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Development of Multi-Target Directed Ligands for Neurodegenerative Disorders: A Medicinal Chemistry Approach

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Abstract:

Alzheimer and Parkinson disease are neurodegenerative disorders which are multi-factorial and have few treatment alternatives. Conventional single-effect medications usually cannot be effective against the rich variety of pathological methods involved, such as oxidative stress, cholinergic dysfunction, neuroinflammation, and protein aggregation. This review discusses the novel potential that Multi-Target Directed Ligands (MTDLs) offer within medicinal chemistry as a new way of working to overcome such limitations. MTDLs are single molecules designed rationally and having the capacity to affect several targets related to the disease at a time, which shows enhanced efficacy, fewer side effects, and better compliance by patients. Preclinical models of diverse MTDLs, - e.g. donepezil-built-in ferulic acid, and rasagiline hybrids have actually demonstrated cognitive and neuroprotective capability in rodent designs. Medicinal chemistry methods that were employed in the development of these ligands including pharmacophore hybridization, fragment-based design and structure-based optimization are also identified in the review. Despite the promising therapeutic indication associated with to the use of MTDLs, limitations with regards to the predictability, model-predictivity of long-term toxicity data, and conventional evaluation tools remain to be the barrier towards translational efforts. The development of this field will also involve interdisciplinary science, the use of enhanced AI tools in the design of drugs, and the use of biomarkers to perform clinical measurements to design effective, disease-modifying drugs.

Keywords: Neurodegenerative disorders, Multi-target directed ligands (MTDLs), Medicinal chemistry, Alzheimer's disease, Parkinson's disease, Cholinesterase inhibition, Oxidative stress, Drug design.

1. INTRODUCTION

Neurodegenerative diseases such as Alzheimer disease (AD), Parkinson disease (PD), Huntington disease (HD), and amyotrophic lateral sclerosis (ALS) are a series of debilitating progressive neurological disorders which are the result of progressive neuronal breakdown in structure and in its functionality. Complicated, multifactorial pathogenesis of these disorders with oxidative stress, abnormalities in mitochondrial functioning, misfolded protein, neuroinflammation, and neurotransmitter balance creates important clinical and social problems[1]. The conventional drug development methods that normally aim at only one pathological mechanism have shown modest clinical success in altering the disease course. Accordingly, the pressing demand to develop more potent therapy has directed the attention to a polypharmacological strategy in the sense in which medicines could bind multiple targets of molecules due to the complexity of neurodegenerative diseases to be tackled more effectively within that contextual framework.

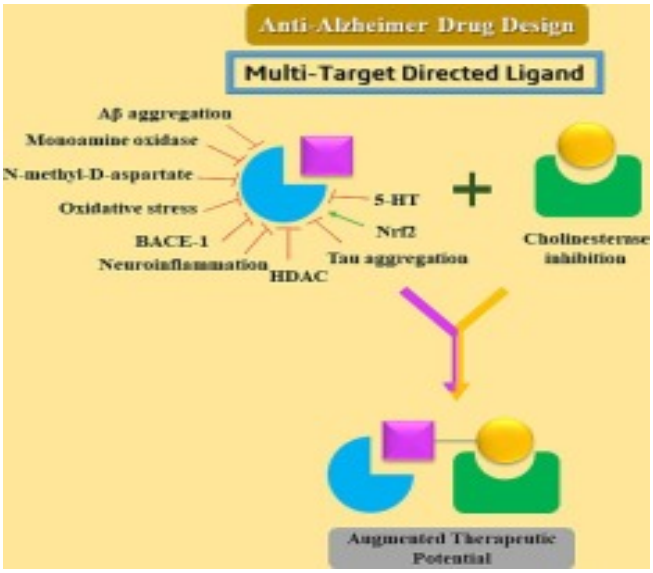

Figure 1: Multi-Target Directed Ligands (MTDLs)[2]

The emergence of multi-target directed ligands (MTDLs) as an innovative paradigm of Medicinal chemistry is seen. The MTDLs are single molecule designed rationally for targeting multiple targets implicated in disease processes. As compared to combination therapies, the MTDLs have benefits on pharmacokinetics and pharmacodynamics such as, bioavailability, minimized drug-drug interactions, and patient compliance. Medicinal chemists use various approaches like pharmacophore hybridization, molecular conjugation and structure-based optimization in order to design ligands which have multiple activities like being a cholinesterase inhibitor, an antioxidant agent and metal chelator, monoamine oxidase and anti-inflammatory agent. So these are revolutionary breakthroughs that not only mediate the symptoms, but also the course of the disease in neurodegenerative diseases[3].

1.1.Background Information and Context

Neurodegenerative diseases, including Alzheimer, Parkinson, and Huntington diseases, are becoming sharply rising in the world, especially under the conditions of raising life expectancy as well as the risk factors associated with the lifestyle. Although a large body of literature has already been developed, the existing pharmacological therapy is seen as being mostly symptomatic, rather than preventing the neurodegenerative processes. This treatment deficit indicates the drawbacks of postulated single-target agents that will not be effective in treating these disorders since they are multifactorial in nature. Consequentially, there is an increase in the build-up of multi-target directed ligands (MTDLs) that are meant to regulate multiple pathological pathways at once, such as, oxidative stress, neuroinflammation, protein aggregation, neurotransmitter imbalance. The development of computational drug design methods, high-throughput screening, chemical biology and systems pharmacology has allowed medicinal chemists to conceptually design and optimize such ligands to engage multiple disease-related targets precisely. The combined, multi-modal management provides a stronger

treatment management, which could address the possible changes in effectiveness, reduce adverse effects, and deliver significant disease-changing outcomes to patients with such complicated neurological disorders[4].

1.2.Objectives of the Review

- Evaluate the therapeutic potential of MTDLs in neurodegenerative disorders.
- Review key preclinical studies and assessment methods for MTDLs.
- Classify MTDLs based on targeted pathological mechanisms.
- Explore medicinal chemistry strategies for MTDL design.
- Identify strengths, limitations, and translational challenges of MTDLs.

1.3.Importance of the Topic

Considering the increased rate of neurodegenerative diseases that have taken place across the globe in-the-main due to the aging generation and the little therapeutic value of the current single-drug intervention, the breakthrough of multi-target directed ligand (MTDL) is a revolutionary paradigm in the drug discovery process. In contrast to the conventional single-targeting agents that generally cannot help versatile pathogenesis of such diseases like Alzheimer, Parkinson, etc, MTDLs were aimed at targeting several pathological pathways at a time, providing an improved and more comprehensive form of therapy. This plan is of extreme importance because this would be in line with a creeping scientific accord that mechanism-based and polypharmacological interventions are principal to curbing or preventing disease-driven development but not just acclimatizing the symptoms[5]. Besides, the creation of MTDLs is a pivotal point of combat between medicinal chemistry and translational neuroscience as it encourages interdisciplinary experiences involving chemical biology, pharmacology, and clinical studies. Not only does such convergence help us understand more complex diseases processes, but it will also speed up the discovery of new, disease-modifying drug candidates with better efficacy and safer profiles, which will ultimately bring hope of a better patient outcome to the challenges of these devastating diseases.

2. PRECLINICAL STUDIES AND ASSESSMENT OF MTDLS IN AD AND PD MODELS

Multi-target directed ligands (MTDLs) preclinical research has revealed growing promise of treating neurodegenerative disorder like Alzheimer and Parkinson. Hybrid drugs known as donepezil-ferulic acid and donepezil-curcumin have demonstrated improvement in cognition and antioxidative stress in rodent model amnesia. Equally, Rasagiline hybrids with coumarin or melatonin have demonstrated combination inhibition of MAO-B and AChE as well as neuroprotective and anti-apoptotic effects in Parkinsonian mice. Tacrine-based metal-chelating

hybrids were able to decrease the number of amyloid fibrils and oxidative stress as they could bind the excessive metal ions. These results demonstrate therapeutic potential of MTDLs to target several pathological mechanisms at the same time, something that no single-target drug can achieve[6]**.**

MTDLs are evaluated using behavioral tests including the Morris Water Maze and rotarod to analyze cognitive and motor abilities as well as by biochemical tests of oxidative stress, inflammation, and neurotransmitter concentrations. Immunostaining histological examinations of disease pathogenesis using markers such as GFAP, Iba-1 and amyloid plaques as well as pharmacokinetic analysis of drug absorption, distribution, and the permeability across the blood-brain-barrier of drug constituents. Limitations are reflected in the absence of long-term toxicity studies, low translatability of the models to human and variable experimental protocols, all of which impair the immediate clinical transferability of results**.**

Table 1: Summary of MTDL Studies in Alzheimer's Drug Discovery

Author(s)	Study	Focus Area	Methodology	Key Findings
Patil et al. (2023)[7]	Multi-Target-Directed Ligand Approach in Anti-Alzheimer's Drug Discovery	Development of MTDLs for Alzheimer's Disease	Literature review and structure-based drug design principles	Emphasizes the importance of designing ligands that act on multiple pathological targets like cholinesterases, β-amyloid aggregation, and oxidative stress to combat Alzheimer's effectively
Yang et al. (2020)[8]	Recent advances in the rational drug design based on multi-target ligands	Rational design strategies of MTDLs	Review of recent MTDL development strategies, including pharmacophore linking and structure-based design	Highlights technological advancements like molecular docking and ADMET profiling, enhancing drug efficacy and

				reducing side effects
de Freitas Silva et al. (2018)[9]	Multi-target directed drugs as a modern approach for drug design towards Alzheimer's disease: an update	Modern MTDL drug design approaches for AD	Compilation of MTDL candidates and in vitro/in vivo testing results	Demonstrates the utility of hybrid compounds (e.g., tacrine-based) in improving cognitive function and inhibiting key AD enzymes
Alarcón-Espósito et al. (2021)[10]	From hybrids to new scaffolds: the latest medicinal chemistry goals in MTDLs for Alzheimer's disease	Innovation in scaffold design for MTDLs	Comparative evaluation of hybrid molecules and novel scaffolds	Advocates the shift from classical hybrids to scaffold-hopping and de novo designs for better selectivity and brain penetration
Albertini et al. (2021)[11]	From combinations to multitarget-directed ligands: A continuum in Alzheimer's disease polypharmacology	Transition from drug combinations to MTDLs	Critical review of polypharmacological strategies	Proposes that MTDLs provide a more effective and safer alternative to combination therapy by reducing drug-drug interactions and improving p

2.1.Key Preclinical Research Studies

Multi-target directed ligands (MTDLs) are a broad family of ligands that have been used to test in preclinical models of animals that have mimicked the symptoms of many neurodegenerative disorders including Alzheimer disease (AD) and Parkinson disease (PD). Some examples are donepezil-based hybrids with antioxidant scaffolds (ferulic acid and curcumin)[12]. These conjugates were shown to have better cognitive performance and lower indicators of oxidative

stress (i.e., malondialdehyde [MDA], nitric oxide) in models of amnesia (scopolamine or amyloid-beta [Abeta]) in rodents. Concurrently, in rasagiline-coumarin and rasagiline-melatonin hybrids, their presence provides MPTP-induced Parkinsonian mice interesting results, inculcated dual inhibition of monoamine oxidase-B (MAO-B) and acetylcholinesterase (AChE), as well as robust anti-apoptotic and mitochondrial protective. Tacrine hybrids linked to metal-chelators (e.g. 8- hydroxyquinoline) have been evaluated to reduce Abeta aggregation and chelate excessive Cu 2 + and Fe 2 + ions thereby reducing the oxidative burden as well as neuroinflammation. Such studies emphasize the potential of MTDLs in harnessing the involvement of several pathogenic modules, which provides a comprehensive treatment strategy to complicated neurodegenerative diseases[13].

2.2.Methodologies and Evaluation Metrics

Behavioral, biochemical, pharmacokinetic and histological analyses done during the preclinical study of MTDLs are performed together. Of the commonly used behavioral tests to assess cognitive and motor deficits in models of AD and PD, respectively, include the Morris water maze, Y-maze, radial arm maze, rotarod and the novel object recognition tasks[14]. Oxidative stress markers (e.g. MDA, superoxide dismutase [SOD], glutathione [GSH], catalase], pro-inflammatory cytokines (e.g. TNF-infection, IL-1infection, neurotransmitter levels (e.g. acetylcholine, dopamine) in brain tissues are measured using biochemical assays. Immunohistochemical histopathological assessment in terms of astrocytic (GFAP), microglial (Iba-1), and amyloid (A beta plaques) or alpha-synuclein deposits offers information regarding neuroinflammation and protein clogging. Besides, such pharmacokinetic parameters as blood-brain barrier (BBB) permeability, oral bioavailability, metabolic stability, and half-life are assessed by such methods as LC-MS/MS and in situ perfusion techniques. All these measures specify whether the compound is drug-like with in vivo therapeutical applicability[15].

2.3.Strengths and Weaknesses

- **Strengths**

An added strategic value of the MTDL method is that it can modulate various disease targets at once, which is especially useful in multifactorial and multidimensional diseases such as AD, and PD. In comparison to monotherapies, the MTDLs tend to have synergistic effects, e.g. the combination of cholinesterase inhibition with antioxidant and anti amyloid effects which results in increased neuroprotection. Animal studies make possible controlled, repeatable analyses of behavioral alteration, neurochemical changes and disease process. The imaging, histology, and biomarker-based real-time monitoring of bioactivity and pharmacology increase the mechanistic insights and drugs screening and require quantitative integration[16].

- **Weaknesses**

Although these applications have these advantages, they do have a number of limitations. Numerous studies are devoted to the acute treatment courses, which are not produced with the

long-term toxicity and pharmacokinetic (PK) profiling, which is essential in clinical translation. Though instructive, rodent models might not reproduce the sequential nature and multidimensional nature of human neurodegenerative diseases, which hinder translational research. Also, the inconsistent use of induction methodologies, dosing schedules and endpoint results do not allow direct comparisons across studies. Mathbanttex, rarely are the chronic administration or multi-dose protocols studied which are critical to test the drug safety and efficacy in long term[17].

3. THEMATIC CLASSIFICATION OF MTDLS BASED ON TARGETED MECHANISMS IN NEURODEGENERATIVE DISORDERS

Cholinergic dysfunction and oxidative stress are being addressed with multi-target directed ligands (MTDLs) which have been proving beneficial in the early stage of Alzheimer diseases. The hybrids of acetylcholinesterase (AChE) inhibitors such as tacrine with antioxidants such as lipoic acid, ferulic acid or melatonin are dual neuroprotectants. These chemicals can improve cognitive ability in Abetreated rodents, and maintain redox balance by increasing antioxidant enzyme (SOD, CAT, GSH) activity and decreased lipid peroxidation. Anti-inflammatory and anti-aggregating MTDLs, i.e., curcumin-rivastigmine and melatonin-donepezil hybrids, are acted against neuroinflammation and A o or t pathology, respectively. They suppress the action of pro-inflammatory cytokines (TNF- 0, IL-6) and NF- 0 B signaling, as well as preventing protein aggregates and plaque formation thus alleviating major pathological Alzheimer characteristics[18].

More so, combination MTDLs of metal-chelating bacteria such as clioquinol with monoamine oxidase-B (MAO-B) inhibitors such as rasagiline has been found to be very helpful in Parkinson diseases. These agents limit oxidative stress, re-establish normal dopamine levels and nigrostriatal neuron protects. It does not undergo redox cycling, and it does not allow the Abeta aggregation due to metal-chelating properties. MAO-B inhibition decreases the formation of hydrogen peroxide. Also, mitochondria-targeted MTDLs to lipophilic cations such as TPP+ have direct benefits by maintaining mitochondrial physiology, forestalling apoptosis, and decreasing infarct region in stroke and injury designs. The presence of structures to pass the blood-brain barrier and accumulate in the mitochondria increases their therapeutic value in limiting the progression of neurodegenerative diseases.

3.1.Cholinergic and Antioxidant MTDLs

Oxidative stress and cholinergic dysfunction are subsequent related phenomena of early development of Alzheimer disease (AD). The multi-target directed ligands (MTDLs) against acetylcholinesterase (AChE) with antioxidant properties give such protection in both directions. An example would be the tacrine (a known AChE inhibitor) hybrids with antioxidant lipoic acid, ferulic acid or melatonin, which were created in order to take care of the issue of cholinergic deficits as well as the damage brought on by free radicals. These hybrids enhanced

cognitive functions that were impaired by A beta (1-42) peptide in rodent models which was depicted through their better performance in the Morris Water Maze and novel objects recognition tests. At a biochemical level, they led to the remarkable decrease in the index of lipid peroxidation in hippocampus as well as the increase in the activity of antioxidant enzymes including superoxide dismutase (SOD), catalase (CAT), and glutathione (GSH), which connotes redox homeostasis. Moreover, the integrative stability of antioxidant scaffolds further helps in hindering the mitochondrial dysfunction and weakening of the membrane to maintain the originality of neurons[19].

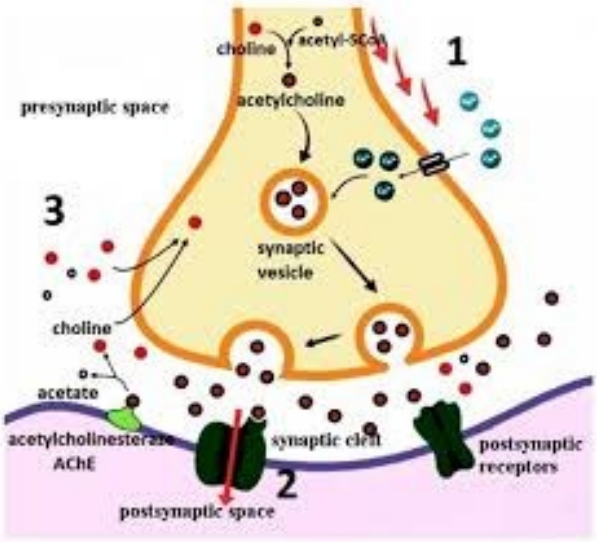

Figure 2: Cholinergic Dysfunction System[20]

3.2.Anti-inflammatory and Anti-aggregatory Ligands

Crucial factors of neurodegenerative processes are neuroinflammation and protein misfolding. MTDLs that suppress the expression of pro-inflammatory cytokines and at the same time do not allow aggregation of β-amyloid (A,) have shown promising outcomes. In case example, hybrids of curcumin-rivastigmine and melatonin-donepezil have dual action reducing microglial activation and amyloid burden of lipopolysaccharide (LPS) induced transgenic mouse model. They inhibit the synthesis of tumor necrosis factor-alpha (TNF-alpha), interleukin-6 (il-6), nitric oxide (NO) and nuclear factor-kappa B (NF-kappa B) signal. Also, they were found to prevent hyperphosphorylation of tau and fibril forming, and thereby target both inflammatory and proteinopathy arms of AD. It is a recurrent strategy to combine fragments of polyphenolic and non-steroidal (anti-inflammatory) drugs (NSAID) with scaffold of MTDL to improve their therapeutic scopes[21].

3.3.Metal Chelating and Monoamine Oxidase Inhibitors

Dyshomeostasis of metal ions, especially iron, copper, and zinc, both stimulates an increase in reactive oxygen species (ROS) production and promotes aggregation of A. Metal chelating

agent combinations have been investigated together with monoamine oxidase- B (MAO-B) inhibitors to aid in the management of oxidative stress and dopaminergic neurodegeneration, in particular, Parkinson disease (PD), namely, metal-chelator dopamine-levodopa transporter complexes (MTDLs) including combinations of 8-hydroxyquinoline/ clioquinol metal chelating agents with rasagiline MAO-B inhibitor. Clioquinol-rasagiline hybrids delivered strong inhibition of MAO-B and lower level of oxidative stress markers, as well as the enhancement of motor coordination of 6-hydroxydopamine (6-OHDA) lesioned rat models. These compounds evenly regulated the dopamine levels and also avoided further destruction in the nigrostriatal neurons. Binding the metal with the metal chelation agent can help destroy the metalA 11 association, thereby preventing the redox cycle/neuronal death process, whereas by using an inhibitor of the MAO-B enzyme, we reduce the amount of hydrogen peroxide and sustain the mitochondrial status[22].

3.4.Mitochondrial Protective Ligands

Neurodegenerative diseases are characterized by dysfunction of mitochondria, which can result in the failure to generate ATP and excess formation of ROS, which subsequently results in apoptotic cell death. The cationic lipophilic moieties like triphenylphosphonium (TPP+) have been used on the MTDLs that are designed to specifically target mitochondria. These mitochondrial specific ligands maintain the mitochondrial membrane potential (Dpm), decrease the cytochrome c withdrawal, and prevent the caspase-3 enactment in the situations of ischemia injuries, and also in the scenario of excitement injury[23]. As the case may be, TPP-conjugation with antioxidants or cholinesterase inhibitors not only prevents the mitochondrial swelling and fragmentation, but enables cellular respirations and energy production. These MTDLs protect against oxidative burden and promote survival of neurons in rodent models of stroke or traumatic brain injury and yield reduced experimental infarct volumes. They can enter the brain across the blood-brain barrier and accumulate in the mitochondria, and hence can be a strong source of agent against early pathologies of the mitochondrion regarding the neurodegenerative diseases.

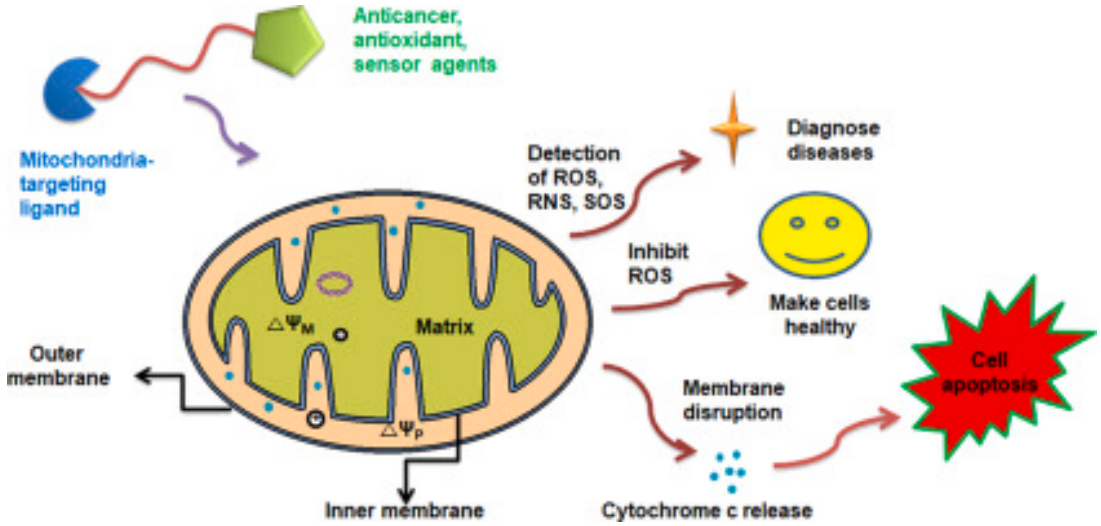

Figure 3: Mechanism of Mitochondria-Targeting Ligands in ROS Detection and Cell Apoptosis Prevention[24]

4. MEDICINAL CHEMISTRY STRATEGIES FOR MTDL DESIGN

Multi-Target Directed Ligands (MTDLs) Chemistry is a novel medicinal chemistry strategy to combat the complexity of diseases such as neurodegenerative diseases (i.e. Alzheimer and Parkinson). As opposed to the conventional rule of one drug one target scenario, MTDLs are single molecular entities that can inhibit or stimulate multiple biological pathway(s) simultaneously. This is specially beneficial to illnesses that have range of and interacting pathological processes like oxidative stress, inflammation, protein folding and neurotransmitter imbalance. Medicinal chemistry: Medicinal chemistry is important with regards to recognizing and refining pharmacophore(s), particular structural motifs that trigger biological actions of molecules; and inserting and also linking these pharmacophores in to a single entity to preserve or boost the activity on various targets[25].

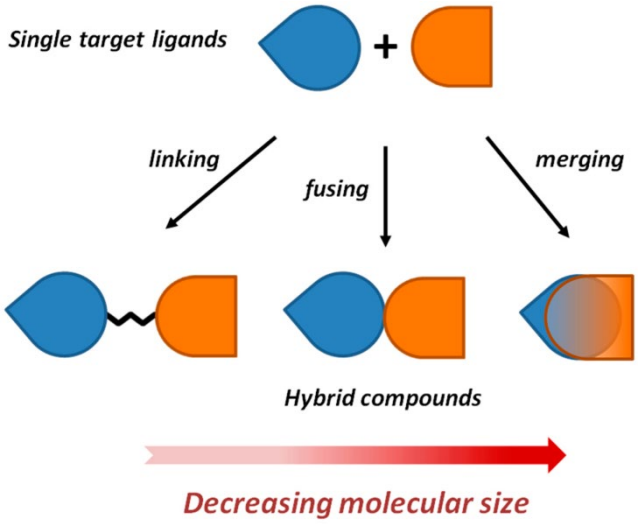

Figure 4: MTDL Design Strategies Linking Fusing Merging Hybrids[26]

Pharmacophore hybridization is one of the central MTDL design strategies; it implies the merging or connection of two or more separate pharmacophores with known target specificity. Such hybrids may be generated by direct conjugation (conjugates), shared chemical scaffold (merged hybrids), or generated with variable length and flexibility linkers to conserve activity at both sites (fused hybrids)[25]. As an example, a hybrid molecule containing an AChE inhibitor (e.g. tacrine) and an antioxidant scaffold (e.g. lipoic acid or ferulic acid) can target both cholinergic neurotransmission and oxidative damage. A delicate balance of electronic and steric properties is necessary in such hybridization so as to provide good pharmacokinetics target accessibility and blood-brain barrier (BBB) penetration[27].

The other strategic approach entails the use of structure based drug design (SBDD) whereby 3D structure of various biological targets have been used to inform the design of ligands that fit many active sites in the rationale[28]. Computational methods such as molecular docking, virtual screening and molecular dynamics simulations are used to optimise ligand-target interactions and this technique is helpful to medicinal chemists to make interactions prior to the synthesis. The so-called fragment-based drug design (FBDD) is regularly used, in which low individual potency molecular fragments are found against distinct targets and then chemically combined or expanded into a high potency MTDL. Such computational aid led to substantive speed-up of the design process, less trial-and-error and more successful development of molecules that came to be therapeutically useful[29].

Moreover, redesigning modification is a very important aspect of MTDL design in terms of physicochemical and pharmacokinetic optimization[30]. It is the mandate of the medicinal chemists to make sure that the MTDLs possess appropriate solubility, metabolic stability and absorption properties without compromising on efficacy. This may include tactical changes e.g. addition of polar group to enhance the solubility, or use of bioisosteric replacements to enable an increase in metabolic resistance. In order to be able to penetrate the CNS in the case of neurodegenerative diseases target, lipophilicity should be well balanced together with molecule weight as well as propensity to a hydrogen bond. Finally, the effectiveness, safety, and druglikeness should be optimized in a multidimensional process; hence, effectively translating mechanistic knowledge into clinically actionable therapy[31].

5. DISCUSSION

The review provides an insight into Multi-Target Directed Ligands (MTDLs) that may serve as an alternate solution to single-target therapy to neurodegenerative diseases by the multi-faceted ability to inhibit cholinesterase, display antioxidant, anti-inflammatory, and metal-chelating roles. Such compounds including donepezil-ferulic acid and rasagiline hybrids have better cognitive performances in preclinical studies[32]. MTDLs are in parallel with precision medicine because they tackle inlining complex disease processes in addition to possible elimination of

side effects and interactions. Nevertheless, there are still impediments to clinical translation because of the shortage of long-term safety outcomes and the insufficiency of the available animal models. The next areas in the field of research are advanced humanized models, biomarker-mediated assessment, and the AI-aided design of drugs to provide faster clinical applicability[33].

5.1. Interpretation and Analysis of the Findings

The information provided in the preclinical data and medicinal chemistry sections has shown that Multi-Target Directed Ligands (MTDLs) are a feasible and possibly a superior alternative to the single-target approach to neurodegenerative disorders[34]. The analyzed studies indicate that the synergistic therapeutic effects of MTDLs are related to the combinations of such functions as cholinesterase inhibition, antioxidant effects, anti-inflammatory activity, metal chelation properties, and mitochondrial protection. As an example, hybrids of donepezil-ferulic acid and those of rasagiline consistently demonstrated multi-target effect resulting in better cognitive and motor effects in rodents models of Alzheimer and Parkinson diseases. Such results support the idea that the limitation of various pathological pathways improves the total efficacy and neuroprotection[35]. Also, a structure-based and pharmacophore-hybridization approach has facilitated the rational development of optimally blood-brain barrier-penrictive, target-binding, and drug-like compounds, which substantiate the medicinal chemistry as a focal point of MTDL advancement.

5.2. Implications and Significance

The introduction of MTDLs is a paradigm shift in the treatment of neurodegenerative diseases. The discussed data support this idea that single target approach cannot help in managing a multifactorial disease process[36]. The MTDL strategy has great clinical value as it may postpone the progress of a disease and brings a symptomatic improvement with fewer side effects and better patient adherence. The strategy also conforms to the bigger trend in drug discovery involving the focus on precision medicine and polypharmacology. Also, therapy may be simplified by avoiding cocktail therapies with the use of MTDLs and decrease the likelihood of drug-drug interactions. In scientific perspective, MTDLs can be used effectively as intervention tools to interrogate intricate disease pathways and identify the cross-talk of different biological targets. Combining medicinal chemistry and pharmacology, pharmacological systems and computer models in MTDL design demonstrate the strength of interdisciplinary partnership in producing new drug candidates[37].

5.3. Gaps and Future Research Directions

Although there is positive development, there are some fatal gaps. A majority of preclinical studies do not have long-term toxicity data or a set evaluation protocol and it is thus hard to extrapolate observations into clinical observations[38]. The validity of animal models is reduced

because they usually cannot reproduce the chronicity and heterogeneity of neurodegenerative conditions in humans. What is more, most of the MTDLs exhibit favorable in vitro and in vivo performance, but only a handful got through to the clinical trials, and this signifies a translational block. The future research needs to be focused on the development of disease-relevant humanized models, prolonged pharmacokinetics and toxicity studies, and efficacy measures that are based on biomarkers[39]. Moreover, the optimization of ligand specificity and target selection might be further advanced by the further development of AI-based drug design technology and the integration of multi-omics data. Academic-industry-clinical research partnerships will play a central role in transforming bench research discoveries into bedside, eventually into viable products as effective treatments of neurodegenerative patients by identifying the effective candidates of MTDL[40].

6. CONCLUSION

The advancement of the Multi-Target Directed Ligands (MTDLs) is a revolutionary step towards the treatment plan of a neurodegenerative disease, especially Alzheimer and Parkinson diseases. MTDLs have a strong advantage over conventional single-target therapeutic agents because they can simultaneously target multiple pathogenic pathways simultaneously; cholinergic dysfunction, oxidative stress, neuroinflammation, protein aggregation, metal ion imbalance, and mitochondrial dysfunction are all known to occur in AD, which makes MTDLs a new type of holistic/omniberic medicine. Preclinical data show that MTDLs, some of which are hybrids containing various donepezil, tacrine, and rasagiline morphologies, the novel MTDLs have displayed synergistic efficacy in neuroprotection, cognitive improvement, and motor functioning in potent animal models. Medicinal chemistry is central to this innovation, and the techniques used include pharmacophore hybridization, fragment-based design and structure-based optimization of ligands to attain positive pharmacokinetic and penetration of the ligand into the central nervous system. Nevertheless, translating them to the clinical setting is a significant challenge since they hold little long-term safety evidence, have poor predictability by animal-model translation, and their assessment methods are imprecise. The potential of MTDLs will not be fully achieved, and in the future, researchers need to concentrate on further developing humanized disease models, guided by biomarkers, and the development of AI and multi-omics to be utilized in rational drug design. This kind of work, which reaches across medicinal chemistry, pharmacology, systems biology, and clinical research, is highly interdisciplinary, highlighting the necessity of cooperation in such a web of complications related to neurodegenerative diseases and the potential usefulness of contributing to the feasibility of the disease-modifying therapy in patients across the globe.

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