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Natural Product Chemistry and Computer Aided Drug Design an Approach to Drug Discovery: A Review Article

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Abstract

Natural products have been an inherent part of sustaining acculturation because of their medicinal properties. Past discoveries of bioactive natural products have relied on serendipity and accidental experience, and these compounds serve as inspiration for the generation of analogs with desired physicochemical properties. Bioactive natural products with therapeutic potential are abundantly available in nature and some of them are beyond exploration by conventional methods. However there has been a great breakthrough in the study of computer aided drug design (CADD) as many unfruitful lab researches have been averted and money, time and energies saved through CADD. Computer-aided drug design is a stimulating, arousing and manifold discipline where various aspects of applied and basic research integrate and induce each other. The empirical basis of CADD involves quantum mechanics and molecular modeling studies like structure based drug design; ligand-based drug design; database searching and binding affinity based on the knowledge of a biological target. In this present review we present the areas where natural product chemistry and CADD tools support drug discovery processes.

Keywords: Natural Product; Computer Aided Drug Design; Molecular Modeling and Drug Discovery Processes

Abbreviations: CADD: Computer Aided Drug Design; VLS: Virtual Library Screening; LBDD: Ligand-Based Drug Discovery; SBDD: Structure Based Drug Design.

Introduction

A disease is a particular abnormal condition that negatively affects the structure or function of all or part of an organism, and that is not due to any immediate external injury [1]. Diseases are often known to be medical conditions that are associated with specific symptoms and signs. A disease may be caused by external factors such as pathogens or by internal dysfunctions. For example, internal dysfunctions of the immune system can produce a variety of different diseases, including various forms of immunodeficiency, hypersensitivity, allergies and autoimmune disorders [1].

Healing with medicinal plants is as old as mankind itself. The connection between man and his search for drugs in nature dates from the far past of which there is ample evidence from various sources, written documents, preserved monuments, and even original plant medicines. Awareness of medicinal plants usage is a result of the many years of struggles against illnesses due to which man learned to pursue drugs in barks, seeds, fruit bodies, leaves and other parts of the plants. Contemporary science has acknowledged their active action, and it has included in modern pharmacotherapy a range of drugs of plant origin, known by ancient civilizations and used throughout the millennia.

The knowledge of the development of ideas related to the usage of medicinal plants as well as the evolution of

awareness has increased the ability of pharmacists and physicians to respond to the challenges that have emerged with the spreading of professional services in facilitation of man's life [2]. The high impacts of natural products on human being have been noted for centuries in the realms of home remedies and medicines. Historical evidence of the first natural products was revealed through the scientific study of the ancient human remains in which pollen deposits were found in the grave of Shanidar in present-day Iraq, which is estimated to date back to more than 60,000 years ago [3].

The effectiveness of computational approaches as competent tools for facilitating drug discovery and development has been recognized for decades, without exception, in the case of natural products. In the post-genomic era, scientists are bombarded with data produced by advanced technologies. Thus, rendering these data into knowledge that is interpretable and meaningful becomes an essential issue. In this regard, computational approaches utilize the existing data to generate knowledge that provides valuable understanding for addressing current problems and guiding the further research and development of new natural-derived drugs. Furthermore, several medicinal plants have been continuously used in many traditional medicine systems since antiquity throughout the world, and their mechanisms have not yet been elucidated. Therefore, the utilization of computational approaches and advanced synthetic techniques would yield great benefit to improving the world's health population and well-being.

The processes of drug discovery from idea to market involve seven basic steps which include: Disease selection, target selection, lead compound identification, lead optimization, and preclinical trial testing, clinical trial testing and pharmacogenomics optimization. The compounds for testing can be obtained from natural sources (plants, animals, microorganisms) and by chemical synthesis. These compounds can be rejected as obsolete owing to absence or low activity, existence of toxicity or carcinogenity, complexity of synthesis, insufficient efficiency, etc. As a result only one of 100000 investigated compounds may be introduced to the market, and now average cost of development of new drug rose up to 800million dollars. The reduction of time-consuming and cost of the last stages of drug testing is unlikely due to strict state standards on their realization. Therefore main efforts to increasing efficiency of development of drugs are directed to stages of discovery and optimization of ligands [4].

Methodology

Materials such as journal articles, conference/workshop/seminar papers that were published online were used for sourcing information. Publications from 2000 till date were focused on in other to maintain current information and evolutions. All searches were restricted to articles from peer reviewer articles written in English, information not backed by empirical data was avoided.

Drug Discovery Process

The drug discovery and development process is a long and costly venture. Drug discovery is a series of processes which when followed identify the drug compounds for the effective treatment or control of disease targets. It starts with the screening of large number of chemical compounds to optimize the disease targets [5]. It requires insight information about the structure of the drug receptor so that the drug molecules can be adjusted to the binding site. It takes almost 10 year and one Billion dollar to get 1 drug as shown in the pictures below [6] (Figure 1).

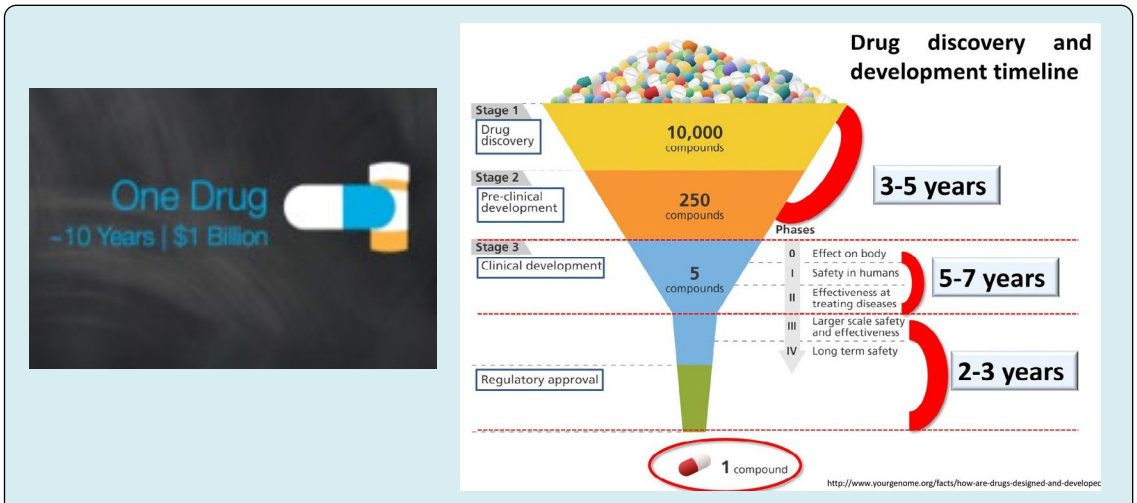


Figure 1: Drug Discovery and Development Timeline.

During the last decades the field of drug discovery process that direct to new ligands finding turns into the modern science employing of computer, bioinformatics and experimental approaches, which are denominated as "rational drugs design". The latter includes two directions: experimental and computer methods (CADD – computer aided drug design). The main experimental methods are combinatorial chemistry and high-throughput screening [4]. Factors affecting drugs discovery have been reported to include Medicinal requirements, screening facilities, expenses of drug development process, and many parameters have been reported to be considered in drug designing which states that drug should be safe and effective, bioavailable, metabolic stable with minimal side effect and be selectively distribute to the target tissue [7,8].

Computer Aided Drug Design

Computer-Aided Drug Design (CADD) or Computational Drug Design is a specialized discipline that uses computational methods to simulate drug-receptor interactions. Below are the stages of CADD and the drug discovery and development pipeline (Figures 2 & 3).

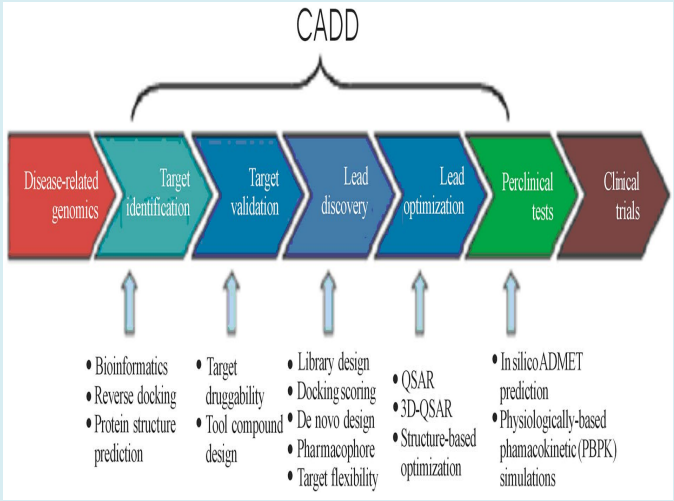


Figure 2: Drug discovery and development pipeline.

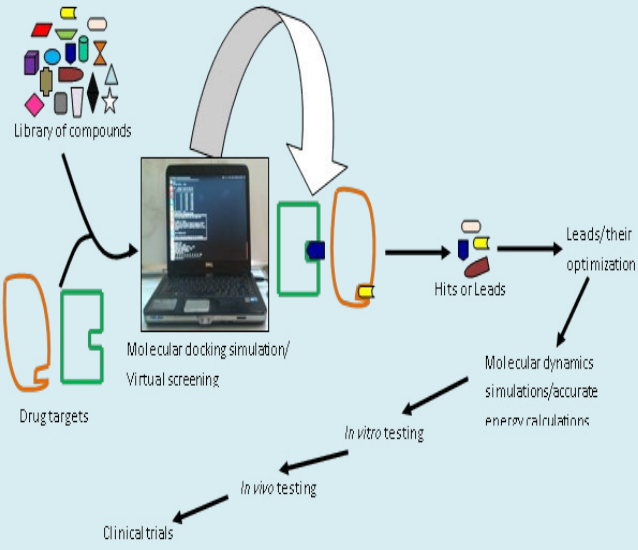


Figure 3: Drug discovery and development chart.

Computer methods of drugs design are based on a postulate that pharmacologically active compounds act by interaction with their macromolecule-targets, mainly proteins or nucleic acids. Major factors of such interaction include steric complementarily of interacting surfaces of molecules, electrostatic force, hydrophobic interaction and hydrogen bonds formation. These factors are mainly considered during analysis and prediction of interaction of two molecules. Both computational and experimental techniques have important roles in drug discovery and development and represent complementary approaches. CADD entails: [9]. Use of computing power to streamline drug discovery and development process [10]. Leverage of chemical and biological information about ligands and/or targets to identify and optimize new drugs [11]. Design of insilico filters to eliminate compounds with undesirable properties (poor activity and/or poor absorption, distribution, metabolism, excretion and toxicity, ADMET) and select the most promising candidates. Applications of CADD include target of structure analysis that is possible binding site detection, candidate molecule generation, docking of generated molecules with target [12,13].

In silicon drug discovery process have been reported to consist of 3 main stages which include identification of therapeutic target and generation of small compounds library for the testing and screening against the target molecule, interaction testing of selected hits by docking at binding sites and subjection of selected compounds to pharmacokinetic studies and the compound that passes the pharmacokinetic parameters is used as a lead compound [14]. Some drugs have been discovered through CADD approaches these drugs include Captopril discovered 1981 used as Antihypertensive drug, Saquinavir discovered 1995 used as HIV inhibitor, Dorzolamide discovered in 1995 used as carbonic anhydrase inhibitor. Indinavir and Ritonavir which were discovered in 1996 and used as HIV inhibitor. Triofiban discovered in 1998 used as fibrinogen antagonist, Zanamivir discovered in 1999 used as Neuraminidase inhibitor, Oseltamivir discovered in 1999 active against influenza A and B viruses. Raltegravir discovered in 2007 used as HIV inhibitor, Aliskiren discovered in 2007 used as Human rennin inhibitor [15].

Natural Products and Drug Discovery

Natural product is a chemical compound or substance produced by a living organism that is, found in nature. There is a strong biological and ecological rational for plants to produce novel bioactive secondary metabolite. Natural products have historically provided many major new drugs. They also provide drugs that would be inaccessible by other routes. They can provide templates for future drug design. The process of drug discovery from natural products have been reported to involves, several steps, from sample collection and vouching through the preparation of extracts to bioassay of the extracts and isolation and structural elucidation of bioactive constituents [16].

Some of the identified natural products or phytochemicals are classified as flavonoids, alkaloid, steroid, terpenoids, phenolic compounds, steroids etc. and all of them have antimicrobial activities which vary from antibacterial, antifungal, antiviral, antimalarial [17].

Drug discovery relied solely on natural products as the primary source of medicines that have significantly influenced the advances in biology and inspired drug discovery and development. Natural drugs or naturally derived drugs are those that contain pharmacologically active ingredients derived from biological or mineral sources and intended for use in the diagnosis, cure, mitigation and prevention of diseases. Evidently, several pathologies were reported to have been successfully treated with natural or naturally derived medicines. Traditionally, natural medicines were extensively used both as concoctions or concentrated plant extracts without isolation of active compounds but advances in experimental procedures in the nineteenth century enabled the isolation and purification of active principles from these plants. Nevertheless, natural products have been the single most productive source of leads for the development of drugs [18].

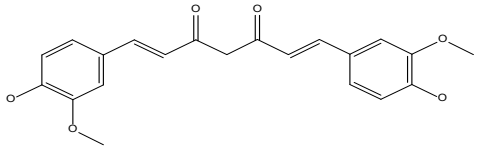
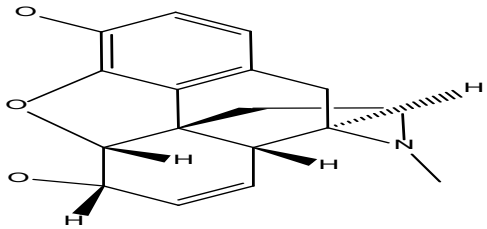
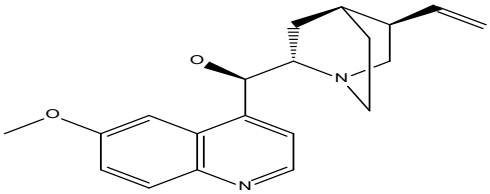
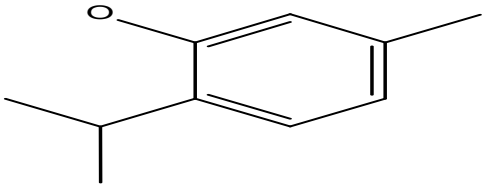
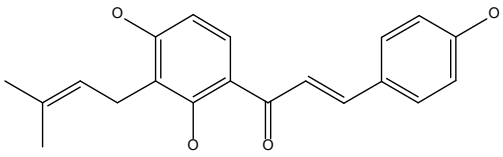
Natural Products and Computer Aided Drug Design an Approach to Drug Discovery

Some researchers have conducted research on drug discovery using computer aided drug design or Insilico method to check the leading drug potential of some natural products some of their results are shown below. Ashish, et al. [19] performed virtual screening of 329 flavonoids obtained from naturally occurring plant-based anti-cancer compound-activity-target (NPACT) database to identify novel PARP inhibitors. The Virtual screening was carried out using different insilico methods which includes molecular docking studies, prediction of druglikeness and insilico toxicity studies, their result revealed Fifteen out of 329 flavonoids achieved better docking score as compared to rucaparib which is an FDA approved PARP inhibitor. These 15 hits were again rescored using accurate docking mode and drug-likeliness properties were evaluated. Accuracy of docking method was checked using re-docking. Finally NPACT00183 and NPACT00280 were identified as potential PARP inhibitors with docking score of -139.237 and -129.36 respectively. These two flavonoids were also showed no AMES toxicity and no carcinogenicity which was predicted using admetSAR. Their finding suggests that NPACT00183 and NPACT00280 have promising potential to be further

explored as PARP inhibitors [19].

Ciddi Veeresham, et al. [20] reported that plants have remained an important source of novel pharmacologically active compounds with many drugs being directly or indirectly derived from plants, the contribution of plants to disease treatment and prevention remain enormous, He stated that 11% of the 252 drugs considered basic and essential in this 21st century by WHO were exclusively of flowering plant origin several recent plants derived compound which have undergo development and have been marketed as drugs include Paclitaxel from Taxus brevifolia for long, ovarian and breast cancer, Artemisinin from traditional Chinese plant Artemisia annua to combat multidrug resistant malaria, Silymarin extracted from the seeds of Silybum marianum for the treatment of liver disease. In recent decade few plant drugs have been launched Arteether, endoperoxide sesquiterpene lactone and semisynthetic natural product derived from Artemisinin used in malarial treatment. Nitisinone derived from natural product Leptospermoe (Callistemon citrinus) is used in treatment of anti tyrosinaemia, galantamine a natural alkaloid (from Galanthus nivalis) for Alzhemer's apomorph is a semi synthetic compound from morphine (Papaver somniferum) used in Parkinson's disease, Tiotropium a derivative of atropine from Atropa belladonna in chronic obstructive pulmonary disease, Dronabinol and Cannabidiol obtained from cannabis plant (Cannabis sativa) and Capsaicin active compound from Capsicum annuum are used as pain relievers [20].

Recent reports have shown some commercially available phytocompound drugs their structure and medicinal properties [21] (Table 1).

Phytocompound	Medicinal properties	Structure
Curcumin	Antibacterial, anticancer, antidiabetic, anti-inflammatory	
Morphine	Analgesic, Pain relievier	
Quinine	Antibacterial, Antimalarial	
Thymol	Antifungal, antibacterial dental care.	
Isobavachalcone	Antiplatelet, antioxidative, antitumor, neuroprotective, anti-inflammatory.	

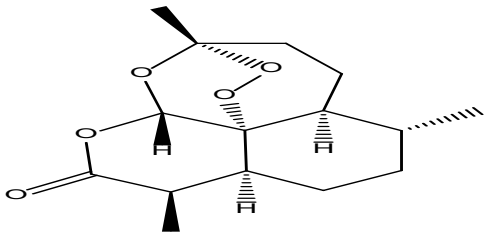
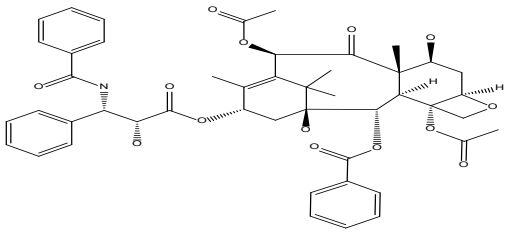
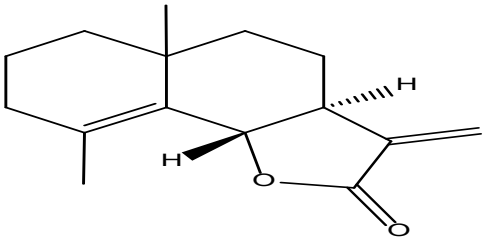
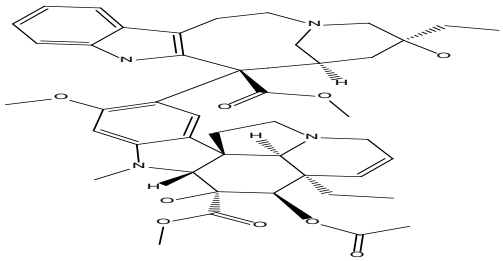
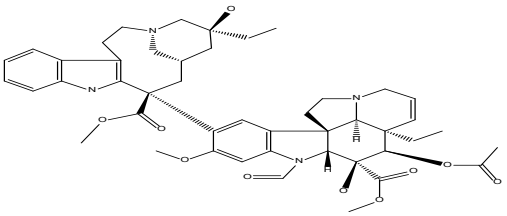
Artemisinin	Antimalarial, antibacterial, autoimmune diseases, anticancer.	
Taxol	Anticancer, antineoplatic	
Arbusculin	Melanin inhibitor	
Vinblastine	Anticancer	
Vincristine	Anticancer, antitumor	

Table 1: phytocompound drugs their structure.

Phytocompounds have been reported to have several advantages over chemical entities like low cost, lower side effects, and higher bioavailability [22]. Computational approaches have shown to help in exploring pharmacokinetic properties, e.g. absorption, metabolism, distribution, excretion, and lethality, and pharmacodynamics data, i.e., affinity, potency, efficiency, and selectivity [23]. As most of the modern medicines have been reported to be derived from plant sources, many phytocompounds are being explored for their pharmacological properties. Computer-aided drug discovery (CADD) has been report as one of the advanced tools in recent times that have certainly increased the effectiveness of the drug discovery process [24]. In addition, other cutting-edge technologies, such as virtual library screening (VLS), ligand-based drug discovery (LBDD), and structure-based drug design (SBDD), have further complemented the drug invention. Several of the commercial and free tools, such as Auto Dock, Schrodinger suite, Discovery Studio, Flex, and many more, are being used in CADD to identify the novel inhibitors for numerous targets. At present, researchers are increasingly using the molecular modeling method as a powerful medicinal chemistry tool to study structure-activity relationships [22,23].

Numerous researches have been reported on the growth of natural product as insight to drug discovery. Some samplings of them have yielded in many significant discoveries for modern medicine in the form of drugs or supplements [25]. Currently, investigation of the chemical diversity of natural products and application of CADD methodologies in combination with experimental validation techniques has been important in identifying and proposing new drug molecules [26,27]. Natural products structures have played a great role in the search for novel agents against many diseases [28]. CADD can be applied either by structure-based method or ligand base method. Structure-based methods utilizes the knowledge of the target binding site (mainly obtained from X-ray, crystallographic or NMR studies) for the construction of a three dimensional (3D) model that can be used for molecular docking or pharmacophore generation and screening on molecular dynamics simulations, some examples are reported by Simoben, et al. [25] while ligand-based method aimed at identifying those structural features that are important and responsible for the observed biological activity of a molecule by considering sets of known active and inactive decay molecule [25].

Conclusion

The diverse therapeutic activity of bioactive molecules present in the numerous organisms applied in traditional medicine justices their use in the treatment of ailments for centuries, however natural products occupy tremendous chemical structural space unmatched by any other small molecule families, but one of the major limiting factors in natural products drug discovery industry is that pharmaceuticals have been traditionally designed to target individual factors in a disease system, but diseases are complex in nature and vulnerable at multiple attacks. Therefore, a systematic novel synergistic drug screening approach based on a multifactorial principle is urgently needed hence the need to combining the knowledge of CADD and natural products as an approach for drug design is paramount. These techniques can proved to be effective in various stages of drug discovery process thus reducing both cost and time taken for developing a drug than conventional methods.

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