The Fall of Fol: In Silico Identification of Antimicrobial Peptides Targeting SIX Effectors of *Fusarium oxysporum* f. sp. *lycopersici*

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ABSTRACT

Introduction: *Fusarium oxysporum* f. sp. *lycopersici* (Fol) is a globally notorious fungal pathogen responsible for vascular wilting in *Lycopersicon esculentum* (tomato), one of the most highly cultivated crops worldwide. The culprit penetrates the plant via the roots, and extends upwards after hijacking the vascular tissue, causing widespread clogging of vessels and inducing water stress. In Pakistan, an already economically-grieving country, a loss of up to 50-80% crop yield caused by Fol is a staggering obstacle. While farmers are generally recommended to use certified resistant see, for example, Salaar, Sandal, and Sahil, the resistance genes inferred in these seeds can easily be overcome by Fol upon variation or mutation in fungal pathogenic features. Rapid evolution of the fungus is also the main reason why fungicides are not very effective against preventing Fol infections in tomato plants, although the use of fungicides is the secondary guideline provided to farmers countrywide. Moreover, crops that do succumb to infection are fated to meet a tragic end, where they are burned as a sanitation measure to prevent further spread of the pathogen.

Objectives: In our study, we explore the efficacy of previously recorded antimicrobial peptides (AMPs) in binding to and blocking four essential effector proteins involved in the pathogenesis of *F. oxysporum* f. sp. *lycopersici*- induced vascular wilt in tomato. These proteins are called SIX (Secreted in Xylem) effectors, which function by suppressing plant immunity, facilitating colonization, acting as virulence factors, and triggering or evading host resistance. This study is purely computational, and follows a classical pipeline for in vitro identification of antimicrobial peptides.

Methodology: Amino acid sequences of target proteins (SIX1, SIX4, SIX6, and SIX8) were retrieved from RCSB Protein Data Bank (PDB). Antimicrobial peptides were selected from Database of Antimicrobial Activity and Structure of Peptides (DBAASP) and shortlisted on the basis of length, molecular weight, isoelectric point, aromaticity, hydrophobicity, and other physicochemical parameters. Suitable candidates were modeled using PEP FOLD-3 and docked against our proteins of interest via ClusPro 2.0. Docked models with highest binding affinities were highlighted as our study results.

Key Findings: Preliminary docking analyses identified several antimicrobial peptides with favorable physicochemical properties and consistently strong predicted interactions with SIX-family proteins. Among the shortlisted AMPs, a subset demonstrated stable binding orientations across clusters and high-scoring poses in ClusPro 2.0. A notable example is Python Cathelicidin CATHPb1. These peptides exhibited structural complementarity to key functional regions of SIX1, SIX4, SIX6, and SIX8, suggesting their potential as candidate inhibitors. The study highlights promising AMP–SIX protein interactions that warrant further validation.

Conclusion: Our computational pipeline revealed a subset of AMPs that consistently exhibited favorable docking behavior with SIX-family proteins, supporting their potential role as inhibitors. While further verification is required, these preliminary insights demonstrate the feasibility of AMP-based targeting of SIX proteins and open new avenues for therapeutic exploration.

Keywords: *Fusarium oxysporum*, Antimicrobial Peptides, Molecular Docking, SIX Effectors, Tomato Wilt.

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