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Computational drug design and exploration of potent phytochemicals against cancer through in silico approaches

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Abstract

Bioinformatics is the study of informatics processes in biotic systems by utilizing of computational techniques. Cancer remains one of the main causes of death in World. Plants based medicines are considered effective source along with computer aided drug designing as an effective approach for drug discovery and development. Herbal medicines are naturally occurring compounds that have number of medicinal properties. The phytochemicals including Aegle marmelos, Aloe barbadensis and Andrographolide are active compounds to be valuable source for anti-cancer drugs. Phytochemicals have potential inhibitory activity on cancer invasion and metastasis. Various computational approaches including stages of designing, docking, pharmacophore modelling and homology modelling are considered as the backbone of this process. Phytochemicals are those compounds in plants which protect plants against fungi, bacteria, and viruses. Phytochemicals with anti-cancer possessions are capable candidates. Phytocompounds are being well recognized potentially potent for cancer treatment. Some phytocompounds are being actively explored for use as anticancer therapies. The drug-likeness properties of compounds are key characteristics for novel drug. Lipinski's Ro5 and ADMET properties are important rule for the evaluation of drug likeness properties which can be used for treatment against different diseases such as cancer.

Bioinformatics is an emerging field of biological sciences that utilize the combined approaches of mathematics, statistics, and computer sciences to solve the biological problems [1]. Bioinformatics includes the data organization that allows researcher to access the exiting information and to submit new entries of data as they are produced [2]. Bioinformatics also helps to develop new fast tools to analyse the biological data and interpretation of biological results [3].

Bioinformatics mainly focuses on computer-aided analyses, homology modelling and *ab intio* modelling, structure prediction of genes/proteins followed by computational drug designing and to predict the biological mechanisms in different diseases [4]. Computational techniques help researchers to design and discover new drugs for the treatment of diseases [5]. *In silico* approaches, molecular docking and molecular dynamic simulations are broadly used in computational drug discovery for identification of novel compound [6-7]. The structural bioinformatics and drug designing help to discovery the potent novel compounds [8-9]. In addition, computer aided drug design works as a bridge between structural biologists, computational biologists, pharmacists and biophysicists for the purpose of new entities of active compounds [10]. The tools of bioinformatics and computer aided drug design gives fruitful favors such as ligand-receptor interactions, drug-drug interactions, time management, and insight knowledge about development of drug discovery [11]. Computer aided drug design have two groups including ligand based and structure-based methods for drug discovery [12]. Ligand based approaches based on the information of small compounds that bind to the target of interest [13,14]. Pharmacophore modeling and QSAR are major approaches for ligand-based drug designing [15]. Comparative molecular docking and *de novo* ligand design are considered as the effective approaches for drug designing [16]. From the FDA studies, structure-based drug designing has successful rates at clinical trials [17]. The detailed promising methodology has been reported for novel drug designing followed by molecular docking and computational approaches [18].Computational approaches and bioinformatics techniques help in computational peptide designing [19] and bioequivalence analyses of drugs [20].

In ancient times, in pursuit for the liberation of their sickness, the people were considered the plants as medicines. The therapeutic plants were usually used for the treatment of different diseases of animals as well as human beings [21]. Various herbs and shrubs were used for certain infectious diseases [22]. 365 drugs (dried parts of medicinal plants) has also been reported as drugs including *Rhei rhisoma*, camphor, *Theae folium*, *Podophyllum*, the great yellow gentian, ginseng, jimson weed, cinnamon bark, and ephedra [23]. The secondary metabolites of plants have been reported as an exceptional pool of effective medical complexes. Several anti-cancer agents have also been isolated from several plant sources like Catharanthus roseus, Podophyllum species, Taxus brevifolia, Camptotheca acuminate, Betula Alba, Cephalotaxus species, Erythroxylum pervillei, Curcuma longa, Ipomoeca batatas and Centaurea schischkinii. 'Researchers are trying to discover the bioavailability of anti-cancerous agents from unfamiliar plant families [24]. Cancer is a group of diseases which are involving in abnormal cell growth with the potential to invade or spread to other parts of the body [25]. The growth of cancerous cells is irregular and different from the growth of normal cells. Cancer cells have the potential to generate new cancer cells and increasing irregularly. The irregular growth of cancer cells have the ability to invade other tissues and disturb the normal functioning of the cell. It has been reported that the lump is formed by the cancer cells while some cancers such as leukemia, scarcely form tumors. The cancer cells are present in both blood and bone marrow [26]. The cancer cell competes with many normal homeostatic mechanisms that regulate normal process of production. The cancer cells invade the neighboring tissues followed by getting into the blood flow and moved far away from the site of their origin for multiplying [27].

Cancer is considered as the second most deadly disease in all over the world. Cancer is increasing day by day due to aging and increasing population along with increasing implementation of carcinogenic activities, specially smoking, in economically emerging nations [28].

Bael (Aegle marmelos) is an Indian medicinal plant, which has huge significance towards numerous diseases and many bioactive complexes have also been sequestered from this plant [29, 30]. Singanan *et al.*, (2007) worked on the shoot extract of Aegle Marmelos at the alcoholic liver injury of albino rats and observed effective hepato-protective effects [31]. Ramnik *et al.*, (2008) reported that the aqueous removal of bael fruit and spores are effective against hepatic CCL4 agents [32]. Arul *et al*., (2005) reported that the leaves of Aegle Marmelos has the ability of analgesic antipyretic and anti-inflammatory and also observed that most of the extracts initiate a vital inhibition of the carrageenan-induced paw oedema

and cotton-pellet granuloma in rats. The extracts of the leaves also have analgesic action by decline the initial and dawn phases of paw trouncing in mice. The significance decrease in hyperpyrexia in rats was also observed by most of the extract sources [33].

The aqueous extract of Aegle mannelos for anti-inflammatory action by means of rat paw edema exemplary was also reported followed by the anti-inflammatory actions of Aegle Marmelos [34]. The anti-cancer activity of bael fruit is effective against carcinoma at the beginning of cell proliferation [35] The anti-cancer characteristics of traditional drug Bangladesh have the extracts of Aegle Marmelos for cytotoxic action using brine shrimp lethality analyse; sea urchin eggs assay, and MTT assay analyses by using tumour cell lines. The extract of Aegle marmelos helped to reveal the harmfulness on all the utilized assays [36].

Aloe barbadensis miller is the botanical name of Aloe vera and belongs to Asphodelaceae (Liliaceae) family. It is an arborescent, shrubby perennial, xerophytic, succulent, pea- green colour shrub. It has effective growth rate in dry zones [37]. An *anti-inflammatory act of* Aloe vera is to discontinue the cyclooxygenase track and decreases the prostaglandin E2 invention from arachidonic acid. The novel anti-inflammatory compound known as C-glucosyl chromone was sequestered from gel extracts [38]. The extract of some species of the Amoora shrub extractfrom different areas of Bangladesh have significant therapeutic properties against inflammation, cancer, and infections of the liver [39, 40, 41]. The Amoora rohituka [42] is conventionally used as a herbal medicine against cancer, liver, and spleen sicknesses [43]. Amoora rohituka is familiar to be effective against colon cancer, cervical cancer, and breast cancer and leukaemia cell panels [44].

The products of Andrographolide have been reported to have anti-inflammatory properties in trial models of stroke asthma, and arthritis and the patient having upper respiratory tract infections showed improvement. The drops of Andrographolide help in the formation of cytokines and adhesion molecules, nitric oxide and lipid intermediaries, most likely through hang-up of the nuclear feature (NF)-jB gesturing pathway. The anti-cancer process for andrographolide, which hold inhibition process of signalling proteins such as Janus tyrosine kinase-signal transducers and activators of phosphatidylinositol 3-kinase and NF-jB motioning pathways overthrow of heat shock protein 90, cyclins and cyclin-dependent kinases and metalloproteinase. Furthermore, some tumor suppressor biological markers including p53 and p21 chief to inhibition of cancer cell production, existence, metastasis and angiogenesis [26]. Andrographolide drug discovery is considered as a significant development of a unique class of anti-inflammatory and anti-cancer drugs [45]. Plants have active ingredients which plays significant role in drug design and development [46]. The phytochemicals significantly contribute as anti-cancer agents in the process of drug designing [47]. The meditational chemistry proved that the phytochemicals are very important source for novel drug targets [48]. Scientific studies showed that more than 60% of drugs are based on plants and their derivatives [49].

Computational drug designing is a key technique for novel drug targets and a less time-consuming approach, cheaper, effective strategy and quick analyses as compared to conventional drug designing process [50, 51, 52]. The conventional drug designing process almost takes 10-15 years [53, 54] and very expensive economic ranges from 0.8 to 1.0 billion USD [55]. By utilizing the computational approaches to design micro molecules and bio-macro molecules for novel drug discovery are considered effective. The computational approaches utilized as preclinical studies such as target identification, target modeling, target validation, compounds accessibility and compound toxicity to lead discovery and optimization which help for drug development process [56, 57, 58, 59, 60]. The pharmacophore modeling, QSAR analyses, virtual screening and molecular docking are key aspects for computational approaches [61, 62, 63, 64]. GOLD, FlexX, DOCK, Surflex, Glide, MOE, and AutoDock Vina docking tools used for molecular docking analyses [65, 66, 67, 68, 69, 70, 71]. These docking tools help to increase the process of accuracy of molecular docking [72]. Various approaches including ADMET properties and drug-likeness properties assessed that how much phytocompounds contains potential therapeutics features [73]. Drug likeness properties are assessed by Lipinski rule of five. The RO5 has some key factors about a drug like candidate such as less than 5 HBD, less than 10 HBA, molecular weight less than 500 Da and logP is less than 5 [74]. The drug likeness properties are calculated by mCule server, admetSAR and Osiris property explorer [75, 76, 77].

Hence, plants based phytocompounds are valuable therapeutic source for novel drugs. Scientific community can easily assess potential therapeutic effects of phytocompounds based on their drug likeness properties. Additionally, computational approaches have better profile of phytocompounds

including physiochemical properties, 2D chemical structure, toxicities, and therapeutics identifications against targeted biological markers which can fruitful information for development of novel drugs from phytocompounds. Currently, researchers are focused to discover potent phytocompounds against cancer. Computational studies also proved that the phytocompounds will bring new breakthroughs against cancerous targeted proteins which plays key role in the development of tumor inhibition.

It is very necessary to develop more phytomedicines as compared to conventional medicines against cancer. Phytocompounds have better binding affinity to inhibits or suppressor tumor proliferation. The success of phytomedicines in drug discovery is very important for pharmaceutical industry and research community.

CONCLUSION

Computational approach for drug discovery is shown an emerging discipline with the potential to significantly improve how new drugs are found for different diseases such as cancer. Computational approaches can be supposed as a central hub for new drug designing. Computational drug designing is a very keen field that applies computational techniques to makes novel drugs from plants based phytocompounds. Phytocompounds could be used as therapeutic agents for drug designing. This review shows that phytochemicals as more potent agent for the treatment of number of cancers.

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