INSILICO DESIGN OF NOVEL MICROBICIDES
IN CONTROLLING HIV AND SEXUALLY TRANSMITTED DISEASES

INTRODUCTION

Heterosexual transmission particularly affecting women is driving the HIV epidemic today in many resource-poor countries, where most of the infections are occurring. The current statistical report denotes more than 30 million people living with HIV-1 infection after 28 years when AIDS was first recognized. The HIV/AIDS poses to be a destructive pandemic to humans worldwide. It has been estimated that there are 60 million individuals infected with HIV-1 and 25 million individuals dead [1]. In India, about 2.5 million people are living with HIV and it is prevalent in Southern states like Andhra Pradesh, Maharashtra, Tamil Nadu and Karnataka accounting for 63% of the infected population [2].

HIV is found in varying concentrations or amounts in blood, semen, vaginal fluid, breast milk, saliva, urine and tears. The rate of transmission by saliva, urine and tears are negligible The transmission of HIV occurs from infected person to a healthy person through three main means where heterosexual transmission accounts the highest rate (65% to 80%), secondly mother to child transmission (25%) and thirdly the transmission through HIV infected blood and blood products (0.15% to 7%) [4]. Behavioral interventions and structural interventions and Antiretroviral therapy are considered to be the major methods implemented for the prevention and accounts for 80% control of HIV transmission [5]. Vaccine development is also found to be unsuccessful till date due to challenges like high genetic
variability of the virus, improper immune correlation, animal model limitations and problems associated with clinical trials [6].

**NOVEL FEATURES OF RESEARCH PROPOSAL**

The potential prevention method for HIV/AIDS today lays in a method the use of topical microbicides (Carraguard, Polynaphthalene, sulphonate and Cellulose sulfate). So, microbicides play an important role in controlling HIV/AIDS.

Microbicides are defined as substances that can be applied to vagina or rectum during sexual activity to prevent the spread of HIV and other sexually-transmitted diseases and/or to act as a contraceptive. More specifically vaginal microbicides are chemical agents used topically by women within the vagina in order to prevent infection by HIV and potentially by other enveloped viruses and sexually transmitted pathogens. They can be formulated as creams, gels, films, or suppositories, that would substantially reduce the transmission of HIV—and possibly other sexually transmitted infections (STIs)—when applied topically. Topical microbicides are pharmaceutical products, which function through a variety of mechanisms disrupting the entry or the life cycle of the HIV virus. An added advantage of microbicides is that they have properties which make them effective against other sexually transmitted infections too. These are initially developed to protect uninfected women but infected women would also use them to reduce transmission of HIV and other sexually transmitted infections to male partners.
Microbicides are self-administered prophylactic agents that impede transmission of HIV. These products can be administered either by parenteral route or enteral route [7]. The microbicidal compounds having poor oral bioavailability are being developed as topical microbicides [8]. The number of microbicide candidates in preclinical development is approximately 50 where the number of compounds in advanced development is 14 [9]. The microbicides are based on antiretroviral (ARV) drugs that specifically target HIV. These include nucleotide reverse transcriptase inhibitors (NtRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs) and Entry inhibitors. The present study focuses on entry inhibitors because they target the viral life cycle at an initial stage of infection itself. Literature review revealed that several entry inhibitors (Eg: SCH-351125, AMD 3100, AMD 070, TAK -779, GW 873140, Aplaviroc, RANTES analogs) are unsuccessful in clinical trials due to side effects [10]. Hence there is an urgent need of newer drug compounds to fight against HIV. The insilico approach helps us to design newer drugs in an easy manner based upon the properties of the compounds selected for study. It helps us to search for new CCR5, CXCR4 antagonists as well as dual tropic antagonists with enhanced activity against CCR5 and CXCR4 receptors rather than targeting the rapidly mutating viral epitopes.

In vitro studies have been carried out to recognize many molecules as potential vaginal microbicides so far. The present work proposes to investigate insilico design of novel vaginal microbicides in controlling HIV and other Sexually Transmitted Diseases.
ENTRY AND FUSION MECHANISM

Entry inhibitors act very early in the HIV life cycle long before integration occurs. HIV infects a cell by binding to CD4 receptor of the target cell membrane. In addition to binding to CD4, HIV must also bind with a co-receptor ie., chemokine receptors CCR5 and CXCR4 [11] expressed on the cell membrane to enter a T cell. Blockade of these receptors has been shown to be effective in arresting the life cycle of HIV [12]. Based upon the literature survey, most sexual transmission of HIV is believed to occur by CCR5-tropic strains [11], it is CCR5-blockers that have greater potential as microbicides, and a number of these compounds are under investigation for this purpose [13]. The phenotypic switch from R5 to X4 viruses *in vivo* typically occurs only after several years of infection [14] and dual tropic antagonists are applied against R5/X4 tropic strains (Fig1).

Based on the literature review, it can be concluded that both *in vitro* and *in vivo* studies are reported related to microbicidal activity [15, 16, 17] and protein ligand interaction [18]. The present work aimed to explore newer microbicides by *insilico* approaches with the following objectives.

![Fig1: Entry and fusion mechanism of HIV](image-url)
OBJECTIVES:

1. *Insilico* study on the proteins of viruses which are responsible for sexually transmitted diseases.

2. To explore the structures of various microbicidal compounds and to study the structure-function relationships and mechanism of action of microbicides.

3. Comparative studies of the protein-ligand interaction among the microbicide and the receptor site.


5. Prediction and design of novel compounds with less side effects which are closely similar to the microbicides.

BRIEF RESEARCH PLAN:

- Even though research work is going in microbicides at clinical level, bioinformatics can play crucial role in exploring these microbicides.

- Various proteins sequence and structure databases available, which can provide detailed information about proteins involved in replication of virus involved in diseases. The information about these proteins will be very useful in studying the mechanism of action of microbicides.

- The detailed exploration about the structural details of microbicides can be extracted from small molecule databases.
• The compounds, which are closely similar to microbicides, can be extracted from various databases, specialized packages etc.

• The interaction between microbicides and the targeted protein can be analyzed using docking softwares.

• Derivation of the best fitted protein-ligand complex with more binding affinity and least energy can be done using force field optimization.

EXPECTED OUTCOME:

• Detailed information about the role of proteins involved in replication of virus causing HIV infection will be provided.

• The structure and function relationship and the mechanism of action of microbicides can be reported.

• The protein-ligand interactions and their molecular mechanics force field calculations will be reported.

• Prediction and design of novel microbicides with fewer side effects for HIV/AIDS.
REFERENCES


