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Research Article

CHIKUNGUNYA DRUG TARGET DATABASE: A COMPREHENSIVE DATABASE OF CHIKUNGUNYA DRUG TARGETS

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ABSTRACT

Objective: Chikungunya is a viral infection transmitted by the *Aedes* mosquito to humans. Currently, there is no approved treatment for the infection. Clinical trials have been carried out to identify candidate drug molecules. There is no existing repository for determining the information pertaining to drug targets of chikungunya. The current study aims to develop a comprehensive database of chikungunya drug targets.

Methods: Literature review is carried out to determine the available drug targets for chikungunya with the help of several open source biological repositories. The database consists of 23 viral strains, 19 drugs targets, and 7 drugs. Further manual annotation is performed to identify the relevant drug targets. For each of these drug targets identified, an illustrative pathway is constructed depicting the role of drug targets in the viral infection.

Results: The chikungunya drug target database (CDTD) was constructed based on the three-tier architecture in XAMPP (Windows Apache MySQL Perl PHP) platform. The database comprised 23 viral isolates, 19 drug targets, and 7 currently used drugs specific to chikungunya infection. For each of the drug targets, a mechanistic pathway is designed to illustrate the role of drug targets and the mechanical pathway in chikungunya infection.

Conclusion: CDTD is a specialized database which is designed to provide comprehensive information pertaining to viral drug targets. The database can be utilized from researchers interested in the virology of chikungunya further providing drug target information.

Availability: The database is freely available at http://www.biocdtd.org/.

Keywords: Chikungunya virus, Drug targets, Viral isolates, Drugs, Pathways.

INTRODUCTION

Chikungunya viral infection transmitted by *Aedes* mosquitoes is characterized by numerous outbreaks in the Indian subcontinent, Indian Ocean and other parts of Asia since 2004. According to National Vector Borne Diseases Control Programme (NVBDCP), there were 18,639 new cases reported with chikungunya infection in 2013 [1]. The virus was first isolated from Tanzania in the 1950s [2,3].

Chikungunya virus (CHIKV) belongs to the alphavirus genus and family Togaviridae [4,5]. They usually have RNA as their genetic material. The size of the virus is about 50-70 nm, having an icosahedral-like nucleocapsid surrounded by an envelope embedded with viral glycoproteins. There are nine genes encoded in the virus. They include non-structural polyproteins (nsP1-nsP4 proteins), structural polyproteins (E1-3 and 6K), and polyadenylation sites [6,7]. The penetration of the virus into the host cell is facilitated by the E1 protein. The viral genome is around 11.8 kb in size having multiple copies of the capsid protein of about 30 KDa. Symptoms normally start 4-7 days after the bite of the chikungunya mosquito. Severe infection lasts for 1-10 days and is characterized by sudden onset of fever, headache, fatigue, nausea, vomiting, rash, myalgia, and severe arthralgia [8,9]. Knowledge of environmental epidemiology of CHIKV infectivity is very necessary for better control of the disease. Among the affected population considerable discomfort and morbidity have been caused by CHIKV to a certain extent. CHIKV has broadened its vector competence through viral adaption which has increased its potential to cause human disease. In concomitance, it has been observed that the death rate is not particularly high, but excess mortality with large CHIKV outbreaks. Chikungunya is mainly a non-fatal disease but can lead to death only in case of elderly people. Recovery from the disease chikungunya differentiates with age; younger patients recover within 5-15 days. The recovery from the acute phase of chikungunya was slow in diabetics, and their blood sugar used to go up quite early during the disease. The capability of RNA viruses to appear and cause human disease often reflects their ability to develop new ecologic contacts and swiftly adapt to new amplification hosts or vectors. The chikungunya disease has diagnosis problems associated with it due to the clinical features that match with that of dengue fever asthenia, myalgia rash, and hypotension was found common in both dengue and chikungunya fever. Treatment gets delayed due to the problem in diagnosis which results in a worsening of the situation and chances of a disease to become an epidemic.

The treatment of a viral infection can be provoked by designing new and better drugs against chikungunya. An approach to facilitate the drug development is by targeting the potential drug targets expressed in chikungunya infection. The information pertaining to chikungunya is depicted in some of the databases discussed below.

There are several databases available to depict the information regarding CHIKV namely, CHIKVPRO - A database comprising of chikungunya proteins and their annotation [10], G2H: Chikungunya Database [11], Viral Pathogen Database and Analysis Resource [12], and CHIKV information Diseases Database [13]. The above-mentioned databases feature general information regarding CHIKV and its annotation. Currently, there is no single repository having comprehensive information about drug targets and mechanism of lead molecules binding to such drug targets for CHIKV. There is a need for a comprehensive drug target database for CHIKV. It guides the researchers to focus on the drug targets engaging toward the development of new drugs for the viral infection. The database comprises of viral isolates information, drug targets information, and information regarding currently available drugs for the treatment chikungunya viral infection. The pathways have been derived for each of the drug target illustrating the role of the drug target in the infection.

This study is an attempt to annotate the available drug targets of CHIKV into a single repository by the development of a comprehensive chikungunya drug targets database (CDTD). The database serves as a repository for scientific community working in the field of virology subjected to CHIKV.

METHODS

The methodology adopted for the development of CDTD comprised two parts:

a. Data compilation
b. Database construction.

Data compilation

Literature review for diverse data collection

The data pertaining to chikungunya viral isolates, drug targets, and available drugs were collected from various literature sources. The search strategy was implemented by referring to a number of biological repositories namely: NCBI PubMed [14], UniProt [15], RCSB - Protein Data Bank (PDB) [16], ClinicalTrials [17], and MESH [18].

The data were retrieved from these biological repositories using different search keywords. The keywords "chikungunya" and "virus" were used to retrieve the synonyms and general description of the virus from MESH repository. It was followed by retrieving the literature collection referring to CHIKV from different parts of the world. The search resulted in 1793 hits from PubMed. Advanced search was focused on the information pertaining to CHIKV in the year 2013 which resulted in 78 articles. The search hits were further processed to identify the hits pertaining to drug targets for CHIKV. It resulted in 13 hits. The research articles were further screened to identify the relevance of hits. The same procedure was repeated for the collection of information pertaining to viral isolates and drugs of chikungunya. The screening of information resulted in 23 different viral isolates, 19 drug targets, and 6 drugs for CHIKV.

Annotation and validation of the identified drug targets

The data derived from the literature review had basic information pertaining to each drug target from different biological sources. Thereby manual annotation was performed to identify the detailed description for each drug target. The information for each drug target comprised: (i) Target name, (ii) gene name, (iii) synonyms, (iv) PDB ID of the target protein, (v) general description of the target protein, (vi) function of the protein in chikungunya viral infection, and (vii) corresponding citation of the target protein.

Derivation of an illustrative pathway of therapeutic mechanism of drug target

The data derived from the literature review for each drug target were used for deriving a pictorial representation of a mechanistic pathway of the therapeutic action of any drug molecule binding to such a drug target**.** The cascade of reactions occurring pre-binding and post-binding has been represented in the illustrative pathway.

Construction of CDTD

Database architecture

The architecture of CDTD is a classical three-tier web application comprising of:

1. User-interface or client tier
2. Business logic or application tier
3. Data storage tier or data access tier.

Database schema

The organized relational database schema was developed to implement as a comprehensive repository for chikungunya drug targets. The database was implemented using X-Any Platform Apache MySQL PHP (XAMPP) which is an RDBMS web server. The scripts are written in PHP. Client-side programing is implemented using HTML, CSS, and PHP having Apache as the web server for delivering the web interface. The schema is implemented to support and accommodate the information regarding chikungunya viral isolates, drug targets of chikungunya, currently available chikungunya drugs, and the predicted pathway for each drug target. The database supports additional information related to chikungunya drug targets by referring to different biological repositories such as PubMed, PDB, and DrugBank. The designed pathway for each drug target is stored in the database to depict the target and drug interaction. The information for each entity is accessed using PHP scripts.

Database construction

The flowchart demonstrating the methodology used for the construction of CDTD is shown in Fig. 1. The construction of the database is a multistep protocol comprising of the viral strains, drug targets, available drugs, and pathway interpretation for each target.

Database contents

- Drug information: The information regarding currently available drugs for the treatment of chikungunya viral infection is depicted in the drug information table. The 6 available drugs are depicted in the table and retrieved using MySQL queries
- Drug target information: The database identifies 19 potential chikungunya drug targets known to have significant roles in the chikungunya viral infection. The influence of these drug targets in the chikungunya infection is depicted by pathway analysis. The data are retrieved using MySQL queries
- Pathway information: For each drug targets the mechanistic pathway depicting the role of the target in the viral infection is designed. A suitable candidate drug molecule can be designed to inhibit the action of the drug target
- Isolated strain information: The information comprises of 23 different chikungunya viral isolates deposited from different regions of the world. Each viral isolate is known to have a characteristic feature pertaining to the virology.

Each web page for the query has been designed as a simple interface without the loss of precision. The connectivity to the database is established to the homepage of the database followed by retrieving the appropriate hits for the viral strains, drug targets, and the available drugs. Each entity is identified by an identifier (viral ID, target ID, and drug ID) for extracting the relevant information. Once the entity is clicked, the description about it is deciphered from the viral information page followed by the target information page and the drug information page. The reliability of the hits can be determined by the user.

Once a user clicks the ID, the display is taken to the information page which is hyperlinked to different biological repositories. On clicking the target ID in the target page, the display is taken to the target information page depicting the name of the target, its common gene name, the respective PDB entry of the protein target, the general description of the protein target, the role of the drug target in chikungunya infection and the respective PubMed ID of the target protein providing the citation for the drug target in chikungunya infection.

The user-interface diagram for CDTD is displayed in the Fig. 2. The Fig. 2 interprets the complete user-interface builds for the system considering many key factors such as specificity, simplicity, speed for accessing, and clear in the data. External databases are referred in Green color like PDB ID, PubMed ID, and DrugBank ID.

The results depict CDTD database capturesinformation regarding the CHIKV emphasizing on the drug targets for the virus. The drug targets were identified by a preliminary literature review and further validated by manual annotation. The hypothetical pathway is designed for each drug target to identify the role of the protein in causing the viral infection. Apart from drug targets, the database comprises of

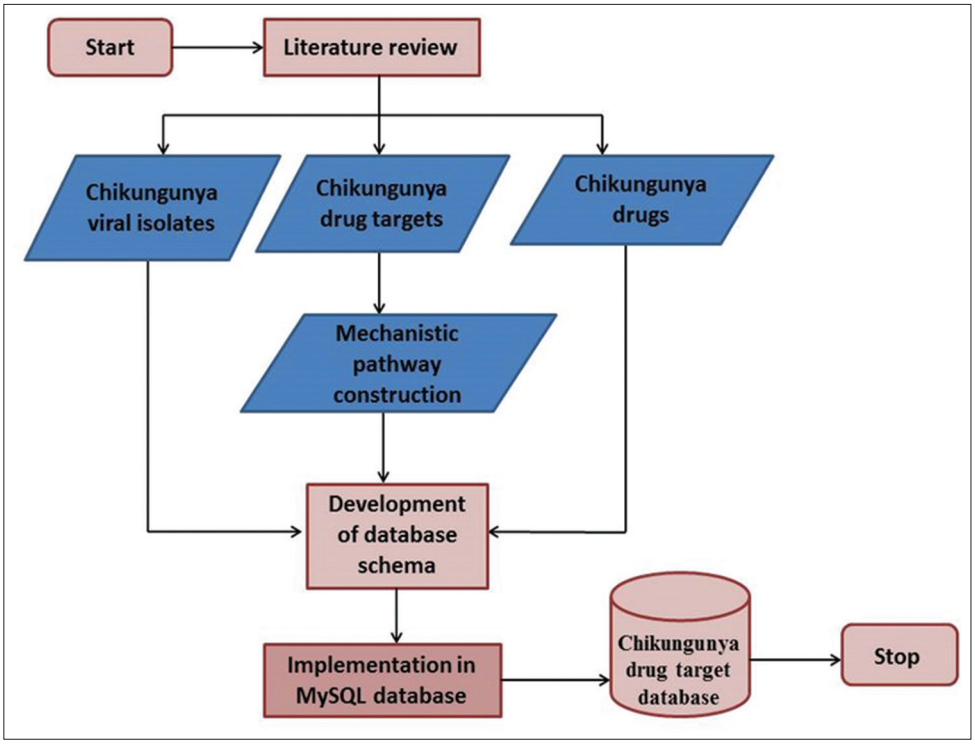

Fig. 1: Methodology used for construction of chikungunya drug target database

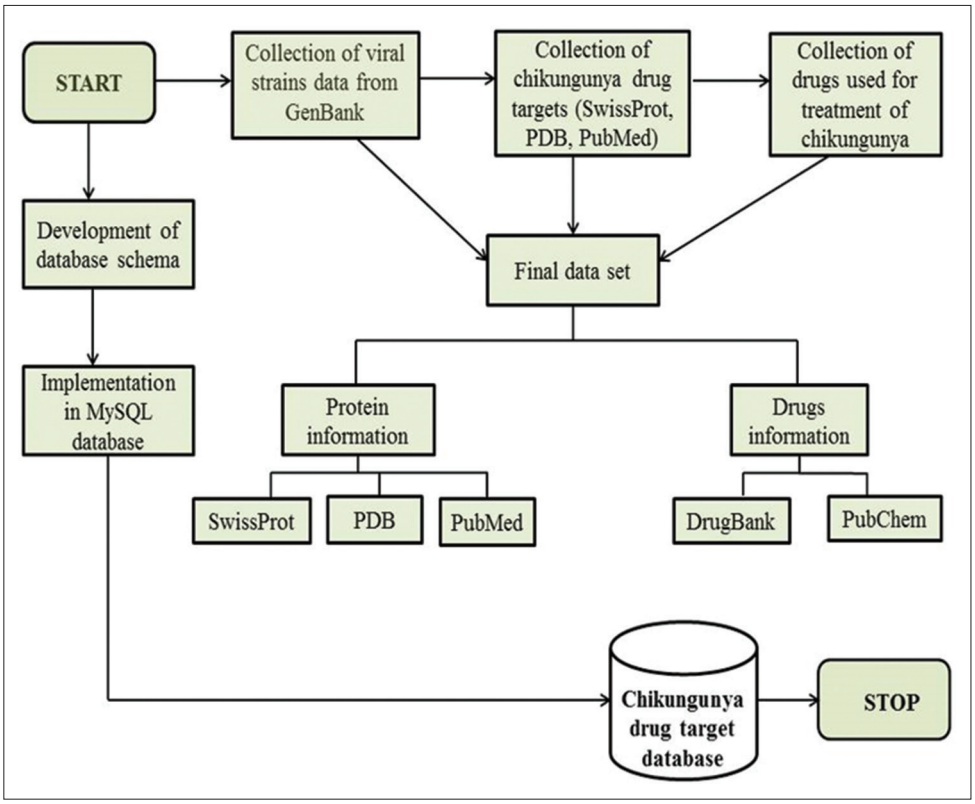

Fig. 2: User-interface diagram for chikungunya drug target database

the different chikungunya isolates and the currently available drug information for the infection. Information from the database is cross-referenced to other external databases such as NCBI, PDB, PubMed, UniProt, DrugBank, and MESH. These biological repositories provide explicit information about the role of drug targets in the viral infection for users.

RESULT

The CDTD was constructed based on the three-tier architecture in XAMPP (Windows Apache MySQL Perl PHP) platform. The database comprised of 23 viral isolates, 19 drug targets, and 7 currently used drugs specific to chikungunya infection. For each of the drug targets, a

mechanistic pathway is designed to illustrate the role of drug targets in chikungunya infection.

DISCUSSION

CDTD is an annotated, specialized database of chikungunya drug targets. The targets are further validated by manual curation. CDTD database explores the biologically active drug targets in chikungunya and further demonstrates the role of the drug target in the viral infection by designing the probable pathway for the drug target. The database also implements the information regarding the chikungunya viral isolates and the currently available drugs for the viral treatment. The database enables users to identify drug targets of CHIKV identified from previous literature evidence. The database further supports the identification of new drug targets for the viral infection which could be targeted by prominent drugs. Until date, there is no comprehensive database for the drug targets of CHIKV. Hence, this database can be utilized as an alternative source of information for the chikungunya drug targets. This database is an attempt to depict the drug targets for CHIKV to aid further drug discovery in this arena. The purpose of this study is to make the database available on the World Wide Web for free access by researchers interested in the field of chikungunya virology.

CONCLUSION

CDTD is a specialized database designed to provide comprehensive information pertaining to viral drug targets. The database can be utilized from researchers interested in the virology of chikungunya further providing drug target information.

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