

4.5.1.Multi-Drug Targeting Strategies differ in Alzheimer's treatment

Multi-Drug Targeting Strategies in Alzheimer's treatment aim to address the multifactorial nature of the disease by simultaneously targeting multiple biological pathways[28] [2] [3] [4] [53]. These strategies involve the development of multi-target directed ligands (MTDLs) or compounds that can act on various enzymes and receptors implicated in Alzheimer's pathogenesis, such as acetylcholinesterase (AChE), soluble epoxide hydrolase (sEH), and fatty acid amide hydrolase (FAAH). By targeting multiple pathways like Aβ and tau aggregation, metal toxicity, oxidative stress, and neuroinflammation, these strategies offer a holistic approach to treatment. Additionally, combining neuromodulator targeting with innovative drug delivery methods can enhance therapeutic outcomes by overcoming traditional treatment limitations. Overall, Multi-Drug Targeting Strategies provide a promising avenue for more effective and comprehensive Alzheimer's disease management.

4.6. What challenges remain in the comprehensive review of these strategies, and how can they be addressed?

Multi-Drug Targeting Strategies for Alzheimer's Disease face challenges due to the disease's multifactorial nature and the limitations of conventional single-target treatments.[1][2] Despite advancements in targeting amyloid beta and tau proteins, current therapies only provide temporary symptomatic relief.[54] The complexity of AD, with genetic, transcriptomic, and proteomic variations, complicates drug discovery efforts.[55] The need for a paradigm shift towards multi-target approaches is emphasized to address the diverse pathophysiological pathways involved in AD progression.[56] This shift is crucial for developing more effective therapies that can simultaneously target multiple aspects of the disease, offering a more comprehensive treatment strategy to combat the multifaceted challenges posed by Alzheimer's disease.

4.6.1. Multi-Drug Targeting Strategies impact Alzheimer's Disease treatment

Multi-Drug Targeting Strategies, such as Multi-Target Directed Ligands (MTDLs), play a crucial role in Alzheimer's Disease (AD) treatment by simultaneously inhibiting multiple enzymes involved in the disease's pathogenesis[28][57]. These strategies target key enzymes like acetylcholinesterase (AChE), monoamine oxidase B (MAO-B), soluble epoxide hydrolase (sEH), and fatty acid amide hydrolase (FAAH), aiming to address the multifactorial nature of AD[27][4]. By inhibiting these enzymes, MTDLs can potentially provide significant anti-AD effects, including anti-inflammatory, neuroprotective, and neurogenesis-promoting effects[58]. Computational approaches aid in the design and identification of novel multi-target compounds, offering a promising avenue for developing effective AD therapeutics. These multi-drug targeting strategies represent a holistic approach to AD treatment, addressing various pathological factors simultaneously for enhanced efficacy and potential disease-modifying effects.

5.SUMMARY

Combination therapies, polypharmacology approaches, repurposed drugs, gene therapy, and cross-species studies are promising approaches to Alzheimer's Disease (AD). Combination therapies target multiple mechanisms, such as FDA-approved drugs, metabolic activators, herbal medicine, and music therapy, to improve cognitive function and reduce pathological markers. Polypharmacology targets multiple pathways simultaneously, providing neuroprotective and cognitive benefits. Repurposed drugs, such as Fasudil, Lonafarnib, and fingolimod, show potential in reducing amyloid-β and tau pathologies and improving memory performance. Gene therapy and RNA-based approaches target amyloid pathway intermediates, tau protein, APOE4 downregulation, and neurotrophin expression, offering potential disease-modifying effects. Environmental factors and cross-species studies provide valuable insights into AD pathogenesis and identify new therapeutic targets.

The discussion around Alzheimer's disease (AD) treatment is evolving rapidly, with innovative strategies emerging to address the complex nature of the disease. One key area of focus is combination therapies, which target multiple mechanisms simultaneously to improve cognitive function and reduce pathological markers in AD patients. These therapies offer a holistic approach to treatment, combining FDA-approved drugs, metabolic activators, herbal medicine, and music therapy to enhance therapeutic outcomes.

6.DISCUSSION

Polypharmacology approaches are also gaining traction, aiming to provide neuroprotective and cognitive benefits by modulating various pathways involved in AD pathogenesis. By targeting neuroinflammation, oxidative stress, and amyloid aggregation, polypharmacology offers potential disease-modifying effects and may improve memory functions while protecting neurons.

Repurposed drugs present another promising avenue in AD treatment, with compounds like Fasudil, Lonafarnib, and fingolimod showing potential to mitigate cognitive decline and disease progression.

However, careful consideration of potential side effects is necessary for safe and effective use in AD patients.

Gene therapy and RNA-based approaches offer innovative strategies to target key genes and pathways implicated in AD. By regulating gene expression in AD-affected brains, these approaches aim to provide disease-modifying effects and enhance therapeutic outcomes.

Environmental factors and cross-species studies also play a crucial role in understanding AD etiology and progression. Pollution and other environmental factors have been linked to AD development, highlighting the need for further research in this area. Cross-species studies, particularly in non-human primates, provide valuable insights into AD pathology and may help identify new therapeutic targets.

Overall, the discussion around AD treatment is multifaceted, with researchers exploring a range of innovative strategies to combat this devastating disease. By taking a holistic approach and integrating insights from various disciplines, we can enhance our understanding of AD and develop more effective therapies to improve the lives of patients and their families.

7.CONCLUSION

In conclusion, the landscape of Alzheimer's disease (AD) treatment is rapidly evolving, with a growing emphasis on holistic approaches that target multiple facets of the disease's pathology. Combination therapies, polypharmacology, repurposed drugs, gene therapy, and RNA-based approaches offer promising avenues for addressing the complex nature of AD and improving patient outcomes. Combination therapies, incorporating FDA-approved drugs, metabolic activators, herbal medicine, and music therapy, have shown potential in enhancing cognitive function and reducing pathological markers in AD patients. Polypharmacology approaches aim to provide neuroprotective and cognitive benefits by simultaneously targeting neuroinflammation, oxidative stress, and amyloid aggregation.

Repurposed drugs like Fasudil, Lonafarnib, and fingolimod offer new possibilities for mitigating cognitive decline and disease progression in AD. However, careful consideration of potential side effects is crucial for safe and effective use. Gene therapy and RNA-based approaches hold promise in targeting key genes and pathways implicated in AD, with the potential to provide disease-modifying effects and enhance therapeutic outcomes. Environmental factors and cross-species studies provide valuable insights into AD etiology and progression, highlighting the importance of considering external influences in disease management.

In conclusion, by adopting a multifaceted approach and integrating insights from various disciplines, we can advance our understanding of AD and develop more effective therapies to improve the lives of patients and their families. Continued research and collaboration across scientific fields are essential to further progress in AD treatment and ultimately find a cure for this devastating disease.

7.1.Weaknesses and Drawbacks in Approaches

- The complexity of neurodegenerative diseases may not be fully addressed by multitarget drugs due to the interconnected pathological processes involved .
- While multitargeted bioactive natural molecules offer a promising approach for Alzheimer's disease, the variability in their pharmacokinetics and potential for drug-drug interactions when used in combination therapies could limit their effectiveness .
- The reliance on high-throughput screening for identifying potential multi-target compounds may overlook less explored but potentially significant targets in Alzheimer's disease pathogenesis .
- Herbal medicine's effectiveness and the mechanisms of action in Alzheimer's disease remain underexplored, posing challenges for their integration into mainstream therapeutic strategies .
- The development of diagnostic and therapeutic strategies based on circulating biomarkers and neuroinflammation targeting faces challenges in proving efficacy and safety in clinical trials .

7.2.Enhancement of Existing Knowledge

- Highlight the importance of multitarget drugs in neurodegenerative diseases, emphasizing the need for therapies that address multiple pathological processes simultaneously .
- Provide insights into the structure-activity relationship (SAR) of bioactive natural molecules, advancing the understanding of their potential in Alzheimer's disease treatment .
- Expand the scope of potential therapeutic targets in Alzheimer's disease, including less explored kinases, thereby broadening the horizon for drug discovery .
- Illustrate the potential of herbal medicine in Alzheimer's disease therapy through a multi-target and multi-time strategy, contributing to the holistic treatment approaches .
- Discuss novel diagnostic and therapeutic strategies, including the use of circulating biomarkers and targeting neuroinflammation, thus enriching the toolkit for Alzheimer's disease management .

7.3.Future Research Directions

- Further exploration of the pharmacokinetics and drug-drug interactions of multitargeted bioactive natural molecules to enhance their therapeutic efficacy in Alzheimer's disease .
- Investigation into the less explored targets related to Alzheimer's disease pathogenesis for potential inclusion in multi-target drug discovery .
- Development of more comprehensive studies on the effectiveness and mechanisms of action of herbal medicines in Alzheimer's disease, including their impact on the peripheral system .
- Advancement in the development of diagnostic tools that can multiplex and multimodally detect multiple biomarkers for Alzheimer's disease, improving early diagnosis and personalized treatment strategies .

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