

***THERAPEUTIC EFFECTS OF GEDUNIN AND  
DERIVATIVE***



**Thesis submitted in partial  
fulfillment for the Award of  
Degree**

**Doctor of Philosophy**

**By**

***Priya Dagar***

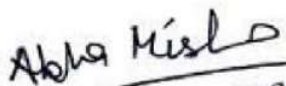
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**DEDICATED TO MY BELOVED HUSBAND, MY PARENTS  
FOR THEIR LOVE, SUPPORT, AND ENCOURAGEMENT**

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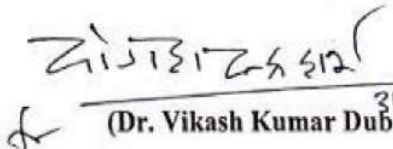
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**(PRIYA DAGAR)**

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## **LIST OF ABBREVIATIONS AND SYMBOLS**

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MAPC	Multipotent adult progenitor cells
JAK/SAT	Janus kinase signal transducers/activators of transcription
HSP90	Heat shock protein 90
PARP	Poly adenosine diphosphate ribose polymerase
PAMPs	Pathogen-associated molecular patterns
QSAR	Quantitative structure-activity relationships
L-AAO	L- amino acid oxidase
ASV	Anti-snake venom
PLA	Phospholipase A
CROFAB	Crotalidae polyvalent immune fab
DDT	Dichloro diphenyl trichloroethane
BRCA	Breast cancer gene
TMPRSS	Transmembrane serine protease
PTEN	Phosphate and tensin homolog
TP53	Tumor protein 53
MCF-7	Michigan cancer foundation -7
BRs	Brassino steroids
NADPH	Nicotinamide adenine dinucleotide phosphate
NADH	Nicotinamide adenine dinucleotide
NADK	Nicotinamide adenine dinucleotide kinase
MNADK	Mitochondria localized Nicotinamide adenine dinucleotide kinase
KRAS	Kirsten rat sarcoma virus
GLT-1	Glutamate transporter
ROS	Reactive oxygen species
TEM	Transmission electron microscope
DM	Diabetes mellitus
HPLC	High-performance liquid chromatography

HRLCMS-Q-TOF High-resolution liquid chromatograph mass spectrometer

	quadruple time of flight
AJS-ESI	Agilent Jet Stream -Electrospray ionization mass spectrometry
CCL <sub>4</sub>	Carbon tetrachloride
LC	Liquid chromatography
PDB	Protein data bank
ADMET	Absorption, Distribution, Metabolism, Excretion, and toxicity
TPSA	Topological polar surface area
BBB	Blood-brain barrier
LD <sub>50</sub>	Lethal dose 50
MD	Molecular dynamics
OPLS	Optimized Parameters for Liquid Simulations All Atom
DLID	Drugs like density
CNS	Central nervous system
CYP	Cytochrome P
GI	Gastrointestinal tract
HIA	Human intestinal absorption
HBD	Hydrogen bond donor
HBA	Hydrogen bond acceptor
HERG	Human ether-a-go-related gene
5'NT	5'Nucleotidase
CSL	Composite site lability
WHO	World health organization
DG	Free energy change
ACHE	Acetylcholinesterase
PMF	Potential mean scores
RMSD	Root mean square density
RMSF	Root mean square fluctuations
SASA	Solvent accessible surface area
PGP	P-glycoprotein
IC <sub>50</sub>	Inhibitory concentration
OCHEM	Organic chemistry
DNN	Deep neural network
CDK2	Cyclin-dependent kinase

MTT3-	[4,5-dimethylthiazol-2-yl]-2,5 diphenyl tetrazolium bromide
R <sup>2</sup>	Coefficient of determination
Q <sup>2</sup>	goodness of prediction
RMSE	Root mean square error
MAE	Mean absolute error
CNN	Convolutional neural network
AI	Artificial intelligence
INCHI	International chemical identifier
RNN	Recurrent neural network
NLP	Natural language processing
LSTM	Long Short-Term Memory networks
VGGNET	Visual Geometry Group network
RELU	Rectified Linear Unit activation function
DNS	3,5-Dinitrosalicylic acid
GBSA	Generalized Born and surface area continuum solvation
PNPG	4-Nitrophenyl- $\beta$ -D- glucopyranoside
DMSO	Dimethyl Sulfoxide
HEPG2	Human liver cancer cell line
DPBS	Dulbecco's phosphate buffer saline
FBS	Fetal bovine serum
PBS	phosphate buffer saline
H2DCFDA	Dichlorodihydrofluorescein diacetate
GLN	Glutamine
ASP	Aspartic acid
TYR	Tyrosine
HIS	Histidine
LEU	Leucine
TRP	Tryptophan
ILE	Isoleucine
PHE	Phenylalanine
KDA	Kilo dalton
OC	Ovarian cancer
CEA	Carcino embryogenic antigen

PA1	Ovarian teratocarcinoma cell line
PC3	prostate cancer cell line
FITC	Fluorescein isothiocyanate
FL1	fluorescence parameter 1

## Preface

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The work in the thesis has been published, and most of the chapters are reworking of these published work. The entire Thesis work has been divided into 11 chapters: Chapter 1 deals with a general introduction about Gedunin( $C_{28}H_{34}O_7$ ) and its relation with cancer, Diabetes mellitus, and snake anti-venom. It also highlights the motivations and significance of the research work. Chapter 2 presents the literature survey covering the uses and applications of gedunin against snake venom, diabetes, liver, prostate, and ovarian cancer. Chapter 3 describes the ripen fruit materials, various techniques (polarity-based extraction using soxhlet, HPLC, HRLCMS, and Column chromatography ) involved in the Extraction, purification, and characterization of gedunin from *Azadirachta indica* and their results and discussion. Chapter 4 presents the methods of computational analysis including docking, simulation, and pharmacokinetics analysis of gedunin against snake venom enzymes and their results and discussion. Chapter 5 deals with *insilico* analysis of modified gedunin derivative  $C_{26}H_{31}N_2O_6F$  with their methods, results, and discussion. Chapter 6 deals with methods, results, and discussion of QSAR and Retrosynthesis of  $C_{26}H_{31}N_2O_6F$ . Chapter 7 deals with methods, results, and discussion of molecular property prediction of  $C_{26}H_{31}N_2O_6F$ (modified gedunin derivative) using LSTM, CNN, VGGNET, and k-means clustering. Chapter 8 deals with the method, results, and discussion of the antidiabetic potential of gedunin using alpha-glucosidase and alpha-amylase enzymes. Chapter 9 covers the materials, methods, results, and discussion of the anti-cancer activity of gedunin using liver cancer cell HepG2, PA1, and PC3 where ROS activity, Apoptosis activity, scratch assay/migration assay and colony

formation assay/proliferation assay has been shown. Chapter 10 deals with Transcriptomics studies of gedunin using the HeLa cell line with methods, results, and discussion. Chapter 11 presents a brief summary and conclusions of experimental findings.

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