In Silico Studies in Antimicrobial Peptides Design and Development

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Abstract. Antimicrobial peptides (AMPs) are a group of natural-derived molecules exhibited broad spectrum antimicrobial activity. Currently these molecules have been investigated comprehensively due to their interesting features regarding antimicrobial and immunomodulatory mode of actions which placed them as promising therapeutics agents in this post antibiotics era. Numerous strategies have been implemented in order to develop a novel AMP for biotechnology and therapeutics applications, one of which is in silico study. This approach offers a rapid and cost effective manner in AMPs design and development. In silico studies provide additional and substantial information for in vitro techniques. In this paper, we deliver an overview of the applicable in silico approaches that have been used in designing and developing AMPs.

1. Introduction
Antimicrobial peptides (AMPs) are small and ubiquitous molecules exhibited antimicrobial activity. These molecules are expressed in both eukaryotic and prokaryotic organisms and play role as first line defense or as an addition to existing immune system. Recently AMPs have become popular target of drug development since the rapid ability of AMPs in performing broad spectrum activity, include antibiotic-resistant microbes has been revealed [1,2,3]. There are several AMPs already present in the market and others are still being evaluated in clinical trial [4,5]. However, there are some limitations regarding the commercial development of AMPs, such as high cost production and time consuming (especially in application of recombinant techniques), low efficacy in animal models, high susceptibility to protease degradation and loss of activity in certain physiological conditions [1]. All these shortcomings can be elucidated by applying a cost effective method in AMPs design and modification, namely in silico study [1,6,7].

In silico study is a logical extension of in vitro method where biological and physiological processes are simulated in computer. This approach permit the researcher to perform a virtually unlimited assortment of parameters, which offer more suggestions or predictions of applicable results [8]. There have been increasing reports on in silico study in predicting, designing and modifying AMPs and they compromise promising approaches [9,10]. This paper will discuss further about the application of in silico studies in AMPs design and predictions of their mode of actions.
2. **In silico Studies and Antimicrobial Peptides Design**

The design of peptides (or proteins) refers to re-arranging of amino acids sequences to either generate an exclusively novel peptide or to fit the existing structural template. The design should be conducted in rational manner [10]. Computer-assisted AMP design is very useful for estimating or predicting the desired biological activity from the primary peptide structure [6]. There are five types of prediction methods for AMPs; (1) prediction based on mature peptide sequences only (2) prediction based on precursor sequences only, (3) prediction based on both mature and precursor sequences, (4) prediction based on sequence similarity of the modifying enzymes and (5) prediction based on genomic information [9].

Bioinformatics has provided abundant genomics and proteomics data permitted the use of **silico**-associated molecular tools in identification and screening of novel AMPs [11]. The databases not only provide the AMPs sequences but also render the related information such as structural, complexities, specific target, antimicrobial activity and cytotoxicity, and also link to external related database (National Centre for Bioinformatics, Swiss Prot, etc) and certain prediction tools [12,13,14]. The information can accelerate the peptide design pipeline. These following are some of available and commonly use AMPs databases:

a. **Collection of Anti-Microbial Peptides (CAMP).** The database can be accessed at [http://www.camp.bicnirrh.res.in/](http://www.camp.bicnirrh.res.in/) and provide collection of 6756 AMPs sequences and also 3D structures of 682 AMPs [15].

b. **Linking AMPs database (LAMP).** To date, this database curated almost 5,547 AMPs sequences of consist of 3,904 natural AMPs and 1,643 synthetic peptides. This database is available at [http://biotechlab.fudan.edu.cn/database/lamp/index.php](http://biotechlab.fudan.edu.cn/database/lamp/index.php) [13].

c. **Database of Antimicrobial Activity and Structure of Peptides (DBAASP).** The database is available at [https://dbaasp.org/](https://dbaasp.org/) and the latest version of this database provide more interesting features, namely as molecular dynamic simulation, which is useful in presenting structural description based on empirical data calculation [16].

d. **Bactibase.** The database is dedicated to information related to AMPs produced by bacteria, namely as Bacteriocin. It contains physicochemical properties of 230 bacteriocin (calculated or predicted). Therefore it is very useful in exploitation of this AMPs in medicine and biotechnology application. The database is available at [http://bactibase.hamamamilab.org/main.php](http://bactibase.hamamamilab.org/main.php) [17].

e. **Yet Another Database of Antimicrobial Peptides (YADMP).** The database provides more information regarding the Quantitative Structure-Activity Relationship (QSAR) analysis and prediction of activity on the target bacteria. It can be accessed at [http://yadamp.unisa.it/default.aspx](http://yadamp.unisa.it/default.aspx) [18].

f. **The Antimicrobial Peptide Database (APD).** The latest version of database offers comprehensive information about AMPs from human, animals, bacteria, fungi, plants, archaea and a number of synthetics peptides. There are also 403 unique 3D crystal structures that can be accessed in this database. APD can be accessed at [http://aps.unmc.edu/AP/](http://aps.unmc.edu/AP/) [19,20].

g. **Antiviral Peptides Database (AVPdb).** The database in the first inclusive database for antiviral peptides (AVPs). There are more than 60 pathogenic viruses targeted by the curated AVPs in this database. The database also affords important information related to targeted viruses, cell line, assays and experimental efficacy data of the AVPs. AVPdb is available at [http://crdd.osdd.net/servers/avpdb/index.php](http://crdd.osdd.net/servers/avpdb/index.php) [21].

Generating AMPs sequences also can be done by using mathematical algorithm and modelling. Most of AMPs databases are constructed using certain algorithms. Previous study revealed the use of sequence alignment method, Lempel-Ziv (LZ) complexity, and support vector machines- (SVMs-) pairwise algorithm in combination. The integrated algorithm enabled to detect the evolutionary and structural relationship of the peptides and exhibited higher sensitivity performance on AMPs prediction than CAMP method [22].
Another study of computational method discovered the use of decision tree model in AMPs design. In this approach, the known AMPs (parental peptide) were used as a backbone of designed AMPs. Later the amino acids residues of the parental peptides were substituted by other amino acids. The substitution were based on (1) total hydrophobic ratio (%), (2) net charge, (3) distribution of positive charge of hydrophobic residues on the same exterior, (4) Boman Index, and (5) amphiphilic character. The modify sequences were then submitted to predictive tools which was available at APD database to validate the antimicrobial activity. The process were continued by synthesis of peptide analog and analysed further by decision tree modelling which generated using J48 algorithm from Weka. Decision tree modelling placed each AMPs on several partition which classify based on the certain criterion and interpreted further as none (no activity), low (activity occurred on single organism), medium (activity was observed in two kinds of organisms) and high (activity was observed on three or more organisms) [23]. Amino acids substitution was also used in modifying short length AMPs generated from scrambled peptide and QSAR analysis [24].

Computational approach could be applied on categorizing and clustering abundant data of AMP’s physicochemical properties. In this method, Genetic algorithm (GA) and k-means algorithm obtained better clustering results compared to other algorithm. The study also revealed specific region on AMPs with enrichment of physicochemical properties and on the other hand, there were specific region with depleted physicochemical properties [25]. Other previous study used Artificial Neural Network (ANN) to determine the precise correlation between physicochemical properties of AMPs and its antimicrobial activity and defined the fundamental differences between AMPs and non-AMPs molecules based on their physicochemical characteristics [26].

Recent study showed the application of AmPEP, a sequence based prediction of AMPs. This computational method provided an accurate prediction method using random forest algorithm. The prediction was based on the pattern of amino acids distribution along the referred sequences [7].

Peptide mimics or also known as peptidomimetics can be used to overcome limitation of AMPs. A Rational design of peptidomimetics can recover the performance of the active peptide while demonstrating the significant improvement on bioavailability and stability. The construction of peptidomimetics also involve the in silico approach such as QSAR analysis [6,27].

3. Conclusions

In silico approach has offer a robust method in AMPs design and development. To date, the application of bioinformatics, computational method, mathematical modeling are commonly used in the pipeline of AMPs development, for both medicine and biotechnology purposes. In silico studies not only enable to overcome the shortcoming of AMPs but also offer a rapid and cost effective method in developing AMPs.

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