APPLICATION OF MEMBRANE ACTIVE PEPTIDES FOR MANAGEMENT OF MICROBIAL KERATITIS

ADITI ARORA

KUSUMA SCHOOL OF BIOLOGICAL SCIENCES
INDIAN INSTITUTE OF TECHNOLOGY DELHI
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Application of Membrane Active Peptides for Management of Microbial Keratitis

by

Aditi Arora

Kusuma School of Biological Sciences

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CERTIFICATE

This is to certify that the thesis entitled **"Application of Membrane Active Peptides for Management of Microbial Keratitis"** being submitted by **Ms. Aditi Arora** to the **Kusuma School of Biological Sciences, Indian Institute of Technology Delhi** for the award of the degree of **"Doctor of Philosophy"** is a record of the bonafide research work carried out by her, prepared under my supervision, in conformity with the rules and regulations of the 'Indian Institute of Technology Delhi'. The research report and the results present in the thesis have not been submitted to any other University or Institute for the award of any other degree or diploma.

Date:

Place:

Dr. Archana Chugh

Professor
Kusuma School of Biological Sciences
Indian Institute of Technology Delhi
New Delhi 110016, India

Acknowledgments

"Scientific breakthroughs do not happen in isolation; progress depends on the collective contributions of many."

— David Baker, Nobel Prize in Chemistry, 2024

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Friendship has been a cornerstone of my PhD experience. I am especially grateful to **Dr. Pragati**, a true friend who has stood by me throughout these six years. Her unwavering encouragement and support helped me overcome numerous hurdles, and we celebrated every milestone together. Our cherished moments were made even more special with the company of **Nidhi and Maryam**, whose presence during hostel movie nights and dining outings added immense joy to my PhD life.

Living away from home in a hostel is never easy, but my close friends Pragati and Maryam made it feel like a second home. Through every high and low, they were there for me, making hostel life both bearable and enjoyable. From late-night conversations in our rooms to indulging in 'night wali' Maggi and parathas, their companionship was invaluable. I am also thankful to **Ram and Vikas** for their insightful discussions about both research and life. They were always there whenever I needed help, even on short notice. The bonds we formed not only provided emotional support during challenging times but also enriched my overall experience as a graduate student. These friendships have truly made my PhD journey memorable and fulfilling.

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I also take a moment to acknowledge and appreciate **myself** for the determination and patience I exhibited, particularly in the final stages of my PhD. Staying alone in the hostel and traveling to Sonipat for my last crucial experiments tested my endurance, but I persevered. **My father's** unwavering support during those arduous times was invaluable, and I am deeply grateful for his encouragement.

This acknowledgment would be incomplete without recognizing the unwavering love and support of **my family**. Their encouragement has been the driving force behind my achievements, and no words can fully express my gratitude. My Late mother's steadfast belief in my potential and my sister's unwavering support have been my pillars of strength throughout this journey.

Lastly, I express my gratitude to the **Almighty** for blessing me with incredible people who have been an integral part of this journey, guiding and supporting me at every step.

ABSTRACT

Ocular diseases represent a significant challenge to visual health and contribute substantially to the global burden of disease. The World Health Organization estimates that over 2.2 billion individuals worldwide suffer from vision impairment, with corneal opacities accounting for approximately 6 million cases and contributing to 1.5–2.0 million instances of unilateral blindness annually. Microbial keratitis (MK) emerges as a leading cause of corneal opacification, posing serious public health implications and adversely affecting quality of life.

MK can arise from fungal, bacterial, or viral etiologies, with fungal keratitis frequently associated with elevated rates of blindness. Notable fungal pathogens such as *Fusarium, Aspergillus, and Candida* species present considerable therapeutic challenges due to the limitations of existing antifungal treatments, which often suffer from issues related to low solubility, inadequate tissue penetration, and high toxicity. Similarly, bacterial keratitis, primarily attributed to *Staphylococcus spp. and Pseudomonas aeruginosa*, is further complicated by the rising prevalence of antibiotic resistance. Collectively, these challenges highlight the urgent need for innovative therapeutic strategies in ocular medicine.

Membrane-active peptides (MAPs) have emerged as promising candidates for addressing these limitations. MAPs are a diverse class of short, often cationic, peptides that interact with biological membranes, either disrupting them to exert antimicrobial effects or translocating through them to deliver therapeutic cargo. Two prominent subclasses of MAPs are antimicrobial peptides (AMPs) and cell-penetrating peptides (CPPs). AMPs are known for their broad-spectrum antimicrobial activity, typically by compromising membrane integrity, while CPPs are primarily recognized for their ability to traverse cell membranes and facilitate intracellular delivery of various molecules. Notably, the distinction between AMPs and CPPs is increasingly recognized as fluidic, with many peptides exhibiting both antimicrobial and cell-penetrating properties due to shared physicochemical traits such as amphipathicity, cationicity, and the ability to adapt helical structures.

This thesis explores the therapeutic potential of these multifunctional peptides, focusing on Corneal Targeting Sequence 1 (CorTS 1) and its novel derivatives for the treatment of keratitis caused by *Fusarium dimerum* and *Pseudomonas aeruginosa*.

In the initial phase of the study, CorTS 1 was assessed for its antifungal efficacy against *Fusarium* keratitis. The peptide demonstrated significant inhibition of *Fusarium dimerum* hyphal growth through modulation of membrane permeability *in vitro.* Additionally, it exhibited successful trans-epithelial penetration in rabbit eyes and effectively treated keratitis induced by *Fusarium* spp. in a murine model. With its corneal-targeting characteristics and

favourable solubility profile, CorTS 1 showed considerable promise as a therapeutic candidate for late-stage deep stromal fungal keratitis.

In the subsequent phase of the study, novel derivatives of CorTS 1 were developed to broaden its antimicrobial spectrum and enhance efficacy against Gram-negative pathogens. Among these derivatives, CorTS 1 Derived Antimicrobial Peptide 2 (CDAP 2), characterized by a highly α-helical structure, exhibited potent bactericidal activity against both Gram-positive and Gram-negative bacteria including *Staphylococcus aureus, S. epidermidis,* methicillin-resistant *S. aureus (MRSA), Pseudomonas aeruginosa*, multidrug resistant *P. aeruginosa* and carbapenem-resistant *Acinetobacter baumannii*, while demonstrating minimal cytotoxicity to human corneal epithelial cells. Mechanistic investigations revealed that CDAP 2 exerts its antimicrobial effects through the induction of oxidative stress and membrane permeabilization in *P. aeruginosa*. Beyond its antimicrobial properties, CDAP 2 displayed successful cellular internalization and cargo delivery in human corneal epithelial cells, indicating its dual role as both a therapeutic agent and a nanocarrier for ocular drug delivery.

These findings position CorTS 1 and its derivative CDAP 2 as novel peptide-based therapeutics with significant potential for effective management of fungal and bacterial keratitis.

सार

नेत्र संबंधी रोग दृश्य स्वास्थ्य के लिए एक महत्वपूर्ण चुनौती का प्रतिनिधित्व करते हैं और रोग के वैश्विक बोझ में महत्वपूर्ण योगदान देते हैं। विश्व स्वास्थ्य संगठन का अनुमान है कि दुनिया भर में 2.2 बिलियन से अधिक व्यक्ति दृष्टि हानि से पीड़ित हैं, जिसमें कॉर्नियल अपारदर्शिता लगभग 6 मिलियन मामलों के लिए जिम्मेदार है और सालाना एकतरफा अंधेपन के 1.5-2.0 मिलियन मामलों में योगदान करती है।

माइक्रोबियल केराटाइटिस (एमके) कॉर्नियल अपारदर्शीकरण का एक प्रमुख कारण बनकर उभरता है, जो गंभीर सार्वजनिक स्वास्थ्य प्रभाव पैदा करता है और जीवन की गुणवत्ता पर प्रतिकूल प्रभाव डालता है। एमके फंगल, बैक्टीरियल या वायरल एटियलजि से उत्पन्न हो सकता है, फंगल केराटाइटिस अक्सर अंधेपन की बढ़ी हुई दरों से जुड़ा होता फ्यूजेरियम, एस्परगिलस और कैंडिडा प्रजाति जैसे उल्लेखनीय फंगल रोगजनक मौजूदा एंटीफंगल उपचारों की सीमाओं के कारण काफी चिकित्सीय चुनौतियां पेश करते हैं, जो अक्सर कम घुलनशीलता, अपर्याप्त ऊतक प्रवेश और उच्च विषाक्तता से संबंधित मुद्दों से ग्रस्त होते हैं। इसी तरह, बैक्टीरियल केराटाइटिस, जो मुख्य रूप से स्टैफिलोकोकस एसपीपी और स्यूडोमोनस एरुगिनोसा के कारण होता है, एंटीबायोटिक प्रतिरोध के बढ़ते प्रचलन से और भी जटिल हो जाता है। सामूहिक रूप से, ये चुनौतियाँ नेत्र चिकित्सा में नवीन चिकित्सीय रणनीतियों की तत्काल आवश्यकता को उजागर करती हैं।

झिल्ली-सक्रिय पेप्टाइड्स (MAPs) इन सीमाओं को संबोधित करने के लिए आशाजनक उम्मीदवार के रूप में उभरे हैं। MAPs छोटे, अक्सर धनायनिक, पेप्टाइड्स का एक विविध वर्ग है जो जैविक झिल्लियों के साथ परस्पर क्रिया करते हैं, या तो उन्हें रोगाणुरोधी प्रभाव डालने के लिए बाधित करते हैं या चिकित्सीय कार्गो पहुंचाने के लिए उनके माध्यम से स्थानांतरित होते हैं। MAPs के दो प्रमुख उपवर्ग रोगाणुरोधी पेप्टाइड्स (AMPs) और सेल-पेनेट्रेटिंग पेप्टाइड्स (CPPs) हैं। AMPs अपनी व्यापक-स्पेक्ट्रम रोगाणुरोधी गतिविधि के लिए जाने जाते हैं, आमतौर पर झिल्ली अखंडता से समझौता करके, जबकि CPPs मुख्य रूप से कोशिका झिल्लियों को पार करने और विभिन्न अणुओं की इंट्रासेल्युलर डिलीवरी को सुविधाजनक बनाने की उनकी क्षमता के लिए पहचाने जाते हैं विशेष रूप से, एएमपी और सीपीपी के बीच अंतर तेजी से तरल के रूप में पहचाना जाता है, जिसमें कई पेप्टाइड्स साझा भौतिक-रासायनिक लक्षणों जैसे एम्फीपैथिसिटी, कैटायनिकिटी और हेलिकल संरचनाओं को अपनाने की क्षमता के कारण रोगाणुरोधी और कोशिका-भेदक दोनों गुणों का प्रदर्शन करते हैं।

यह थीसिस इन बहुक्रियाशील पेप्टाइड्स की चिकित्सीय क्षमता का पता लगाती है, जो फ्यूजेरियम डिमेरम और स्यूडोमोनस एरुगिनोसा के कारण होने वाले केराटाइटिस के उपचार के लिए कॉर्नियल टारगेटिंग सीक्वेंस 1 (CorTS 1) और इसके उपन्यास व्युत्पन्न पर ध्यान केंद्रित करती है।

अध्ययन के प्रारंभिक चरण में, कॉर्टीएस 1 का मूल्यांकन फ्यूजेरियम केराटाइटिस के खिलाफ इसकी एंटीफंगल प्रभावकारिता के लिए किया गया था। पेप्टाइड ने इन विट्रो में झिल्ली पारगम्यता के मॉड्यूलेशन के माध्यम से फ्यूजेरियम डिमेरम हाइफल वृद्धि के महत्वपूर्ण अवरोध का प्रदर्शन किया। इसके अतिरिक्त, इसने खरगोश की आँखों में सफल ट्रांस-एपिथेलियल प्रवेश का प्रदर्शन किया और एक म्यूरिन मॉडल में फ्यूजेरियम एसपीपी द्वारा प्रेरित केराटाइटिस का प्रभावी ढंग से इलाज किया। अपनी कॉर्नियल-लक्ष्यीकरण विशेषताओं और अनुकूल घुलनशीलता प्रोफ़ाइल के साथ, कॉर्टीएस 1 ने देर-चरण के गहरे स्ट्रोमल फंगल केराटाइटिस के लिए एक चिकित्सीय उम्मीदवार के रूप में काफी वादा दिखाया।

अध्ययन के बाद के चरण में, कॉर्टीएस 1 के नए व्युत्पन्न विकसित किए गए ताकि इसके रोगाणुरोधी स्पेक्ट्रम को व्यापक बनाया जा सके और ग्राम-नेगेटिव रोगजनकों के खिलाफ प्रभावकारिता को बढ़ाया जा सके। इन व्युत्पन्नों में, कॉर्टीएस 1 व्युत्पन्न रोगाणुरोधी पेप्टाइड 2 (सीडीएपी 2), जिसकी विशेषता अत्यधिक α-हेलिकल संरचना है, ने स्टैफिलोकोकस ऑरियस, एस. एपिडर्मिडिस, मेथिसिलिन-प्रतिरोधी एस. ऑरियस (एमआरएसए), स्यूडोमोनस एरुगिनोसा, बहुऔषधि प्रतिरोधी पी. एरुगिनोसा और कार्बापेनम-प्रतिरोधी एसिनेटोबैक्टर बाउमानी सहित ग्राम-पॉजिटिव और ग्राम-नेगेटिव दोनों बैक्टीरिया के खिलाफ शक्तिशाली जीवाणुनाशक गतिविधि का प्रदर्शन किया, जबकि मानव कॉर्नियल उपकला कोशिकाओं के लिए न्यूनतम साइटोटॉक्सिसिटी का प्रदर्शन किया। यांत्रिक जांच से पता चला कि सीडीएपी 2 ऑक्सीडेटिव तनाव और पी. एरुगिनोसा में झिल्ली पारगम्यता के प्रेरण के माध्यम से अपने रोगाणुरोधी प्रभावों को लागू करता है। अपने रोगाणुरोधी गुणों से परे, CDAP 2 ने मानव कॉर्नियल उपकला कोशिकाओं में सफल सेलुलर आंतरिककरण और कार्गो डिलीवरी प्रदर्शित की, जो नेत्र संबंधी दवा वितरण के लिए एक चिकित्सीय एजेंट और नैनोकैरियर दोनों के रूप में इसकी दोहरी भूमिका को दर्शाता है।

ये निष्कर्ष कॉर्टीएस 1 और इसके व्युत्पन्न सीडीएपी 2 को नए पेप्टाइड-आधारित चिकित्सा के रूप में स्थापित करते हैं, जिनमें फंगल और बैक्टीरियल केराटाइटिस के प्रभावी प्रबंधन की महत्वपूर्ण क्षमता है।

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ABBREVIATIONS AND SYMBOLS

%	Percent
®	Registered
™	Trade Mark
°C	Degree Celsius
α	Alpha
β	Beta
µ	Micro
µg	Microgram
µL	Microliter
4CzIPN	Tetra(9H-carbazol-9-yl)-1,4-dicyanobenzene
α-MSH	Alpha-Melanocyte-Stimulating Hormone
AAV	Adeno-Associated Viruses
AMD	Age-related Macular Degeneration
AMPs	Antimicrobial Peptides
AMR	Antimicrobial Resistance
ANOVA	Analysis of Variance
ARMOR	Antibiotic Resistance Monitoring in Ocular Microorganisms
ARVO	Association for Research in Vision and Ophthalmology
Ara27	Adenovirus early region 1A protein 27
ARPE 19	Adult Retinal Pigment Epithelium 19
ASO	Antisense Oligonucleotide
ATCC	American Type Culture Collection
ATP	Adenosine Triphosphate
AZM	Acetazolamide
BK	Bacterial Keratitis
BA	Bioavailability
BD	Becton Dickinson
BMAP-27/28	Bovine Myeloid Antimicrobial Peptide 27/28
BRB	Blood Retinal Barrier
BTZ-DMAC	Benzothiadiazole-dimethylacridone,
CAMP	Collection of Anti-Microbial Peptides

CBA	Cytokine Bead Assay
CBT	Cabazitaxel
CD	Circular Dichroism
CD 4/8	Cluster of Differentiation 4/8
CDR	Complementarity-Determining Region
CFU	Colony Forming Unit
CHAT	Choline O-Acetyltransferase peptide
CLW	Contact Lens Wear
CLSI	The Clinical & Laboratory Standards Institute
CLSM	Confocal Laser Scanning Microscopy
CorTS 1	Corneal Targeting Sequence 1
CDAPs	CorTS 1 Derived Antimicrobial Peptides
CO_2	Carbon dioxide
CPCSEA	Committee for the Purpose of Control and Supervision of Experiments on Animals
CPP	Cell Penetrating Peptide
CS	Chitosan
CO	Corneal Opacities
CN	Collagen Nanosheets
CV	Crytal Violet
CXL	Corneal Collagen Crosslinking
DALK	Deep Anterior Lamellar Keratoplasty
Da	Dalton
DBAASP	Database of Antimicrobial Activity and Structure of Peptides
DED	Dry Eye Diseases
DIC	Differential Interference Contrast
DM	Descemet’s Membrane
DME	Diabetic Macular Edema
DMEM	Dulbecco's Modified Eagle Medium
DMSO	Dimethyl Sulfoxide
DNA	Deoxyribonucleic acid
DPX	Dibutyl phthalate Polystyrene Xylene
DR	Diabetic retinopathy

EAU	Experimental automimmune uveitis
ECM	Extracellular matrix
EDTA	Ethylenediaminetetraacetic Acid
EGF	Epidermal Growth Factor
ex/em	Excitation/emission
FACS	Fluorescence-activated cell sorting
FCAP	Flow Cytometric Analysis Program
FBS	Fetal Bovine Serum
FDA	Food and Drug Administration
FGF	Fibroblast Growth Factor
FITC	Fluorescein Isothiocyanate
FK	Fungal Keratitis
FLT1	Fms-like Tyrosine Kinase 1,
GLP-2	Glucagon-like peptide-2
gm	Gram
H2DCFDA	2',7'-Dichlorodihydrofluorescein Diacetate
HA	Hyaluronic Acid
hBD-3	Human β-Defensin-3
HCE	Human Corneal Epithelial
HDPs	Host Defense Peptides
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
HPLC	High Performance Liquid Chromatography
HSPs	Heat Shock Proteins
IAEC	Institutional Animal Ethics Committee
IFN	Interferon
IL	Interleukin
IRF3	Interferon Regulatory Factor 3
I-TASSER	Iterative Threading ASSEmbly Refinement
JNK	c-Jun N-terminal Kinase
Kg	Kilogram
KAMPs	Keratin 6a-derived antimicrobial peptides
LK	Lamellar Keratoplasty

LASIK	Laser-Assisted In Situ Keratomileusis
LRR	Leucine Rich Repeat
LB	Luria Broth
^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate	Lutetium-177 DOTA-Tyr^{3}-Octreotate (DOTA (1,4,7,10-Tetraazacyclododecane-1,4,7,10-tetraacetic acid))
MAPs	Membrane Active Peptides
MAP	Model Amphipathic Peptide
MART 1	Melanoma Antigen 1
MDR	Multi Drug Resistant
MRSA	Methicillin-Resistant *Staphylococcus aureus*
MK	Microbial Keratitis
mg	Milligrams
MIC	Minimum Inhibitory Concentration
MBC	Minimum Bactericidal Concentration
MMP9	Matrix metalloproteinase-9
min	Minute
ml	Milliliter
mM	Millimolar
MRP	Multi-drug Resistance Protein
MHB	Mueller Hinton Broth
mtDNA	Mitochondrial DNA
MTT	3-(4,5-Dimethylthiazol-2-yl)-2,5-Diphenyltetrazolium Bromide
MTS	Membrane Translocating Sequence
MVP	Multivariant Penetratin
NAI-DPAC	9,9′-(2,2′-Dipyridylamino)-9H,9′H-3,3′-bicarbazole
NCT	National Clinical Trial number
NDNP-5.7	Newcastle Disease Virus-derived Neuropeptide 5.7
NF-κB	Nuclear Factor kappa-light-chain-enhancer of activated B cells
NFW	Nuclease Free Water
NHC	Normal Human Conjunctival Cells
NIB	National Institute of Biologicals
nm	Nanometer
NO	Nitric Oxide

NPs	Nanoparticles
NPDR	Non-proliferative diabetic retinopathy
NRFU	Normalized Relative Fluorescence Unit
OD	Optical Density
OH-CATH 30	Odorranine Heptad-Cathelicidin 30
Oxal	Oxaliplatin
PK	Penetrating keratoplasty
PACAP	Pituitary Adenylate Cyclase-Activating Polypeptide
PAS	Penetration Accelerating Sequences
PDA	Potato Dextrose Agar
PDB	Potato Dextrose Broth
PEG	Polyethylene Glycol
PBS	Phosphate Buffered Saline
PGIMER	Postgraduate Institute of Medical Education and Research
PI	Propidium Iodide
PLGA/PEI	Poly (lactic-co-glycolic acid) / Polyethylenimine
PMNs	Polymorphonuclear Neutrophils
PMOs	Phosphorodiamidate Morpholino Oligomers
PDA	Potato Dextrose Agar
POD	Peptide for Ocular Delivery
PRR	Pattern-Recognition Receptors
PDR	Proliferative diabetic retinopathy
rhNGF	recombinant Human Nerve Growth Factor
RIPA	Radioimmunoprecipitation Assay
RNA	Ribonucleic Acid
ROS	Reactive Oxygen Species
RO	Reverse Osmosis
rpm	Revolutions per minute
RPE	Retinal Pigment Epithelial cells
RPMI	Roswell Park Memorial Institute
RGC	Retinal Ganglion Cells
ROS	reactive oxygen species
RT	Room Temperature

SD	Standard Deviation
SEM	Scanning Electron Microscopy
SDS	Sodium dodecyl-sulfate
SLRPs	Small Leucine Rich Proteoglycan
SIM	Structured Illumination Microscopy
SMAP-29	Sheep Myeloid Antimicrobial Peptide 29
STAT 3	Signal Transducer and Activator of Transcription 3
Tβ4	Thymosin β4
TAT	Transactivator of Transcription
TADF	Thermally Activated Delayed Fluorescence
Tat_2	TAT Dimer
TFE	Trifluoroethanol
TLR	Toll-like Receptor
TNF	Tumor Necrosis Factor
ToAP2	Tityus obscurus Antimicrobial Peptide 2
TRP 1	Tyrosinase-Associated Protein 1
TUNEL	Terminal deoxynucleotidyl transferase dUTP nick end labeling
UM	Uveal Melanoma
USA	United States of America
UV	Ultraviolet
UVA	Ultraviolet-A
VEGF	Vascular Endothelial Growth Factor
VRE	Vancomycin-resistant Enterococci
VISA	Vancomycin-intermediate resistant *Staphylococcus aureus*
VIP	Vasoactive Intestinal Peptide
VGCV	Valganciclovir
WHO	World Health Organization