Bibliography

Abbott, J. A. (2001). Cardiovascular physiology: mechanisms of control. Complex Adaptive Structures, SPIE.

Agrawal, S., et al. (2022). "Design and synthesis of benzo [d] thiazol-2-yl-methyl-4-(substituted)-piperazine-1-carbothioamide as novel neuronal nitric oxide inhibitors and evaluation of their neuroprotecting effect in 6-OHDA-induced unilateral lesioned rat model of Parkinson's disease." **156**: 113838.

Ahmad, M. H., et al. (2021). "Naringenin alleviates paraquat-induced dopaminergic neuronal loss in SH-SY5Y cells and a rat model of Parkinson's disease." **201**: 108831.

Ahmed, M. B., et al. (2008). "Protective effects of extract from dates (Phoenix dactylifera L.) and ascorbic acid on thioacetamide-induced hepatotoxicity in rats."

Albarmawi, H., et al. (2022). "The economic burden of Parkinson disease among Medicare beneficiaries." **28**(4): 405-414.

Albrecht, W., et al. (2019). "Prediction of human drug-induced liver injury (DILI) in relation to oral doses and blood concentrations." **93**: 1609-1637.

Atsumi, S., et al. (1992). "Inhibition of glucocerebrosidase and induction of neural abnormality by cyclophellitol in mice." **297**(2): 362-367.

Audano, M., et al. (2018). "Mitochondria, lysosomes, and dysfunction: their meaning in neurodegeneration." **147**(3): 291-309.

Ayto, R., et al. (2010). "Long-term outcomes of liver transplantation in type 1 Gaucher disease." **10**(8): 1934-1939.

Baccam, G. C., et al. (2022). "Glucosylceramide synthase inhibition protects against cardiac hypertrophy in chronic kidney disease." **12**(1): 9340.

Baek, J.-H., et al. (2019). "GRP78 level is altered in the brain, but not in plasma or cerebrospinal fluid in Parkinson's disease patients." **13**: 697.

Beavan, M. S. and A. H. J. A. o. m. Schapira (2013). "Glucocerebrosidase mutations and the pathogenesis of Parkinson disease." **45**(8): 511-521.

Bedi, O. and P. J. N.-S. s. a. o. p. Krishan (2020). "Investigations on acute oral toxicity studies of purpurin by application of OECD guideline 423 in rodents." **393**: 565-571.

Bendikov-Bar, I., et al. (2013). "Ambroxol as a pharmacological chaperone for mutant glucocerebrosidase." **50**(2): 141-145.

Berger, K., et al. (1991). "Retrograde degeneration of nigrostriatal neurons induced by intrastriatal 6-hydroxydopamine injection in rats." **26**(2): 301-307.

Berger, Z., et al. (2015). "Tool compounds robustly increase turnover of an artificial substrate by glucocerebrosidase in human brain lysates." **10**(3): e0119141.

Bhandari, R. and I. P. J. J. C. S. T. Kaur (2012). "A sensitive HPLC method for determination of isoniazid in rat plasma, brain, liver and kidney." **3**(2).

Bhardwaj, H. C., et al. (2016). "Neuroprotective and anti-nociceptive potential of ambroxol in oxaliplatin induced peripheral neuropathic pain in rats." **8**(2): 1.

Bi, H., et al. (2016). "Spectroscopic analysis on the binding interaction between tetracycline hydrochloride and bovine proteins β-casein, α-lactalbumin." **178**: 72-83.

Blandini, F., et al. (2008). "The 6-hydroxydopamine model: news from the past." **14**: S124-S129.

Bo, R.-X., et al. (2022). "The neuroinflammatory role of glucocerebrosidase in Parkinson's disease." **207**: 108964.

Boix, J., et al. (2018). "Gait analysis for early detection of motor symptoms in the 6-OHDA rat model of Parkinson's disease." **12**: 39.

Braak, H., et al. (2006). "Pathology associated with sporadic Parkinson's disease—where does it end?": 89-97.

Bradford, M. M. J. A. b. (1976). "A rapid and sensitive method for the quantitation of microgram quantities of protein utilizing the principle of protein-dye binding." **72**(1-2): 248-254.

Brand, M., et al. (2013). "The role of mitochondrial function and cellular bioenergetics in ageing and disease." British Journal of Dermatology **169**: 1-8.

Bustin, S. A., et al. (2009). The MIQE Guidelines: Minimum Information for Publication of Q uantitative Real-Time PCR Experiments, Oxford University Press.

Cai, P., et al. (2016). "Inhibition of endoplasmic reticulum stress is involved in the neuroprotective effect of bFGF in the 6-OHDA-induced Parkinson's disease model." **7**(4): 336.

Cairns, J. R. K., et al. (2015). "β-Glucosidases: multitasking, moonlighting or simply misunderstood?" **241**: 246-259.

Campion, S., et al. (2013). "The current status of biomarkers for predicting toxicity." **9**(11): 1391-1408.

Chatterjee, D. and D. J. J. o. M. B. Krainc (2023). "Mechanisms of Glucocerebrosidase Dysfunction in Parkinson's Disease." 168023.

Chen, M., et al. (2022). "Pharmacokinetics, bioavailability and tissue distribution of chitobiose and chitotriose in rats." **9**(1): 13.

Chiasserini, D., et al. (2015). "Selective loss of glucocerebrosidase activity in sporadic Parkinson's disease and dementia with Lewy bodies." Molecular neurodegeneration **10**(1): 1-6.

Chinta, S. J., et al. (2005). "Dopaminergic neurons." **37**(5): 942-946.

Chopade, P., et al. (2023). "Alzheimer's and Parkinson's disease therapies in the clinic." **8**(1): e10367.

Chwiszczuk, L. J., et al. (2023). "The ANeED study–ambroxol in new and early dementia with Lewy bodies (DLB): protocol for a phase IIa multicentre, randomised, double-blinded and placebo-controlled trial." **15**: 1163184.

Cohen, J. J. S. p. a. f. t. b. s. (1988). "The effect size." 77-83.

Costa, C. A. d., et al. (2020). "The endoplasmic reticulum stress/unfolded protein response and their contributions to Parkinson's disease physiopathology." **9**(11): 2495.

Dai, T., et al. (2019). "Investigation the interaction between procyanidin dimer and α-glucosidase: Spectroscopic analyses and molecular docking simulation." **130**: 315-322.

Dawson, T. M. and V. L. J. N. n. Dawson (2002). "Neuroprotective and neurorestorative strategies for Parkinson's disease." **5**(Suppl 11): 1058-1061.

Deng, Y.-x., et al. (2013). "Toxicological evaluation of neem (Azadirachta indica) oil: acute and subacute toxicity." **35**(2): 240-246.

Dhanve, P., et al. (2023). "AMBROXOL: A POTENTIAL THERAPEUTICS AGAINST NEURODEGENERATION." 100096.

Ding, X., et al. (2022). "Interaction between active compounds from Rosa roxburghii Tratt and β-glucosidase: Characterization of complexes and binding mechanism." **165**: 113707.

Do, J., et al. (2019). "Glucocerebrosidase and its relevance to Parkinson disease." **14**: 1-16.

Dong, Y.-w., et al. (2018). "Structural flexibility and protein adaptation to temperature: Molecular dynamics analysis of malate dehydrogenases of marine molluscs." **115**(6): 1274-1279.

Eo, H., et al. (2019). "Ukgansan protects dopaminergic neurons from 6-hydroxydopamine neurotoxicity via activation of the nuclear factor (erythroid-derived 2)-like 2 factor signaling pathway." **122**: 208-215.

Foltynie, T. and J. J. J. o. n. Kahan (2013). "Parkinson's disease: an update on pathogenesis and treatment." **260**: 1433-1440.

Furbish, F. S., et al. (1984). Interaction of human placental glucocerebrosidase with hepatic lectins. The molecular basis of lysosomal storage disorders, Academic Press Orlando**:** 219-232.

Furderer, M. L., et al. (2022). "Neuropathological features of gaucher disease and gaucher disease with Parkinsonism." **23**(10): 5842.

Fuster, J. M. J. I. J. o. P. (2000). "Cortical dynamics of memory." **35**(2-3): 155-164.

Fuster, J. n. M. J. T. i. n. (1997). "Network memory." **20**(10): 451-459.

Gaballah, H. H., et al. (2016). "Modulatory effects of resveratrol on endoplasmic reticulum stress-associated apoptosis and oxido-inflammatory markers in a rat model of rotenone-induced Parkinson's disease." **251**: 10-16.

Ganeshpurkar, A., et al. (2018). "Design, synthesis and collagenase inhibitory activity of some novel phenylglycine derivatives as metalloproteinase inhibitors." **107**: 1491-1500.

Ganeshpurkar, A., et al. (2020). "Structure-based screening and molecular dynamics simulation studies for the identification of potential acetylcholinesterase inhibitors." **46**(3): 169-185.

Ganeshpurkar, A., et al. (2022). "Identification of sulfonamide based butyrylcholinesterase inhibitors through scaffold hopping approach." **203**: 195-211.

Ganeshpurkar, A., et al. (2022). "Improved machine learning scoring functions for identification of Electrophorus electricus's acetylcholinesterase inhibitors." 1-25.

Gatto, E. M., et al. (2019). "Parkinsonisms and glucocerebrosidase deficiency: A comprehensive review for molecular and cellular mechanism of glucocerebrosidase deficiency." **9**(2): 30.

Gegg, M. E., et al. (2012). "Glucocerebrosidase deficiency in substantia nigra of parkinson disease brains." Annals of neurology **72**(3): 455-463.

Gegg, M. E., et al. (2012). "Glucocerebrosidase deficiency in substantia nigra of parkinson disease brains." **72**(3): 455-463.

Gegg, M. E., et al. (2022). "Glucocerebrosidase-associated Parkinson disease: Pathogenic mechanisms and potential drug treatments." **166**: 105663.

Gegg, M. E. and A. H. J. T. F. j. Schapira (2018). "The role of glucocerebrosidase in Parkinson disease pathogenesis." **285**(19): 3591-3603.

GeW, C. P. J. (1998). "The rat brain in stereotaxic coordinates."

Ghosh, R., et al. (2021). "Evaluation of green tea polyphenols as novel corona virus (SARS CoV-2) main protease (Mpro) inhibitors–an in silico docking and molecular dynamics simulation study." **39**(12): 4362-4374.

Goldin, E., et al. (2012). "High throughput screening for small molecule therapy for Gaucher disease using patient tissue as the source of mutant glucocerebrosidase." **7**(1): e29861.

Gómez-Suaga, P., et al. (2018). "ER–mitochondria signaling in Parkinson's disease." **9**(3): 337.

Goswami, P., et al. (2016). "Endoplasmic reticulum stress plays a key role in rotenone-induced apoptotic death of neurons." **53**: 285-298.

Greenfield, N. J. J. N. p. (2006). "Using circular dichroism spectra to estimate protein secondary structure." **1**(6): 2876-2890.

Guardia-Laguarta, C., et al. (2015). "A new role for α-synuclein in Parkinson's disease: Alteration of ER–mitochondrial communication." **30**(8): 1026-1033.

Guo, S., et al. (2005). "Protective effect of green tea polyphenols on the SH-SY5Y cells against 6-OHDA induced apoptosis through ROS–NO pathway." **39**(5): 682-695.

Gutti, G., et al. (2019). "Development of pyrazole and spiropyrazoline analogs as multifunctional agents for treatment of Alzheimer's disease." **90**: 103080.

Hammond, J. C., et al. (2012). "AMPA receptor subunit expression in the endoplasmic reticulum in frontal cortex of elderly patients with schizophrenia." **7**(6): e39190.

Han, L., et al. (2017). "Inhibitory effect of phloretin on α-glucosidase: Kinetics, interaction mechanism and molecular docking." **95**: 520-527.

Hansson, T., et al. (2002). "Molecular dynamics simulations." **12**(2): 190-196.

Hassan, M., et al. (2018). "Molecular docking and dynamic simulation of AZD3293 and solanezumab effects against BACE1 to treat Alzheimer's disease." **12**: 34.

Hetz, C., et al. (2003). "Caspase-12 and endoplasmic reticulum stress mediate neurotoxicity of pathological prion protein." **22**(20): 5435-5445.

Hitomi, J., et al. (2004). "Apoptosis induced by endoplasmic reticulum stress depends on activation of caspase-3 via caspase-12." **357**(2): 127-130.

Hoozemans, J., et al. (2007). "Activation of the unfolded protein response in Parkinson's disease." **354**(3): 707-711.

Jacob, R. and M. J. I. J. o. C. D. i. W.-W. Khan (2018). "Cardiac biomarkers: what is and what can be." **3**(04): 240-244.

Jana, S., et al. (2018). "Multiple 3D-QSAR modeling, e-pharmacophore, molecular docking, and in vitro study to explore novel AChE inhibitors." **8**(69): 39477-39495.

Jonsson, M., et al. (2013). "Application of OECD Guideline 423 in assessing the acute oral toxicity of moniliformin." **53**: 27-32.

Joseph, O., et al. (2019). "Toxicity study of ethanol leaf extract of ocimum canum on heart and lipid profile of wister rats."

Jothy, S. L., et al. (2011). "Acute oral toxicity of methanolic seed extract of Cassia fistula in mice." **16**(6): 5268-5282.

Jung, O., et al. (2016). "Progress and potential of non-inhibitory small molecule chaperones for the treatment of Gaucher disease and its implications for Parkinson disease." **13**(5): 471-479.

Kalia, L. V., et al. (2015). "Disease-modifying strategies for Parkinson's disease." **30**(11): 1442-1450.

Kang, S., et al. (2022). "DA-9805 protects dopaminergic neurons from endoplasmic reticulum stress and inflammation." **145**: 112389.

Kang, Z.-L., et al. (2017). "Structural changes evaluation with Raman spectroscopy in meat batters prepared by different processes." **54**: 2852-2860.

Karatas, M., et al. (2020). "Enzyme kinetics and inhibition parameters of human leukocyte glucosylceramidase." **6**(11).

Ketudat Cairns, J. R., et al. (2010). "β-Glucosidases." **67**: 3389-3405.

Khan, M. F., et al. (2016). "A simple RP-HPLC method development and validation for the simultaneous estimation of naproxen and Rabeprazole." **6**(11): 147-152.

Kip, E. and L. C. J. A. R. R. Parr-Brownlie (2022). "Reducing neuroinflammation via therapeutic compounds and lifestyle to prevent or delay progression of Parkinson's disease." **78**: 101618.

Kluwe, W. M. J. T. and A. Pharmacology (1981). "Renal function tests as indicators of kidney injury in subacute toxicity studies." **57**(3): 414-424.

Kopytova, A., et al. (2021). "Ambroxol increases glucocerebrosidase (GCase) activity and restores GCase translocation in primary patient-derived macrophages in Gaucher disease and Parkinsonism." **84**: 112-121.

Kumar, B., et al. (2018). "4, 6-Diphenylpyrimidine derivatives as dual inhibitors of monoamine oxidase and acetylcholinesterase for the treatment of Alzheimer's disease." **10**(1): 252-265.

Kumar, S., et al. (2021). "Molecular dynamics simulations identify the regions of compromised thermostability in SazCA." **89**(4): 375-388.

Kuo, S.-H., et al. (2022). "Mutant glucocerebrosidase impairs α-synuclein degradation by blockade of chaperone-mediated autophagy." **8**(6): eabm6393.

Kuo, S.-H., et al. (2022). "Misfolded GBA/β-glucocerebrosidase impairs ER-quality control by chaperone-mediated autophagy in Parkinson disease." **18**(12): 3050-3052.

Li, T., et al. (2018). "Comparing the binding interaction between β-lactoglobulin and flavonoids with different structure by multi-spectroscopy analysis and molecular docking." **201**: 197-206.

Li, Y., et al. (2020). "Ucf-101 protects in vivo and in vitro models of PD against 6-hydroxydopamine toxicity by alleviating endoplasmic reticulum stress via the Wnt/β-catenin pathway." **71**: 217-225.

Lieberman, R. L., et al. (2009). "Effects of pH and iminosugar pharmacological chaperones on lysosomal glycosidase structure and stability." **48**(22): 4816-4827.

Liu, G., et al. (2015). "Increased oligomerization and phosphorylation of α-synuclein are associated with decreased activity of glucocerebrosidase and protein phosphatase 2A in aging monkey brains." **36**(9): 2649-2659.

López-Guillermo, A., et al. (1991). "Liver dysfunction following splenectomy in idiopathic myelofibrosis: a study of 10 patients." **85**(4): 184-188.

Lowry, O., et al. (1951). "Protein measurement with the Folin phenol reagent." **193**(1): 265-275.

Luo, F., et al. (2012). "HtrA2/Omi is involved in 6-OHDA-induced endoplasmic reticulum stress in SH-SY5Y cells." **47**: 120-127.

Mächtel, R., et al. (2022). "From lysosomal storage disorders to Parkinson's Disease–Challenges and opportunities." 167932.

Maegawa, G. H., et al. (2009). "Identification and characterization of ambroxol as an enzyme enhancement agent for Gaucher disease." **284**(35): 23502-23516.

Magalhaes, J., et al. (2018). "Effects of ambroxol on the autophagy-lysosome pathway and mitochondria in primary cortical neurons." **8**(1): 1385.

Manning-Boğ, A. B., et al. (2009). "Alpha-synuclein-glucocerebrosidase interactions in pharmacological Gaucher models: a biological link between Gaucher disease and parkinsonism." **30**(6): 1127-1132.

Marí, M. and J. C. J. L. I. Fernández-Checa (2007). "Sphingolipid signalling and liver diseases." **27**(4): 440-450.

Maynard, D. M. J. T. P. o. C. (1960). "Circulation and heart function." **1**: 161-226.

Mazzulli, J. R., et al. (2016). "Activation of β-glucocerebrosidase reduces pathological α-synuclein and restores lysosomal function in Parkinson's patient midbrain neurons." **36**(29): 7693-7706.

McNeill, A., et al. (2014). "Ambroxol improves lysosomal biochemistry in glucocerebrosidase mutation-linked Parkinson disease cells." **137**(5): 1481-1495.

Mebius, R. E. and G. J. N. r. i. Kraal (2005). "Structure and function of the spleen." **5**(8): 606-616.

Menozzi, E. and A. H. J. C. D. Schapira (2020). "Enhancing the activity of glucocerebrosidase as a treatment for Parkinson disease." **34**: 915-923.

Menozzi, E., et al. (2023). "Targeting the GBA1 pathway to slow Parkinson disease: Insights into clinical aspects, pathogenic mechanisms and new therapeutic avenues." 108419.

Mercolini, L., et al. (2009). "Simultaneous analysis of diazepam and its metabolites in rat plasma and brain tissue by HPLC-UV and SPE." **80**(1): 279-285.

Michel, H. E., et al. (2022). "Omarigliptin attenuates rotenone-induced Parkinson's disease in rats: Possible role of oxidative stress, endoplasmic reticulum stress and immune modulation." **164**: 113015.

Migdalska-Richards, A., et al. (2016). "Ambroxol effects in glucocerebrosidase and α-synuclein transgenic mice." **80**(5): 766-775.

Migdalska-Richards, A. and A. H. J. J. o. n. Schapira (2016). "The relationship between glucocerebrosidase mutations and Parkinson disease." **139**: 77-90.

Minders, C., et al. (2015). "Monoamine oxidase inhibitory activities of heterocyclic chalcones." **25**(22): 5270-5276.

Mishra, A., et al. (2018). "Ambroxol modulates 6-Hydroxydopamine-induced temporal reduction in Glucocerebrosidase (GCase) enzymatic activity and Parkinson's disease symptoms." **155**: 479-493.

Mishra, A. and S. J. N.-S. s. A. o. P. Krishnamurthy (2020). "Neurorestorative effects of sub-chronic administration of ambroxol in rodent model of Parkinson's disease." **393**: 429-444.

Mishra, E. and M. K. J. B. Thakur (2022). "Alterations in hippocampal mitochondrial dynamics are associated with neurodegeneration and recognition memory decline in old male mice." **23**(2): 251-271.

Motawi, T. K., et al. (2022). "Empagliflozin alleviates endoplasmic reticulum stress and augments autophagy in rotenone-induced Parkinson's disease in rats: Targeting the GRP78/PERK/eIF2α/CHOP pathway and miR-211-5p." **362**: 110002.

Mullin, S., et al. (2020). "Ambroxol for the treatment of patients with Parkinson disease with and without glucocerebrosidase gene mutations: a nonrandomized, noncontrolled trial." **77**(4): 427-434.

Munoz, S. S., et al. (2021). "The interplay between Glucocerebrosidase, α-synuclein and lipids in human models of Parkinson's disease." **273**: 106534.

Murray, G. J., et al. (1995). "Studies on the turnover of exogenous mannose-terminal glucocerebrosidase in rat liver lysosomes." **57**(2): 208-217.

Nakagome, I., et al. (2018). "Design of a new α-1-C-Alkyl-DAB derivative acting as a pharmacological chaperone for β-Glucocerebrosidase using ligand docking and molecular dynamics simulation." **23**(10): 2683.

Navarro-Romero, A., et al. (2020). "The emerging role of the lysosome in Parkinson's disease." **9**(11): 2399.

Nikolaev, M., et al. (2022). "Glucocerebrosidase dysfunction and alpha-synuclein accumulation-a pathophysiological duet in GBA-associated Parkinson's disease." **21**(12): 18-22.

Ning, B., et al. (2019). "β-Asarone regulates ER stress and autophagy via inhibition of the PERK/CHOP/Bcl-2/Beclin-1 pathway in 6-OHDA-induced parkinsonian rats." **44**: 1159-1166.

Pastores, G. M. and D. A. Hughes (2018). "Gaucher disease."

Paxinos, G. and C. Watson (2006). The rat brain in stereotaxic coordinates: hard cover edition, Elsevier.

Pazhayattil, G. S., et al. (2014). "Drug-induced impairment of renal function." 457-468.

Peng, T., et al. (2018). "Fluoxetine-mediated inhibition of endoplasmic reticulum stress is involved in the neuroprotective effects of Parkinson's disease." **10**(12): 4188.

Perrone, R. D., et al. (1992). "Serum creatinine as an index of renal function: new insights into old concepts." **38**(10): 1933-1953.

Piao, Y., et al. (2013). "Change trends of organ weight background data in sprague dawley rats at different ages." **26**(1): 29-34.

Poewe, W., et al. (2009). "The clinical progression of Parkinson's disease." **15**: S28-S32.

Radi, Z. A. J. I. j. o. t. (2019). "Kidney pathophysiology, toxicology, and drug-induced injury in drug development." **38**(3): 215-227.

Ramakrishna, K., et al. (2022). "Pharmacokinetic and Pharmacodynamic Properties of Indole-3-carbinol in Experimental Focal Ischemic Injury." **47**(4): 593-605.

Rao, R. V. and D. E. J. C. o. i. c. b. Bredesen (2004). "Misfolded proteins, endoplasmic reticulum stress and neurodegeneration." **16**(6): 653-662.

Real, C. C., et al. (2017). "Treadmill exercise prevents increase of neuroinflammation markers involved in the dopaminergic damage of the 6-OHDA Parkinson's disease model." **63**: 36-49.

Richter, F., et al. (2014). "A GCase chaperone improves motor function in a mouse model of synucleinopathy." **11**: 840-856.

Robak, L. A., et al. (2017). "Excessive burden of lysosomal storage disorder gene variants in Parkinson's disease." **140**(12): 3191-3203.

Rocha, E. M., et al. (2015). "Progressive decline of glucocerebrosidase in aging and P arkinson's disease." **2**(4): 433-438.

Ron, I., et al. (2010). "Interaction between parkin and mutant glucocerebrosidase variants: a possible link between Parkinson disease and Gaucher disease." **19**(19): 3771-3781.

Sadeghian, Z., et al. (2022). "Post treatment with Gastrodin suppresses oxidative stress and attenuates motor disorders following 6-OHDA induced Parkinson disease." **790**: 136884.

Samuels, M. A. J. C. (2007). "The brain–heart connection." **116**(1): 77-84.

Sanchez-Martinez, A., et al. (2016). "Parkinson disease-linked GBA mutation effects reversed by molecular chaperones in human cell and fly models." **6**(1): 31380.

Sanz, E., et al. (2009). "PF9601N [N-(2-propynyl)-2-(5-benzyloxy-indolyl) methylamine] confers MAO-B independent neuroprotection in ER stress-induced cell death." **41**(1): 19-31.

Sawkar, A. R., et al. (2002). "Chemical chaperones increase the cellular activity of N370S β-glucosidase: a therapeutic strategy for Gaucher disease." **99**(24): 15428-15433.

Sayyaed, A., et al. (2023). "A detailed review of pathophysiology, epidemiology, cellular and molecular pathways involved in the development and prognosis of Parkinson's disease with insights into screening models." **47**(1): 1-16.

Schapira, A. H. and M. E. J. P. o. t. N. A. o. S. Gegg (2013). "Glucocerebrosidase in the pathogenesis and treatment of Parkinson disease." **110**(9): 3214-3215.

Schapira, A. H. J. M. and c. neuroscience (2015). "Glucocerebrosidase and Parkinson disease: recent advances." **66**: 37-42.

Schmittgen, T. D. and K. J. J. N. p. Livak (2008). "Analyzing real-time PCR data by the comparative CT method." **3**(6): 1101-1108.

Schneider, C. M., et al. (1995). "Effects of physical activity on creatine phosphokinase and the isoenzyme creatine kinase–MB." **25**(4): 520-524.

Schreiner, B. and M. J. M. P. P. Ankarcrona (2017). "Isolation of mitochondria-associated membranes (MAM) from mouse brain tissue." 53-68.

Schulze, H. and K. J. C. S. H. p. i. b. Sandhoff (2011). "Lysosomal lipid storage diseases." **3**(6): a004804.

Selvaraj, S., et al. (2012). "Neurotoxin-induced ER stress in mouse dopaminergic neurons involves downregulation of TRPC1 and inhibition of AKT/mTOR signaling." **122**(4): 1354-1367.

Shahed, J. and J. J. H. o. c. n. Jankovic (2007). "Motor symptoms in Parkinson's disease." **83**: 329-342.

Sharma, P., et al. (2019). "Design and development of multitarget-directed N-Benzylpiperidine analogs as potential candidates for the treatment of Alzheimer's disease." **167**: 510-524.

Shidore, M., et al. (2016). "Benzylpiperidine-linked diarylthiazoles as potential anti-Alzheimer's agents: synthesis and biological evaluation." **59**(12): 5823-5846.

Shrivastava, P., et al. (2013). "Anti-apoptotic and anti-inflammatory effect of Piperine on 6-OHDA induced Parkinson's rat model." **24**(4): 680-687.

Shukla, R., et al. (2018). "Structure-based screening and molecular dynamics simulations offer novel natural compounds as potential inhibitors of Mycobacterium tuberculosis isocitrate lyase." **36**(8): 2045-2057.

Siebert, M., et al. (2014). "Glucocerebrosidase is shaking up the synucleinopathies." **137**(5): 1304-1322.

Silva, R. M., et al. (2005). "CHOP/GADD153 is a mediator of apoptotic death in substantia nigra dopamine neurons in an in vivo neurotoxin model of parkinsonism." **95**(4): 974-986.

Silveira, C., et al. (2019). "Ambroxol as a novel disease-modifying treatment for Parkinson's disease dementia: protocol for a single-centre, randomized, double-blind, placebo-controlled trial." **19**(1): 1-10.

Silveira, C., et al. (2019). "Ambroxol as a novel disease-modifying treatment for Parkinson's disease dementia: Protocol for a single-centre, randomized, double-blind, placebo-controlled trial." **19**: 1-10.

Singh, R., et al. (2020). "Identifying potential GluN2B subunit containing N-Methyl-D-aspartate receptor inhibitors: An integrative in silico and molecular modeling approach." **38**(9): 2533-2545.

Smith, L., et al. (2017). "Insights into the structural biology of Gaucher disease." **298**: 180-190.

Soni, R., et al. (2023). "Uncovering Novel Therapeutic Targets for Parkinson's Disease."

Stojkovska, I., et al. (2018). "Molecular mechanisms of α-synuclein and GBA1 in Parkinson's disease." **373**: 51-60.

Tayebi, N., et al. (2017). "Glucocerebrosidase haploinsufficiency in A53T α-synuclein mice impacts disease onset and course." **122**(4): 198-208.

Thangavelu, L., et al. (2020). "Evaluation of the sub-acute toxicity of Acacia catechu Willd seed extract in a Wistar albino rat model." **113**: 104640.

Thummel, K. E., et al. (2006). "Design and optimization of dosage regimens: pharmacokinetic data." 1787-1888.

Tong, Q., et al. (2016). "Inhibition of endoplasmic reticulum stress-activated IRE1α-TRAF2-caspase-12 apoptotic pathway is involved in the neuroprotective effects of telmisartan in the rotenone rat model of Parkinson's disease." **776**: 106-115.

Trapero, A., et al. (2012). "Potent aminocyclitol glucocerebrosidase inhibitors are subnanomolar pharmacological chaperones for treating gaucher disease." **55**(9): 4479-4488.

Trapero, A. and A. J. A. m. c. l. Llebaria (2011). "The myo-1, 2-diaminocyclitol scaffold defines potent glucocerebrosidase activators and promising pharmacological chaperones for Gaucher disease." **2**(8): 614-619.

Travlos, G., et al. (1996). "Frequency and relationships of clinical chemistry and liver and kidney histopathology findings in 13-week toxicity studies in rats." **107**(1): 17-29.

Tripathi, P., et al. (2022). "Generation of wild-type rat Glucocerebrosidase homology modeling: Identification of putative interactions site and mechanism for chaperone using combined in-silico and in-vitro studies." **126**: 105871.

Tripathi, P., et al. (2023). "Identification of novel glucocerebrosidase chaperone for potential treatment of Parkinson's disease: An approach using in silico virtual screening, molecular docking and molecular dynamics, and in vitro studies." **228**: 453-466.

Venuprasad, M., et al. (2013). "Neuroprotective effects of hydroalcoholic extract of Ocimum sanctum against H 2 O 2 induced neuronal cell damage in SH-SY5Y cells via its antioxidative defence mechanism." **38**: 2190-2200.

Vercammen, L., et al. (2006). "Parkin protects against neurotoxicity in the 6-hydroxydopamine rat model for Parkinson's disease." **14**(5): 716-723.

Victorino, D. B., et al. (2020). "COVID-19 and Parkinson's disease: are we dealing with short-term impacts or something worse?" **10**(3): 899.

Vieira, S. R., et al. (2021). "Glucocerebrosidase mutations: A paradigm for neurodegeneration pathways." **175**: 42-55.

Vysakh, A., et al. (2020). "Acute oral toxicity and anti-inflammatory evaluation of methanolic extract of Rotula aquatica roots in Wistar rats." **11**(1): 45-52.

Wang, H., et al. (2020). "Ghrelin protects dopaminergic neurons against MPTP neurotoxicity through promoting autophagy and inhibiting endoplasmic reticulum mediated apoptosis." **1746**: 147023.

Wang, H. Q., et al. (2007). "Expanding insights on the involvement of endoplasmic reticulum stress in Parkinson's disease." **9**(5): 553-561.

Wang, S.-F., et al. (2017). "Baicalein prevents 6-OHDA/ascorbic acid-induced calcium-dependent dopaminergic neuronal cell death." **7**(1): 8398.

Wang, X., et al. (2023). "The Crucial Roles of Pitx3 in Midbrain Dopaminergic Neuron Development and Parkinson's Disease-Associated Neurodegeneration." **24**(10): 8614.

Weiser, T. J. C. n. and therapeutics (2008). "Ambroxol: a CNS drug?" **14**(1): 17-24.

Wen, H., et al. (2017). "Acute toxicity and genotoxicity of silver nanoparticle in rats." **12**(9): e0185554.

Westbroek, W., et al. (2011). "Exploring the link between glucocerebrosidase mutations and parkinsonism." **17**(9): 485-493.

Wood-Kaczmar, A., et al. (2006). "Understanding the molecular causes of Parkinson's disease." **12**(11): 521-528.

Wu, K.-J., et al. (2023). "Prosaposin PS18 reduces dopaminergic neurodegeneration in a 6-hydroxydopamine rat model of Parkinson's disease." **13**(1): 8148.

Xiao, F., et al. (2014). "Spectroscopic investigation on the interaction of hyperbranched poly (amine) ester with model plasma protein: Effect on the structural and conformational changes." **118**: 1106-1112.

Xu, X.-L., et al. (2011). "Raman spectroscopic study of heat-induced gelation of pork myofibrillar proteins and its relationship with textural characteristic." **87**(3): 159-164.

Yang, J., et al. (2023). "Recent advances in novel mutation genes of Parkinson's disease." 1-10.

Yang, Y., et al. (2005). "Determination of plasma and brain levels of isotretinoin in mice following single oral dose by high-performance liquid chromatography." **37**(1): 157-163.

Yu, Z., et al. (2007). "Pharmacologic chaperoning as a strategy to treat Gaucher disease." **274**(19): 4944-4950.

Yu, Z., et al. (2007). "Isofagomine-and 2, 5-anhydro-2, 5-imino-D-glucitol-based glucocerebrosidase pharmacological chaperones for Gaucher disease intervention." **50**(1): 94-100.

Zagórska, A., et al. (2023). "Drug Discovery and Development Targeting Dementia." **16**(2): 151.

Zeuner, K. E., et al. (2019). "Progress of pharmacological approaches in Parkinson's disease." **105**(5): 1106-1120.

Abbott, J. A. (2001). Cardiovascular physiology: mechanisms of control. Complex Adaptive Structures, SPIE.

Agrawal, S., et al. (2022). "Design and synthesis of benzo [d] thiazol-2-yl-methyl-4-(substituted)-piperazine-1-carbothioamide as novel neuronal nitric oxide inhibitors and evaluation of their

neuroprotecting effect in 6-OHDA-induced unilateral lesioned rat model of Parkinson's disease." **156**: 113838.

Ahmad, M. H., et al. (2021). "Naringenin alleviates paraquat-induced dopaminergic neuronal loss in SH-SY5Y cells and a rat model of Parkinson's disease." **201**: 108831.

Ahmed, M. B., et al. (2008). "Protective effects of extract from dates (Phoenix dactylifera L.) and ascorbic acid on thioacetamide-induced hepatotoxicity in rats."

Albarmawi, H., et al. (2022). "The economic burden of Parkinson disease among Medicare beneficiaries." **28**(4): 405-414.

Albrecht, W., et al. (2019). "Prediction of human drug-induced liver injury (DILI) in relation to oral doses and blood concentrations." **93**: 1609-1637.

Atsumi, S., et al. (1992). "Inhibition of glucocerebrosidase and induction of neural abnormality by cyclophellitol in mice." **297**(2): 362-367.

Audano, M., et al. (2018). "Mitochondria, lysosomes, and dysfunction: their meaning in neurodegeneration." **147**(3): 291-309.

Avenali, M., et al. (2020). "Glucocerebrosidase defects as a major risk factor for Parkinson's disease." **12**: 97.

Ayto, R., et al. (2010). "Long-term outcomes of liver transplantation in type 1 Gaucher disease." **10**(8): 1934-1939.

Baccam, G. C., et al. (2022). "Glucosylceramide synthase inhibition protects against cardiac hypertrophy in chronic kidney disease." **12**(1): 9340.

Baek, J.-H., et al. (2019). "GRP78 level is altered in the brain, but not in plasma or cerebrospinal fluid in Parkinson's disease patients." **13**: 697.

Beavan, M. S. and A. H. J. A. o. m. Schapira (2013). "Glucocerebrosidase mutations and the pathogenesis of Parkinson disease." **45**(8): 511-521.

Bedi, O. and P. J. N.-S. s. a. o. p. Krishan (2020). "Investigations on acute oral toxicity studies of purpurin by application of OECD guideline 423 in rodents." **393**: 565-571.

Bendikov-Bar, I., et al. (2013). "Ambroxol as a pharmacological chaperone for mutant glucocerebrosidase." **50**(2): 141-145.

Berger, K., et al. (1991). "Retrograde degeneration of nigrostriatal neurons induced by intrastriatal 6-hydroxydopamine injection in rats." **26**(2): 301-307.

Berger, Z., et al. (2015). "Tool compounds robustly increase turnover of an artificial substrate by glucocerebrosidase in human brain lysates." **10**(3): e0119141.

Bhandari, R. and I. P. J. J. C. S. T. Kaur (2012). "A sensitive HPLC method for determination of isoniazid in rat plasma, brain, liver and kidney." **3**(2).

Bhardwaj, H. C., et al. (2016). "Neuroprotective and anti-nociceptive potential of ambroxol in oxaliplatin induced peripheral neuropathic pain in rats." **8**(2): 1.

Bi, H., et al. (2016). "Spectroscopic analysis on the binding interaction between tetracycline hydrochloride and bovine proteins β-casein, α-lactalbumin." **178**: 72-83.

Blandini, F., et al. (2008). "The 6-hydroxydopamine model: news from the past." **14**: S124-S129.

Blanz, J. and P. J. J. o. n. Saftig (2016). "Parkinson's disease: acid-glucocerebrosidase activity and alpha-synuclein clearance." **139**: 198-215.

Bo, R.-X., et al. (2022). "The neuroinflammatory role of glucocerebrosidase in Parkinson's disease." **207**: 108964.

Boix, J., et al. (2018). "Gait analysis for early detection of motor symptoms in the 6-OHDA rat model of Parkinson's disease." **12**: 39.

Braak, H., et al. (2006). "Pathology associated with sporadic Parkinson's disease—where does it end?": 89-97.

Bradford, M. M. J. A. b. (1976). "A rapid and sensitive method for the quantitation of microgram quantities of protein utilizing the principle of protein-dye binding." **72**(1-2): 248-254.

Brand, M., et al. (2013). "The role of mitochondrial function and cellular bioenergetics in ageing and disease." British Journal of Dermatology **169**: 1-8.

Bustin, S. A., et al. (2009). The MIQE Guidelines: M inimum I nformation for Publication of Q uantitative Real-Time PCR E xperiments, Oxford University Press.

Cai, P., et al. (2016). "Inhibition of endoplasmic reticulum stress is involved in the neuroprotective effect of bFGF in the 6-OHDA-induced Parkinson's disease model." **7**(4): 336.

Cairns, J. R. K., et al. (2015). "β-Glucosidases: multitasking, moonlighting or simply misunderstood?" **241**: 246-259.

Campion, S., et al. (2013). "The current status of biomarkers for predicting toxicity." **9**(11): 1391-1408.

Chatterjee, D. and D. J. J. o. M. B. Krainc (2023). "Mechanisms of Glucocerebrosidase Dysfunction in Parkinson's Disease." 168023.

Chen, M., et al. (2022). "Pharmacokinetics, bioavailability and tissue distribution of chitobiose and chitotriose in rats." **9**(1): 13.

Chiasserini, D., et al. (2015). "Selective loss of glucocerebrosidase activity in sporadic Parkinson's disease and dementia with Lewy bodies." Molecular neurodegeneration **10**(1): 1-6.

Chiasserini, D., et al. (2015). "Selective loss of glucocerebrosidase activity in sporadic Parkinson's disease and dementia with Lewy bodies." **10**: 1-6.

Chinta, S. J., et al. (2005). "Dopaminergic neurons." **37**(5): 942-946.

Choi, M.-G., et al. (2018). "Sequestration of synaptic proteins by alpha-synuclein aggregates leading to neurotoxicity is inhibited by small peptide." **13**(4): e0195339.

Chopade, P., et al. (2023). "Alzheimer's and Parkinson's disease therapies in the clinic." **8**(1): e10367.

Chwiszczuk, L. J., et al. (2023). "The ANeED study–ambroxol in new and early dementia with Lewy bodies (DLB): protocol for a phase IIa multicentre, randomised, double-blinded and placebo-controlled trial." **15**: 1163184.

Cohen, J. J. S. p. a. f. t. b. s. (1988). "The effect size." 77-83.

Costa, C. A. d., et al. (2020). "The endoplasmic reticulum stress/unfolded protein response and their contributions to Parkinson's disease physiopathology." **9**(11): 2495.

Dai, T., et al. (2019). "Investigation the interaction between procyanidin dimer and α-glucosidase: Spectroscopic analyses and molecular docking simulation." **130**: 315-322.

Dawson, T. M. and V. L. J. N. n. Dawson (2002). "Neuroprotective and neurorestorative strategies for Parkinson's disease." **5**(Suppl 11): 1058-1061.

Deng, Y.-x., et al. (2013). "Toxicological evaluation of neem (Azadirachta indica) oil: acute and subacute toxicity." **35**(2): 240-246.

Dhanve, P., et al. (2023). "AMBROXOL: A POTENTIAL THERAPEUTICS AGAINST NEURODEGENERATION." 100096.

Ding, X., et al. (2022). "Interaction between active compounds from Rosa roxburghii Tratt and β-glucosidase: Characterization of complexes and binding mechanism." **165**: 113707.

Do, J., et al. (2019). "Glucocerebrosidase and its relevance to Parkinson disease." **14**: 1-16.

Domenicale, C. (2024). "Age-dependent modulation of G2019S LRRK2 on α-synuclein pathology and β-Glucocerebrosidase activity."

Dong, Y.-w., et al. (2018). "Structural flexibility and protein adaptation to temperature: Molecular dynamics analysis of malate dehydrogenases of marine molluscs." **115**(6): 1274-1279.

Eo, H., et al. (2019). "Ukgansan protects dopaminergic neurons from 6-hydroxydopamine neurotoxicity via activation of the nuclear factor (erythroid-derived 2)-like 2 factor signaling pathway." **122**: 208-215.

Foltynie, T. and J. J. J. o. n. Kahan (2013). "Parkinson's disease: an update on pathogenesis and treatment." **260**: 1433-1440.

Furbish, F. S., et al. (1984). Interaction of human placental glucocerebrosidase with hepatic lectins. The molecular basis of lysosomal storage disorders, Academic Press Orlando**:** 219-232.

Furderer, M. L., et al. (2022). "Neuropathological features of gaucher disease and gaucher disease with Parkinsonism." **23**(10): 5842.

Fuster, J. M. J. I. J. o. P. (2000). "Cortical dynamics of memory." **35**(2-3): 155-164.

Fuster, J. n. M. J. T. i. n. (1997). "Network memory." **20**(10): 451-459.

Gaballah, H. H., et al. (2016). "Modulatory effects of resveratrol on endoplasmic reticulum stress-associated apoptosis and oxido-inflammatory markers in a rat model of rotenone-induced Parkinson's disease." **251**: 10-16.

Ganeshpurkar, A., et al. (2018). "Design, synthesis and collagenase inhibitory activity of some novel phenylglycine derivatives as metalloproteinase inhibitors." **107**: 1491-1500.

Ganeshpurkar, A., et al. (2020). "Structure-based screening and molecular dynamics simulation studies for the identification of potential acetylcholinesterase inhibitors." **46**(3): 169-185.

Ganeshpurkar, A., et al. (2022). "Identification of sulfonamide based butyrylcholinesterase inhibitors through scaffold hopping approach." **203**: 195-211.

Ganeshpurkar, A., et al. (2022). "Improved machine learning scoring functions for identification of Electrophorus electricus's acetylcholinesterase inhibitors." 1-25.

Gatto, E. M., et al. (2019). "Parkinsonisms and glucocerebrosidase deficiency: A comprehensive review for molecular and cellular mechanism of glucocerebrosidase deficiency." **9**(2): 30.

Gegg, M. E., et al. (2012). "Glucocerebrosidase deficiency in substantia nigra of parkinson disease brains." Annals of neurology **72**(3): 455-463.

Gegg, M. E., et al. (2012). "Glucocerebrosidase deficiency in substantia nigra of parkinson disease brains." **72**(3): 455-463.

Gegg, M. E., et al. (2022). "Glucocerebrosidase-associated Parkinson disease: Pathogenic mechanisms and potential drug treatments." **166**: 105663.

Gegg, M. E. and A. H. J. T. F. j. Schapira (2018). "The role of glucocerebrosidase in Parkinson disease pathogenesis." **285**(19): 3591-3603.

GeW, C. P. J. (1998). "The rat brain in stereotaxic coordinates."

Ghosh, R., et al. (2021). "Evaluation of green tea polyphenols as novel corona virus (SARS CoV-2) main protease (Mpro) inhibitors–an in silico docking and molecular dynamics simulation study." **39**(12): 4362-4374.

Goker-Alpan, O., et al. (2008). "The spectrum of parkinsonian manifestations associated with glucocerebrosidase mutations." **65**(10): 1353-1357.

Goker-Alpan, O., et al. (2010). "Glucocerebrosidase is present in α-synuclein inclusions in Lewy body disorders." **120**: 641-649.

Goldin, E., et al. (2012). "High throughput screening for small molecule therapy for Gaucher disease using patient tissue as the source of mutant glucocerebrosidase." **7**(1): e29861.

Gómez-Suaga, P., et al. (2018). "ER–mitochondria signaling in Parkinson's disease." **9**(3): 337.

Goswami, P., et al. (2016). "Endoplasmic reticulum stress plays a key role in rotenone-induced apoptotic death of neurons." **53**: 285-298.

Granek, Z., et al. (2023). "GBA1 gene mutations in α-Synucleinopathies—molecular mechanisms underlying pathology and their clinical significance." **24**(3): 2044.

Greenfield, N. J. J. N. p. (2006). "Using circular dichroism spectra to estimate protein secondary structure." **1**(6): 2876-2890.

Guardia-Laguarta, C., et al. (2015). "A new role for α-synuclein in Parkinson's disease: Alteration of ER–mitochondrial communication." **30**(8): 1026-1033.

Guo, S., et al. (2005). "Protective effect of green tea polyphenols on the SH-SY5Y cells against 6-OHDA induced apoptosis through ROS–NO pathway." **39**(5): 682-695.

Gutti, G., et al. (2019). "Development of pyrazole and spiropyrazoline analogs as multifunctional agents for treatment of Alzheimer's disease." **90**: 103080.

Hammond, J. C., et al. (2012). "AMPA receptor subunit expression in the endoplasmic reticulum in frontal cortex of elderly patients with schizophrenia." **7**(6): e39190.

Han, L., et al. (2017). "Inhibitory effect of phloretin on α-glucosidase: Kinetics, interaction mechanism and molecular docking." **95**: 520-527.

Hansson, T., et al. (2002). "Molecular dynamics simulations." **12**(2): 190-196.

Hassan, M., et al. (2018). "Molecular docking and dynamic simulation of AZD3293 and solanezumab effects against BACE1 to treat Alzheimer's disease." **12**: 34.

Hetz, C., et al. (2003). "Caspase-12 and endoplasmic reticulum stress mediate neurotoxicity of pathological prion protein." **22**(20): 5435-5445.

Hitomi, J., et al. (2004). "Apoptosis induced by endoplasmic reticulum stress depends on activation of caspase-3 via caspase-12." **357**(2): 127-130.

Hoozemans, J., et al. (2007). "Activation of the unfolded protein response in Parkinson's disease." **354**(3): 707-711.

Jacob, R. and M. J. I. J. o. C. D. i. W.-W. Khan (2018). "Cardiac biomarkers: what is and what can be." **3**(04): 240-244.

Jana, S., et al. (2018). "Multiple 3D-QSAR modeling, e-pharmacophore, molecular docking, and in vitro study to explore novel AChE inhibitors." **8**(69): 39477-39495.

Jonsson, M., et al. (2013). "Application of OECD Guideline 423 in assessing the acute oral toxicity of moniliformin." **53**: 27-32.

Joseph, O., et al. (2019). "Toxicity study of ethanol leaf extract of ocimum canum on heart and lipid profile of wister rats."

Jothy, S. L., et al. (2011). "Acute oral toxicity of methanolic seed extract of Cassia fistula in mice." **16**(6): 5268-5282.

Jung, O., et al. (2016). "Progress and potential of non-inhibitory small molecule chaperones for the treatment of Gaucher disease and its implications for Parkinson disease." **13**(5): 471-479.

Kalia, L. V., et al. (2015). "Disease-modifying strategies for Parkinson's disease." **30**(11): 1442-1450.

Kang, S., et al. (2022). "DA-9805 protects dopaminergic neurons from endoplasmic reticulum stress and inflammation." **145**: 112389.

Kang, Z.-L., et al. (2017). "Structural changes evaluation with Raman spectroscopy in meat batters prepared by different processes." **54**: 2852-2860.

Karatas, M., et al. (2020). "Enzyme kinetics and inhibition parameters of human leukocyte glucosylceramidase." **6**(11).

Ketudat Cairns, J. R., et al. (2010). "β-Glucosidases." **67**: 3389-3405.

Khan, M. F., et al. (2016). "A simple RP-HPLC method development and validation for the simultaneous estimation of naproxen and Rabeprazole." **6**(11): 147-152.

Kip, E. and L. C. J. A. R. R. Parr-Brownlie (2022). "Reducing neuroinflammation via therapeutic compounds and lifestyle to prevent or delay progression of Parkinson's disease." **78**: 101618.

Kluwe, W. M. J. T. and A. Pharmacology (1981). "Renal function tests as indicators of kidney injury in subacute toxicity studies." **57**(3): 414-424.

Kopytova, A., et al. (2021). "Ambroxol increases glucocerebrosidase (GCase) activity and restores GCase translocation in primary patient-derived macrophages in Gaucher disease and Parkinsonism." **84**: 112-121.

Kumar, B., et al. (2018). "4, 6-Diphenylpyrimidine derivatives as dual inhibitors of monoamine oxidase and acetylcholinesterase for the treatment of Alzheimer's disease." **10**(1): 252-265.

Kumar, S., et al. (2021). "Molecular dynamics simulations identify the regions of compromised thermostability in SazCA." **89**(4): 375-388.

Kuo, S.-H., et al. (2022). "Mutant glucocerebrosidase impairs α-synuclein degradation by blockade of chaperone-mediated autophagy." **8**(6): eabm6393.

Kuo, S.-H., et al. (2022). "Misfolded GBA/β-glucocerebrosidase impairs ER-quality control by chaperone-mediated autophagy in Parkinson disease." **18**(12): 3050-3052.

Li, T., et al. (2018). "Comparing the binding interaction between β-lactoglobulin and flavonoids with different structure by multi-spectroscopy analysis and molecular docking." **201**: 197-206.

Li, Y., et al. (2020). "Ucf-101 protects in vivo and in vitro models of PD against 6-hydroxydopamine toxicity by alleviating endoplasmic reticulum stress via the Wnt/β-catenin pathway." **71**: 217-225.

Lieberman, R. L., et al. (2009). "Effects of pH and iminosugar pharmacological chaperones on lysosomal glycosidase structure and stability." **48**(22): 4816-4827.

Liu, G., et al. (2015). "Increased oligomerization and phosphorylation of α-synuclein are associated with decreased activity of glucocerebrosidase and protein phosphatase 2A in aging monkey brains." **36**(9): 2649-2659.

López-Guillermo, A., et al. (1991). "Liver dysfunction following splenectomy in idiopathic myelofibrosis: a study of 10 patients." **85**(4): 184-188.

Lowry, O., et al. (1951). "Protein measurement with the Folin phenol reagent." **193**(1): 265-275.

Luo, F., et al. (2012). "HtrA2/Omi is involved in 6-OHDA-induced endoplasmic reticulum stress in SH-SY5Y cells." **47**: 120-127.

Mächtel, R., et al. (2022). "From lysosomal storage disorders to Parkinson's Disease–Challenges and opportunities." 167932.

Mächtel, R., et al. (2023). "From Lysosomal Storage Disorders to Parkinson's Disease–Challenges and Opportunities." **435**(12): 167932.

Maegawa, G. H., et al. (2009). "Identification and characterization of ambroxol as an enzyme enhancement agent for Gaucher disease." **284**(35): 23502-23516.

Magalhaes, J., et al. (2018). "Effects of ambroxol on the autophagy-lysosome pathway and mitochondria in primary cortical neurons." **8**(1): 1385.

Magalhaes, J., et al. (2016). "Autophagic lysosome reformation dysfunction in glucocerebrosidase deficient cells: relevance to Parkinson disease." **25**(16): 3432-3445.

Manning-Boğ, A. B., et al. (2009). "Alpha-synuclein-glucocerebrosidase interactions in pharmacological Gaucher models: a biological link between Gaucher disease and parkinsonism." **30**(6): 1127-1132.

Marí, M. and J. C. J. L. I. Fernández-Checa (2007). "Sphingolipid signalling and liver diseases." **27**(4): 440-450.

Maynard, D. M. J. T. P. o. C. (1960). "Circulation and heart function." **1**: 161-226.

Mazzulli, J. R., et al. (2016). "Activation of β-glucocerebrosidase reduces pathological α-synuclein and restores lysosomal function in Parkinson's patient midbrain neurons." **36**(29): 7693-7706.

McNeill, A. (2013). Glucocerebrosidase mutations and Parkinson's disease, UCL (University College London).

McNeill, A., et al. (2014). "Ambroxol improves lysosomal biochemistry in glucocerebrosidase mutation-linked Parkinson disease cells." **137**(5): 1481-1495.

Mebius, R. E. and G. J. N. r. i. Kraal (2005). "Structure and function of the spleen." **5**(8): 606-616.

Menozzi, E. and A. H. J. C. D. Schapira (2020). "Enhancing the activity of glucocerebrosidase as a treatment for Parkinson disease." **34**(9): 915-923.

Menozzi, E. and A. H. J. C. D. Schapira (2020). "Enhancing the activity of glucocerebrosidase as a treatment for Parkinson disease." **34**: 915-923.

Menozzi, E., et al. (2023). "Targeting the GBA1 pathway to slow Parkinson disease: Insights into clinical aspects, pathogenic mechanisms and new therapeutic avenues." 108419.

Mercolini, L., et al. (2009). "Simultaneous analysis of diazepam and its metabolites in rat plasma and brain tissue by HPLC-UV and SPE." **80**(1): 279-285.

Michel, H. E., et al. (2022). "Omarigliptin attenuates rotenone-induced Parkinson's disease in rats: Possible role of oxidative stress, endoplasmic reticulum stress and immune modulation." **164**: 113015.

Migdalska-Richards, A., et al. (2016). "Ambroxol effects in glucocerebrosidase and α-synuclein transgenic mice." **80**(5): 766-775.

Migdalska-Richards, A. and A. H. J. J. o. n. Schapira (2016). "The relationship between glucocerebrosidase mutations and Parkinson disease." **139**: 77-90.

Minders, C., et al. (2015). "Monoamine oxidase inhibitory activities of heterocyclic chalcones." **25**(22): 5270-5276.

Mishra, A., et al. (2018). "Ambroxol modulates 6-Hydroxydopamine-induced temporal reduction in Glucocerebrosidase (GCase) enzymatic activity and Parkinson's disease symptoms." **155**: 479-493.

Mishra, A. and S. J. N.-S. s. A. o. P. Krishnamurthy (2020). "Neurorestorative effects of sub-chronic administration of ambroxol in rodent model of Parkinson's disease." **393**: 429-444.

Mishra, E. and M. K. J. B. Thakur (2022). "Alterations in hippocampal mitochondrial dynamics are associated with neurodegeneration and recognition memory decline in old male mice." **23**(2): 251-271.

Motawi, T. K., et al. (2022). "Empagliflozin alleviates endoplasmic reticulum stress and augments autophagy in rotenone-induced Parkinson's disease in rats: Targeting the GRP78/PERK/eIF2α/CHOP pathway and miR-211-5p." **362**: 110002.

Mullin, S., et al. (2020). "Ambroxol for the treatment of patients with Parkinson disease with and without glucocerebrosidase gene mutations: a nonrandomized, noncontrolled trial." **77**(4): 427-434.

Munoz, S. S., et al. (2021). "The interplay between Glucocerebrosidase, α-synuclein and lipids in human models of Parkinson's disease." **273**: 106534.

Murray, G. J., et al. (1995). "Studies on the turnover of exogenous mannose-terminal glucocerebrosidase in rat liver lysosomes." **57**(2): 208-217.

Nakagome, I., et al. (2018). "Design of a new α-1-C-Alkyl-DAB derivative acting as a pharmacological chaperone for β-Glucocerebrosidase using ligand docking and molecular dynamics simulation." **23**(10): 2683.

Navarro-Romero, A., et al. (2020). "The emerging role of the lysosome in Parkinson's disease." **9**(11): 2399.

Neumann, J., et al. (2009). "Glucocerebrosidase mutations in clinical and pathologically proven Parkinson's disease." **132**(7): 1783-1794.

Nikolaev, M., et al. (2022). "Glucocerebrosidase dysfunction and alpha-synuclein accumulation-a pathophysiological duet in GBA-associated Parkinson's disease." **21**(12): 18-22.

Ning, B., et al. (2019). "β-Asarone regulates ER stress and autophagy via inhibition of the PERK/CHOP/Bcl-2/Beclin-1 pathway in 6-OHDA-induced parkinsonian rats." **44**: 1159-1166.

Pastores, G. M. and D. A. Hughes (2018). "Gaucher disease."

Paxinos, G. and C. Watson (2006). The rat brain in stereotaxic coordinates: hard cover edition, Elsevier.

Pazhayattil, G. S., et al. (2014). "Drug-induced impairment of renal function." 457-468.

Peng, T., et al. (2018). "Fluoxetine-mediated inhibition of endoplasmic reticulum stress is involved in the neuroprotective effects of Parkinson's disease." **10**(12): 4188.

Perrone, R. D., et al. (1992). "Serum creatinine as an index of renal function: new insights into old concepts." **38**(10): 1933-1953.

Piao, Y., et al. (2013). "Change trends of organ weight background data in sprague dawley rats at different ages." **26**(1): 29-34.

Poewe, W., et al. (2009). "The clinical progression of Parkinson's disease." **15**: S28-S32.

Radi, Z. A. J. I. j. o. t. (2019). "Kidney pathophysiology, toxicology, and drug-induced injury in drug development." **38**(3): 215-227.

Ramakrishna, K., et al. (2022). "Pharmacokinetic and Pharmacodynamic Properties of Indole-3-carbinol in Experimental Focal Ischemic Injury." **47**(4): 593-605.

Rao, R. V. and D. E. J. C. o. i. c. b. Bredesen (2004). "Misfolded proteins, endoplasmic reticulum stress and neurodegeneration." **16**(6): 653-662.

Real, C. C., et al. (2017). "Treadmill exercise prevents increase of neuroinflammation markers involved in the dopaminergic damage of the 6-OHDA Parkinson's disease model." **63**: 36-49.

Richter, F., et al. (2014). "A GCase chaperone improves motor function in a mouse model of synucleinopathy." **11**: 840-856.

Robak, L. A., et al. (2017). "Excessive burden of lysosomal storage disorder gene variants in Parkinson's disease." **140**(12): 3191-3203.

Rocha, E. M., et al. (2015). "Progressive decline of glucocerebrosidase in aging and P arkinson's disease." **2**(4): 433-438.

Ron, I., et al. (2010). "Interaction between parkin and mutant glucocerebrosidase variants: a possible link between Parkinson disease and Gaucher disease." **19**(19): 3771-3781.

Rubilar, J. C., et al. (2024). "The lysosomal β-glucocerebrosidase strikes mitochondria: Implications for Parkinson's therapeutics." awae070.

Sadeghian, Z., et al. (2022). "Post treatment with Gastrodin suppresses oxidative stress and attenuates motor disorders following 6-OHDA induced Parkinson disease." **790**: 136884.

Samuels, M. A. J. C. (2007). "The brain–heart connection." **116**(1): 77-84.

Sanchez-Martinez, A., et al. (2016). "Parkinson disease-linked GBA mutation effects reversed by molecular chaperones in human cell and fly models." **6**(1): 31380.

Sanz, E., et al. (2009). "PF9601N [N-(2-propynyl)-2-(5-benzyloxy-indolyl) methylamine] confers MAO-B independent neuroprotection in ER stress-induced cell death." **41**(1): 19-31.

Sawkar, A. R., et al. (2002). "Chemical chaperones increase the cellular activity of N370S β-glucosidase: a therapeutic strategy for Gaucher disease." **99**(24): 15428-15433.

Sayyaed, A., et al. (2023). "A detailed review of pathophysiology, epidemiology, cellular and molecular pathways involved in the development and prognosis of Parkinson's disease with insights into screening models." **47**(1): 1-16.

Schapira, A. H. and M. E. J. P. o. t. N. A. o. S. Gegg (2013). "Glucocerebrosidase in the pathogenesis and treatment of Parkinson disease." **110**(9): 3214-3215.

Schapira, A. H. J. M. and c. neuroscience (2015). "Glucocerebrosidase and Parkinson disease: recent advances." **66**: 37-42.

Schmittgen, T. D. and K. J. J. N. p. Livak (2008). "Analyzing real-time PCR data by the comparative CT method." **3**(6): 1101-1108.

Schneider, C. M., et al. (1995). "Effects of physical activity on creatine phosphokinase and the isoenzyme creatine kinase–MB." **25**(4): 520-524.

Schreiner, B. and M. J. M. P. P. Ankarcrona (2017). "Isolation of mitochondria-associated membranes (MAM) from mouse brain tissue." 53-68.

Schulze, H. and K. J. C. S. H. p. i. b. Sandhoff (2011). "Lysosomal lipid storage diseases." **3**(6): a004804.

Selvaraj, S., et al. (2012). "Neurotoxin-induced ER stress in mouse dopaminergic neurons involves downregulation of TRPC1 and inhibition of AKT/mTOR signaling." **122**(4): 1354-1367.

Shahed, J. and J. J. H. o. c. n. Jankovic (2007). "Motor symptoms in Parkinson's disease." **83**: 329-342.

Sharma, P., et al. (2019). "Design and development of multitarget-directed N-Benzylpiperidine analogs as potential candidates for the treatment of Alzheimer's disease." **167**: 510-524.

Shidore, M., et al. (2016). "Benzylpiperidine-linked diarylthiazoles as potential anti-Alzheimer's agents: synthesis and biological evaluation." **59**(12): 5823-5846.

Shrivastava, P., et al. (2013). "Anti-apoptotic and anti-inflammatory effect of Piperine on 6-OHDA induced Parkinson's rat model." **24**(4): 680-687.

Shukla, R., et al. (2018). "Structure-based screening and molecular dynamics simulations offer novel natural compounds as potential inhibitors of Mycobacterium tuberculosis isocitrate lyase." **36**(8): 2045-2057.

Siebert, M., et al. (2014). "Glucocerebrosidase is shaking up the synucleinopathies." **137**(5): 1304-1322.

Silva, R. M., et al. (2005). "CHOP/GADD153 is a mediator of apoptotic death in substantia nigra dopamine neurons in an in vivo neurotoxin model of parkinsonism." **95**(4): 974-986.

Silveira, C., et al. (2019). "Ambroxol as a novel disease-modifying treatment for Parkinson's disease dementia: protocol for a single-centre, randomized, double-blind, placebo-controlled trial." **19**(1): 1-10.

Silveira, C., et al. (2019). "Ambroxol as a novel disease-modifying treatment for Parkinson's disease dementia: Protocol for a single-centre, randomized, double-blind, placebo-controlled trial." **19**: 1-10.

Singh, R., et al. (2020). "Identifying potential GluN2B subunit containing N-Methyl-D-aspartate receptor inhibitors: An integrative in silico and molecular modeling approach." **38**(9): 2533-2545.

Smith, L., et al. (2017). "Insights into the structural biology of Gaucher disease." **298**: 180-190.

Soni, R., et al. (2023). "Uncovering Novel Therapeutic Targets for Parkinson's Disease."

Stojkovska, I., et al. (2018). "Molecular mechanisms of α-synuclein and GBA1 in Parkinson's disease." **373**: 51-60.

Takahashi, H., et al. (2024). "Reduced progranulin increases tau and α-synuclein inclusions and alters mouse tauopathy phenotypes via glucocerebrosidase." **15**(1): 1434.

Tayebi, N., et al. (2017). "Glucocerebrosidase haploinsufficiency in A53T α-synuclein mice impacts disease onset and course." **122**(4): 198-208.

Thangavelu, L., et al. (2020). "Evaluation of the sub-acute toxicity of Acacia catechu Willd seed extract in a Wistar albino rat model." **113**: 104640.

Thummel, K. E., et al. (2006). "Design and optimization of dosage regimens: pharmacokinetic data." 1787-1888.

Tong, Q., et al. (2016). "Inhibition of endoplasmic reticulum stress-activated IRE1α-TRAF2-caspase-12 apoptotic pathway is involved in the neuroprotective effects of telmisartan in the rotenone rat model of Parkinson's disease." **776**: 106-115.

Trapero, A., et al. (2012). "Potent aminocyclitol glucocerebrosidase inhibitors are subnanomolar pharmacological chaperones for treating gaucher disease." **55**(9): 4479-4488.

Trapero, A. and A. J. A. m. c. l. Llebaria (2011). "The myo-1, 2-diaminocyclitol scaffold defines potent glucocerebrosidase activators and promising pharmacological chaperones for Gaucher disease." **2**(8): 614-619.

Travlos, G., et al. (1996). "Frequency and relationships of clinical chemistry and liver and kidney histopathology findings in 13-week toxicity studies in rats." **107**(1): 17-29.

Tripathi, P., et al. (2022). "Generation of wild-type rat Glucocerebrosidase homology modeling: Identification of putative interactions site and mechanism for chaperone using combined in-silico and in-vitro studies." **126**: 105871.

Tripathi, P., et al. (2023). "Identification of novel glucocerebrosidase chaperone for potential treatment of Parkinson's disease: An approach using in silico virtual screening, molecular docking and molecular dynamics, and in vitro studies." **228**: 453-466.

Venuprasad, M., et al. (2013). "Neuroprotective effects of hydroalcoholic extract of Ocimum sanctum against H 2 O 2 induced neuronal cell damage in SH-SY5Y cells via its antioxidative defence mechanism." **38**: 2190-2200.

Vercammen, L., et al. (2006). "Parkin protects against neurotoxicity in the 6-hydroxydopamine rat model for Parkinson's disease." **14**(5): 716-723.

Victorino, D. B., et al. (2020). "COVID-19 and Parkinson's disease: are we dealing with short-term impacts or something worse?" **10**(3): 899.

Vieira, S. R., et al. (2021). "Glucocerebrosidase mutations: A paradigm for neurodegeneration pathways." **175**: 42-55.

Vysakh, A., et al. (2020). "Acute oral toxicity and anti-inflammatory evaluation of methanolic extract of Rotula aquatica roots in Wistar rats." **11**(1): 45-52.

Wang, H., et al. (2020). "Ghrelin protects dopaminergic neurons against MPTP neurotoxicity through promoting autophagy and inhibiting endoplasmic reticulum mediated apoptosis." **1746**: 147023.

Wang, H. Q., et al. (2007). "Expanding insights on the involvement of endoplasmic reticulum stress in Parkinson's disease." **9**(5): 553-561.

Wang, S.-F., et al. (2017). "Baicalein prevents 6-OHDA/ascorbic acid-induced calcium-dependent dopaminergic neuronal cell death." **7**(1): 8398.

Wang, X., et al. (2023). "The Crucial Roles of Pitx3 in Midbrain Dopaminergic Neuron Development and Parkinson's Disease-Associated Neurodegeneration." **24**(10): 8614.

Weiser, T. J. C. n. and therapeutics (2008). "Ambroxol: a CNS drug?" **14**(1): 17-24.

Wen, H., et al. (2017). "Acute toxicity and genotoxicity of silver nanoparticle in rats." **12**(9): e0185554.

Westbroek, W., et al. (2011). "Exploring the link between glucocerebrosidase mutations and parkinsonism." **17**(9): 485-493.

Wood-Kaczmar, A., et al. (2006). "Understanding the molecular causes of Parkinson's disease." **12**(11): 521-528.

Wu, K.-J., et al. (2023). "Prosaposin PS18 reduces dopaminergic neurodegeneration in a 6-hydroxydopamine rat model of Parkinson's disease." **13**(1): 8148.

Xiao, F., et al. (2014). "Spectroscopic investigation on the interaction of hyperbranched poly (amine) ester with model plasma protein: Effect on the structural and conformational changes." **118**: 1106-1112.

Xu, X.-L., et al. (2011). "Raman spectroscopic study of heat-induced gelation of pork myofibrillar proteins and its relationship with textural characteristic." **87**(3): 159-164.

Yang, J., et al. (2023). "Recent advances in novel mutation genes of Parkinson's disease." 1-10.

Yang, Y., et al. (2005). "Determination of plasma and brain levels of isotretinoin in mice following single oral dose by high-performance liquid chromatography." **37**(1): 157-163.

Yu, Z., et al. (2007). "Pharmacologic chaperoning as a strategy to treat Gaucher disease." **274**(19): 4944-4950.

Yu, Z., et al. (2007). "Isofagomine-and 2, 5-anhydro-2, 5-imino-D-glucitol-based glucocerebrosidase pharmacological chaperones for Gaucher disease intervention." **50**(1): 94-100.

Zagórska, A., et al. (2023). "Drug Discovery and Development Targeting Dementia." **16**(2): 151.

Zeuner, K. E., et al. (2019). "Progress of pharmacological approaches in Parkinson's disease." **105**(5): 1106-1120.

Zhang, G. and Y. J. F. c. Ma (2013). "Mechanistic and conformational studies on the interaction of food dye amaranth with human serum albumin by multispectroscopic methods." **136**(2): 442-449.

Zhang, P., et al. (2022). "Ambroxol chaperone therapy for Gaucher disease type I-associated liver cirrhosis and portal hypertension: A case report." **22**(6): 658-662.

Zhang, Y., et al. (2017). "Echinacoside's nigrostriatal dopaminergic protection against 6-OHDA-Induced endoplasmic reticulum stress through reducing the accumulation of Seipin." **21**(12): 3761-3775.

Zhao, L., et al. (2020). "Interaction mechanism between α-glucosidase and A-type trimer procyanidin revealed by integrated spectroscopic analysis techniques." **143**: 173-180.

Zheng, J., et al. (2016). "Design and synthesis of potent quinazolines as selective β-glucocerebrosidase modulators." **59**(18): 8508-8520.

Zhou, H., et al. (2021). "A simple LC-MS/MS method for simultaneous determination of cilostazol and ambroxol in Sprague-Dawley rat plasma and its application to drug-drug pharmacokinetic interaction study following oral delivery in rats." **1179**: 122766.

Zhou, Y., et al. (2017). "The sodium-glucose co-transporter 2 inhibitor, empagliflozin, protects against diabetic cardiomyopathy by inhibition of the endoplasmic reticulum stress pathway." **41**(6): 2503-2512.

Zhu, Y., et al. (2012). "Overview of tyrosine hydroxylase in Parkinson's disease." **11**(4): 350-358.

Appendices

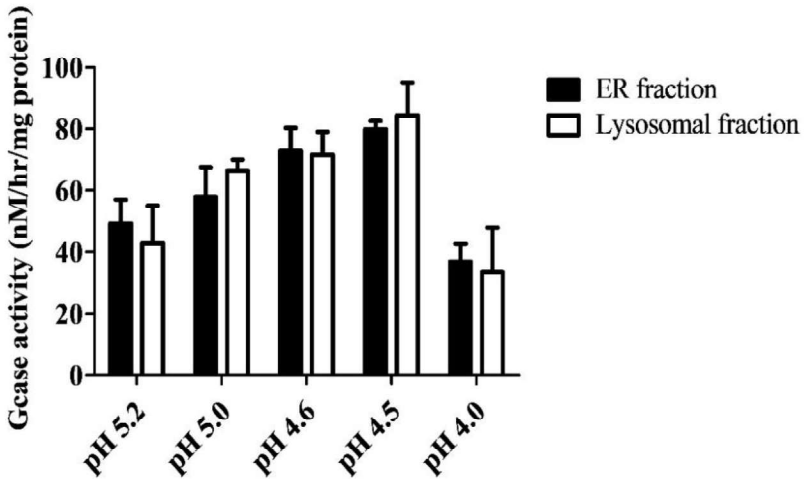


Figure 2.1 rGCase activity of lysosomal fractions *versus* acidified ER fractions. There was no difference in the activity of rGCase was observed between acidic pH of lysosome and the acidified ER fractions All values are shown in the form of mean ±SD; n = 3.

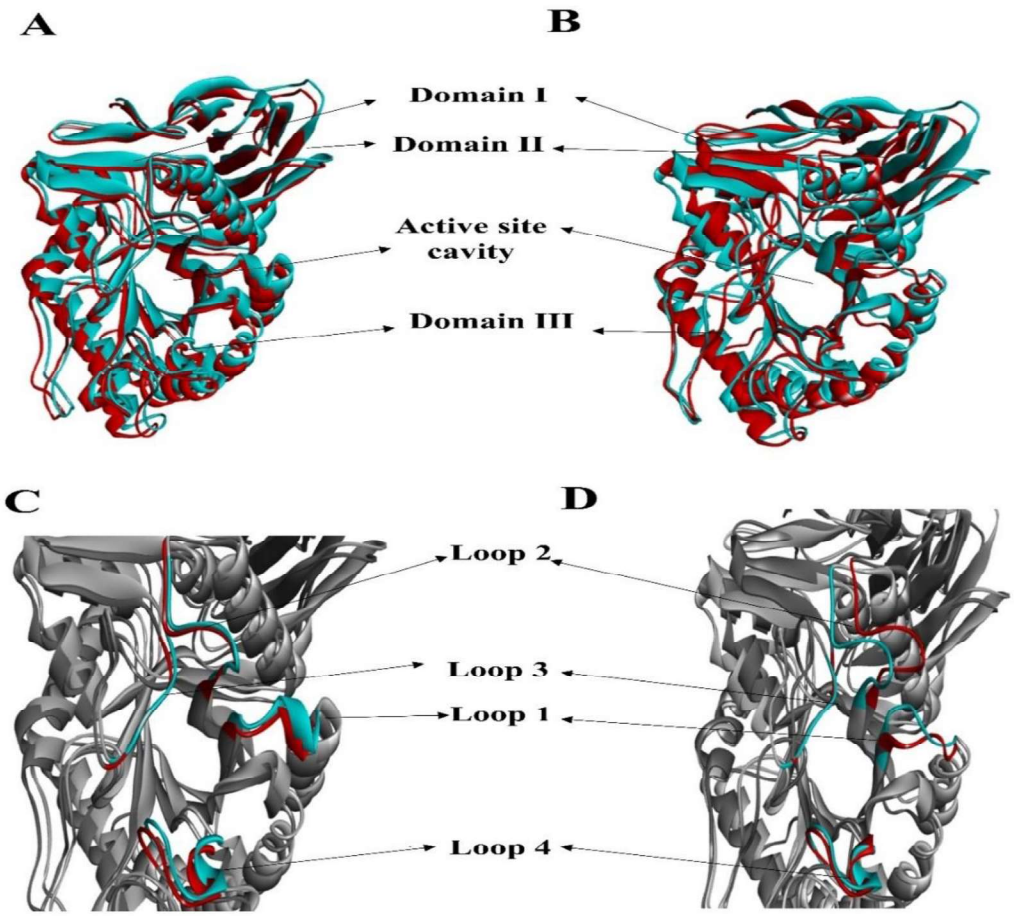


Figure 2.2 Superimposition of the domain (A) and loops (C) of human-GCase protein (hGCse, PDB: 3NT1, colored red) over constructed rat- GCase homology model (rGCase, colored turquoise) at neutral pH (7.0). Superimposition of the domain (B) and loops (D) of hGCse (PDB: 3GXD, colored red) over constructed rGCase homology model (colored turquoise) at acidic pH (4.5).

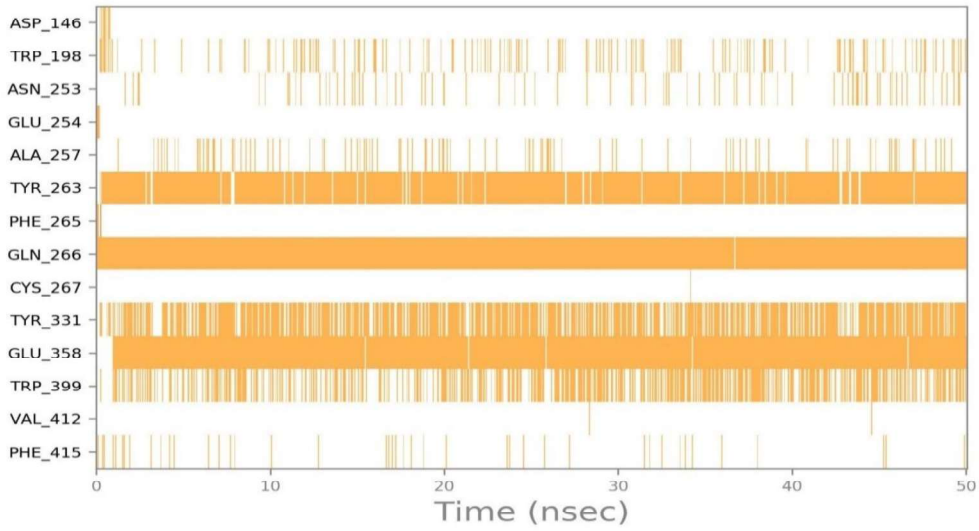


Figure 2.3. Timeline portrayal of the protein-ligand (rGCase-AMB) contacts throughout the simulation on the pH 7.0.

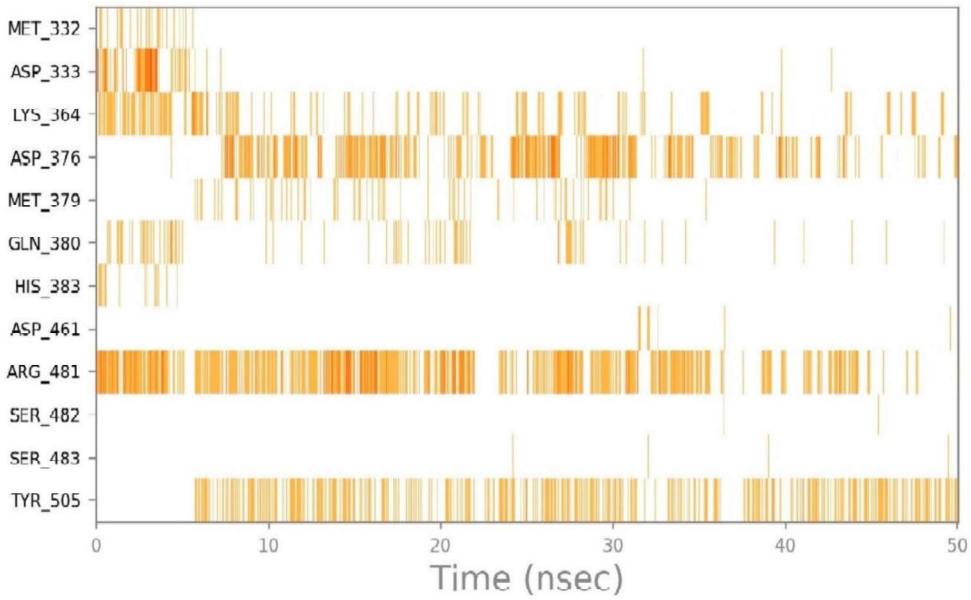


Figure 2.4 Timeline portrayal of the protein-ligand (rGCase-AMB) contacts throughout the simulation on pH 4.5.

Methods

2. Method of Isolation of GCase enriched Endoplasmic reticulum (ER) and lysosomal fractions

2.1 Requirements: Tris-HCL was purchased from Merck. Triton X-100 and Protease inhibitor was acquired from Sigma-Aldrich (St. Louis, MO, USA). EGTA [ethylene glycol-bis (2-aminoethylether)-N,N,N',N'-tetraacetic acid], bovine serum albumin (BSA), sucrose, citric acid, sodium phosphate dibasic, and mannitol were supplied by Hi-media (Mumbai). All other reagents were analytical grade.

2.2 Compliance with ethical standards

The experiments were conducted on the Charles-Foster strain of adult albino male rats (250 + 20 g), procured by Central Animal House of the Institute of Medical Sciences (IMS-BHU). All experimental protocols were carried out as per the approved guideline of principles of laboratory animal care (National Research Council US Committee for the Update of the Guide for the Care and Use of Laboratory Animals 2011) and approved by the Institutional animal ethical committee, Banaras Hindu University (Dean/2019/IAEC/1243).

2.3 Preparation of Buffers:

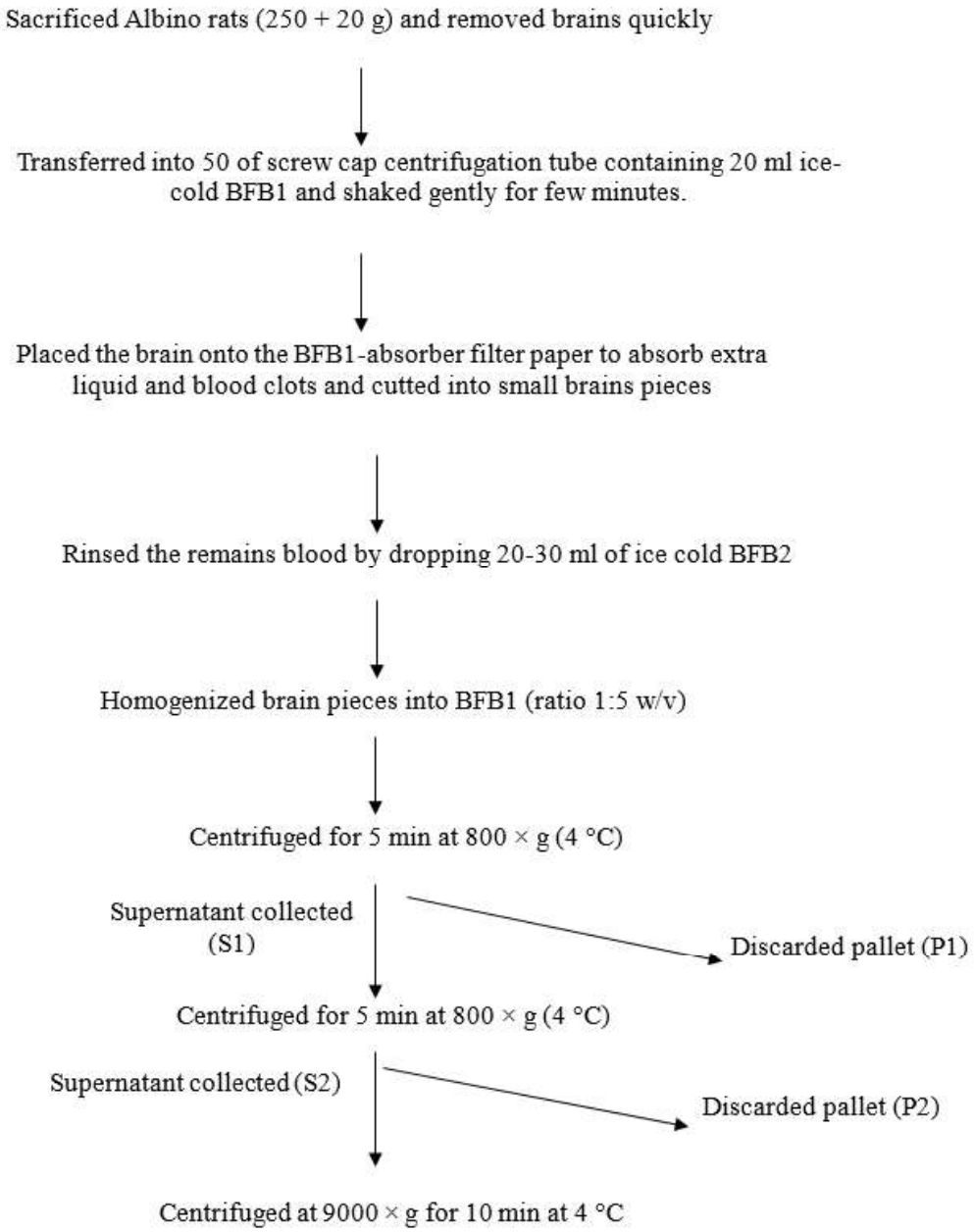
2.3.1 Brain fractionation buffer 1 (BFB1): 225 mM mannitol, 75 mM sucrose, 0.5 mM EGTA, 0.5% bovine serum albumin, 30 mM Tris–HCl, pH 7.4. Prepared in tripled-distilled water (1 day before the experiments). To this, add a fresh protease inhibitor (dilution 1:100) to avoid sample proteolysis just before starting the experiments.

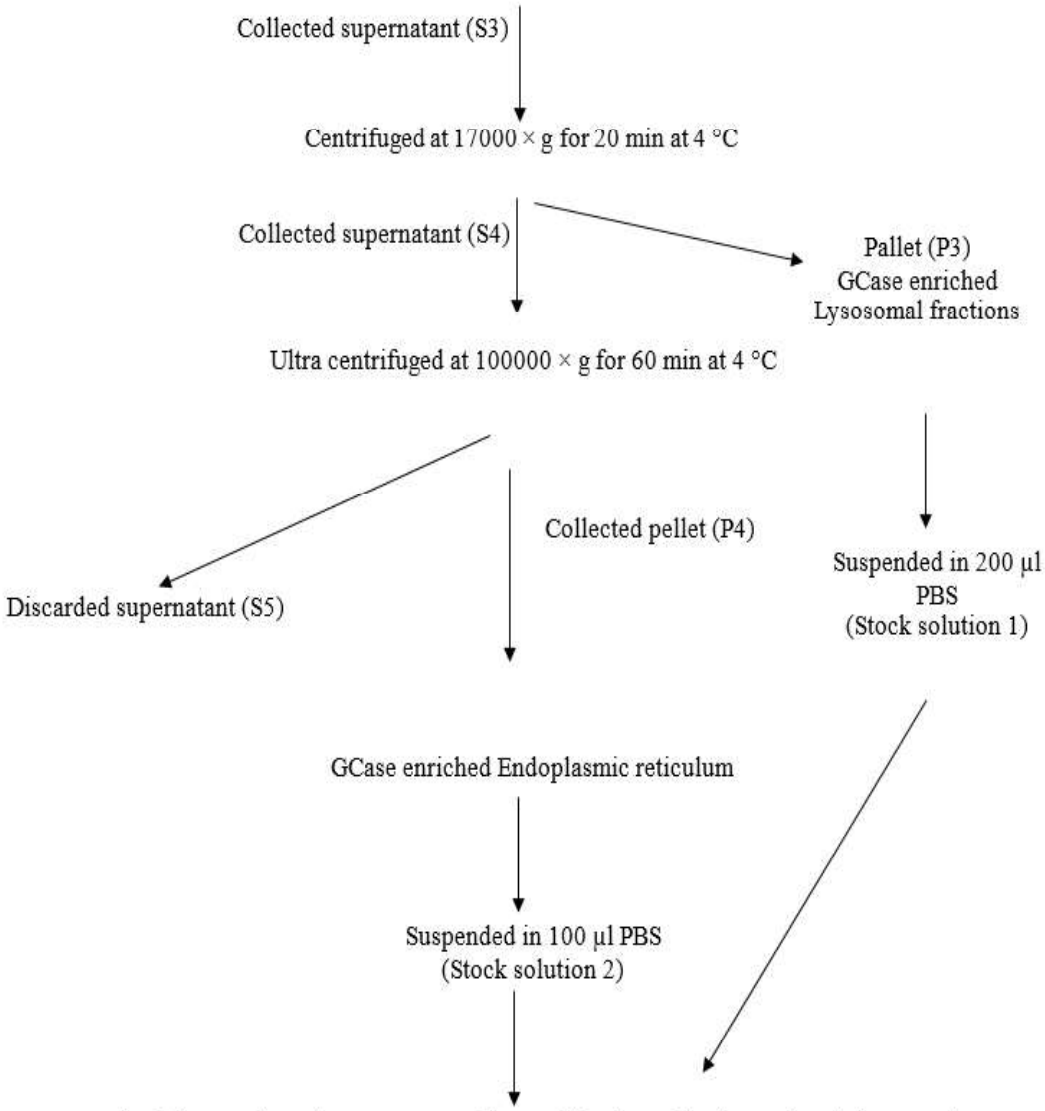
2.3.2 Brain fractionation buffer 2 (BFB2): 225 mM mannitol, 75 mM sucrose, 30 mM Tris–HCl, pH 7.4. Prepared 1 day before the experiment in tripled-distilled.

2.3.3 Enzyme activity assay buffer (McIlvaine buffer): 100 mM sodium citrate, 200 mM sodium phosphate buffer, 0.2% TDC and 0.1% Triton-100, pH 7.0, 5.5, 5.2, 5.0, 4.5 and 4.0. Freshly prepared in tripled-distilled water.

2.3.4 Note. Isolation procedures must be carried out at 4^0C. Equipment and solutions should be pre-cooled before use. Protein concentration was determined by the Lowry method (Lowry, Rosebrough et al. 1951, Hammond, Meador-Woodruff et al. 2012, Berger, Perkins et al. 2015, Schreiner and Ankarcrona 2017).

2.4 Procedure:


Sacrificed Albino rats (250 + 20 g) and removed brains quickly
Transferred into 50 of screw cap centrifugation tube containing 20 ml ice-cold BFB1 and shaked gently for few minutes.
Placed the brain onto the BFB1-absorber filter paper to absorb extra liquid and blood clots and cutted into small brains pieces
Rinsed the remains blood by dropping 20-30 ml of ice cold BFB2
Homogenized brain pieces into BFB1 (ratio 1:5 w/v)
Centrifuged for 5 min at 800 × g (4 °C)
Supernatant collected (S1)
Discarded pallet (P1)
Centrifuged for 5 min at 800 × g (4 °C)
Supernatant collected (S2)
Discarded pallet (P2)
Centrifuged at 9000 × g for 10 min at 4 °C


Collected supernatant (S3)
Centrifuged at 17000 × g for 20 min at 4 °C
Collected supernatant (S4)
Pallet (P3)
GCase enriched
Lysosomal fractions
Ultra centrifuged at 100000 × g for 60 min at 4 °C
Collected pellet (P4)
Discarded supernatant (S5)
Suspended in 200 µl
PBS
(Stock solution 1)
GCase enriched Endoplasmic reticulum
Suspended in 100 µl PBS
(Stock solution 2)
To examined the pH-dependent rGCase activity profiles, immediately stock solution 1 and 2 were diluted into each pH of activity assay buffer (McIlvaine buffer, pH 7.0, 5.5, 5.2, 5.0, 4.5, and 4.0) to give a working solution of 0.5 microgram of protein per microliter (0.5 µg/µl) for each.

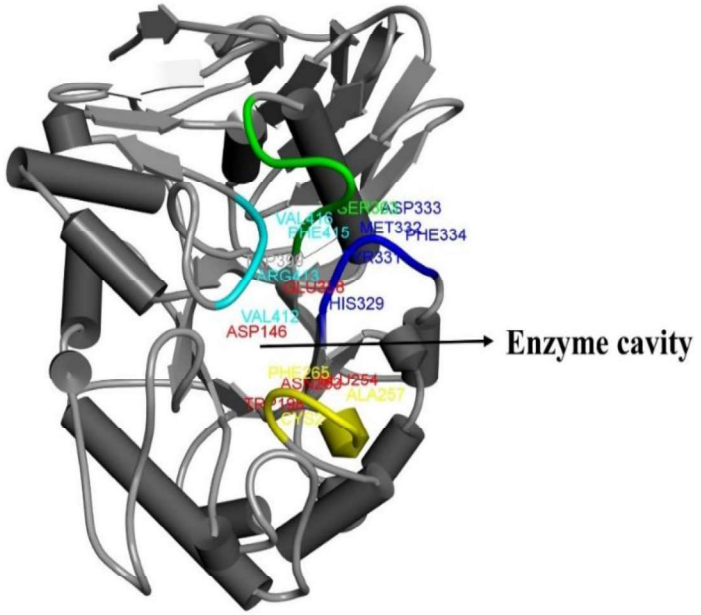


Figure 3.1 rGCase active site residues. Loop 1, loop 2, loop 3, and loop 4 are denoted by Blue, Green, Turquoise, and Yellow colour, respectively.

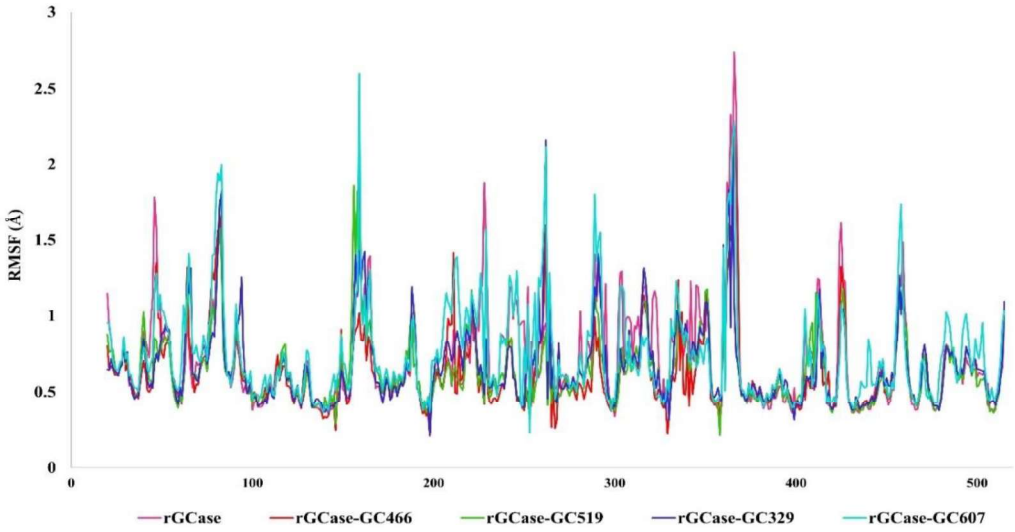


Figure 3.2 Influence of pH 7.0 on protein (C-α atoms) RMSF plots before and after ligand binding during a 50 ns simulation.

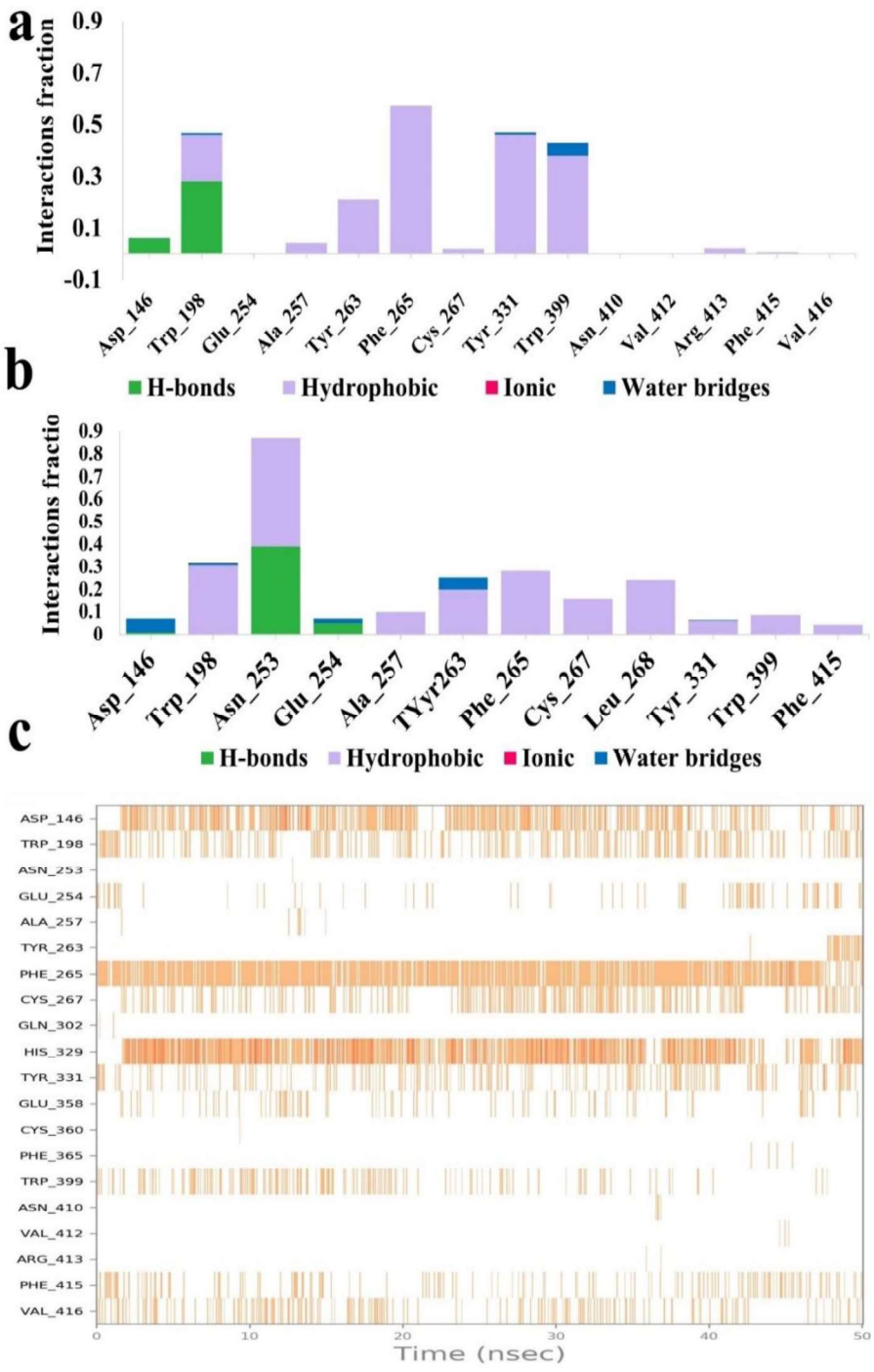


Figure 3.3 GC329 (a) and GC607 (b) 50 ns PL-contact time frame plots at pH 7.0. A value of 0.8 indicates that the specific interaction is maintained 80% of the time during the simulation.

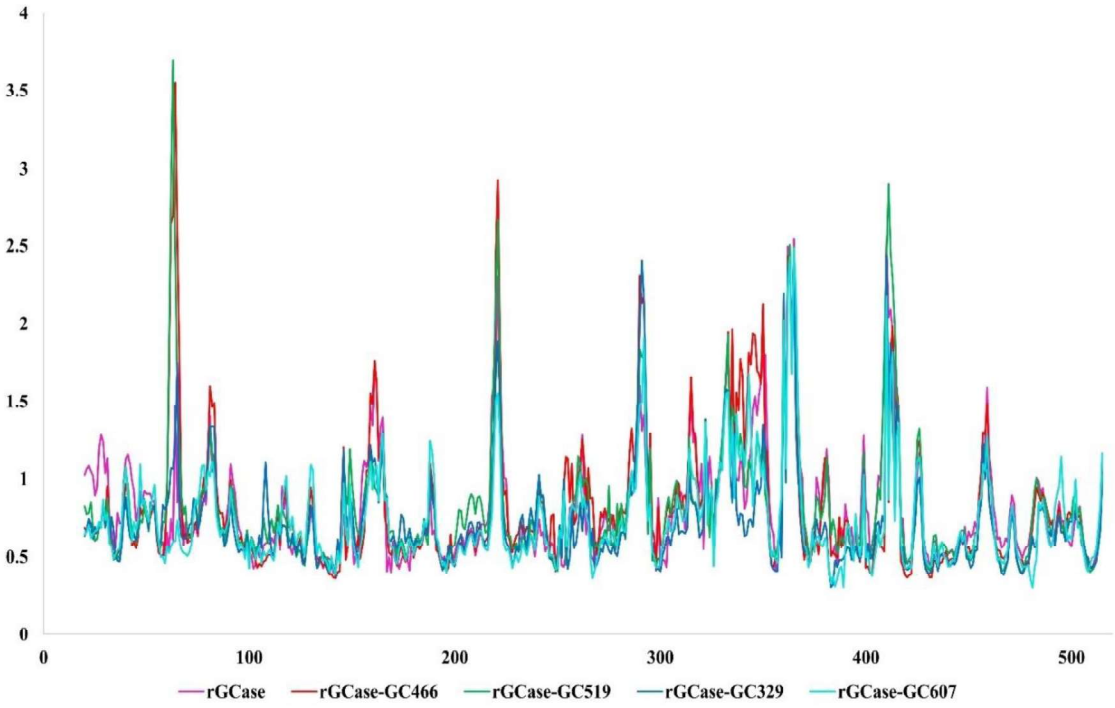


Figure 3.4 Effect of pH 4.5 on protein (C-α atoms) RMSF plots before and after ligand binding during a 50 ns simulation.

Contacts timeline representation (c) of the top ligand (GC466) with protein throughout the trajectory (50 ns) at pH 7.0.

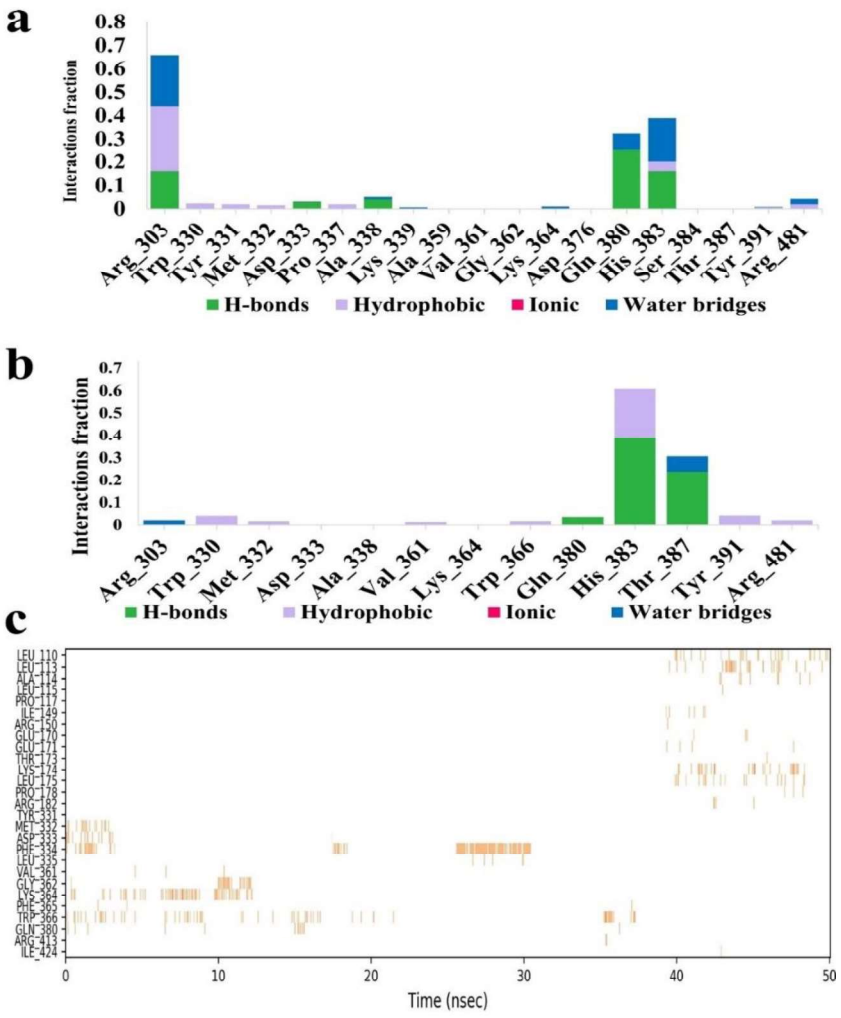


Figure 3.5 GC329 (a) and GC607 (b) 50 ns PL-contact time frame plots at pH 4.5. A value of 0.1 indicates that the specific interaction is maintained 10% of the time during the simulation. Contacts timeline representation (c) of the top ligand (GC466) with protein throughout the trajectory (50 ns) at pH 4.5.

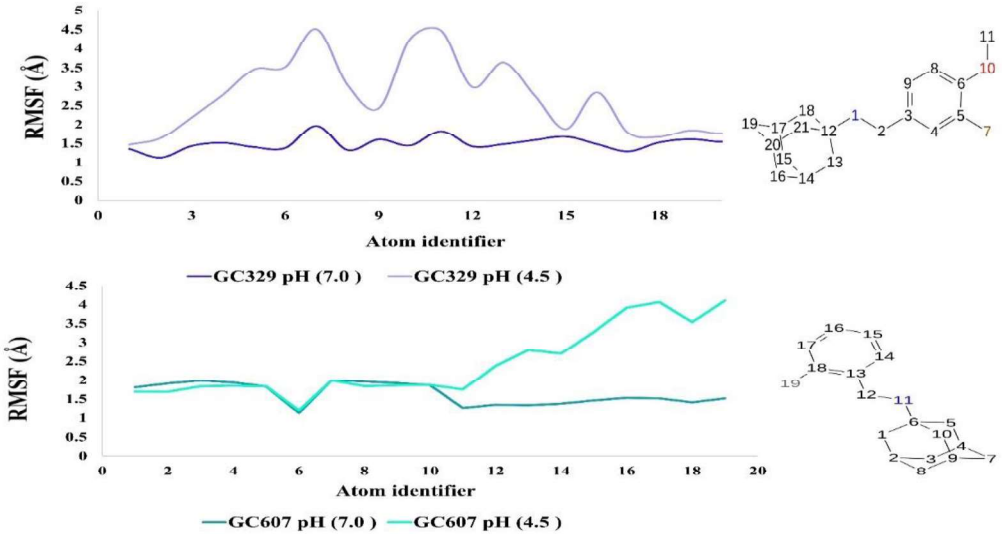


Figure 3.6. A comparative RMSF plot between pH 7.0 and 4.5 of ligands GC329 (blue) and GC607 (turquoise).

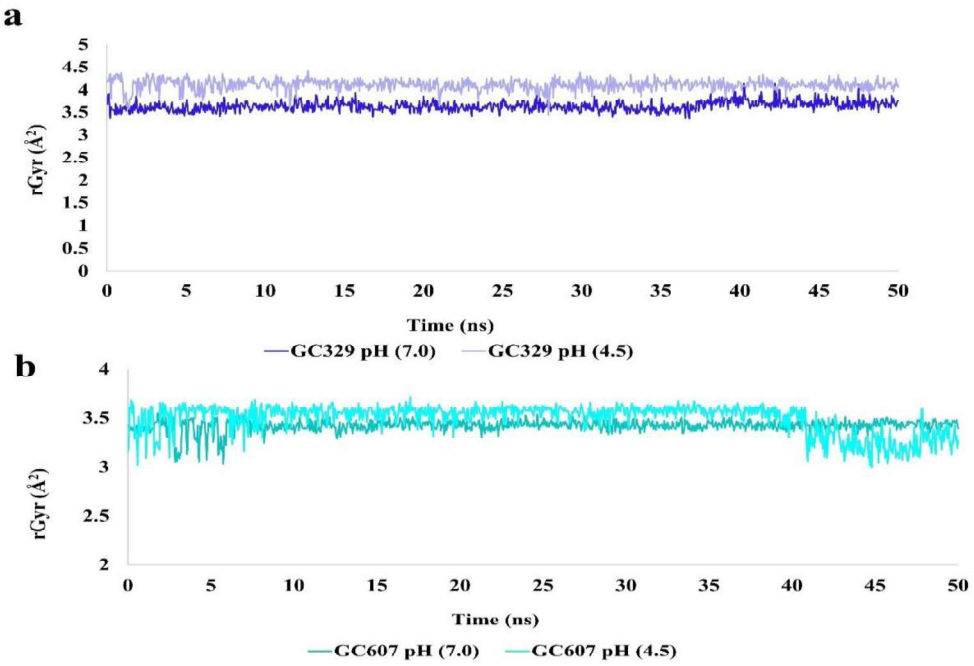


Figure 3.7 A comparative radius of gyration (rGyr) plots between pH 7.0 and 4.5 of ligands GC329 (blue) and GC607 (turquoise).

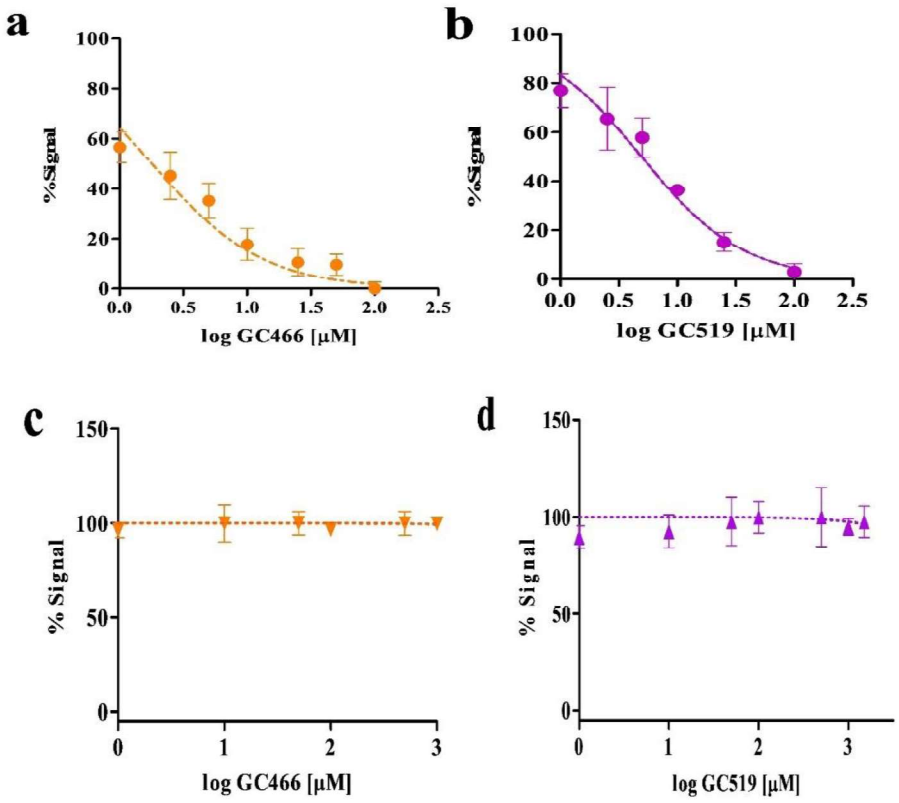


Figure 3.8 The concentrations and pH-dependent sigmoidal plots of top two ligands for rGCase are depicted graphically. a and b, plots depict for pH 7.0. c and d, show for pH 4.5. rGCase activity is represented as a % of the fluorescent signal. rGCase isolated from Charles-Foster strain of adult albino male rats (250 + 20 g) provided by Central Animal House of the Department of Zoology, Institute of Science, Banaras Hindu University. The Institutional Animal Ethical Committee approves experimental protocol (IAEC, Reference No; BHU/DoZ/IAEC/2021-2022/047).

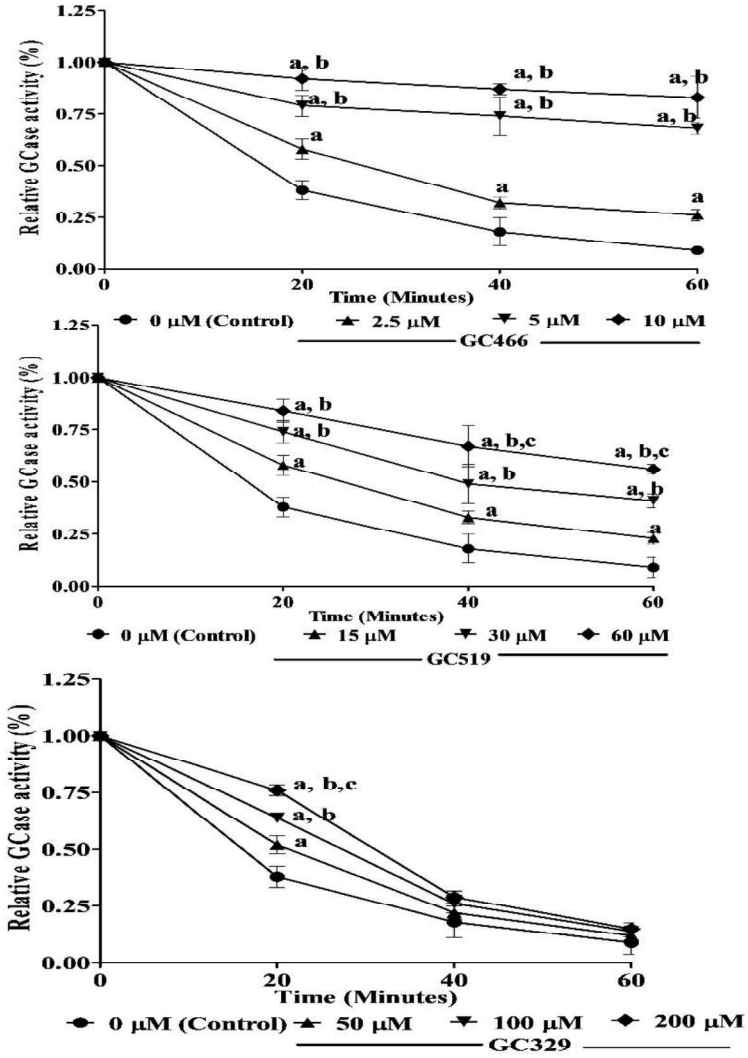


Figure 3.9 Relative GCase activity after thermal denaturation (TD, 48 ^{o}C) during 1 hr at the indicated compounds concentrations (µM), compared to the corresponding 0 ^{0}C (control) assay. All values are shown in the form of mean ± SD; n = 3. $^{a}p < 0.05$ compared to the corresponding time of the untreated group (control). $^{b}p < 0.05$ compared to the corresponding time of 2.5 µM, 15 µM, and 50 µM for GC466, GC519, and GC329, respectively. $^{c}p < 0.05$ compared to the corresponding time of 30 µM and 100 µM for GC519 and GC329, respectively [Two-way ANOVA followed by Bonferroni multiple comparison tests, Graph Pad Prism 5.1 Software, Inc].

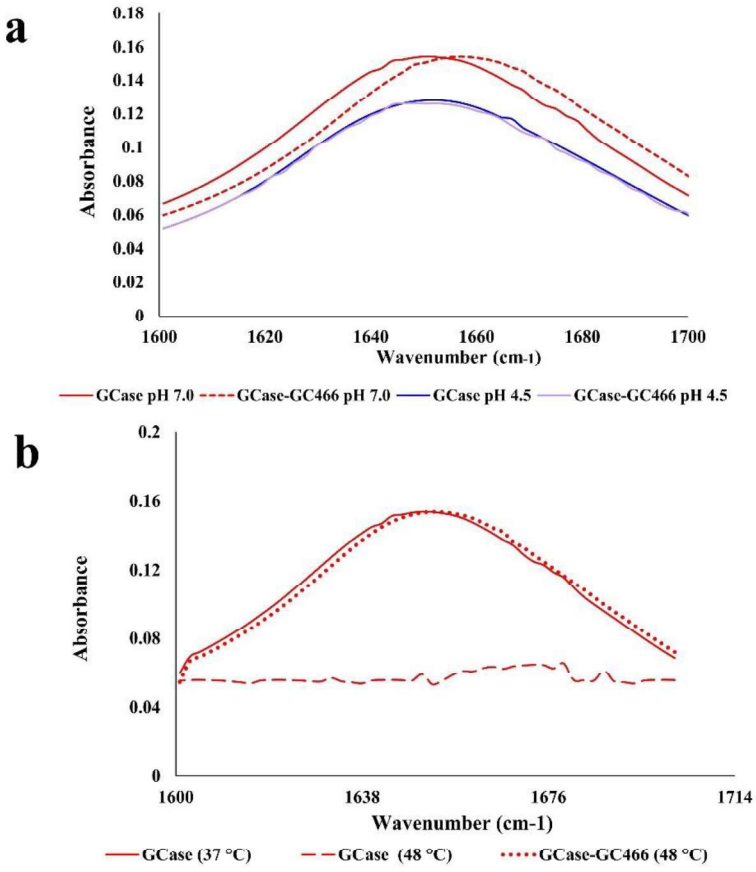


Figure 3.10 The FT-IR spectra of free rGCase and rGCase-GC466 complex at 37 ^{0}C (under body temperature condition, Fig. a) and thermal denaturation condition (48 ^{0}C, Fig b) at the region of 1700–1600 cm−1. rGCase protein kept at 37 ^{0}C (body temperature) is considered a control for thermal denaturation conditions.

3.1 Circular dichroism (CD) spectroscopy studies

Circular dichroism (CD) spectroscopy (Jasco J-810 Analytical Instruments) was used to examine changes in the secondary structure of the rGCase protein induced by pHs or ligands in accordance with a procedure previously described with a few modifications (Xiao, Gu et al. 2014, Li, Hu et al. 2018, Dai, Chen et al. 2019). There were two different sets of experiments run. In the first set, we determined the rGCase's spectra (10 µg, 0.5 µg / µl) from 190 to 250 nm at pH 7.0 and 4.5 of McIlvaine buffer (100 mM citric acid, 200 mM sodium phosphate buffer) in the presence or absence of the test compound GC466 (0.65 µM, concentration selected based on our *in vitro* kinetics study where we found 0.65 µM have good binding affinity for rGCase], after subtracting the background spectra of the corresponding test buffer solution. The top compound selected for this study was based on our *in silico* and *in vitro* study. This experiment was performed under normal conditions (37 ^{0}C, body temperature).

The second series of experiments, however, involved recording CD spectra at pH 7.0 after thermally exposing the rGCase (200 µg, 20 /µl) at 48 °C for 60 min in either the presence or absence of GC466 (10 µM). rGCase protein kept at 37 ^{0}C (body temperature) is considered as control GCase. Our thermal denaturation assay experiment (section 2.2.4.2) served as the basis for selecting the temperature, concentration, and time. The instrument was set at a 1 mm path-length cell, 100 nm/min scanning speed, 1 nm bandwidth, 4 s response time, and a 1.0 nm data pitch. Nitrogen was continually pumped through all samples during all of the measurements. Each spectrum represented the average of three scans. The CD spectroscopic data were analyzed using the online

BESTSEL software (https://bestsel.elte.hu/index.php) to determine the secondary structure, such as α-helix, β-sheet, and random coil.

3.1.1 Observations

The investigation of the secondary conformation forms of proteins using CD spectroscopy has been proven to be a trustworthy technique. In light of this, it may be possible to better comprehend how pH variations or the presence of ligands affect protein conformation (Xiao, Gu et al. 2014, Dai, Chen et al. 2019). With these facts in mind, in the first set, we discovered changes in the structure of the rGCase protein at lysosomal pH 4.5 in comparison to ER pH 7.0 in both the presence and absence of the test substance GC466 at normal body temperature (37 ^{0}C). At pH 7.0, two negative bands, characteristic of helix structures, were discernible in the rGCase CD profile. They were located around 209 and 222 nm (**Figure 3.16a in Chapter 3**). When the pH was altered from 7.0 to 4.5, the values of % α-helix (pH 7:0 to 4.5: 18.40 ± 0.15% to 15.42 ± 0.13%) and negative ellipticity decreased, but the % random coil increased (pH 7:0 to 4.5: 22.01 ± 0.25% to 25.72 ± 0.16%), indicating alterations in the rGCase secondary structure at pH 4.5 as compared to 7.0. Similarly, in our *in silico* work, we observed conformational alterations when comparing rGCase pH 7.0 to 4.5 (**Figure 3.1 in appendices**). Also, similar observations were found in our earlier study (Tripathi, Ganeshpurkar et al. 2022). As previously described, changes in the position of hydrogen bond formation may cause changes in the secondary structure of proteins (Zhao, Wen et al. 2020). In the meantime, the protein-ligand interaction in terms of protein's structural alterations in the presence of GC466 at both pHs has also been examined. The contents of the β-sheet and random coil in rGCase at pH 7.0 after the addition of GC466 increased from 21.20 ± 0.14% to 23.18

± 0.16% and 22.01 ± 0.25% to 26.20 ± 0.17%, respectively. In contrast, the contents of the α-helix significantly decreased from 18.4 ± 0.15% to 17.5 ± 0.26%. These findings suggested that the binding of GC466 may cause conformational changes in the rGCase, characterized by a decrease in the α-helix and an increase in the random coil, as reported in other studies (Zhao, Wen et al. 2020). This research-backed with our findings from the MD simulation, where we observed stable interactions between rGCase and GC466. According to an *in vitro* investigation, this persistent association may also be the cause of the enzyme's inhibition at pH 7.0 (**Section 3.3.4 and Table 3.2 in chapter 3 and, Figure 3.8 in appendices**). However, at pH 4.5, the contents of rGCase protein secondary structure in either free or complex form were similar [α-helix: 15.42 ± 0.13% (rGCase) and 15.41 ± 0.17% (rGCase –GC466); β-sheet: 20.5 ± 0.18% (rGCase) and 20.51 ± 0.12% (rGCase –GC466; random coil: 25.72 ± 0.16% (rGCase) and 25.70 ± 0.14% (rGCase –GC466]. These results demonstrated no persistent interactions between them at pH 4.5, as discovered in our MD simulation. This might be the result of the enzyme activity losing its inhibition around pH 4.5, according to *in vitro* research.

In the second series of tests (**Figure 3.16a in Chapter 3**), using CD spectroscopy and thermal denaturation conditions, we assessed the stability of interactions of the rGCase-GC466 complex by evaluating rGCase secondary structural changes under thermal conditions. In this context, free rGCase and rGCase-GC466 complex were thermally exposed at 48 °C for 60 min The rGCase Since GC466 only interacts with rGCase in stable ways at pH 7.0; thus, we have chosen this pH. The structural alterations or denaturation of the protein by CD spectra was evaluated online for a free or complex form of rGCase by the online BESTSEL software approach. We observed that the rGCase was denatured after being exposed to heat (48 °C) for 60 minutes, as seen by a very low elliptical negative peak at 210 nm and a negative band close to 198 nm while compared

to its control rGCase (37 ^{0}C, body temperature) (Greenfield 2006).These data indicated a complete loss in α-helix structures. On the other hand, the complex form was able to retain the α-helix structures even after 60 minutes of thermal denaturation, as evidenced by two sharp negative bands at approximately 209 and 222 nm. These observations are enough to comprehend that GC466 may have the ability to bind with rGCase and stabilize it before it becomes denatured. The chaperoning capacity of GC466 is demonstrated by its ability to bind to rGCase and stabilize it. This result corroborated the findings of our MD simulation and *in vitro* thermal denaturation assay.

3.2 Fourier transform infrared (FT-IR) spectra measurements

The FT-IR spectra of rGCase and its GC466 complex were measured for the first set of the experiment in the range of 1700–1400 cm^{-1} at pH 7.0 and 4.5. However, the second set involved recording FT-IR spectra at pH 7.0 after thermally exposing the rGCase at 48 °C for 60 min in either the presence or absence of the GC466 (**detailed in Section 3.1)**. The ATR method of the FT-IR spectrometer (Bruker Optics, Germany) was employed for detection at wavenumbers between 1600 and 1700 cm−1 with a resolution of 4 cm^{-1} and 60 scans. Meanwhile, the corresponding absorbance values of free GC466 and buffer solutions were recorded and subtracted with the same instrumental parameters. Data were analyzed using Origin software (version 6.0, Origin Lab, Northampton, MA, USA(Han, Fang et al. 2017).

3.2.1 Observations

Further evidence for conformational changes in rGCase and protein-ligand interactions affected by pHs was further confirmed by FT-IR spectroscopy. In the IR region, proteins exhibit a number of amide bands in different ranges of wavenumbers, representing different vibrations of the peptide moiety. Among these amide bands of protein, amide I bands of IR spectra, which mainly originated from the C = O stretching vibration

severally and occur in the region 1700–1600 cm-1, have been extensively used in the characterization of protein-ligand interactions and conformational studies of proteins (Han, Fang et al. 2017). Thus, in the first set (**Figure 3.10 in appendices**), the FT-IR spectra of free rGCase and rGCase-GC466 complex in the region of 1700–1600 cm−1 were investigated at pH 7.0 and 4.5. It can be seen that the peak position of the amide I band of free rGCase was shifted from 1654 to 1657 cm−1 after shifting the pH from 7.0 to 4.5. The spectral ranges between1650–1660 cm-1 are ascribed to the α-helix by the well-known assignment criterion(Han, Fang et al. 2017). In light of this, the changes above in peak positions, particularly in these areas, might be the result of changes to the rGCase α-helix conformation. This conclusion is supported by the results of the CD spectroscopy and MD simulation (**Figure 3.10 in chapter I and 3.1 appendices)**, in which a change in α-helix has been observed while lowering the pH from 7.0 to 4.5. Meanwhile, the protein-ligand stability in terms of protein's structural alterations in the presence of GC466 at both pHs have also been examined. At pH 7.0, upon the addition of GC466 to rGCase, the peak position of the amide I band shifted from 1654 to 1658 cm-1. This phenomenon suggested that GC466 makes a stable complex with rGCase by interacting with the C=O group in the protein structure subunits. However, no shifts in peaks were observed at pH 4.5 after the addition of GC466 to rGCase (free rGCase: 1656 cm-1; rGCase-GC466 complex: 1656 cm-1), indicating no interaction between them at this pH. A similar observation was also found in our MD study, where GC466 has only stable interaction with rGCase at pH 7.0.

In the second set (**Figure 3.10 in appendices**), using FT-IR spectroscopy, we measured the stability of interactions of the rGCase-GC466 complex in terms of structural changes at pH 7.0 in either presence or absence of GC466 under thermal denaturation (48 ^{0}C) conditions. We have found that the peak position of the amide I band for control rGCase

(kept at 37 ^{0}C) was 1654 cm-1 which displayed the characteristic feature of the α-helix structure. However, the protein was denatured after being exposed to heat for 60 min at 48 ^{0}C, as seen by the loss in intensity of the amide I band between 1650-1660 cm-1 position. With the addition of GC466 to rGCase, a sharp amide I band can be seen at the position of 1656 cm-1, indicating the retaining of amide I. However, when this peak position was compared to its control GCase (37 ^{0}C) peak (1654 cm-1), a shift in the amide I band (1656 to 1654 cm-1) was noticed. The changes in these peak positions signified that GC466 makes a stable complex with rGCase at pH 7.0 by interacting with the C=O group of protein subunits and stabilizing it before denatured under thermal denaturation. Similar findings were made in our MD investigation, which showed that GC466 interacts with rGCase most consistently at pH 7.0.

3.3. RAMAN spectra measurements

Raman (Witec alpha 300R, WITEC-RAMAN instrument) spectra of both sets of experiments (**detailed mentioned in section 3.1 in appendices**) at pH 7.0 and 4.5 were determined in the ranges of 400–3050 cm−1 (Xu, Han et al. 2011, Kang, Li et al. 2017). The protein samples were spread on a glass slide during the measurement and focused on the excitation laser beam (785 nm). The spectra were recorded in the range of 400–3050 cm−1. Each spectrum was obtained under the following conditions: 3 scans, 60 s exposure time and 2 cm−1 resolution. The time required for the acquisition of 1 spectrum was about 2 min. Raman spectral data were averaged over multiple scans, smoothed, baseline corrected, and were plotted using Origin software.

3.3.1 Observations

Raman spectroscopy further confirmed the pH-dependent conformational changes in rGCase protein and protein-ligand interactions seen in CD, FT-IR, and MD simulation studies. Amide I is the most useful Raman band for determining the secondary structure

of proteins in Raman. Unambiguously, the amide I vibrational mode, which primarily consists of C=O stretching vibrations, has been ascribed to the strong Raman band in the area 1645–1685 cm-1 (Xu, Han et al. 2011). Thus, in both sets of experiments, we focus on this region (1645-1685 cm-1) to investigate protein-ligand interactions and pH-dependent conformational changes of the protein. In the first set **(Figure 3.10b in chapter 3)** it can be seen that when pH changed from 7.0 to 4.5, the amide I band of the Raman spectra of pH 7.0 was displaced from 1656 to 1650 cm-1. However, it is well known, the Raman spectral ranges from, 1650–1660 cm-1 are assigned to α-helix
(Xu, Han et al. 2011, Kang, Li et al. 2017). As a result, the shift in Raman spectra could be attributed to conformational changes in the α-helix structure of rGCase, as observed in our MD simulation (**Figure 3.1 in appendices**). In the meantime, the protein-ligand interaction at both pHs has also been examined in terms of structural alteration. At pH 7.0, after mixing the GC466 to rGCase, the Raman spectrum of the amide I band shifted from 1656 to 1652 cm-1, signifying that GC466 interacted with the C=O group in the protein structure subunits and made a stable complex with it, which also seen in MD simulation. This persistent association may also be the cause of the enzyme's inhibition at pH 7.0 (**Section 3.3.4 and Table 3.2 in chapter 3 and, Figure 3.8 in appendices**).). However, no changes in the Raman shift of amide I band were visible at pH 4.5 when comparing free rGCase (1650 cm-1) Raman shift to rGCase-GC466 complex (1650 cm-1) Raman shift, indicating no interaction between them. The MD simulation produced results that were very similar; interactions were only seen at pH 7.0. Also, an *in vitro* study suggests that this may be caused by the enzyme activity losing its inhibition around pH 4.5. To dig further, we measured the stability of interactions between rGCase and GC466 at pH 7.0 under thermal denaturation conditions (**Figure 3.10b in Chapter 3)**. pH 7.0 was chosen for this study because GC466 has only stable interaction with rGCase

at this pH. For control rGCase (kept at 37 ^{0}C), we found sharp Raman spectra of the amide I band at 1656 cm-1, which displayed the characteristic feature of α-helix structure as previously reported (Xu, Han et al. 2011, Kang, Li et al. 2017). However, after heat exposure for 60 min, the loss in Raman spectral of amide I band between 1645- 1685 cm-1 has been seen signified protein denaturation under thermal exposure conditions. In the addition of GC466 to rGCase under thermal denaturation conditions, a sharp amide I Raman spectral band can be seen at 1650 cm-1. A shift in the amide I (1656 to 1650 cm-1) band was observed when this Raman spectral peak position was compared to that of the control GCase (37 ^{0}C). The changes in these peak positions signified that GC466 may interact with the C=O group of protein subunit and stabilize it before being denatured under thermal denaturation. A stable interaction between rGCase protein and GC466 has also been seen in our MD simulation.

Table 4.1 Effect of single-dose oral administration of compound GC466 at a dose of 2000 mg/kg on hematological parameters of rats after their death on Day -1

Rats	Hb (g/dL)	RBC (x 10^6 cells/mL)	WBC (x 10^3 Cell/mL)	PLT Platelets (x 10^5 Cells/mL)
1	11.71	5.45	6.01	7.72
2	10.60	4.24	4.11	3.65
3	11.32	6.21	5.78	3.52
4	7.82	2.74	3.58	4.24
5	8.47	4.56	3.88	3.77

Table 4.2 Effect of single-dose oral administration of compound GC466 at a dose of 2000 mg/kg on the liver, kidneys and heart coefficient of the rats after their death on Day -1

Rats	Liver (g)	Kidneys (g)	Heart (g)
1	4.62	0.74	0.45
2	6.10	0.47	0.37
3	4.23	0.28	0.38
4	5.72	0.54	0.45
5	5.88	0.42	0.35

Table 4.3 Effect of single-dose oral administration of compound GC466 at a dose of 2000 mg/kg on the lungs, brain and spleen coefficient of the rats after their death on Day -1

Rats	Lung (g)	Brain (g)	Spleen (g)
1	1.31	1.11	0.49
2	1.25	1.34	0.52
3	0.78	0.84	0.56
4	0.98	1.03	0.39
5	1.60	0.75	0.56

Table 4.4 Effect of single-dose oral administration of compound GC466 at a dose of 2000 mg/kg on serum hepatic enzyme parameters of the rats after their death on Day -1

Rats	AST(IU/L)	ALT(IU/L)	ALP (IU/L)
1	126.54	50.72	150.86
2	154.32	42.14	144.72
3	290.52	34.82	200.70
4	210.65	56.57	168.91
5	286.85	61.22	131.43

Table 4.5 Effect of single-dose oral administration of compound GC466 at a dose of 2000 mg/kg on the serum creatinine and CK-MB (heart) parameters of the rats after their death on Day -1.

Rats	Creatinine (mmol/L)	CK-MB (ng/mL)
1	70.82	22.27
2	91.53	40.60
3	76.32	36.65
4	80.06	48.71
5	76.53	42.62

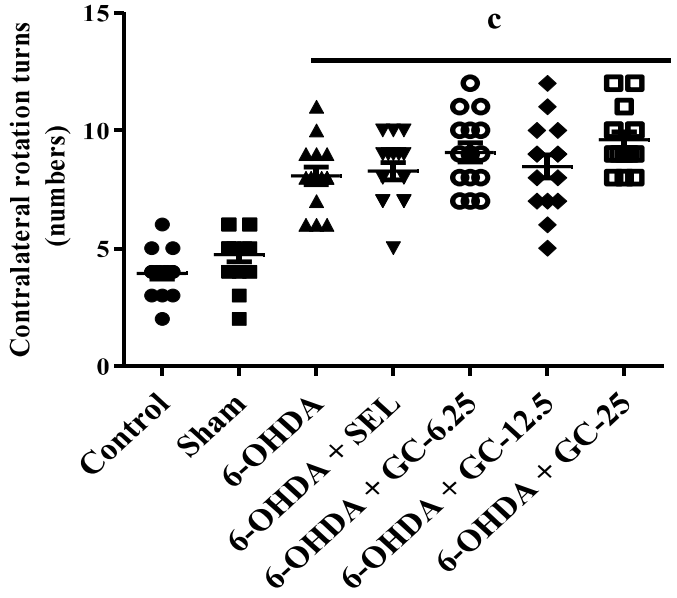


Figure 5.1 Effect of GC466 on 6-OHDA-induced alteration in apomorphine-induced rotations on Day-4. All values are shown as mean ± SD; n = 16; $^{c}p< 0.05$ compared to control and sham [One-way ANOVA followed by Tukey Post-hoc test, Graph Pad Prism 5.1 Software, Inc].

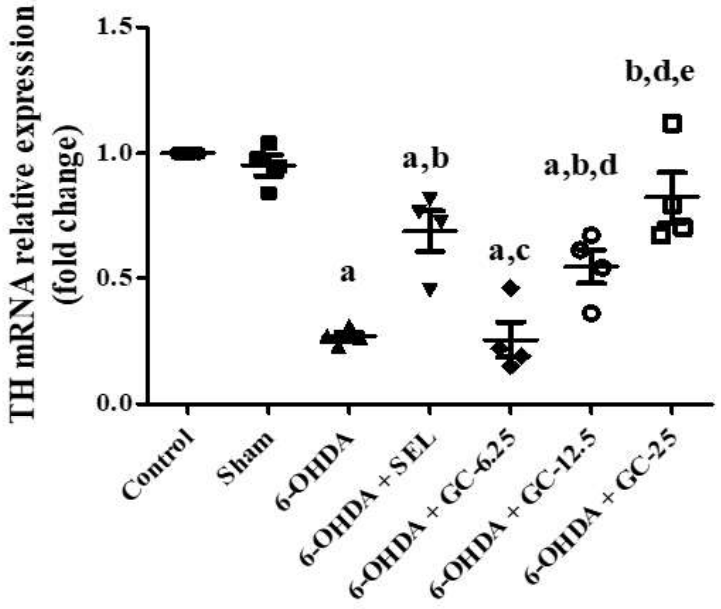


Figure 5.2 Effect of GC466 on 6-OHDA-induced alteration in Tyrosine hydroxylase (TH) mRNA level. Results are expressed as mean ± SD; n = 4; $^{a}p< 0.05$ compared to sham, $^{b}p< 0.05$ compared to 6-OHDA and $^{c}p< 0.05$ compared to 6-OHDA + SEL, $^{d}p< 0.05$ compared to 6-OHDA + GC-6.25 and $^{e}p< 0.05$ compared to 6-OHDA + GC-12.5 [One-way ANOVA followed by Tukey post-hoc test, Graph Pad Prism 5.1 Software, Inc].

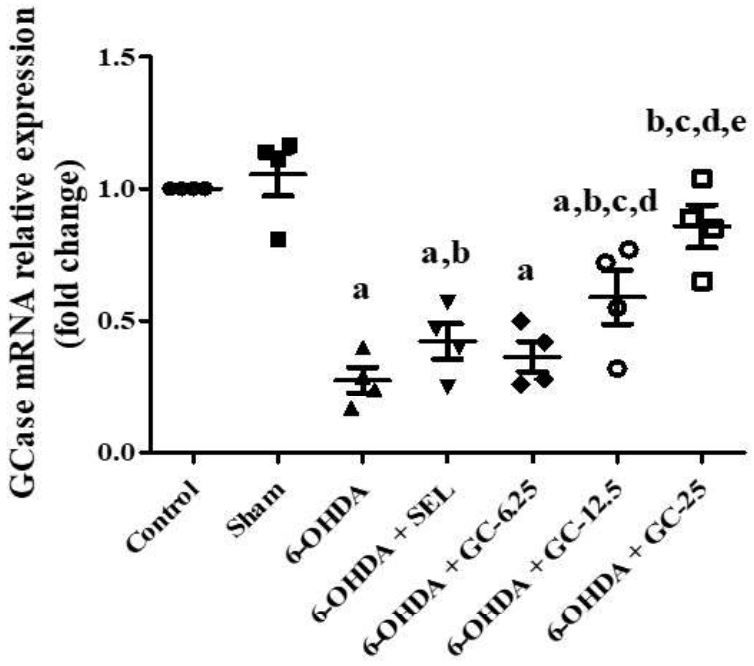


Figure 5.3 Effect of GC466 on 6-OHDA induced alterations in glucocerebrosidase (GCase) mRNA levels in PD rats. Results are reported as mean ± SD; n = 4; [a]p< 0.05 compared to sham, [b]p< 0.05 compared to 6-OHDA and [c]p< 0.05 compared to 6-OHDA + SEL, [d]p< 0.05 compared to 6-OHDA + GC-6.25 and [e]p< 0.05 compared to 6-OHDA + GC-12.5 [One-way ANOVA followed by Tukey post-hoc test, Graph Pad Prism 5.1 Software, Inc].

- **List of publications from thesis:**

- **Pratigya Tripathi**, Ankit Ganeshpurkar, Sushil Kumar Singh, S. Krishnamurthy, Generation of wild-type rat Glucocerebrosidase homology modeling: Identification of putative interactions site and mechanism for chaperone using combined in silico and invitro studies, *Bioorganic Chemistry* 126 (2022) 105871. DOI: 10.1016/j.bioorg.2022.105871.

- **Pratigya Tripathi**, Ankit Ganeshpurkar, Sushil Kumar Singh, S. Krishnamurthy, Identification of novel glucocerebrosidase chaperone for potential treatment of Parkinson's disease: An approach using i*n silico* virtual screening, molecular docking and molecular dynamics, and *in vitro* studies. *International Journal of Biological macromolecules*, 228(4) (2023) 453-466. DOI: 10.1016/j.ijbiomac.2022.12.217.

- **List of publications during Ph.D**

- Ankit Ganeshpurkar, Ravi Singh, **Pratigya Tripathi**, Qadir Alam, Sairam Krishnamurthy, Ashok Kumar, Sushil Kumar Singh, Effect of sulfonamide derivatives of phenylglycine on scopolamine-induced amnesia in rats" *Ibrain*, 9(2023) 13-31. DOI: doi.org/10.1002/ibra.12092.

- **Under review from the Thesis**

- **Pratigya Tripathi,** Ela Mishra, Mahendra Kumar Thakur, and Sairam Krishnamurthy, Modulation of ER stress- glucocerebrosidase pathway involved in the neuroprotective effect of novel compound GC466 in the 6-OHDA-induced Parkinson's disease model: A new molecular mechanism and treatment approach for Parkinson's disease is under review in "*Progress of Neurobiology*."

- **<u>Under review from the other projects during PhD</u>**

- Ankit. Ganeshpurkar, Ravi. Singh, **Pratigya Tripathi**, Qadir Alam, Sairam Krishnamurthy, Ashok Kumar, Sushil Kumar Singh, Effect of sulfonamide derivatives of para-aminobenzoic acid on scopolamine-induced amnesia in rats communicated in *"Experimental Brain Research"*