RESEARCH PAPER

Lysosomal Storage Disorder Pathobiology and Horizons: Pharmacological Chaperones in the Era of Precision Medicine

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ABSTRACT
Lysosomal storage disorders (LSDs) are inherited metabolic diseases caused by the deficient activity of specific lysosomal enzymes leading to the progressive accumulation of unmetabolized substrates in the lysosomes and resulting in systemic and neurological dysfunction. Some of the main clinically meaningful LSDs are Niemann-Pick disease, Gaucher disease, Tay-Sachs disease and Fabry disease In spite of advances with enzyme replacement and substrate reduction therapies, limited effective treatments are available. The objective of this review article is to compare recent progress in the design of small molecule inhibitors of Gaucher, Tay-Sachs, Fabry and Niemann-Pick disease employing structure-based computational methods. Literature searches were conducted to identify molecular docking, molecular dynamics (MD) simulations and ligand-protein interactions analyses of lysosomal enzymes, towards the natural products, small molecules, and pharmacological chaperones within the four diseases of interest. Computational studies investigated powerful and selective inhibitors of the disease-specific enzymes β-glucocerebrosidase (Gaucher disease), β-hexosaminidase A (Tay-Sachs disease), α-galactosidase A (Fabry disease), and proteins that transport lipids in cells (Niemann-Pick disease). Molecular docking was used to perform rapid screening of virtual chemical libraries for potential inhibitors and to predict their binding modes. The molecular dynamics and simulations provided additional details regarding ligand dynamics, conformational stability, and binding energetics. Hydrogen bonding, hydrophobic contacts, and active-site complementarities contributed towards inhibition. Computational techniques based on structural information have considerably improved the knowledge of enzyme-inhibitor interaction studies related to lysosomal storage diseases and led to the discovery of new drug targets. A comparison of the four diseases – namely, Gaucher, Tay-Sachs, Fabry, and Niemann-Pick – reveals that similar molecular pathways exist among these diseases, which can pave the way for creating specific treatment regimens.

Keywords: *Lysosomal Storage Disorders, Pharmacological Chaperones, Precision Medicine, Enzyme Replacement Therapy, Artificial Intelligence, Fabry Disease, Gaucher Disease.*

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1. INTRODUCTION

Lysosome, the cellular recycle bin, was discovered by Christian de Duve in the1950[1]. It plays key role in nutrient sensing, regulating secretion, repairing damage to the plasma membrane and coordinating key metabolic signalling pathways. As a result, lysosomal storage disorders (LSD) are no longer seen as simple failures of cellular disposal, but as deep and systemic disturbances that disrupt the finely tuned coordination of cellular function and survival[2]. Although each of these genetic metabolic conditions is individually rare and more than 70 are known in total, together they affect a surprisingly large number of people, with an estimated occurrence of 1 in every 5,000 to 10,000 live births worldwide[3]. The LSDs are a group of inherited metabolic disorders that arise primarily from deficiencies in acid hydrolases, leading to the accumulation of undegraded substrates. This enzymatic deficiency leads to the build-up of undegraded materials within lysosomes, including glycosphingolipids, glycosaminoglycans and cholesterol, which progressively disrupt normal cellular function[4]. The accumulation of these substances is setting off a much broader and more complex chain of events that drive disease progression. The downstream effects include impaired autophagy which allows toxic protein aggregates to build up inside the cell. It also includes mitochondrial dysfunction leading to oxidative stress to the cell. It sometimes causes calcium

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imbalance and activation of chronic inflammatory pathways[5]. These disorders cause a multiorgan damage of heart, skeleton and central nervous system[5] (Figure 1).

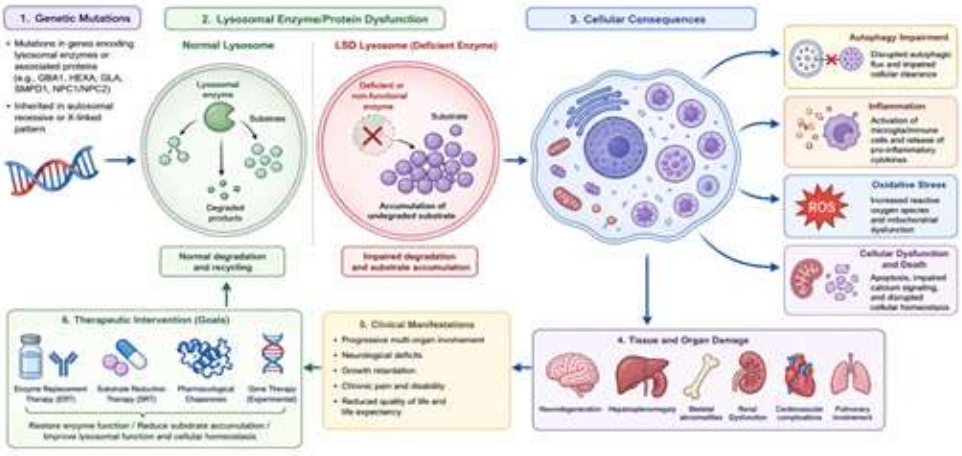

Fig 1. Lysosomal storage disease pathogenesis. Mutation in genes leads to reduced levels of activity of enzymes or transport proteins involved in lysosome functions. Such defects cause substrate build-up within the lysosomes. The excess build-up causes disruption in the cells' homeostasis, autophagy, oxidative stress, inflammation, and apoptosis mechanisms.

The therapeutic approaches of LSD were principally governed by symptoms relief but little ability to alter the course of the disease. The inclusion of enzyme replacement therapy (ERT) in the 1990 made a significant breakthrough in the LSD therapy[6]. The recombinant enzymes were delivered to cells through mannose-6-phosphate receptors making the Fabry disease and the Gaucher disease type 1 into controllable range[7]. The Indian patient first received enzyme replacement therapy in 1999 for treatment of Gaucher disease[8]. Despite the success of ERT, there are several practical challenges. These include its inability to cross the blood-brain barrier, which leaves neurological symptoms. The patients develop neutralizing anti-drug antibodies which reduces effectiveness of ERT over time. The inability to reach certain tissues particularly organs affected by fibrosis is another disadvantage of the ERT[9, 10]. The inclusion of computational biology, artificial intelligence and structural biology are changing the research landscape from protein replacement to protein correction. The Pharmacological Chaperone Therapy (PCT) and substrate management via substrate reduction therapy require the predictive power of artificial intelligence. The objective of this review article is to provide an exhaustive analysis of challenges and opportunities in chemical biology for treating Fabry's, Gaucher, Niemann-Pick and Tay-Sachs disease.

2. DEFINITION AND CLASSIFICATION AND BIOCHEMICAL PATHWAY LEADING TO LSD

The LSD is a group of disorder that affect specific enzymes. It is usually caused by lysosomal dysfunction usually deficiency of single enzyme. The classification of LSD is based on their storage products e.g glyco proteinoses, mucopolysaccharidoses, mucolipidoses, glycogen storage, sphingolipidoses, lipid storage disorders and transport defects (Table 1) [11]. Since, the detailed classification of LSD is out of the scope of this review, we will be interested in the category Sphingolipidoses with associated sphingolipid activator defects— Fabry's, Gaucher, Niemann-Pick and Tay-Sachs disease. The biochemical pathway of sphingolipid breakdown within lysosome occurred by specific enzymes for production of ceramide. The GM-ganglioside is converted into GM3, while alpha-galactosidase A and sphingomyelinase act on ceramide trihexoside and sphingomyelin, respectively. Intermediate molecules of glucocerebroside and galactocerebroside are also funnelled towards ceramide through the actions of glucocerebrosidase and galactocerebrosidase (Gb3) and globotriaosylsphingosine (lyso-Gb3) (Fig. 2).

Table 1. Classification of lysosomal storage disease[11]

Disorder	Metabolic deficiency	Accumulated substance
Sphingolipid activator protein deficiency disorders		
Fabry disease	α- Galactosidase A	Galactosylated glycolipids
Farber disease	Lysosomal ceramidase	Ceramide
Gaucher disease	β- Glucocerebrosidase	Glucocerebroside and glucosylsphingosine
Tay- Sachs disease B variant including B1 variant	β- Hexosaminidase A&B (β polypeptide)	GM2- ganglioside, GA2- glycolipid and oligosaccharides
Krabbe disease	β- Galactoceramidase	Galactosylceramide and psychosine
Niemann- Pick A and B	Sphingomyelinase	Sphingomyelin
Mucopolysaccharidoses		
Hurler syndrome	α- L- iduronidase	Dermatan sulphate, oligosscharides, heparan sulphate,
Glycoproteinoses		
Galactosialidosis	Cathepsin A deficiency	Sialylated oligosaccharide and glycopeptide compounds
α- Mannosidosis	Lysosomal α- D- mannosidase	α-Linked terminal mannose–containing oligosaccharides
Schindler disease	α- N- acetyl- galactosaminidase	Peptide- and sphingolipid-linked glycoconjugates
Sialidosis (mucolipidosis I)	Lysosomal neuraminidase	Sialic acid–rich oligosaccharide and glycopeptide substrates
Multiple enzyme deficiencies resulting from lysosomal protein processing defects		
Mucolipidosis type II (I-cell disease)	α/β subunits of N-acetylglucosamine-1-phosphotransferase	Mixed glycoconjugates: oligosaccharides, glycosaminoglycans, and glycosphingolipids
Defect in soluble non- enzymic lysosomal protein		
Niemann- Pick type C2	NPC2 (Niemann–Pick type C2) cholesterol-binding protein	Cholesterol and associated lipids
Lysosomal membrane protein defects		
LIMP-2 (lysosomal integral membrane protein-2) deficiency causing action myoclonus–renal failure syndrome	LIMP-2 (lysosomal integral membrane protein-2), also known as SCARB2 (scavenger receptor class B, member 2)	Characterization not established
Neuronal ceroid lipofuscinosis group of disorders		
Palmitoyl-protein thioesterase-1 deficiency	Lysosomal enzyme palmitoyl-protein thioesterase-1 (PPT1)	Lipofuscin containing saposins A and D
Deficiencies of lysosomal cathepsins		
Galactosialidosis due to protective protein/cathepsin A (PPCA) deficiency	Protective protein/ cathepsin A (PPCA)	Sialylated oligos and glycopeptides
Disorders of nucleic acid metabolism		
Aicardi–Goutières syndrome	“DNase III	Enhanced type I interferon response
Abnormal biosynthesis of lysosome-related organelles		
Chediak–Higashi syndrome	LYST (lysosomal trafficking regulator) gene/protein	Defective lysosomal size, regulation and positioning

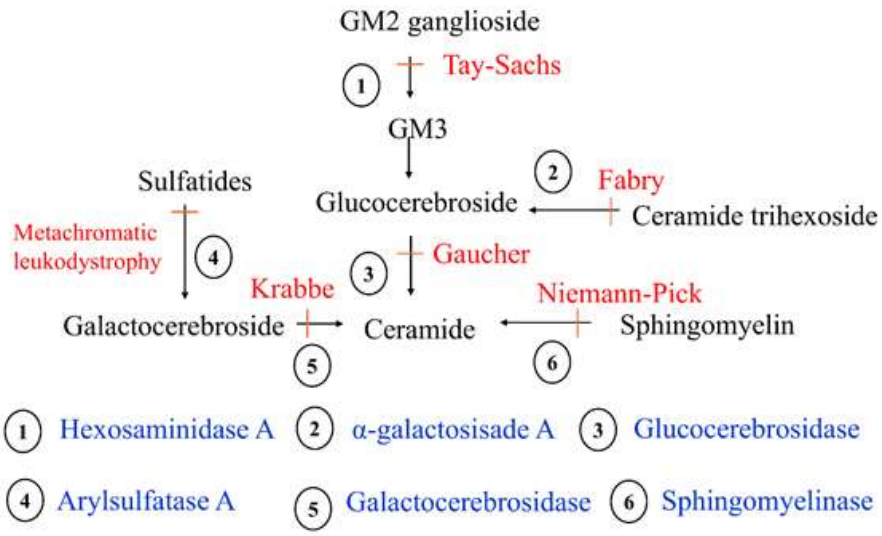

Fig. 2. The diagrammatic pathway of sphingolipid breakdown with the enzymes involved. The disease caused by the deficiency of enzymes is marked in the ray diagram.

2.1. Tay-Sachs Disease

The conversion of GM2 gangliosides to GM3 gangliosides is carried out in normal lysosome by β-hexosaminidase A (*HexA*) gene. The mutation in the β-hexosaminidase A (*HexA*) gene located on the chromosome number 15 is the reason for hereditary disorder, Tay-Sachs disease (TSD; OMIM: 272800) [12, 13]. Because of the mutation of *Hex A*, the activity of Hex A enzyme reduces in the lysosomes which causes accumulation of GM2 gangliosides to toxic level. This toxic product accumulation causes irreversible damage to the nerves of the brain and spinal cord (Fig. 2).

2.2 Fabry Disease

Fabry disease (FD; OMIM:301500) is a rare X-linked inherited condition that affects multiple organ which is caused by the mutation in the *GLA* gene. The chromosomal location of *GLA* gene is the Xq22.1 and it encodes lysosomal enzyme alpha-galactosidase A (alpha-GalA). The deficiency of alpha-GalA leads to the accumulation of globotriaosylceramide (Gb3) and globotriaosylsphingosine (lyso-Gb3). The lipid molecule builds up in many parts of the body including blood vessels, kidneys, heart, nerves, eyes and connective tissues[11]. The life expectancy is reduced by 15 years for males and by 10 years for females. The cardiovascular disease is the leading cause of death in those patients (Fig. 2).

2.3 Gaucher Disease

Gaucher disease (GD, OMIM: 610539) is caused by mutation in the ß-glucosylceramidase 1 (*GBA1*) gene encoding lysosomal beta-glucocerebrosidase (*GBA*)[14]. The GD is characterized by accumulation of glucosylceramide (GlcCer) in cells of the macrophage-monocyte lineage, giving rise to “Gaucher cells” (Fig. 2).

2.4 Niemann-Pick Disease

Niemann-Pick disease type A (NPD, OMIM: 257200) is a rare autosomal recessive LSD marked by mutation in the sphingomyelin phosphodiesterase-1 gene (*SMPD1*), which encodes acid spingomyelinase (ASM) on chromosome 11p15. Spingomyelin, a structural component of cell membrane is the primary accumulating lipid. The primary organs affected by ASM deficient patient are liver, spleen and lung (Fig. 2).

3. METHODS

To investigate LSD, ‘lysosomal storage disorder’ was used for the literature review using the databases PubMed. We covered two centuries of the databases (January 1945 to April 2026). All systematic review (N = 195) identified by the search engines were downloaded and independently analysed three times by the co-authors of this review article. We compared the progress summaries of seven Web of Science (WoS)-cited scientific review manuscripts to identify current research trends in this field (Table 2). Moreover, we have graphically represented the number of research articles published in PubMed on Fabry’s, Gaucher, Niemann-Pick and Tay-Sachs disease to compare the research trends among the studied LSDs.

Table 2. The list of literatures used for writing the synthesis of LSDs

Serial number	Article summary	References
1	This review summaries the Fabry disease caused by the accumulation of globotriaosyl-ceramide due to α-galactosidase A deficiency. The article gives concise information on cardiomyopathy, fibrosis and heart failure caused by Gb3 accumulation. The genetic testing and imaging are the diagnosis method as suggested by the author. The enzyme replacement and chaperone therapy are shown as the management options.	15
2	This systematic review illustrates lyso-Gb3 as the biomarker for Fabry disease. The precise diagnostic accuracy particularly in males and efficient disease monitoring potential are shown by it. Nonetheless, in late onset females, the systematic review pinpoints search of other diagnostic tools.	16
3	This systematic review showed that there are approximately 50 different types of LSD were identified. Amongst them, the citizen of Asia and the USA were compared for Hunter syndrome in 2022. The study showed the higher prevalence in Asia compared to USA.	17
4	This systematic review assesses the psychological impact of parenting a child with LSD. The study revealed financial strain, social isolation and anxiety in parents while dealing with their children of intense behavioural change.	18
5	This review synthesis the risk of developing heart failure associated with LSD. It also lists a set of enzymes responsible for developing lysosomal storage disorders.	19
6	This review summarizes harmful single nucleotide polymorphisms (SNP) associated with glucocerebrosidase (*GBA1*) gene. The study reviews that the different variants of GBA1 gene mutation leads to the development of Parkinson's disease. The study identifies pathogenic SNPs of glucocerebrosidase (*GBA1*) gene associated with development of Gaucher disease are N409S among Jewish and Whites), L483P among Asians and Hispanics, E365K and T408M among whites. This review also shows the risk of development of Parkinson's disease.	20
7	This review has shown that lack of awareness among Indian citizen about LSD. The authors showed that LSD was found in India in between 1970-2000. The study also thrusts that lysosomal storge disorder was also reported in Calcutta in 1986. Hence, based on the observation, Department of Health Research and Indian Council of Medical Research developed the taskforce to understand the pathobiology of lysosomal storage disorders.	4

4. PRELIMINARY STATEMENTS

4.1 Research Trend in the Field of LSD under this review

The PubMed database search about the total number of manuscripts published in LSD revealed a total of 35,000 articles amongst which there are 4992 review articles and 192 systematic review articles. The trends of research articles published after 2000 were found to be dramatically increased to 24193 articles whereas only 13,611 articles were published during 1945 to 2000 period. Hence, an increase in awareness and increase in diagnosis has been reflected (Fig. 3a). When the research articles published in PubMed were compared on each individual diseases, it was found that Gaucher disease is the most researched entity among the four LSDs studied in this research followed by Fabry's disease (Fig 3b). Whenever, we have compared the number of review article in each of the four LSDs, we found that Fabry's disease is leading the list with 87 review articles and the least number of review articles published in the Tay-Sachs disease (Fig 3c). The keyword search in the PubMed 'Fabry's disease' AND 'Gaucher Disease' yielded 5 systematic review articles. The keyword search 'Fabry's disease AND 'Niemann-Pick' yielded one systematic review article. When we searched these four diseases together, we did not find any systematic review article in PubMed database which shows the importance of this review article (Fig 3d).

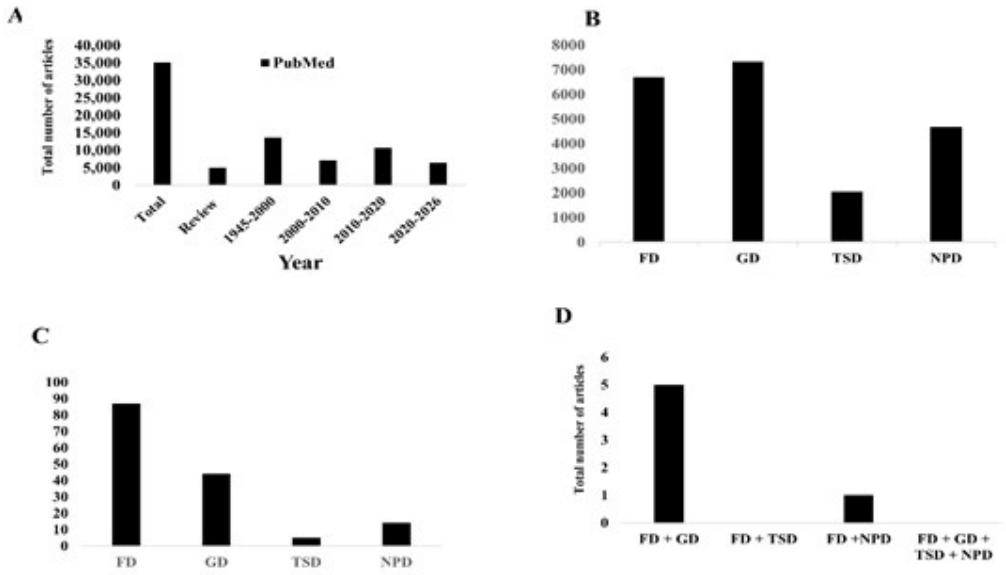

Fig. 3. Analysis of research trends and publication data for Lysosomal Storage Disorders (LSDs) in the PubMed database. A. Total number of manuscripts and review articles published in the field of LSD, categorized by time periods from 1945 to 2026, showing a dramatic increase in research output after the year 2000. B. Comparative representation of the total number of research articles published in PubMed for individual diseases: Fabry disease (FD), Gaucher disease (GD), Tay-Sachs disease (TSD), and Niemann-Pick disease (NPD), highlighting GD as the most researched entity. C. Distribution of review articles among the four studied LSDs, indicating that Fabry disease has the highest number of published reviews, while Tay-Sachs disease has the fewest. D. Number of systematic review articles identified through combined keyword searches for multiple LSDs; the absence of systematic reviews covering all four diseases together underscores the significance of the current synthesis.

4.2 Epidemiological studies on LSD in Different Countries

This study identifies the most common LSDs in India, mirroring patterns observed in China, Portugal, Australia, Netherlands and the Czech Republic[21, 22, 23], with a notably higher frequency of GD (Fig. 3). The highest percentage of GD was found in Portugal (40.6) followed by China (39). The GM2 gangliosidosis accounted for 10% of cases in India comprising TSD (10%) in comparison to 23.6% in Portugal. This distribution matches the Portuguese cohort, particularly for Tay-Sachs disease (13.8%), though it exceeds rates in Australia (11.8%) and the Netherlands (11.8%). Elevated GM2 gangliosidosis prevalence has also been noted among children with neurological disorders in southern India, where consanguinity is common[24]. The higher contribution of TSD is thought to be caused by mutation in the HEXA gene within Scheduled Caste community in Gujrat[25]. High carrier frequencies of FD have been reported in the Czech Republic (19%) and Australia (14.8%)[23, 25, 26] (Fig. 3). This low incidence FD in other countries is to be caused by low clinician awareness, especially in cardiac and renal management of adults with FD. Unlike cohorts from the China[21, 22, 23], the NPD was the least common LSD in the other countries. Contributing factors include overlapping clinical features (e.g., hepatosplenomegaly, neonatal jaundice, psychiatric disturbances[27]) and limited diagnostic facilities for NPD in those countries. Overall, the low prevalence of disorders like FD, NPD likely arises from clinician unawareness and scarce enzyme diagnostic facilities across much of India. In contrast, countries with higher reported incidences benefit from greater awareness and infrastructure.

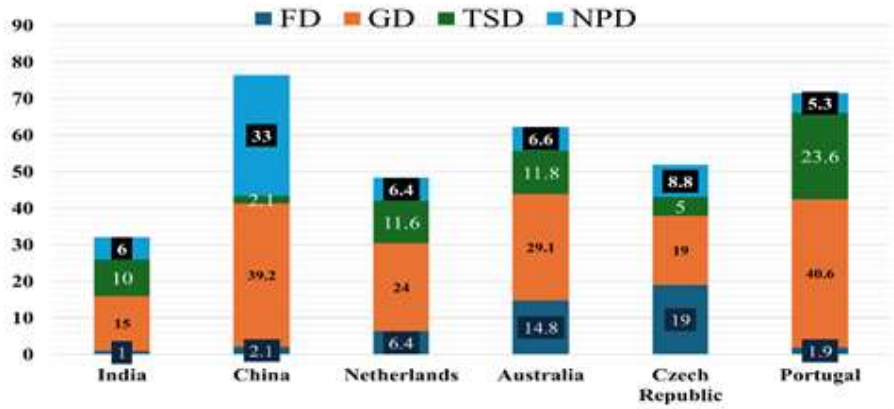

Fig. 4 Incidence of various LSDs in different countries

4.3 Mechanism of detection of LSD considered under this review

4.3.1 Enzymatic assay

The GD is diagnosed by estimating the β-glucocerebrosidase (GBA) activity in peripheral blood cells. The FD is diagnosed by assessing α- galactosidase A activity in plasma, serum or leukocytes. The TSD diagnosis is carried out by the deficiency of β-hexosaminidase A (Hex A) fluorometrically. The NPD is characterized by measuring ASM activity in white blood cells[11].

4.3.2 DNA sequencing analysis to find out the mutation spectrum

Single nucleotide polymorphism (SNP) is the study of mutation in a DNA sequence at a single nucleotide. In LSD, different SNPs were identified as the causative agent (Table 3). The mutations R535C and L444P of GBA enzyme were responsible for GD as characterized by Sheth et al. and Ankleshwaria et al. respectively[4, 28]. For TSD, the p.E462V mutation in HexA enzyme is suggested as per Mistri et al[25]. The Niemann-Pick disease types A and B are associated with the p.R542* variant of ASM enzyme[29], The D92Y mutation in GLA enzyme was found to be the leading cause of the FD[31].

Table 3 Comparative Overview of the selected Lysosomal Storage Disorders and Their Therapeutic Targets

Serial Number	Diseases Name	Gene	Enzyme / Protein	Accumulated Substrate	Major Clinical Features	Current Therapies	Common variant	References
1	Gaucher disease (GD)	GBA1	β-glucocerebrosidase	Glucosylceramide	Hepatosplenomegaly, anemia, bone disease	ERT, SRT	R535C(c.1603C>T) L444P(c.1448T>C) L444P(c.1448T>C)	32 28
2	Tay-Sachs disease (TSD)	HEXA	β-hexosaminidase A	GM2 ganglioside	Neurodegeneration, developmental delay	Supportive, experimental gene therapy	p.E462V	25
3	Niemann Pick disease A/B (NPD)	SMPD1	Acid sphingomyelinase	Sphingomyelin	Hepatosplenomegaly, pulmonary dysfunction	ERT (limited), SRT	p.R542* p.R542*	29 30
4	Fabry disease (FD)	GLA	α-galactosidase A	Globotriaosylceramide (Gb3)	Vascular dysfunction, renal & cardiac issues	ERT, pharmacological chaperones	D92Y	31

4.4 Aid of computational method to develop drugs

Computational methods have become key components in contemporary drug design processes. For instance, structure-based approaches, which include molecular docking and molecular dynamics (MD) simulations, have helped in designing and improving possible drugs through determining the binding affinity and mode, as well as stability of protein-ligand interactions at an atomic level [33, 34]. Molecular docking makes it easier to screen compounds for their efficacy as drugs, whereas MD helps in understanding flexibility, solvation, and stability of interactions between the proteins and ligands. Various studies have recently shown the success of computational techniques in discovering novel inhibitors against LSDs. For instance, docking-based virtual screening for natural products and iminosugars has provided potential inhibitors that can target β-glucocerebrosidase, an enzyme involved in Gaucher disease [35, 36]. Likewise, structure-based designs have been used in developing inhibitors, including transition state analogues and substrate mimetics, of β-hexosaminidase A, which is associated with Tay-Sachs disease, with particular attention on active site interactions[37,38]. In Fabry disease, pharmacological chaperones that can enhance the stability of misfolded α-galactosidase A have been discovered using computational modelling techniques[39, 40]. Additionally, developments in Niemann-Pick disease have involved molecular simulations of lipid-protein interactions and identification

of modulators targeting NPC1 and associated pathways [41, 42].

4.4.1 Therapeutic Targeting of β-Glucocerebrosidase

Molecular docking has found widespread application in identifying potential inhibitors and regulators of β-glucocerebrosidase through their ability to interact with and bind to the enzyme's catalytic site. The active site of GCase consists of crucial residues that are important for its enzymatic activity and act as binding sites for small ligands. Recent investigations have focused on a broad array of compounds, from natural products, iminosugars, and their synthetic analogs. Flavonoids and other plant compounds have been found to show favourable binding properties mainly because of the hydrogen bonds and hydrophobic interactions formed inside the catalytic pocket[36]. Likewise, iminosugars like N-butyl-deoxynojirimycin (NB-DNJ) are highly specific to GCase; not only do they act as competitive inhibitors, but they also help in maintaining enzyme stability[35]. The application of structure-based screening techniques has led to the discovery of new molecular structures with improved binding properties. In summary, all these investigations highlight the significance of non-covalent interactions such as hydrogen bonds, hydrophobic contacts, and electrostatic complementarity in facilitating ligand binding[34]. While molecular docking provides a static view of the complexation between enzymes and ligands, MD simulations can provide valuable information about the dynamics and stability of the complexes. MD simulations of the complexes formed between GCase and its ligands have shown that stable binding occurs when there are low RMSD values and continuous interactions along the trajectory[34]. In addition, MD simulations indicate that successful inhibition by ligands is accomplished by ensuring continuous interactions with the catalytic residues without disrupting the structure of the enzyme. The calculation of binding free energy using methods such as MM-PBSA and MM-GBSA has been useful for understanding the interaction strengths and validating docking results. Some of the main factors that characterize efficient inhibitors, as found in the comparative analysis of computational studies focused on β-glucocerebrosidase, include significant complementarity of ligands to the catalytic site, especially with regards to the interactions between the ligand and residues like Glu235 and Glu340. Hydrogen bonds and hydrophobic interactions play major roles in increasing binding specificity and stabilizing ligands inside the enzyme core, respectively. In addition, the ability of the ligand to undergo conformational changes is vital for compensating differences at the active site. In addition to competing inhibitors, another type of drug worth mentioning are pharmacological chaperones. These drugs bind to dysfunctional forms of the enzyme to stabilize its structure and help it to reach lysosomes.

4.4.2 Therapeutic Targeting of β-Hexosaminidase A

There is currently no cure for Tay-Sachs disease, with only management of symptoms being possible. This condition cannot be treated using enzyme replacement because the enzymes used cannot cross the blood-brain barrier. This has led to scientists exploring other methods of treatment, which include substrate reduction therapy, gene therapy, pharmacologic chaperones, and small-molecule modulators. The one that has come into limelight is computationally aided research since it helps discover molecules that can modulate the activity of enzymes or stabilize the residual activity of the enzyme. The docking approach has been extensively used to study the binding of ligands to the active site of β-Hex A enzyme. The catalytic action of the enzyme entails some residues that are responsible for the hydrolysis of GM2 gangliosides. Therefore, the active site is considered one of the most crucial targets for the development of inhibitors. The use of computers to simulate molecular actions in the enzyme has mainly been employed in the design of transition state analogs, substrate mimetics, and glycomimetic inhibitors, which mimic the structure and chemistry of the natural substrates. Such molecules can create strong hydrogen bonds with the catalytic residues in the enzymes due to their high selectivity and binding affinity[37, 38]. Recent in-silico screening studies have shown promising results in exploring natural ligands with inhibition activity. Stereochemical and functional complementarity have proved to be key factors to achieve successful binding because of the complex nature of GM2 gangliosides. The MD simulations play an important role in determining the stability and conformational behaviour of enzyme-ligand complexes. Considering the complexities associated with the structure of the enzyme and substrate, MD simulations are important in providing insight into the influence of ligand binding on flexibility and stability. Studies using simulation models have established that effective ligands bind to enzymes through stable interactions with catalytic amino acids and reduce conformational movements. RMSD, RMSF, and the radius of gyration can be used as parameters for assessing the stability of enzyme-ligand complexes[34]. In addition, binding energies can be determined using computational techniques to validate docking studies by providing information on affinity of the ligands. Ligand binding is often influenced by water molecules. In complex enzymes like Hex A, solvation effects contribute significantly towards maintaining the binding of the ligand. Whereas β-glucocerebrosidase involved in Gaucher disease has its own set of structural and functional properties that play an important role in the design of effective inhibitors, β-hexosaminidase A has unique attributes as well. Being structurally complicated,

GM2 gangliosides require inhibitors to be designed according to certain stereochemistry requirements and arrangement of functional groups. Additionally, a large molecule can be used in targeting the enzyme. Moreover, the fact that Tay-Sachs is characterized by neuronal specificity requires inhibitors designed to penetrate through the blood-brain barrier. It increases difficulty in the process but, nevertheless, common mechanisms of effective binding should be considered. Hydrogen bonds, electrostatic interactions, and hydrophobic effects represent key elements that should be used to increase the efficiency of ligand binding.

4.4.3 Therapeutic Targeting in Niemann–Pick Disease

Different therapeutic approaches can be employed to treat Niemann–Pick disease, depending on the form of the disease. In type A and B, enzyme replacement and substrate reduction have been attempted as possible treatment options; however, in NPC, treatment strategies concentrate on re-establishing lipid transport in cells and lowering cholesterol content. In contrast to other storage disorders such as Gaucher, Tay-Sachs, and Fabry diseases, which focus on the degradation of soluble lysosomal enzymes, Niemann-Pick disease, especially type C, needs to target membrane-bound protein and lipid transport. Small molecules like cyclodextrins and sterols have proven effective in promoting cholesterol efflux and establishing a proper balance in intracellular lipid levels. Nevertheless, toxicity, poor efficacy, and inadequate BBB permeability continue to pose major hindrances to clinical implementation. In the case of Niemann-Pick disease, molecular docking has been extensively applied to understand the molecular interactions between small ligands and the NPC1 protein domains and, to some degree, acid sphingomyelinase in types A and B. In this regard, it is important to note that the sterol-sensing domain present in NPC1 is crucial for cholesterol binding and transport. Through molecular docking analysis, researchers have discovered different types of ligands such as sterols, cholesterol analogs, and cyclodextrins which interact with the hydrophobic regions of the NPC1 protein. These molecular interactions help in stabilizing certain conformations of NPC1 which are essential for cholesterol transport. Hydrogen bonding and hydrophobic interactions are significant in ensuring ligand stability within the active site [41]. As for acid sphingomyelinase, researchers have carried out computational studies to investigate potential inhibitors that can act on its catalytic site. Molecular dynamics simulations play a very crucial role in NP diseases since membrane associated proteins are dynamic by nature. As compared to other soluble enzymes, NPC1 is found to work within a membrane bound state, thus necessitating a more sophisticated approach for simulating protein-lipid systems in aqueous environments. Through molecular dynamics simulations, much knowledge was gained on the flexibility and structural stability of NPC1 protein domains, stability of ligand binding sites, and the effect of lipid-protein interactions on cholesterol transportation. The simulations showed that ligand binding leads to protein conformational changes, which increase cholesterol transport. Moreover, MD simulations can provide more accurate information about the contribution of waters as well as membrane constituents in maintaining stable protein-ligand complexes. Molecular dynamics simulations together with calculations of binding free energies help in identifying ligands with high binding affinities[42].

4.4.4 Therapeutic Targeting of α-Galactosidase A

Currently, treatments used for Fabry disease involve the use of enzyme replacement therapy and pharmacological chaperone therapy. Despite the effectiveness of enzyme replacement therapy in minimizing substrate buildup and enhancing patient results, it poses some challenges like being very expensive and associated with side effects such as allergic reactions[43]. Pharmacological chaperones constitute a highly specific therapy that is more applicable to those patients whose mutations are favourable. The small molecules act by binding to α-galactosidase A that is improperly folded; hence, the molecule becomes stable and folds into the right form and gets transported to the lysosome. This means that while in other diseases like Gaucher disease and Tay-Sachs disease, the inhibition of the enzyme becomes key, this is not the case for Fabry disease. The discovery of small molecules able to interact with the catalytic site of α-galactosidase A has greatly depended on molecular docking. Key residues such as Asp170 and Asp231 participate in the catalysis and constitute major targets for drug binding. Computational approaches have been applied mainly to pharmacological chaperones, substrate analogues, and glycomimetics mimicking the natural substrate. Among the most widely studied ligands is migalastat, which acts as a reversible competitive inhibitor by binding at the active site in the neutral pH environment of the cell and thereby facilitating the folding and intracellular delivery of the enzyme[39]. Studies of molecular docking revealed that effective pharmacological chaperones must display high binding affinity, proper orientation at the catalytic site, and the ability to establish stable hydrogen bond interactions with active site residues[40]. Moreover, the application of virtual screening allowed finding new lead molecules demonstrating higher binding efficacy owing to stereochemistry and positioning of functional groups. In this respect, the MD simulations are especially important for Fabry disease, where protein misfolding plays an essential role. Such type of simulations allows us to gain profound insight into the mechanisms underlying the impact of the interaction between molecules on the structural stability of α-galactosidase A. Thus, it was found

that pharmacological chaperone binding resulted in the structural stabilization of enzyme conformation, decreased structural fluctuations, and maintenance of active site geometry. Root means square deviation (RMSD) and root mean square fluctuation (RMSF) can be used as parameters of structural stability and flexibility[34]. At the same time, the binding free energy calculation confirms the thermodynamic feasibility of interactions between chaperone and enzyme as well as docking prediction. Another specific feature of the Fabry disease pathology is the dependence of α-galactosidase A properties on pH values, where chaperone binding takes place at neutral pH in the endoplasmic reticulum, while dissociation occurs in lysosomes at acidic pH. This aspect can also be studied by means of MD simulations (Table 4).

Table 4. Summary of Computational Studies Targeting Lysosomal Storage Disorder Enzymes

Disease	Target Enzyme/Protein	Computational Method	Key Compounds Studied	Binding Energy (kcal/mol)	Key Interacting Residues	Major Findings	Reference
Gaucher	β-glucocerebrosidase	Molecular Docking, MD Simulation	Iminosugars (NB-DNJ), flavonoids	~ -6.5 to -9.2	Glu235, Glu340	Stable binding via hydrogen bonding and hydrophobic interactions; potential enzyme stabilization	32 33
Tay–Sachs	β-hexosaminidase A	Docking, MD Simulation	Transition-state analogs, glycomimetics	~ -7.0 to -10.0	Active-site catalytic residues	High specificity due to structural mimicry of GM2 ganglioside	34 35
Fabry	α-galactosidase A	Docking, MD Simulation	Migalastat, substrate analogs	~ -6.0 to -8.5	Asp170, Asp231	Stabilization of misfolded enzyme; pH-dependent binding behavior	36 37
Niemann–Pick (A/B)	Acid sphingomyelinase	Docking, MD Simulation	Small-molecule inhibitors	~ -5.5 to -8.0	Catalytic residues	Moderate binding; therapeutic targeting still under exploration	38, 39
Niemann–Pick (C)	NPC1 protein	Docking, MD (membrane systems)	Sterol analogs, cyclodextrins	~ -6.0 to -9.0	Sterol-binding domain residues	Ligand binding influences cholesterol transport and protein conformation	38, 39

DISCUSSION

Despite sharing the same underlying pathology based on lysosomal malfunction among other disorders such as Tay-Sachs, Fabry, and Niemann-Pick diseases, Gaucher's disease displays considerable heterogeneity regarding molecular targets, substrates, and treatments[2,44]. This heterogeneity is important for computational-based drug discovery and development approaches (Fig. 5). Gaucher disease, Tay-Sachs disease, and Fabry disease can be classified into a category wherein the major issue lies with soluble lysosomal hydrolases like beta glucocerebrosidase, hexosaminidase A, and alpha galactosidase A, respectively[45, 46].

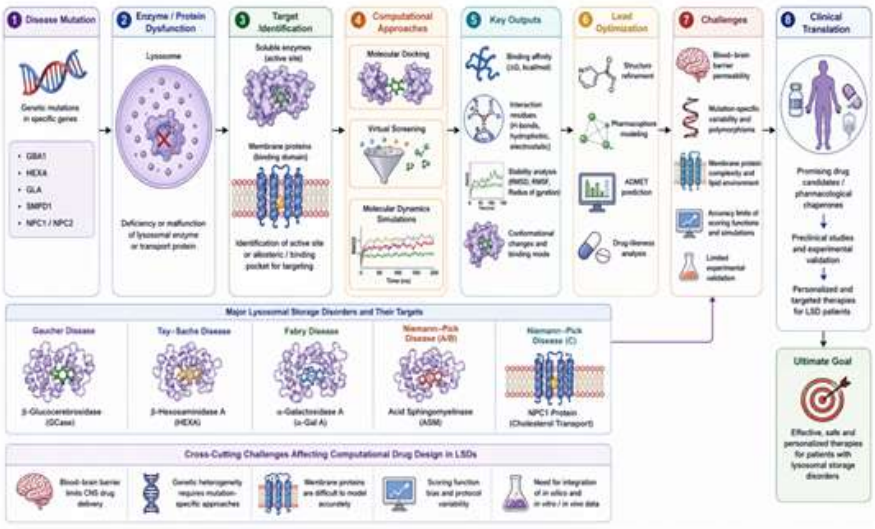

Fig 5. Comparative workflow for computational methods used in drug discovery for lysosomal storage diseases. Mutations cause dysfunction in enzymes/proteins; these targets can be studied via computational techniques including docking and molecular dynamics. Such techniques make it possible to discover potential inhibitors/stabilizers and optimize them based on pharmacokinetic properties. Important limitations in this process include difficulties with crossing the blood-brain barrier, mutation specificity, and complexity of membrane proteins.

On the other hand, Niemann-Pick disease, especially type C, entails membrane-bound protein-related deficiencies involving the function of the NPC1 and NPC2 protein regulators [47,48]. This fact plays a significant role in how computational models would have to be designed since membrane proteins require more advanced simulations than soluble enzymes[34]. The differences in the substrates involved play a pivotal role in the treatment approach. In Gaucher disease, there is an excess of glucosylceramide, whereas Tay-Sachs disease entails the accumulation of complex GM2 gangliosides[49]. In Fabry disease, there is a deposition of globotriaosylceramide in the blood vessels, and in Niemann-Pick disease, there are high levels of cholesterol and sphingomyelin with transport implications[50,51]. Consequently, the approach taken for ligand design will vary greatly due to differences in stereoisomerism and binding properties. Computational methods like molecular docking and MD simulations have been applied to all four disorders, albeit in varying degrees of importance based on the physiological system involved. Molecular docking provides a rapid means of screening compounds for potential drugs and is especially useful in the study of enzymes with a well-known active site, as seen with β-glucocerebrosidase and α-galactosidase A[33]. On the other hand, molecular dynamics simulation plays a greater role when there are complex substrates and membrane-bound proteins whose behaviour is affected by their environment[42]. The therapeutic modalities involved in each of these disorders vary greatly from one another. While enzyme inhibitors and modulators are the common treatment methods in Gaucher and Tay–Sachs diseases via the use of substrate and transition-state analogues[35], Fabry disease involves the use of pharmacological chaperones that prevent the misfolding of the enzyme [39,40]. For Niemann–Pick disorder, lipid transport mechanisms must be targeted[41]. Despite the dissimilarities, there exist some preserved interaction patterns between enzymes and ligands. The non-covalent type of binding, which involves hydrogen bonding, hydrophobic interactions, and electrostatic interactions, is critical in the formation of the enzyme-ligand complex. Additionally, complementarity at the enzyme's active site is another determining factor for the strength of the enzyme-ligand interactions[34]. There are also various limitations that come along with the computational approaches. In this case, these limitations can include lack of consistency between in silico results and experimentally obtained outcomes, as well as poor representation of membrane proteins and lipids, and insufficient incorporation of mutations in structural models[44]. The latest advancements, such as better sampling techniques, machine learning-enabled filtration techniques, and multi-level modelling, have contributed to improving the precision and predictability of computational analyses[52]. In addition, the growing focus on personalized treatment options and mutation-specific treatments can provide promising opportunities for developing effective therapeutic strategies. In summary, despite having a similar biological mechanism, the diversity among lysosomal storage diseases calls for customized computational and medical treatment approaches. Therefore, a thorough comparative understanding of these diseases offers vital information for optimal design of inhibitors and treatment strategies.

CONCLUSION

In this context, lysosomal storage disorders, among which are Gaucher disease, Tay-Sachs disease, Fabry disease, and Niemann-Pick disease, constitute a heterogeneous group of metabolic diseases whose diagnosis and treatment are based on different molecular mechanisms. In this study, special attention is paid to the potential of computational techniques, mainly molecular docking and simulation, in unravelling enzyme-ligand interactions and developing rational therapies. The comparison of the disorders shows that despite a common ethology, i.e., the malfunctioning of lysosomes, each of them calls for therapeutic modalities, depending on its unique molecular pathology. In the case of Gaucher and Tay-Sachs diseases, it involves enzyme inhibition or modulation; Fabry disease needs enzyme stabilization using pharmacological chaperones; and Niemann-Pick disease should be addressed using a different approach, related to lipid transport and membrane proteins. Many interesting results from computational research shed light on several important issues concerning the determination of ligands' activity and affinity, such as network-based interactions, complementary structures, and protein conformations. Nevertheless, certain obstacles still hinder their application in medical practice. The future of progress in this domain is likely to be contingent upon further collaboration between computer modelling approaches and experimental and clinical studies. The use of new simulations, machine learning algorithms, and personalized medicine techniques may increase the accuracy of drug discovery and allow for the creation of new treatments for lysosomal storage diseases.

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