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Virtual screening strategies: Recent advances in the identification and design of anti-cancer agents

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ABSTRACT

Virtual screening (VS) is a well-established technique, which is now routinely employed in computer aided drug designing process. VS can be broadly classified into two categories, i.e., ligand-based and structure-based approach. In recent years, VS has emerged as a time saving and cost effective technique, capable of screening millions of compounds in a user friendly manner. In the area of cancer drug design, VS methods have been widely used and helped in identifying novel molecules as potential anti-cancer agents. Both ligand-based VS (LBVS) structure-based VS (SBVS) methods have been highly useful in the identification of a number of potential anti-cancer agents exhibiting activities in nanomolar range. In tune with the rapid progress in the enhancement of computational power, VS has witnessed significant change in terms of speed and hit rate and in future it is expected that VS will be a preferential alternative to high throughput screening (HTS). This review, discusses recent trends and contribution of VS in the area of anti-cancer drug discovery.

1. Introduction

The word "virtual" is used to signify any instances, which are not directly connected to real world and we human beings cannot perceive them through our senses. In fact the word "virtual" is becoming unambiguous as it is appearing more frequently in real life situations. In the present era of applied science, the term virtual screening is used in the context of Computer Aided Drug Discovery (CADD). VS is a computational technique, which is used to screen novel potential active molecules (called hits) from a chemical database. Pharmaceutical companies and many institutions now routinely employ VS as one of drug discovery methods. The origin of VS dates back to late 1980s, when ALADDIN programme was used to screen a database at ABBOTT laboratory [1].

Currently, the VS methods have evolved to a greater extent in terms of user friendliness, utility and performance. This has led to the increased use of VS methodology and many successful examples covering different disease areas have been published during the last two decades (1994–2014). Availability of supercomputing and cloud computing facilities has made possible to screen a large chemical database (having millions of compounds) within hours without much efforts. There are many published reviews [2–5], which covers the various aspects of VS in detail. However, there is a need of a review covering the recent progress of VS in the area of anti-cancer drug discovery and in this context this review concentrates on recent VS methodologies adopted in the field of anti-cancer drug discovery.

2. Need of VS in anti-cancer drug discovery

Compared to other diseases (parasitic), cancer is a result of malfunction of cellular machinery, where transformed (cancerous) normal cell aggressively divides and spread to other areas of human body through the process of metastasis. Targeting the cancerous cells impose a great hurdle as these are modified normal cells and killing them will also kill healthy dividing cells. This is the reason behind development of targeted therapy, which focuses on specific molecular targets, frequently over-expressed or altered in cancer [6,7]. Traditional cancer therapy such as chemotherapy and radiation therapy target the rapidly dividing cells including cancer cells and few normal cells. The cytotoxic nature of traditional therapy results in serious side effects such as, myelosuppression, gastrointestinal complication and alopecia [6]. Targeted therapy has advantage over both chemotherapy and radiation therapies in aspect that they specifically stop the proliferation of cancer cells or either kill them. During the last 10 years, a large

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number of molecular targets have been identified, which plays an important role in cancer initiation and progression. Most of the targets involved in cancer are either functional proteins or structural proteins. Targeted therapies include monoclonal antibodies (mAb) and small molecules, which bind and modulate the biological function of their targets. The ligand binding site on the targets offers an excellent opportunity to look for new molecules which could optimally fit into it. HTS and VS are some of the techniques that can screen thousands of molecules within short time [8]. VS is considered as a good alternative to HTS, because it is cost effective and fast. No doubt, the high cost of cancer drug discovery can be lowered up to certain extent by employing VS methods.

3. Overview of virtual screening strategies

As mentioned earlier, the VS terminology was conceptualized in the late 1980s and the basic concept of the method has not changed till date. The concept behind VS is simple, that is to retrieve and prioritize the potential active compounds from the virtual library of diverse compounds. First successful attempt of VS was the discovery of novel D1 agonist [1] at the Abbott laboratory. The above discovery can be marked as the beginning of modern VS era. Modern VS techniques are fast, user friendly, advanced and automated. The VS techniques (Fig. 1) are classified mainly in two categories, i.e., ligand-based virtual screening (LBVS) and structure-based virtual screening (SBVS).

4. VS strategies adopted in anticancer drug discovery

VS techniques employed in the drug discovery are mostly generalized and have not been specifically designed for use in discovery of anti-cancer agents. The successful applications of VS have been increasing in recent years towards the contribution for development of anticancer agents. In this section, we highlight the general methodologies and current progress in VS from the selected recent works and provide an overview of the emerged strategies in anti-cancer drug discovery. The key features of presented case studies are tabulated in Table 1.

4.1. Ligand-based virtual screening (LBVS)

VS can be initiated from at least one known ligand of the target, and the method is known as LBVS. Pharmacophore-based VS (PBVS) is considered most popular method under the LBVS approach. Ehrlich first presented the theory of pharmacophore in the year 1909 [9]. He described the pharmacophore as an abstract description of a drug or biologically active molecule that entails (phoros) the necessary features accountable for the drug's (pharmacon) biological activity. [9] During the past few decades, the perception of pharmacophore still remains perpetual but at the same time its application in drug discovery has been magnified extensively. A pharmacophore model may be generated in a ligand based approach for which at least one active query molecule and a search database is an essential prerequisite [8]. However, a set of active molecules can also be used [10]. To execute ligand-based pharmacophore screening using a set of known ligands (which are collectively called as training set), usually common chemical features that illustrate important interactions between a ligand and target are extracted. The PBVS comprises of two major steps-creation of conformational space for the ligands in training set so that the flexibility associated with conformation of ligands can be illustrated and alignment of multiple ligands to figure out the fundamental chemical features so that the pharmacophore can be generated [11]. For the development of pharmacophore model the first crucial step is the selection of accurate chemical feature. Initially the active analog approach was used in which a pharmacophore could have any fragment or atom type [12]. However, recently available techniques utilize a generalized manner for generating pharmacophore models. Presently, various automated software packages/modules are used for the generation of pharmacophore models such as CATALYST/HipHop [13,14], Hypogen [13,15], DISCO [16,17], GASP [16,18] and GALAHAD [16,19], MOE [20], PHASE [21,22], and LigandScout [23]. The software available for pharmacophore generation are based on various algorithms and the variety resides in the alignment rules for the training set molecules and also the approach of handling conformational flexibility. Various studies have been published showing comparison of these software packages [24–26] which may be referred to analyze the differences, advantages and disadvantages of these programs. PBVS has been proved to be successful in identification of a number of potential anticancer agents.

In 2007, Purushottamachar et al. [27] published the first PBVS for the identification of androgen receptor down-regulating agents (ARDAs). This was achieved with the help of a three-dimensional pharmacophore model generated with the help of HipHop software based on a training set of five natural products. The generated pharmacophore was used by them as a query to screen two databases – Maybridge database [28] containing 59,652 compounds and National Cancer Institute (NCI) database [29] containing 238,819 compounds. The hits identified by screening of these two databases were ranked according to their fit score and only

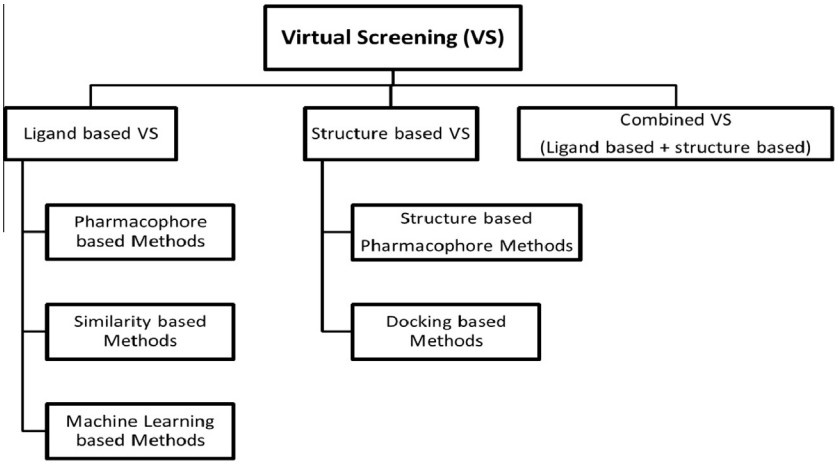

Fig. 1. Different approaches to VS.