I dedicate this thesis to my beloved parents (Maa and Papa), who have been my source of inspiration and my constant pillars of strength. I am forever grateful to them for all their sacrifices in making me what I am today.

To my wonderful family……

Declaration

I hereby declare that the thesis entitled ***"Computational approaches to understand the interactions of small bioactive compounds and cell surface receptors with the SARS-CoV-2 viral proteins"*** has been submitted to Tezpur University in the Department of Molecular Biology and Biotechnology under the School of Sciences for partial fulfillment for the award of the degree of Doctor of Philosophy in Molecular Biology and Biotechnology.

I am the sole author of this thesis. This is a true copy of an original work carried out by me including any required final revisions, as accepted by my examiners.

Further, I declare that no part of this work has been reproduced elsewhere for award of any other degree.

Chainee Das

Date: 23/07/2025
Place: Tezpur University, Tezpur

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CERTIFICATE OF THE PRINCIPAL SUPERVISOR

This is to certify that the thesis entitled ***"Computational approaches to understand the interactions of small bioactive compounds and cell surface receptors with the SARS-CoV-2 viral proteins"*** submitted to the School of Sciences, Tezpur University in partial fulfillment for the award of the degree of Doctor of Philosophy in Molecular Biology and Biotechnology is a record of original research work carried out by **Miss Chainee Das** under my personal supervision and guidance.

All helps received by her from various sources have been duly acknowledged. No part of this thesis has been reproduced elsewhere for award of any other degree.

Date: 23/07/2025
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(Venkata Satish Kumar Mattaparthi)
Supervisor

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Regards,
Chainee Das

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List of Abbreviations

Å	Angstrom
ACE2	Angiotensin Converting Enzyme 2
ARJ	Arjunglucoside-I
AKA	Alpha-ketoamide
AMBER	Assisted Model Building with Energy Refinement
ADMET	Absorption, Distribution, Metabolism, Excretion, and Toxicity
BFE	Binding Free Energy
3CLpro	3-chymotrypsin-like proteases
COVID-19	Coronavirus disease 2019
CTD	C-Terminal Domain
CAN	Carnosol
CASTp	Computed Atlas of Surface Topography of proteins
CoM	Center of Mass
CG	Conjugate Gradient
DM	Double Mutant
DP	Delta-Plus
E protein	Envelope protein
ELE	Electrostatic
EUAs	Emergency Use Authorizations
FAO	Food and Agriculture Organization
FF	Force Field
FFT	Fast Fourier Transform
fs	Femtosecond
FF99SB	Force-field 99 Stony Brook
GI	Gastrointestinal
GBSA	Generalized Born Surface Area
GOR	Garnier-Osguthorpe-Robson
GRAVY	Grand Average of Hydropathicity
g/cc	grams per cubic centimeter
HDAC2	Histone Deacetylase
INSACOG	Indian SARS-CoV-2 Genomics Consortium
kcal/mol	kilocalories per mole
K	kelvin
MW	Molecular Weight
MERS-CoV	Middle East respiratory syndrome
M protein	Membrane protein
Mpro	Main Protease
MHA	Ministry of Home Affairs
MD	Molecular Dynamics
MM	Molecular Mechanics
NDMA	National Disaster Management Authority

List of Abbreviations

NMPA	National Medical Products Administration
N protein	Nucleocapsid protein
NTD	N-Terminal Domain
NHC	National Health Commission
NIH	National Institutes of Health
nsps	nonstructural proteins
ns	nanosecond
nmode	normal mode
NCBI	National Center for Biotechnology Information
nHA	number of hydrogen bond acceptors
nHD	number of hydrogen bond donors
NVT	Nanosecond constant volume
ORFs	Open Reading Frames
PMF	Potential of Mean Force
PRODIGY	PROtein binDIng enerGY prediction
PPIs	Protein-protein interactions
PDB	Protein Data Bank
PLpro	papain-like protease
PONDR	Predictor of naturally disordered regions
PBSA	Poisson-Boltzmann Surface Area
PME	Particle Mesh Ewald
ps	picosecond
pI	Isoelectric point
RT-PCR	Real-Time Reverse-Transcription-Polymerase-Chain-Reaction
RdRp	RNA-dependent RNA-polymerase
RBD	Receptor Binding Domain
RBM	Receptor Binding Motif
RMSD	Root Mean Square Deviation
RMSF	Root Mean Square Fluctuation
RCSB-PDB	Research Collaboratory for Structural Bioinformatics Protein Data Bank
ROS	Rosmanol
RCs	Reaction Coordinates
Rg	Radius of Gyration
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
S protein	Spike Protein
SASA	Solvent-Accessible Surface Area
SD	Steepest Descents
TMPRSS2	Transmembrane Serine Protease-2
TM Domain	Transmembrane Domain
TIP3P	Transferable Intermolecular Potential Three-Point
US	Umbrella Sampling

List of Abbreviations

UCSF	University of California, San Francisco
VOC	Variant of Concern
VUI	Variant Under Investigation
VOI	variant of interest
VMD	Visual molecular dynamics
VDW	van der Waals
WHAM	Weighted Histogram Analysis Method
WOAH	World Organization for Animal Health
WHO	World Health Organization
WT	Wild Type
WHAM	Weighted Histogram Analysis Method

List of Publications

This thesis is partly based on the following original communications:

1. **Das, C**., Das, D., and Mattaparthi, V.S.K. Effect of Mutations in the SARS-CoV-2 Spike RBD Region of Delta and Delta-Plus Variants on its Interaction with ACE2 Receptor Protein. *Letters in Applied NanoBioScience,* 12, 118, 2023. DOI: https://doi.org/10.33263/LIANBS124.118

2. **Das, C**., Hazarika, P.J., Deb, A., Joshi, P., Das, D., and Mattaparthi, V.S.K. Effect of Double Mutation (L452R and E484Q) in RBD of Spike Protein on its Interaction with ACE2 Receptor Protein. *Biointerface Research in Applied Chemistry*, 13, 97, 2022. DOI: https://doi.org/10.33263/BRIAC131.097

3. **Das, C**., Das, D., and Mattaparthi, V. S. K. Computational Investigation on the Efficiency of Small Molecule Inhibitors Identified from Indian Spices against SARS-CoV-2 Mpro. *Biointerface Research in Applied Chemistry*, 13(3), 235, 2023. DOI: https://doi.org/10.33263/BRIAC133.235

4. **Das, C**., and Mattaparthi, V. S. K. Impact of Mutations in the SARS-CoV-2 Spike RBD Region of BA.1 and BA.2 Variants on its Interaction with ACE2 Receptor Protein. *Biointerface Research in Applied Chemistry*, 13(4), 358, 2023. DOI: https://doi.org/10.33263/BRIAC134.358

5. **Das, C**., and Mattaparthi, V.S.K. Efficiency of CAT and L-SIGN as Alternative or Co-receptors for SARS-CoV-2 Spike Protein. *Coronaviruses*, 4 (3), 2023. DOI: https://dx.doi.org/10.2174/0126667975262159230927074645

6. **Das, C**., and Mattaparthi, V.S.K. Computational investigation on the Physio-chemical, Structural and Binding features of BA.2.75 and BA.2.75.2 Omicron variants of SARS-CoV-2. *Letters in Applied NanoBioScience*, 13(4), 191, 2024. DOI: https://doi.org/10.33263/LIANBS134.191

7. **Das, C**., Mohta, A., and Mattaparthi, V.S.K. Computational investigation on the impact of mutations in the SARS-CoV-2 spike RBD region of BA.2.12.1 and BA.4 variants on its interaction with ACE2 Receptor Protein. *Letters in Applied NanoBioScience*, 13, 2, 2024. DOI: https://doi.org/10.33263/LIANBS132.096

8. **Das, C**., and Mattaparthi, V.S.K. Computational Design of Peptide Inhibitors Targeting the SARS-CoV-2 Main Protease. *Coronaviruses*, 5, e130624230993, 2024. DOI: https://doi.org/10.2174/0126667975319992240612053235

Conference Proceedings

1. **Das, C.,** and Mattaparthi, V. S. K. "Effect of Double Mutation (L452R and E484Q) in RBD of Spike Protein on its Interaction with ACE2 Receptor Protein" in the *National Seminar on Advances in Basic and Translational Research in Biology (ABTRiB)* organised by department of Molecular Biology and Biotechnology, Tezpur University on 11-12th March 2022. (Poster Presentation)

2. **Das, C.,** and Mattaparthi, V. S. K. "Effect of Mutations on the RBD of Spike Protein on its Interaction with ACE2 Receptor Protein of human host" in the *12th India-Japan Science and Technology Conclave: International Conference on Frontier Areas of Science and Technology (ICFAST-2022)* held at University of Hyderabad on September 9-10, 2022. (Poster Presentation)

3. **Das, C.,** and Mattaparthi, V. S. K. Participated in the "*National-level mentoring symposium "Gurukul in emerging areas in modern biology and medicine*" organized by Indian National Young Academy of Sciences (INYAS) in collaboration with Dept. of Molecular Biology and Biotechnology, Tezpur University on 2nd & 3rd March, 2023. (Participation)

4. **Das, C.,** and Mattaparthi, V. S. K. "Efficacy of Alternative receptors (CAT and L-SIGN) for SARS-CoV-2 entry: An in-silico study" on the *National seminar on Research at the Interface of Chemical, Biological and Material Sciences* organized by the Dept. of Chemical sciences in collaboration with Students Science Council on March 10, 2023. (Oral presentation)

5. **Das, C.,** and Mattaparthi, V. S. K. Participated in the "*demonstration-cum-hands on session on 'AI and DL in Life Science and Healthcare Research*" organized by the department of Molecular Biology and Biotechnology, Tezpur University on 10th February 2023. (Participation)

6. **Das, C.,** and Mattaparthi, V. S. K. "Computational Investigation on the Efficiency of Small Molecules Identified from Indian Spices acting as inhibitor against SARS-CoV-2 Mpro" in the *TU Science Graduate Research Conclave 2025* organised by the School of Sciences, Tezpur University on 10-11th of February 2025. (Poster Presentation)