Annexure A
Materials and Methods

A.1 MATERIAL

Trehalose was procured from HiMedia. MG132, 2-mercaptoethanol (BME), chloroquine, lactacystin, thapsigargin, DMSO, 3-(4,5-di-methylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT), tunicamycin, and reagents for cell culture were bought from Sigma. Hydrogen peroxide (30%) was obtained from Fisher Scientific and ethidium bromide from Merck. OptiMEM and Lipofectamine™ 2000 was from Life Technologies. Curcumin, Ketorolac, N-acetylcysteine, nocodazole, Propidium Iodide (PI) were acquired from Sigma. TRIzol™ (15596018) Reagent (Invitrogen™) from Thermo Fisher Scientific. Dual-Luciferase® Reporter (DLR™) Assay System (E1910) and DeadEnd™ Fluorometric TUNEL System reagents (G3250) and Proteasome-Glo™ assay reagents (G8622, G8642) were procured from Promega and 5,5′, 6,6′-tetrachloro-1,1′,3,3′ tetraethylbenzimidazol-carbocyanine iodide (JC-1) from Molecular Probes. Annexin V-FITC and Annexin V binding buffer were purchased from BioLegend. 4′,6-diamidino-2-phenylindole (DAPI) were acquired from Invitrogen. The primary and secondary antibodies used in this work are listed in Table A.1 and the various plasmid constructs utilized are listed in Table A.2.

Table A.1: List of antibodies primary and secondary used in the present work

Serial Number	Antibody	Manufacturer	Catalog Number
Primary Antibodies			
1	Actin	Sigma	A2066
2	GAPDH	Santa Cruz Biotechnology	sc-47724
3	γ-tubulin	Sigma	T6557
4	p62	Sigma	WH0008878M1
5	Ubiquitin	Santa Cruz Biotechnology	sc-8017, sc-9133, sc-58448
6	20S proteasome	Santa Cruz Biotechnology	sc-58412, sc-166073
7	p21	Santa Cruz Biotechnology	sc-756
8	p53	Santa Cruz Biotechnology	sc-6243
9	Bax	Santa Cruz Biotechnology	sc-493
10	CHIP	Thermo Scientific	PA1-015
11	CHIP	Santa Cruz Biotechnology	sc-66830
12	cytochrome c	Santa Cruz Biotechnology	sc-13561

13	p27	Santa Cruz Biotechnology	sc-528
14	GFP	Santa Cruz Biotechnology	sc-8334
15	Luciferase	Santa Cruz Biotechnology	sc-74548
Secondary Antibodies			
16	Anti-Mouse IgG Antibody (H+L), Peroxidase	Vector Laboratories	PI-2000
17	Anti-rabbit IgG-Texas Red	Vector Laboratories	TI-1000
18	Anti-rabbit IgG-Fluorescein	Vector Laboratories	FI-1000
19	Anti-mouse IgG-Fluorescein	Vector Laboratories	FI-2000
20	Anti-mouse IgG-Texas Red	Vector Laboratories	TI-2000
21	Anti-Rabbit IgG Antibody (H+L), Peroxidase	Vector Laboratories	PI-1000

Table A.2: List of plasmid constructs and their source detail utilized in the present work

Serial Number	Name of Plasmid Construct	Source Details
1	NF-κB-Luc plasmid	Dr. Aleem Siddiqui (UC San Diego, Gilman Dr. La Jolla, CA)
2	pd1EGFP	Dr. Nihar Ranjan Jana (National Brain Research Centre, Manesar, Gurgaon, India)
3	GFP-Δ9CAT	Dr. Csaba soti (Department of Medical Chemistry, Semmelweis University, Budapest, Hungary)
4	GFP-wtCAT	Dr. Csaba Soti (Department of Medical Chemistry, Semmelweis University, Budapest, Hungary)
5	CHIP	Dr. Nihar Ranjan Jana (National Brain Research Centre, Manesar, Gurgaon, India)
6	EGFP-HDQ23	Dr. A Tunnacliffe (Department of Chemical Engineering and Biotechnology, University of Cambridge, Cambridge, UK)
7	EGFP-HDQ74	Dr. A Tunnacliffe (Department of Chemical Engineering and Biotechnology, University of Cambridge, Cambridge, UK)

8	pEGFP-C1 CFTRΔF508	Dr. Ron R. Kopito (Stanford University, Biology Department Lorry Lokey Bldg Campus Drive Stanford CA)
9	pEGFP-C1-Ataxin3Q84	Addgene: 22123
10	pF148 pSOD1G37RAcGFP1	Addgene: 26409
11	Luciferase-pcDNA3	Addgene: 18964
12	pEGFP-C1-Ataxin3Q28	Addgene: 22122
13	pF141 pAcGFP1 SOD1WT	Addgene: 26402
14	pcDNA3-EGFP	Addgene: 13031
15	pcDNA3-c-myc	Addgene: 16011
16	pEGFP-Hsp70	Addgene: 15215

A.1.1 Cell Lines Used in the Study

Two cell lines used in this present work are COS-7 and A549 which were obtained from the National Centre for Cell Science (NCCS), Pune, India. COS-7 is African green monkey kidney fibroblast-like cell line whereas the A549 cells are human lung epithelial cell adenocarcinoma cells.

A.2 METHODS

A.2.1 Cell Culture Based Experiments: Transfection, Drug Treatment

COS-7 and A549 cells were cultured in Dulbecco's modified Eagle's medium (DMEM), which had fetal bovine serum (10%) and antibiotics penicillin (100U/ml), and streptomycin (100µg/ml), in an incubator at 37° Celsius with carbon dioxide at 5%. The cells were seeded into a variety of culture plates (for example, 6 wells, 96 wells), as well as two-chambered slides, to conduct the studies. When the cells had reached 70% confluency, different plasmid constructs (GFP-wtCAT, pcDNA, pd1EGFP, pEGFP-C1 CFTRΔF508, pEGFP-hsp70, EGFP-HD23Q, and EGFP-HD74Q) were introduced into the culture and transfected into the cells. After the cells had been transfected using Lipofectamine™ 2000 reagent for at least 24 hours in accordance with the directives supplied by the manufacturer, the cells were subjected to a variety of different pharmacological treatments. Cells were also subjected to different stressors with or without Trehalose and in different study Ketorolac, and bright field imaging was done on FLoid™ Cell Imaging Station (Life Technologies).

A.2.2 Cell Sensitivity Assay (MTT Assay)

An MTT experiment was carried out using cultured cells, which had varying doses of Ketorolac and Trehalose added to them, in addition to a control group. The cells were cultured in 96 well plates and subjected to suitable drugs. Subsequently, they were subjected to incubation with MTT (5 mg/ml in PBS) at a concentration of 1:10 (MTT: DMEM) for a duration of 4 hours at a temperature of 37°C and carbon dioxide concentration of 5%. Next, the media was taken out and acidified isopropanol added to dissolve formazan. The measurement of absorbance of solubilized formazan produced was conducted at a wavelength of 595 nm as

described previously (Joshi et al., 2019b). The Student's t-test was carried out, and the findings indicate statistical significance when *p < 0.05 in comparison with control group.

A.2.3 *In Silico* Molecular Docking and LigPlot⁺ Analysis

The *in silico* docking analysis were done using AutoDock Vina (v 1_1_2) (Trott and Olson, 2010). The structural data of proteasome 20S was taken from Protein data bank with ID PDB: 5LE5 (Schrader et al., 2016). Trehalose structure was generated with the help of UCSF Chimera (version 1.15) (Pettersen et al., 2004), and the structure data were taken from PubChem (PubChem CID 7427). For Ketorolac data from (PubChem CID 3826) was taken. The AutoDock Tools (version 1.5.6) (Morris et al., 2009) were deployed for ligand and receptor preparation. For macromolecule preparation, polar hydrogen atoms were added, and water molecules were deleted. Charge on receptor molecule was also balanced. After the primary files were ready, the ADT grid was used to form grid box parameters with 1.000 Å of spacing as follow

(a) Trehalose: The grid parameter was 64 x 44 x 66 and centre parameter was (-1.595, 210.500, 31.091) xyz for the β1 subunit and for the β2 subunit, it was 50 x 56 x 56 and centre (38.556, 169.880, 36.476) xyz. Similarly, for β5 the grid parameter was 50 x 56 x 64 and the centre parameter was (7.569, 180.850, 32.567) xyz.
(b) Ketorolac: The grid parameter for β1 subunit is 58 x 44 x 62 are centre parameters (0.856, 212.332, 26.308) xyz. For β2 subunit are 46 x 50 x 58 and centre parameters (36.693, 172.609, 36.678) xyz and for β5 subunit 52 x 46 x 60 and centre parameter (7.569, 180.85, 29.153) xyz.

After creating a configuration file with optimized grid parameters, the AutoDock Vina command was generated in the command prompt as per the protocols prescribed in Forli et al., (Forli et al., 2016) and blind docking was performed. After docking was completed, the resulting output and log files were further analyzed, and the result was then visualized with PyMOL software (DeLano, 2002). (PyMOL Molecular Graphics System, Version 2.4.1 Schrödinger, LLC http://www.pymol.org). For further investigation of docked results as flattened out 2D representation of ligand-protein interaction LigPlot⁺ software (version 2.2.8) was utilized (Wallace et al., 1995;Laskowski and Swindells, 2011).

A.2.4 Immunofluorescence Analysis

COS-7 cells were seeded onto the 2-well chambered slides; when cells got sub-confluent, they were transfected with different plasmids (for wild types, mutant proteins, Luciferase, and d1EGFP) and subjected to various drugs for a varied period of time and concentration. After completion of drug treatment, cells were extensively washed three times with PBS for 5 minutes each and incubated with paraformaldehyde (4% in PBS) for 15 minutes. After incubation, 3 times washing with PBS was followed and was then for 5 minutes incubated with Triton X-100 (0.5% in PBS). Cells were further washed with PBS 3 times, and then next, blocked with rabbit serum (2% in PBS) for up to 45 min. Next, it was kept overnight at 4˚C with various primary antibodies (1:500) dissolved in PBST (0.05% Tween 20 with PBS). After that, the cells were rinsed in PBS the next day three times. After this, cells were incubated with suitable secondary antibodies (1:5000) for four hours, labeled with fluorescein or Texas Red. Washing with PBS 3 times again is followed by mounting and staining with the antifade solution and 4',6-diamidino-2-phenylindole (DAPI), and cells were analyzed with an epi-fluorescence microscope (Leica DM6000 B).

A.2.5 Proteasome Activity Assay

A549 cells exposed to various drugs for different time and concentration intervals were utilized to quantify the activity of Proteasomes by performing a Proteasome-GloTM Kit assay from Promega. The reagents and samples (Treated cells) were prepared, and the experimentation was executed following the maker's guidelines. All studies were executed in

triplicates, and three independent sets of experiments were performed. GloMax®-Multi Jr Single-Tube Multimode Reader (Promega) was used to record the luminescence data.

A.2.6 TUNEL Assay

A549 cells were subjected with different doses of Ketorolac for 24 hours, including 10 µM, 20 µM, and 40 µM, as well as control. Next, the cells were fixed using a paraformaldehyde (PFA) solution (4% in PBS) for 15 minutes, and then they were rinsed with PBS. For permeabilization, fixed cells were then treated with Triton X-100 (0.5% in PBS) for 5 minutes, afterwards, cells were rinsed with PBS. TUNEL assay afterwards was carried out at 37 degrees Celsius, in compliance with the protocol provided by the manufacturer, and imaged using a fluorescence microscope FLoid Cell Imaging Station; Life Technologies). The apoptotic cells were counted manually and plotted. The nuclear fragmented DNA, which acts a marker of apoptotic cells, is acted upon by TdT to add fluorescein-12-dUTP at 3'-OH of DNA.

A.2.7 Reporter Gene Assay

After cultivating A549 cells, NF-κB luciferase (firefly) and pRL-SV40 *(Renilla)* constructs transfection was done. After transfection, they were then exposed with control or Ketorolac for varying concentrations (10 µM, 20 µM, 30 µM and 40 µM) incubated for 24 hours. Subsequently, the cells were harvested, and the protein isolates were prepared for an experiment in order to examine the level of luciferase activity inside these cells by using the Dual-luciferase reporter gene assay (Promega) in accordance with the instructions from the manufacturer. The luminescence was analysed with GloMax®-Multi Jr. Single-Tube Multimode Reader (Promega).

A.2.8 Misfolded Protein Aggregates Quantification

After being transfected with appropriate plasmid constructs, COS-7 cells were subjected to control (Distilled water) or Trehalose and Ketorolac. The cells post-treatment was analyzed under the fluorescence microscope, and the misfolded protein aggregates were estimated manually. Prominent inclusions were considered where there was more than one aggresome was present in the cell. Statistical evaluations were done by implementing Student's t-test, and aggregate number data are depicted as mean ±SD, and *$p<0.05$ shows statistical significance.

A.2.9 Flow Cytometry and Statistical Analysis

For performing the flow cytometry, the A549 cells were grown and exposed to either control or MG132 (10 µM for 24 h) or Ketorolac (30 µM for 24 h and 48 h). Subsequently, cells were collected and incubated with Annexin V-FITC and PI for 15 min at room temperature (RT) in Annexin V binding buffer. Afterwards, the apoptosis data were collected by using the flow cytometer (BD FACSCanto™ II). The GraphPad Prism software (Version 6.0.1; GraphPad Software Inc, San Diego, California) was utilized for the statistical analysis. Two-way ANOVA was employed to compare means of different groups.

A.2.10 Immunoblotting Analysis

The A549 cells were administered Trehalose or Ketorolac and control (Distilled water) for varied time intervals, and subsequently, the cells were collected, and protein lysates were made by sonication. The cellular extracts were used to perform SDS-PAGE (Bio-Rad) to separate proteins and transfer them to the nitrocellulose membrane afterward. Subsequently, the membrane was subjected to skimmed milk (5% in TBST) (Tris .05 M, pH 7.4 NaCl 0.15 M, 0.05% Tween 20) for blocking for almost 1 hour and thenceforward incubated at 4˚C with various primary antibodies (1:1000) overnight. After overnight incubation, washing of the membrane is done properly and treated with a secondary antibody (1:10000) tagged with horseradish peroxidase (HRP) for 40 min. Afterward, the washing of the membrane is done with TBST. The membrane was developed post-treatment with Luminata Crescendo Western HRP substrate (Merck Millipore). The detection and imaging of chemiluminescence from the membrane was

performed in the Gel Doc XR+ Gel Documentation system (Bio-Rad). Antibodies were diluted in TBST with a pH of 7.4.

A.2.11 JC-1 Staining

A549 cells were exposed to the control, MG132 (10 µM for 12 hours), and various doses of Ketorolac (10 µM, 20 µM, 30 µM and 40 µM) for 24 hours. Following the treatment, a ratiometric fluorescent dye known as JC-1 (5 µM) was given to the cells, and they were then placed in an incubator at 37° Celsius with 5% carbon dioxide for 45 minutes. Next, the media was withdrawn, and prewarmed phosphate-buffered saline (PBS) was added. Following this step, the samples were promptly photographed using a fluorescence microscope (FLoid™ Cell Imaging Station, Life Technologies').

A.2.12 DNA Fragmentation Agarose Gel Electrophoresis and Nucleus Architecture Analysis

Similar set of A549 cells were exposed to control or Ketorolac in a concentration-dependent manner (10 µM, 20 µM, 30 µM, and 40 µM) for a period of 24 hours. Using TRIzol™ following the manufacturer's instructions, we were able to successfully isolate the cells' genomic DNA. The sample was then run through an agarose gel electrophoresis where ethidium bromide was added in gel to visualize DNA. After electrophoresis, gel was imaged using Gel Doc XR+ Gel Documentation System (Bio-Rad). A set of A549 cells were subjected to control, ketorolac (20 and 40 µM, 24 h), and MG132 (10 µM, 12 h). Afterwards, cells were fixed with PFA 4%, washed, and stained with DAPI. The nuclear-stained cells were imaged with fluorescence microscope (FLoid Cell Imaging Station; Life Technologies) to observe nuclear morphology.

A.2.13 Luciferase Activity Assay

The cells expressing exogenous firefly luciferase were treated with Trehalose or control, and few of the sets were also administered MG132 (10 µM), or chloroquine (20 µM) and then given heat stress for 30 min at 43 °C and afterward incubated in normal settings (37 °C, 5% CO2) for 2 hours. Thereafter, the experiment was done to analyze luciferase activity with these cells on GloMax®-Multi Jr Single-Tube Multimode Reader (Promega) utilizing Promega's Dual-luciferase reporter gene assay kit as per the provided guideline from the manufacturer.

A.2.14 Cycloheximide Chase Analysis

For the cycloheximide chase analysis cells were transfected transiently with construct of pd1EGFP for 24 h. Post-transfection the some sets of cells were subjected to either control or Trehalose (1.5 mM). Afterwards, cycloheximide (10 µM) was added for different time points (5 hours and 8 hours) to chase d1EGFP a proteasome modelled protein. Post treatment the cells were observed through fluorescence microscope and were harvested. The harvested cells were later processed for immunoblotting experiments.

A.2.15 Dot blot analysis

To perform Dot blot analysis cells were transfected transiently with different constructs of mutant misfolded proteins. When transfection was done, cells were subjected to control or Trehalose (1.5 mM). Post-treatment cells were harvested and cell lysis was done their extracts were passed through nitrocellulose membrane for performing Dot blot analysis. The anti-actin and anti-GFP antibodies were utilized for analysis of Dot blot. The NIH image analysis software was utilized for quantifying dot blot results.

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