CHAPTER 1: INTRODUCTION

Human oral cavity represents one of the diverse microbial flora that consists of different species of bacteria from both classes viz., Gram-positive and Gram-negative bacteria [1]. *Streptococcus mutans* is one of the primary pathogen involved in the development of dental caries. *S. mutans* mediated dental caries is a multifactorial disease that is being ignored due to its non-life threatening nature [2, 3]. An unknown fact exists as the inflammation process takes its pace slowly and gradually, it would act as a ‘silent killer’ for the patients suffering from dental caries. Therefore, the untreated carious dentine can lead to the development of systemic diseases such as infective endocarditis [2–4]. Furthermore, the emergence of multidrug resistant pathogens has led the researchers worldwide to search for new strategies to overcome the pathogenesis caused by resistant pathogens. Unaware use of antibiotics at high doses specifically in the pathogenic infections has led to the development of multidrug resistant (MDR) microorganisms. Moreover, this will lead to an increased cost in therapeutics with various side effects related to high dose intake of antibiotics [5]. Therefore, this provokes a strong need of research in a better understanding of various regulatory pathways of bacteria for developing alternative drugs that might be a more specific and effective alternate therapy for a particular class of bacteria. One such strategy is to inhibit the quorum sensing mechanism (cell to cell communication) in the bacteria so that the expression of virulence factors can be quenched [5]. In accordance to this phenomenon, the *S. mutans* also harbors a Competing Stimulating Peptide (CSP)-mediated quorum-sensing, ComCDE (Two-component regulatory system) to regulate several virulence-associated traits that includes the formation of the oral biofilm (dental plaque), genetic competence and acidogenicity. The QS-mediated response of *S. mutans* adherence on tooth surface (dental plaque) imparts antibiotic resistance to the
bacterium and further progresses to lead a chronic state, known as periodontitis. Quite a few efforts have been taken to modulate QS to reduce the production of biofilm and associated virulence factors [6–9]. Biofilm cells have been shown to be several folds more tolerant to antibiotics than planktonic cells, and this makes it hard to treat S. mutans with modern medicine [10]. Thus, the importance of developing an anti-quorum compounds as alternate therapy for Multidrug resistant bacteria, has positive future perspectives with respect to medicine. Additionally, this particular approach ensures its success in the fact that, anti-quorum compounds may control virulence traits of pathogenic microbes without significant effects on viability of bacterial cells [11]. The key involvement of ComA (an ABC transporter) in maturation and secretion of CSP made it as a favourable target for QS inhibition of S. mutans. Hence, the present study aims to screen selective inhibitors against ComA leading to downregulation of various virulence genes involved in biofilm formation. In this context, the following objectives were framed for present thesis work:

**Specific aim #1:** Target selection and computational assisted drug designing of plausible target (PEP domain) to attenuate the biofilm formation in S. mutans.

**Specific aim #2:** Synthesize the ComA based biofilm inhibitor (ComAI) and its derivatives.

**Specific aim #3:** In vitro efficacy of drug ComAI and its derivatives to attenuate virulence factors and Target Specific mechanism elucidation of ComA.

**Specific aim #4:** Pre-clinical studies - In vivo rat model to elucidate the preventive effect of ComAI.