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ABSTRACT

Ocular diseases are a major global health concern, with visual impairment (VI) affecting over 2.2 billion individuals. Corneal opacities account for approximately 6 million cases of VI and 1.5–2 million instances of unilateral blindness each year, with microbial keratitis being a leading cause. Fungal keratitis, caused by pathogens such as *Fusarium*, *Aspergillus*, and *Candida* spp., remains difficult to treat due to poor drug penetration, low solubility, and toxicity of current antifungal agents. Similarly, bacterial keratitis, commonly caused due to *Staphylococcus* spp. and *Pseudomonas aeruginosa*, is further complicated by increasing antibiotic resistance, emphasizing the need for alternative therapies.

Membrane Active Peptides (MAPs) have emerged as promising candidates to address these challenges. MAPs are short, often cationic peptides that interact with biological membranes, either disrupting them for antimicrobial action or translocating through them for therapeutic delivery. Two prominent subclasses of MAPs are antimicrobial peptides (AMPs) and cell-penetrating peptides (CPPs). The distinction between AMPs and CPPs is increasingly recognized as fluid, 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 study phase, CorTS 1 demonstrated notable antifungal activity against *F. dimerum* hyphae by disrupting membrane permeability *in vitro*, transepithelial penetration in rabbit eyes, and effectively treated fungal keratitis in mice model, supporting its potential as targeted therapy for deep stromal infections.

In the next phase, CorTS 1 derivatives were developed for enhanced antimicrobial activity, particularly against Gram-negative pathogens. CDAP 2, a highly α-helical peptide, showed potent bactericidal effects against resistant strains like multidrug-resistant *P. aeruginosa*, carbapenem-resistant *A. baumannii and* MRSA, with minimal toxicity to corneal cells. Mechanistic studies showed that CDAP 2 disrupts *P. aeruginosa* via oxidative stress and membrane permeabilization, while also exhibiting efficient cellular internalization and cargo delivery, suggesting its dual function as both antimicrobial and ocular drug delivery vehicle.

These findings position CorTS 1 and CDAP 2 as promising peptide-based therapeutics for treating fungal and bacterial keratitis.