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A STUDY ON DIFFERENT METHODS USED FOR DRUG DESIGNING

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Abstract- Drug design, often referred to as rational drug design or simply rational design, is the inventive process of finding new medicationsbased on the knowledge of a biological target. The drug is most commonly an organic small molecule that activates or inhibits the function of a biomolecule such as a protein, which in turn results in a therapeutic benefit to the patient. In the most basic sense, drug design involves the design of molecules that are complementary in shape and charge to the biomolecular target with which they interact and therefore will bind to it. Drug design frequently but not necessarily relies on computer modelingtechniques.In this paper we studied different methods involved in drug designing such as Ligand based,Structure based and Computer Aided Drug Design[CADD].
Keywords- CADD, SAR.

1. INTRODUCTION

Our body contains proteins, carbohydrates, fats and many more. Every process has a chemical conversion that leads to simple and complex processes. It is provided with important precursors like enzymes and neurotransmitters which help in proper functioning of all life processes. In some cases, some function fail due to exogenous and endogenous factors. The exogenous factors tend to disrupt the body functions. The endogenous factor sometimes leads to disorders. The example of disorders due to endogenous factors is the neurodegenerative disorders. There is no particular drug designed for such disorder instead it is developed to improve quality of life. Hence the external aids called**"**DRUGS" are used which helps in retaining back the normal function of body.

Drugs are chemical entities which can be naturally or synthetically produced.According to US law, a drug is a substance which helps in the diagnosis, cure, relief, treatment, prevention of disease, or meant to affect the structure or function of the body. Usually drug can be defined as any chemical that affects the body and its processes.

The discovery of drug is also called as patient-oriented science for developing newer and safer agents.The discovery of drug was started in nineteenth century by John Langley in 1905 when he proposed the theory of receptive substances. Synthetic drug was developed by SacachiroHata who produced arsphenamine in 1910 by structure activity relationship from atoxylwhich is used in sleeping sickness and syphilis by Paul Ehrlich who is known as father of modern chemotherapy. Now a day pharmaceutical chemists are involved in the assessment of therapeutic compounds and their development. Pharmaceutical chemistry encompasses drug design, drug synthesis, and evaluation of drug efficacy and drug safety. Prior to the nineteenth century, schools of pharmacy trained pharmacists and physicians how to prepare medicinal remedies from natural organic products or inorganic materials. In the ancient Egyptian, Greek, Roman, and Asian societiesherbal medications and folk remedies were administered without any knowledge of their biological mechanism of action. It was not until the early 1800s that scientists began extracting chemicals from plants with purported therapeutic properties to isolate the active components and identify them. Chemists are able to design new drugs with enhanced potency and decreased adverse side effects due to the discovery of compounds,their structure and medicinal activity.

The discovery of drug consists of seven basic steps: disease selection, target selection, lead compound identification, lead optimization, and preclinical trial testing, clinical trial testing and pharmacogenomic optimization. There is always repetition of last five steps. For testing compounds can be obtained from natural sources such as plants, animals, microorganisms and by chemical synthesis. Because of the absence or low activity, existence of toxicity or carcinogenity, complexity of synthesis, insufficient efficiency, etc., these compounds can be rejected . The development of drugs includes stages of discovery and optimization of ligands. Because of the genome decoding of various organisms including man, proteomic investigations, discoveries of molecular mechanisms of many diseases and advances of protein chemistry lead to dramatic increase of number of new potential targets. In the research field nowadays more than doing trials directly on animals instead it is first done in computers using certain softwares which helps in saving the life of experimental animal. Hence it is also same in case

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of drug designing, first it is checked using softwares related to drug discovery. The software doesn't just check the efficiency but also helps in designing new drug and development of those drugs. Two categories of research are:
1) Variable activity of similar molecules.
2) Crystallography also called as NMR or homology modelling. The molecular structure of the target macromolecule and the drug receptor is known from x-ray.
Computational design tool is used by pharmaceutical and biotechnology companies majorly all over the world. The lower level contribution replaces the crude mechanical models with structures which accurately reflects on capability of molecular reality on demonstrating motion and solvents effects. The process of discovering the drug is very difficult as it is very costly and time consuming to produce new drug potentials and enlarge the scope of incurring diseases. There are two methods which are widely used in pharmaceutical industry:
1.) high throughput screening
2.) virtual screening
The drawback of the high throughput screening is that it is very costly so most of the drug discovery is done using virtual screening. Nowadays drug can be discovered in a systematic way instead of relying on old trial and error methods. The drug discovery and development is mainly based on two different approaches. Structure and target based drug discovery. In structure based if the compound exhibits desirable pharmacological activity it is refined and developed further, where as in case of target based strategy putative drug target is identified first.The potential target could be a receptor thought to be involved in disease process or critical enzyme, or another biologically, important molecule in disease pathway. The development of any potential drug starts with years of scientific study to determine the biochemistry behind a disease, for which pharmaceutical intervention is possible. The result is to determine the specific receptors (targets) that must be modulated to alter their activity by some means. Once the target is identified, then the goal is to find compounds that interact with the receptor by mass screening.
The other two methods in designing a drug are 1.) ligand based 2.) structurebased.In ligand-based drug design there are mainly two things - the pharmacophore model and the quantitative structure-activity relationship (QSAR) method. Computer methods of drugs design are based on a postulate that pharmacologically active compounds interact with macromolecule-targets, mainly proteins or nucleic acids. Interaction includes various factors such as steric complementarity of interacting surfaces of molecules, electrostatic force, hydrophobic interaction and hydrogen bonds formation. Factors are mainly important only during analysis and prediction of interaction of two molecules. Computational Drug Discovery and Design [CDDD] has rapidly increased in development to which China has made lot of contributions. Because of the financial support from the government and the hardwork by the researchers they are always in top in case of drug design. If we take the example of Structure based drug design the people of china published a lot of research papers and they were ranked fifth during the year 2006-2010.There are 80 universities and research institutions in China which has drug design research departments. The main reason for the good increase in research is because of the major breakthrough in software development and methodology.
There are various computational techniques that include:

1. Target prediction
2. Drug repositioning approaches
3. Docking
4. Scoring algorithms
5. Virtual screening[VS]
6. Lead optimization techniques
7. Absorption, distribution, metabolism, excretion, toxicity
8. Computer-aided drug design(CADD)

CADD helps in field of drug discovery.Computer-aided drug design(CADD) is interdisciplinary subject which plays major role in discovery and development in new drug research.
CADD strategies depend on structural and other information regarding enzymes and the ligands. CADD is a vast subject which deals with applied and basic research. In initial days of drug discovery researchers had faced little information on Structure Activity Relationship (SAR).Rational drug is designed by firstly finding out which proteins can be the drug targets in pathogenesis. Present report on CADD's brief history tells about DNA as target, receptor theory, structure optimization, structure-based drug design, virtual high-throughput screening (vHTS), graph machines.
In the following Section we have studied some papers where the authors have used different computational drug designing approaches.

2. LITERATURE REVIEW

Baldi, A., in his paper said that the development of new drugs with potential therapeutic applications is one of the most complex and difficult process in the pharmaceutical industry[1]. Nowadays due to the technological advances in areas such as structural characterization of bio macromolecules computer sciences and molecular biology have made rational drug design feasible. CADD is not a promising technique but instead it is a practical and realistic way of helping the medicinal chemist.

The databases that supplement the existing resources of information about small molecules and protein structures which was studied by KristianRother*et al.,* [2]. They also discussed about databases like superLigands and superDrug that provide three-dimensional comparison of small molecules and also topology comparison of PDB ligands with known drugs is done.

Sathyaraj A., in his paper discussed about how the field of pharmaceutical chemistry is diverse[3]. He also discussed about how analytical chemists isolate and identify active components from plant and other natural sources and also how theoretical chemists construct molecular models of existing drugs to evaluate their properties. He also discussed about how pharmaceutical chemists evaluate the bioactivity of drugs and drug metabolites.

How drug discovery process have been revolutionized with the introduction of some newer techniques in molecular biology, biotechnology, genomics, and bioinformatics was discussed byAtharMohd*et al*., in their paper [4].The technique like High Throughput Screening (HTS) is a powerful technique which speeds up the screening process. Target oriented development is a plus point, and receptors especially G-protein coupled receptors (GPCRs) has been successfully targeted.

CADD was discussed by MingyueZheng*et al.,* in their paper [5]. They also illustrated about applications of these methods. They also discussed about how China developed in computational drug design and research work related to it. They discussed about reasons behind the development of China in this matter and about major challenges and its future in this field.

Chia-Hsien Lee *et al.*,in their paper discussed about rational drug design process[6].They also discussed about QSAR and pharmacophore models which are widely used techniques in the rational drug design process. They also discussed about how combining QSAR and pharmacophore models with other drug design methods yields a better result. They also discussed about the basics and pitfalls of computer –aided drug design techniques.

Insilico Drug Design was studied and discussed by Le Anh Vu *et al.*,in their paper [7].They also discussed about its importance in discovering new drugs against important targets.They also discussed about the advancement in fields like structural genomics, bioinformatics, cheminformatics, proteomics and computational power lead to great success in Insilico drug design. They also discussed about how the focused libraries of synthesized compounds based on insilicostrategy can create a promising lead which can continue to clinical trials.They also discussed about how each year new targets are diagnosed and the structure of targets is determined.

A.V. Veselovsky and A.S. Ivanov in their paper discussed about Computer –Aided Drug design [8]. They also discussed about how testing compounds can be obtained from natural sources such as plants, animals and microorganisms and by chemical synthesis. They also discussed about how genome decoding of various organisms including man, proteomic investigations, discoveries of molecular mechanisms of many diseases and advances of protein chemistry lead to dramatic increase of number of new potential targets.

Jie Yang, in his research paper discussed about therapeutic effect of TCM which is a multi-component, multi-path, multi-functional, multi-target approach of integrated regulation.It may be difficult to determine their true targets of many TCM ingredients[9]. Therefore, he studied TCM and its chemical constituents to conduct component-wide qualitative and quantitative data analysis by chemomics technology, including integration of modern separation and analysis, comparative chemical analysis methods, and invitro and invivo metabolic analysis. He also explored the mechanism of Chinese medicine using computer simulation which not only can compensate for the deficiencies of pharmacology experimental methods, but more importantly establish new concepts and advanced research tools in TCM research areas. This helps to provide new ideas and new ways for TCM research which is expected to make modernization of TCM into a track of healthy development, and provide strong support of modern science and technology for TCM into the world.

The successful stories of CADD application in drug discovery in recent years have demonstrated the potential value of CADD in drug development and was discussed by *Pranita P. Kore et al.,* in their paper[10]. They also discussed CADD's approaches which provide valuable information for target identification and validation, lead selection, small-molecular screening and optimization. They also discussed about sub disciplines of CADD which demonstrated promising application for design of drug. They also discussed about the latest technological advances (QSAR/ QSPR, structure-based design, combinatorial library design, chemoinformatics& bioinformatics); the growing number of chemical and biological databases; and an explosion in currently available software tools are providing a much improved basis for the design of ligands and inhibitors with desired specificity. They also discussed that their review would be helpful for design of drug with minimal side effect and high potency.

Elvis A. Martis and Rakesh R. Somaniin their paper discussed that many more approaches like metabolomics, genomics, proteomics also compliment well with the other techniques so that more target specific agents can be discovered with more accuracy[11]. They also discussed about findings of the human genome project which has added more understanding to the target identification. They also discussed about exploring natural sources which is ill-explored should be effectively done as nature is source of countless chemicals which could lead to a successful drug candidates.

Several potential drugs which are far advanced in clinical trials which are the result of structure-based design was discussed byChristophe and wim, in their paper [12]. As they discussed, they said drug design now requires the development of computer programs to cope with flexibility of ligands and proteins, and accurate ways of scoring interactions. Membrane proteins have so far been largely ignored in structure-based drug design processes since so few structures of membrane proteins are known. Recently, however, the structure of prostaglandin synthase, a membrane-associated protein which is the target of aspirin, has been reported. They also discussed about further developments should be done in computer programs

which predict the effect of blocking an enzyme in a pathway on the flow of metabolic or signals through the pathway. They also discussed about many activities going on which is hard to keep up with all developments on so many frontiers.

3. CONCLUSION

Drugs are chemical entities which could be either produced naturally or synthetically.The drug discovery is a patient-oriented science for developing newer and safer agents for patients.In this paper we have discussed various insilico methods for designing a drug.This paper also discusses CADD approaches in drug development, therapeutic effect of TCM andrational drug design process. Because of technological advances, findings of the human genome project, growing number of chemical and biological databases, an explosion in currently available software tools are providing a much improved basis for the design of ligands and inhibitors with desired specificity. All these methods will be helpful for designing of drug with minimal side effect and high potency which is very much needed in the present scenario.

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