PREFACE

Mosquitoes are considered one of the most dangerous creatures on the planet because of their ability to spread deadly diseases. They use the blood for their own nourishment, as a source of protein for their eggs. They are public enemies taken first place for the fight against global infectious disease because they transmit extremely harmful pathogens to human, belonging mosquito born diseases such as Dengue, Malaria, Yellow Fever, Westnile Fever, Encephalitis and Filariasis. Mosquito-borne diseases cause millions of deaths worldwide every year with a disproportionate effect on children and also elders in developing countries. Mosquitoes are estimated to transmit disease to more than 700 million people annually in Africa, South America, Central America, Mexico, Russia and much of Asia. In India there is more than 2, 00,000 deaths are reported every year.

Viruses are so small, a microscope is necessary to visualize them and they have a very simple structure. Viruses are the infectious agents with fairly simple a cellular organization. Viruses possess only one type of nucleic acid either DNA or RNA and only improve their generation in living cells. There are many families of viruses in those flavi viruses are one playing vital role in cause of deadly diseases. Several members of the flavivirus genus, such as the Dengue Virus (DENV), Yellow Fever Virus (YFV), West Nile Virus (WNV), and Japanese Encephalitis virus (JEV) are highly pathogenic to humans and constitute major international health problems such as Dengue Fever, West Nile Fever, and Yellow Fever etc.

The therapeutic drugs (Ribavirin, 6- azauridine, Mycophenolic acid, Triaryl pyrazoline and Castanospermine) for Dengue virus, West Nile Virus and Yellow Fever virus are common for prevention. Due to same family three viruses shown response to same drugs but their EC 50 values are different. Because of these differences we are trying to understand these viruses' genome and progress to drug binding affinity with the non-human proteins and non-structural proteins of three viruses using Bioinformatics with Insilco applications.

Bioinformatics is a conceptualising biology in terms of molecules and applying "informatics techniques" to understand and organise the information associated with these molecules on a large scale.

Comparative genomics deals with the processes of evolution via the alignment and analysis of genes and genomes of living or extinct organisms related by varying degrees of evolutionary divergence from a common ancestor. Comparisons are usually made pairwise with reference to a third genome 'outgroup' or by examination of pairs of paired sequences and summarized in phylogenetic trees. Comparative genome analysis of related species based on motif conservation provides a powerful and general approach for identifying functional elements without previous biological knowledge, and the results show comparative genome analysis of a handful of related species has substantial power to identify genes, define gene structure, highlight rapid and slow evolutionary change, recognize regulatory elements and reveal combinatorial control of gene regulation.

Subtractive genomics approach is one of the recently adopted methodology in which the subtraction of sequence between the host and parasite proteome provides information for a set of proteins that are likely to be essential to the parasite but absent in the host. Computational subtractive genomics approaches , based on the strategy that an essential survival protein non-homologous to any human host protein is a candidate drug target for a given parasite , have been successfully used to identify putative drug targets.

Molecular modelling has become a valuable and essential tool to medicinal chemists in the drug design process. Molecular modelling describes the generation, manipulation or representation of three-dimensional structures of molecules and associated physico-chemical properties. It involves a range of computerized techniques based on theoretical chemistry methods and experimental data to predict molecular and biological properties

Computational methodologies have become a crucial component of many drug discovery programmes, from hit identification to lead optimization and beyond some approaches such as ligand or structure based virtual screening techniques are widely used in many discovery efforts. One key methodology - docking of small molecules to protein binding sites was pioneered during the early 1980 and remains a highly active area of research. When only the structure of a target and its active or binding site is available, docking is primarily used as a hit identification tool. However, similar calculations are often also used later on during lead optimization, when modifications to known active structures can quickly be tested in computer models before compound synthesis.

The present study covers the all the aspect what discussed above and included within five consecutive chapters

1. The chapter 1 deals the case study about Dengue Fever, West Nile Fever and Yellow Fever spread in Tamilnadu.

2. Chapter 2 deals the comparative genome analysis between Dengue Virus, West Nile Virus and Yellow Fever Virus and substractive genome analysis for identification of non-human proteins in three viruses. The molecular modelling and molecular docking of non-human proteins with selected therapeutic drugs

3. Chapter 3 contributes for molecular modelling of non-structural (NS) proteins of three viruses and validation with Ramachandran plot.

4. Chapter 4 deals the molecular docking studies with the selected therapeutic drugs and molecular visualization.

These chapters are preceded by a general introduction, material and methods and succeeded by summery and conclusion followed by bibliography.

Though the present work completely based on bioinformatics approach, this work may contribute much to understand the genome and drug response of the Dengue, West Nile and Yellow Fever Viruses. The keen understanding of genome of virus and their relation with the other viruses explains the homology with each other. The molecular modelling builds the three dimensional structures based on its sequence with the help of homologous crystallographic structures available in protein data bases. Docking studies reveals that the how drugs or lead molecule are interact with the specific proteins effectively, at the same time not effective to the others.

ABBREVIATIONS

%	-	Percent
μ moles (μM)	-	micro moles
2 D	-	Two-Dimensional
3D	-	Three -Dimensional
BLAST	-	Basic Local Alignment Search Tool
BLAST P	-	Basic Local Alignment Search Tool Protein
BLOSUM6	-	Blocks Substitution Matrix
CC	-	Conservation Criteria
CCS	-	category correlation score
CDC	-	Centers for Disease Control and Prevention
CHARMM-22	-	Chemistry at Harvard Macromolecular Mechanics
Cx	-	*Culex*
DEET	-	Diethyltoluamide/ *N,N*-Diethyl-*meta*-toluamide
DENV	-	Dengue Virus
DF	-	Dengue Fever
DHF	-	Dengue Hemorrhagic Fever
DIC	-	Disseminated Intravascular Coagulation
DNA	-	Deoxy Ribo Nucleic Acid
DOPE	-	Discrete Optimized Protein Energy
DSS	-	Dengue Shock Syndrome
EEE	-	Eastern Equine Encephalitis
JEV	-	Japanese Encephalitis Virus
m RNA	-	Messenger RNA
MCS	-	Motif Conservation Score
MM	-	Molecular Modeling
MVE	-	Murray Valley Encephalitis
NCBI	-	National Centre for Biotechnology Information
NIH	-	National Institute of Health

NS P	-	Non-Structural Protein
PAM	-	Point accepted mutation
PDB	-	Protein Data Bank
prM	-	pre-membrane
RNA	-	Ribo Nucleic Acid
RVF	-	Rift Valley Fever
SAVES	-	Structural Analysis and Verification Server
SLE	-	Saint Louis Encephalitis
Spdb	-	Swiss Protein Data Bank
TEV	-	Tick-borne Encephalitis Viruses
ThyA	-	thymidylate synthase
TPZ	-	Triaryl pyrazoline
VCRC	-	Vector Control Research Centre
VHF	-	Viral Hemorrhagic Fever
WNF	-	West Nile Fever
WNV	-	West Nile Virus
YF	-	Yellow Fever
YFV	-	Yellow Fever Virus