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REVIEW ARTICLE

Review on Computational Approaches for Identification of New Targets and Compounds for Fighting Against Filariasis

Manisha Mishra[1] and Prachi Srivastava[2,*]

[1]*Dr. A.P.J. Abdul Kalam Technical University Lucknow, U.P. India*
[2]*AMITY Institute of Biotechnology, AMITY University Uttar Pradesh Campus, Lucknow, India*

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Abstract:

Background:

Lymphatic filariasis is a tropical disease and currently more than 1.4 billion people in 73 countries are at risk but still it is neglected in higher researches. Lymphatic filariasis is wide spread throughout the tropical and subtropical areas of Asia, Africa, the Western Pacific and some parts of the Americas. Though it is a big issue for developing countries but still no proper prophylactic or therapeutic measures are taken out as to protect against filarial infection or to modulate disease.

Objective:

Non availability of proper prevention or cure as well are the major issues for which new scientific computational research approaches towards the management and betterment of this disease is required. Identification of novel compounds or drug targets through advance computational approaches can give new and better alternatives against this social problem or can open a new gate way towards advance approaches of drug designing.

Results:

Current review signifies the contribution of scientist working in different areas are globally thinking about the resolution of this problem and among different approaches these computational based researches will no doubt are a milestone against the fight with filaria. Genomic, proteomic, system biology based concepts, computational drug designing, virtual screening, homology modelling *etc*. are the different advances which altogether will win these problem.

Conclusion:

Compilation of this *in silico* contributions are well establishing their importance in finding out new targets and compounds that could lead a milestone against this social stigma which create humiliation not only for patients or relatives but also burden of society too.

Keywords: Lymphatic filariasis, Computational approaches, Drug targets, Genomic, Proteomic, Microfilaria, Docking.

1. INTRODUCTION

Lymphatic filariasis or elephantiasis is a tropical disease and currently more than 1.4 billion people in 73 countries are at risk but still it is neglected in higher researches [1], it is widespread throughout the tropical and subtropical areas of Asia, Africa, the Western Pacific and some parts of the Americas [2, 3]. In lymphatic filariasis, filarial nematodes *Wuchereria bancrofti* (WB) and *brugia malayi* (BM) resides in the lymphatic system where the thread-like adult worms survive in the bodies of human beings and animals. Lymphatic filariasis afflicts more than 25 million men with genital disease and more than 15 million people with lymphedema in Southeast Asia and African regions [4]. Prevalence and

* Address correspondence to this author at the AMITY Institute of Biotechnology, AMITY University Uttar Pradesh, Malhour (near railway station), Gomti Nagar Extn., Lucknow, U.P., India; Tel: +91-9453141916; E-mail: psrivastava@amity.edu

intensity of infection is very much associated with poverty and illiteracy hence United Nations Millennium Development Goals can contribute to achieve the elimination of it. Infection is usually acquired in childhood, but painful and intense mutilating symptoms are visible appearances of the disease appears later in life. Acute episodes of the disease can cause temporary disability whereas chronic lymphatic filariasis leads to permanent disability [5]. Disease is caused by thin worms transmitted to humans by the bites of mosquitoes in tropical and subtropical regions. Human Lymphatics is the best site for adult filarial parasites. Progression of disease is determined primarily by living adult worms. Inflammatory responses caused by the death of adult worms which later on leads to host reaction and acute filarial lymphangitis. Presence of worms in the scrotal area precipitate the development of hydrocele, chyluria and lymphscrotum. Lymphatic dysfunction caused by dilatation of the lymphatic vessels makes the patient more horizontal to repeated secondary bacterial infection, which precipitates lymphedema and elephantiasis [6].

Filarial problem is not a small issue in human beings as persistent infection of this disease results in very debilitating diseases such as lymphatic blockage resulting in elephantiasis, ocular pathology leading to river blindness and severe dermatitis manifesting as sowed [7]. Microfilariae also play very important role in the pathogenesis of tropical pulmonary eosinophilia [8].

Though it is a big issue for developing countries but still no proper prophylactic or therapeutic measures are taken out as still there is no proper vaccine to protect against filarial infection or to the modulate disease [7]. As per the recent survey of WHO, it has been observed that lymphatic filariasis ranks third after malaria and tuberculosis in terms of disability related to infectious disease. This disease is widespread in both developing and developed countries including India. It causes distress in around 150 million people and over 80 countries with more than 1.5 billion remaining at a risk of infection [8]. These issues suggest that there is a great and necessary need to develop new and advance approaches to overcome this problem.

2. CURRENT ASPECTS OF TREATMENT

Administration of Diethylcarbamazine (DEC), Ivermectin and Albendazole are common against the filarial disorder. As per the recommendation of a Global Program to Eliminate Lymphatic Filariasis (GPELF) in endemic areas, annual mass drug administration of DEC combined with Albendazole [9]. In different floral endemic zones including India DEC-medicated salt has been effectively used. The drug Ivermectin kills only the microfilariae but not the adult worm the adult worm is responsible for the pathology of lymphedema and hydrocele [10]. Instead of the above discussed problematic issues in relation to filariasis, advance researches in this area are still in demand. There is neither any proper treatment nor good prophylactic measures against this problem as researches in this area is deserted and not well funded [11]. Only Ivermectin, Albendazole and Diethylcarbamazine like symptomatic drug treatments are available which target the immature stages but not the long-lived adult worms and also showing adverse side effects [12].

Non-availability of proper prevention or cure as well are the major issues for which new scientific computational research approaches towards the management and betterment of this disease is required. Scientific attention is needed to search out some novel compounds or target those that are able to fight these problems and give better results against filariasis. Identification of novel compounds or drug targets through advance computational approaches can give new and better alternatives against this social problem or can open a new gate way towards advance approaches of drug designing (Table **1**).

Computational biology is helping a lot in testifying the capabilities of better alternatives based on *in silico* methodologies. Rational drug design which is based on target selection and identification using bioinformatics is one of the most important concepts for identification or designing of novel and safe molecule as drug or ligand [13].

3. BIOINFORMATICS APPROACHES AGAINST FILARIAL DRUG DESIGNING

Bioinformatics is an amalgamation of different disciplines. Mainly, it includes combination of information technology and biological sciences used for the different applications like database developments, drug designing, data interpretation, protein modelling, gene identifications *etc*. Bioinformatics is the field based on the applications of computer science in biology which has emerged as a major element in contemporary biology and biomedical research. There is a standard shift in biological research regarding the importance and uses of computers, software tools and computational models [14]. No doubt computational biology is an inter phase between modern biology and information technology and it comprises designing, developments and application of computational algorithms and tools which helps in the understanding of different biological processes and also for betterment of different important sectors like health care and agriculture [15].

Current rational drug designing is based on bioinformatics which has many benefits including reduction in the number of trials in the screening of drug compounds and in identifying potential drug targets for a particular disease using high power computing workstations and software like Insight. It is one of the most conventional, flourishing and dependable processes to overcome these issues related to drug designing [16]. Bioinformatics has a reflective impact on medical sciences. The biological databases are serving physicians to make a diagnosis for disease and develop strategies for its therapy [17].

Bioinformatics has expanded its wing in different basic to advance research applications among which drug designing and virtual screening is the most promising. Bioinformatics tools for virtual screening of molecules, active ingredients of natural herbal products, semi synthetic and synthetic compounds are used to predict if there are possible therapeutic interventions in different kind of disorders including the parasitic ones too. Parasitic infections are worldwide problem and different scientific approaches are in the process of fighting against the issues. These approaches can be classified either in the prophylective or preventive aspects.

Among the different parasitic disorders filariasis is one of the major significant infections which are still on the verge of high negligence. Though scientific communities are putting their valuable efforts for the management of this disease hence many research options including different computational approaches like genomic and proteomic approaches are available to work with the management and cure of the disease. There is an attempt to compile these approaches which are contributing in this issue.

3.1. Genomic Approaches

Genomics is rapidly being used to understand the structure and function of all the genes and other biological features in the entire DNA sequence of the organism along with comparison of genome. It is a discipline that applies DNA sequencing methods, recombinant DNA and bioinformatics to sequence, assemble and analyse the structure and function of genomes (that is a complete set of DNA within a single cell of an organism) [18, 19]. A great revolution has been elicited with the advancement in genomic studies to uncover the complexity of human genome and make easy to understand about the difficulty of biological system [20]. This genomics field includes efforts to standardize the entire DNA sequence of organisms and fine-scale genetic mapping along with genomic structure based studies, which includes genome statistics, repeats, genome rearrangement at both DNA and gene level, synteny and breakpoints; coding regions including gene content, protein content, orthologs, and paralogs; and non coding regions including the prediction of regulatory elements [21]. Comparative genomic studies are based on exploring similarity and differences at gene to genome levels. The main focus of genomic studies is to explore genetic pathway and functional information analysis to elucidate its effect on place in and response to the entire genomes networks to unreveal the effects on system biology [22].

Genome analysis of filarial nematodes as *Wuchereria bancrofti* have 5,103 Expressed Sequence Tag sequences (EST), 19 collected information about gene loci, 22 functional genomics studies, 34 sequence sets from phylogenetic and population studies and *brugia malayi* have 77,882 Expressed Sequence Tag Sequences (EST), 13,331collected information about gene loci, 13 sequence sets from phylogenetic and population studies have been performed which signifies the importance of computational approaches and their relevance in this area [23].

Some genomics based approaches *viz*; SNP based, Microarray based, Sequencing based, NGS related studies have shown the importance of such approaches towards this disease. The importances of FLT4 and FOXC2 genes were reported in lymphatic development or remodelling in lymphatic filariasis. Study of FLT4 signalling and transcription factors such as FOXC2 play an important role in this type of lymph angiogenesis process induced by filarial parasite revolutionized the importance of these genes in development of different problems caused by parasites. Identification of G357A SNP as new variant of FOXC2 gene was identified in Lymphatic filariasis which may show effect on codon usage frequency during translational process [24].

One of the important SNP associated study carried out in different parasites established the resistance development of different veterinary helminthias is against Albendazole and Ivermectin. Resistance to Albendazole in veterinary nematodes is known to be developed by either of the two single amino acid substitutions from phenylalanine to tyrosine in parasite β-tubulin at position 167 or 200. Some assays have developed those are capable of detecting these single nucleotide polymorphisms (SNPs) in *Wuchereria bancrofti* and have applied them to microfilaria obtained from patients in Ghana and Burkina Faso [25].

In the study of Plasma Vascular Endothelial Growth Factor-A (VEGF-A) and VEGF-A gene polymorphism are associated with hydrocele development in lymphatic filariasis. Three VEGF-A promoter polymorphisms were examined. The C/C genotype at -460 was significantly higher in hydrocele patients ([P 0.0007], or 3.8 [95% CI 1.9-8.2]) than in non hydrocele patients [26].

In the same context, another study as association between mannose-binding lectin polymorphisms and *Wuchereria bancrofti* infection in two communities in north-eastern Tanzania have been performed [27].

Study of human lymphatic filariasis in relation to genetic polymorphism of endothelin-1 and tumour necrosis factor receptor II correlates the progression of disease along with the significance of polymorphism in these parasites [28].

Gender-associated genes in filarial nematodes were observed and demonstrated the importance for reproduction and further potential intervention targets. First genome-wide analysis of Gender Associated (GA) gene expression study in a filarial nematode focused its importance in reproductive processes of these parasites [29].

A global gene expression study as lymphangiogenesis and lymphatic remodelling induced by Filarial Parasites implicates the severity of pathogenesis [30].

Another microarray-based analysis of differential gene expression between infective and noninfective larvae of *Strongyloides stercoralis* revealed the untold story of gene expression information [31].

A review genetic variation in immune function and susceptibility to human filariasis precise recent advances in our understanding of genetic contributions to human lymphatic filariasis and addresses the immediate questions facing the field [32].

A case-control study in an east Malaysian population 320 lymphatic filariasis infected individuals and 150 healthy controls with the occurrence of this disease established a potential association of 5 CTLA4 gene promoter single nucleotide polymorphisms with respect to the occurrence of this disorder [33].

These findings are creating a new paradigm for the different kind of association for fighting against this dreadful disorder. These advanced approaches shifted the prototype patterns of scientific contribution and revolutionize the research to come up with the solutions which is still waiting.

3.2. Proteomic Approaches

Functional biological molecule that is made up of one or more polypeptides which are folded into a specific structure is called protein. Proteins can form extremely useful and important chemicals, whose functions largely depend on the detailed chemical properties of their surfaces [34]. Repertoire of twenty amino acids makes different combinations of thousands of proteins which are functionally independent and make our proteome size large [35, 36]. Proteins are dynamic in nature, work at the single-molecule level, and facilitate several biological functions as signal receptors and transmitters, transportation channels, structural elements and enzymes. The structure of a protein is closely associated with its function [37].

Proteomic initiatives are in the terms of decoding the genome and to solve the complexity and functionality of protein and their structure. Initiatives taken in the proteomic studies are a relevant example to show the importance of bioinformatics for the analysis of structure to function relationship of protein analysis. Proteomics approach provides a great stage, which typically assesses proteins in a balanced fashion and provides the means to study the proteomic profile of a complex biological system on a large scale [38].

In continuation to Proteomic based study of *Wuchereria bancrofti* and *Brugia malayi* is showing 20,096 protein sequences in WB and 32,999 protein sequences in BM, no sequence similarity-based protein clusters in WB and 12 sequence similarity-based protein clusters in BM, 2experimentally-determined bio molecular structures (Glutathione S-transferase, MMDB ID: 134122 PDB ID: 5D73 and Thioredoxin, MMDB ID: 112413 PDB ID: 4FYU) in WB and 19 experimentally-determined bio molecular structures (Cyclophilin MMDB ID: 55049 PDB ID: 1A58, Putative Ubiquitin-conjugating Enzyme E2MMDB ID: 111366 PDB ID: 4L83, Calcium-Free (Apo) S100a12MMDB ID: 73787 PDB ID: 2WCF [Metal Binding Protein], Glyceraldehyde 3-phosphate dehydrogenase MMDB ID: 109769 PDB ID: 4K9D *etc*.) in BM [23]. These resolved proteomic issues are helpful in prediction of the new target for the development of novel drug molecule. Surely such efficiency in deciphering the proteomic avenues can help mankind in finding out better, cheap and efficient alternatives for this problem.

3.2.1. Protein structure Predictions

Importance of protein 3D structure and its role in the progression of different diseases is well established. In terms of proteins, 3D structure is the most important as it controls the functionality of complete protein and plays an important part in the progression of the disease hence these 3D structures are better target for further drug designing and relative studies [39]. In case of parasitic disorder the selection of target protein is very specific as the drug is designed against the target protein that should not harm the host where as it could affect the vitality and pathogenicity of the parasite. These 3D structures of selected protein can be used as a better target for drug designing and relative studies against any parasitic disorder [39]. Different computational protocols were used for different studies at protein level *viz*;In *silico* characterization, homology modeling, docking *etc*.

3.2.2. In silico Characterization

It is important in deciphering the important physical and chemical properties along with the prediction of basic configuration of proteins in their secondary structure. Physicochemical characterization of proteins encodes better understanding about the properties like molecular weight, number of hydrogen bonds, theoretical isoelectric point (pI), helices, strands, turns, instability index, number of positive and negatively charged residues, extinction coefficient, grand average hydropathicity (GRAVY) and aliphatic index [39]. Above mentioned parameters are significantly playing an important role in analyzing the properties of protein. *In silico* characterization studies have drawn the positive and progressive relation and attention towards the advance approaches of protein characterization [40]. Different *in silico* characterization based studies related to filariasis and others disorders have already proven their significance and contributed a lot in the area of advance research.

In silico characterization of an RNA binding protein of cattle filarial parasite *Setaria Digitata* has been performed by Nagaratnam *et al*, 2014. In this study, a 549 bp long cDNA (sdrbp) has been sequenced and characterized *in silico*. Due to the difficulties in procuring WB parasite material, *Setaria Digitata* cDNA library has been constructed to identify novel drug targets against HLF and many of the cDNA sequences have been assigned structures and functions to interpret their importance in relation with this disorder [41].

Another study revealed *in silico* structural and functional characterization of a *Vibrio Cholerae* O395 hypothetical protein containing a PDZ1 and an uncommon protease domain, *Vibrio cholerae*, the causative agent of epidemic cholera, has been a constant source of concern for decades. It has constantly evolved itself in order to survive the changing environment [42]. *In silico* identification and characterization of novel drug targets and outer membrane proteins in the fish pathogen *Edward siellatarda* was a land mark for computational approaches with respect to helminths for identification of the new potential drug targets and novel vaccine candidates against it [43].

3.2.3. Homology Modeling

In molecular biology and structural genomics, protein structure determination has become an important area of research. Genome sequencing projects are producing linear amino acid sequences, but full understanding of the biological role of these proteins will require knowledge of their tertiary structures and functions [44]. 3D protein structures are precious sources of information for the functional annotation of protein molecules. These structures are best resolute by experimental methods such as X-ray crystallography and nuclear magnetic resonance (NMR) spectroscopy. However, the experimental methods cannot always be applied. To overcome such issues, prediction of the protein structure by computational methods can frequently result in a useful model [45, 46]. The aim of comparative or homology protein structure modelling is to build a three-dimensional (3D) model for a protein of unknown structure (the target) on the basis of sequence similarity to proteins of known structure (the templates) [47]. Homology modelling can create high-quality structural models when the target and template have close relationship. Like other methods of structure prediction, current run-through in homology modeling is evaluated in a biennial large-scale experiment known as the Critical Assessment of Techniques for Protein Structure Prediction or CASP [48].

Homology modelling is consistently becoming the method of choice for procuring three-dimensional coordinates for proteins because genome projects produce sequences at a much higher rate than NMR and X-ray laboratories can solve the three-dimensional structures [49]. There are some beautiful examples sowing homology modelling studies and their importance with reference to filariasis.

WB and BM three dimensional model of b-tubulin protein (BmBTP) was built using homology modeling approach [50].

Another important 3D structure of Fatty Acid Retinal binding (FAR) protein in *Wuchereria bancrofti* was modelled because of its strong conservation of the biochemical activities with significant role [11].

Filarial protein GP 15/400 poly protein which is an important pathogenic protein of *Wuchereria Bancrofti* was also modeled through *in silico* approaches [39]. It is a well-accepted fact that modelled structure are obtaining remarkable acceptance in scientific community. They have many related applications in virtual screening and drugs as well inhibitor designing based on structure activity relationship.

Synthesis and molecular modelling studies of 3-chloro-4-substituted-1-(8-hydroxy-quinolin-5-yl)-azetidin-2-ones as novel anti-filarial agents is generated an amazing understanding of problem [51]. These supportive findings are very important in helping and guiding of future lead discoveries and optimization efforts [52].

Homology modeling of antioxidant proteins in spinach was adopted to explore Physico-chemical properties and structure of spinach antioxidant proteins [53].

Another study regarding molecular modelling, dynamics and an insight into the structural inhibition of cofactor independent phosphoglycerate mutase isoform 1 from *Wuchereria bancrofti* using cheminformatics and mutational studies explored new interventions of this issue. In this current study, a putative cofactor-iPGM gene was identified in the protein sequence of the *Wuchereria bancrofti* [54].

3.2.4. Molecular Docking

Docking technique is used to form a stable complex between protein and ligand. Molecular docking is one of the most accepted protocol for the computer aided drug designing and structural molecular biology. Prediction of binding orientation with reference to drug candidate and protein targets to calculate the affinity and activity is mostly used by following the detailed docking procedure. This reason justifies the significance of molecular docking or protein ligand interaction in rational drug design [55]. During the docking methodology preferred orientations of different molecules are used to predict in the term of binding affinity association of the molecules through scoring functions [56]. The most interesting and demanding case of the protein-ligand interaction are seen in application of medical sciences. Ligand is a small molecule, which interacts with proteins binding sites. This methodology is used to model the interaction between a small molecule and a protein at the atomic level. This interaction characterizes the behaviour of small molecules with the binding site of target proteins as well as to explicate elementary biochemical processes.

Molecular docking is the most important master program used in structural molecular biology as well as for computer-aided drug design.

Kalani *et al*, 2014 proved the importance of docking study in filariasis by establishing the importance of ursolic acid against the human lymphatic filarial parasite *Brugia malayi* through targeting Glutathione-S-Transferase (GST) parasitic enzyme [57].

Studies on filarial GST as a target for antifilarial drug development *in silico* and *in silico* inhibition of filarial GST by substituted 1, 4-naphthoquinones reveals a good computational contribution in filiarial issues [58].

Structural insights on *Brugia malayi* transglutaminase with cinnamoyl derivatives also proved importance of molecular docking approach [59].

Another study related to filariasis is a systematic study on structure and function of ATPase of *Wuchereria bancrofti* because as till date no effective drug or vaccine has been discovered to treat lymphatic filariasis (LF) and ATPase is one of the most important proteins of *Wuchereria bancrofti* that could be a good target to develop these [60].

4. SOME IMPORTANT FILARIAL INFORMATION SYSTEMS

Above studies and compilation of informative system signifies that scientist of different areas are globally thinking about the resolution of this problem and among different approaches these computational based researches will no doubt be a milestone against the fight with *filaria*. Genomic, proteomic, system biology based concepts, computational drug designing, virtual screening, homology modelling *etc*. are the different advances which altogether will win these problem in terms of proper medication or finding out preventions against the devil of *filaria* which not only causes social stigma but also mental and physical trauma to the victim of this disease. Compilation of this *in silico* contributions are well establishing their importance in finding out new targets and compounds that could lead a milestone against this social stigma, which creates humiliation not only for patients or relatives but also a burden for society.

Table 1. Compilation of Different filarial information systems contributing in computational Approaches.

Name of Database	Link	Discription
Northeast India Helminth Parasite Information Database (NEIHPID)	http://nepiac.nehu.ac.in/index.php	Knowledge base for helminth parasites.
HPIDB" a host-pathogen PPI database	http://agbase.msstate.edu/hpi/main.html	A unified resource for host-pathogen interactions.
ENHanCEd Infectious Diseases (EID2) database	http://www.zoonosis.ac.uk/EID2/	This evidence-based database annotates and integrates existing data on vectors, hosts and their pathogens.
FiloBase	http://filobase.bicpu.edu.in/	A comprehensive drug target database for filariasis.
Global NeglectedTropical Diseases Database (GNTD)	http://www.gntd.org/login.html;jsessionid=EB8DE4822A6548A6F67BFE9BA9EDD6F6	The GNTD project aims to provide a unique open-access, and constantly updated, database on compiled NTD survey data to foster epidemiological research and to obtain recent disease risk estimates applying the compiled data.
GAHI Global Atlas of Helminth Infections	http://www.thiswormyworld.org/	GAHI shows the geographical distribution of neglected tropical diseases transmitted by worms: soil-transmitted helminthiasis, schistosomiasis, and lymphatic filariasis.
WormBase	http://www.wormbase.org/	Explore worm biology facilitating insights into nematode biology.
NEMBASE4	www.nematodes.org	NEMBASE is a comprehensive nematode transcriptome database including 63 nematode species.
Filarial worm genomes	http://www.broadinstitute.org/scientific-community/science/projects/gscid/filarial-worm-genomes	It generates a high quality draft genome assembly and automated annotation for the filarial worm Loa loa, *Wuchereria bancrofti* and *Onchocerca volvulus*.

CONCLUSION

Current study was planned to understand the mechanism involved to explore out the possible therapeutic interventions related to Filariasis disease, commonly known as elephantiasis, is a painful and profoundly disfiguring disease, caused by the parasitic filarial nematodes *Wuchereria bancrofti* (W. bancrofti), *Brugia malayi* (B. malayi), or *Brugia timori* (B. timori). More than 90 percent of infections are due to *Wuchereria bancrofti*.

Above studies and compilation of informative system signifies that scientist of different areas are globally thinking about the resolution of this problem and among different approaches these computational based researches will no doubt are a milestone against the fight with filaria. Genomic, proteomic ,system biology based concepts, computational drug designing, virtual screening, homology modelling *etc*. are the different advances which altogether will won these problem in terms of proper medication or finding out preventions against the devil of filaria which not only causes social stigma but also mental and physical trauma to the victim of this disease. Compilation of this *in silico*

contributions are well establishing their importance in finding out new targets and compounds that could lead a milestone against this social stigma which create humiliation not only for patients or relatives but also burden of society too.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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