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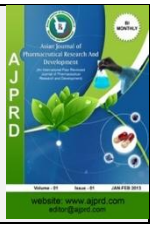

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Review Article

An UpdatedReview onBioinformatics and Pharmacogenomics in Drug Discovery and Development Process

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A B S T R A C T

Drug discovery and development is a time taking process, it has high risk also. Sometimes it get positive result, sometimes not. To discover, development and bring it into the market; pharmaceuticals companies invest millions of money. From drug discovery to bring it into the market these is a step by step procedure, it requires proper human resources, updated technological support and huge investment. A convenient surveillance is needed into the whole process from discovery to marketization that new entity. So these are the reasons for increasing cost in new drug development and research. But in recent time bioinformatics and pharmacogenomics made a huge impact on new drug development. Its helps in drug target identification, drug designing, clinical trial, not only bioinformatics and pharmacogenomics reduces the cost in healthcare management but also improves the selection of proper effective therapy and development of personalized medicines.

Keywords: Drug discovery, development, new drug, bioinformatics, pharmacogenomics, cost factor, personalized medicine

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INTRODUCTION:

There are several approaches which have been taken by pharmaceutical companies to identify new chemical entity. As per data to obtain a new chemical compound there is a need to examine 5000-10000 chemical compounds in the laboratory.[1,2] Amongst these 250 chemical compounds will be selected for preclinical trail. For next clinical trail 5 chemical compounds are selected. To discover, develop a new chemical entity it will take a 10-15 years of hard work to bring that particular drug into the market.[3,4] For these whole procedure a huge amount of financial capital, physical labor and time are invested. To reduce the financial investment, physical labor and time, bioinformatics and pharmacogenomics are one of the prime options nowadays and will be very helpful in future drug development and research.[5]

Bioinformatics In Drug Discovery And Development:

Bioinformatics is a science which employs the computational tools, information technology into the molecular biology such as genes, DNA, RNA, or protein mostly useful in comparing genes and sequences in proteins.[6,7] Bioinformatics stores these data, arrangement and helps in identification, archiving, interpretation, analysis, visualization in further molecular biology research and development. Bioinformatics is one of main branch of pharmaceutical biotechnology, it helps in personalized medical treatment, genomics, proteomics and also used in novel drug discovery and development.[8,9,10]

Designing of new drug: Drug design is one of the most significant step for new drug discovery and development. Advanced bioinformatics is plays an important role on it. The drug design depends upon various factors such as (a)

Identification of new drug targets (b) 3D structure of PDB database (c) advance bioinformatics (d) tools for detecting protein-drug interaction.[11]

Types of drug design: Basically there are two types of drug designing process.

(a) Ligand based drug design: Molecules those are binds with target. In ligand based drug designing 3D quantitative structure activity relationship (3D QSAR) and pharmacophore modeling are mostly used. [12]

(b) Structure based drug design: In structure based drug design using the X-ray crystallography, the protein structure of newly discovered chemical entity are compared with a known protein structure.[13]

Ligand based drug design	Structure based drug design
3D QSAR, ligand structure information, Pharmacophore modeling, ligand based virtual screening	Target structure, ligand docking, De novo design

Drug target identification: Drug target identification is one of the main approaches of bioinformatics. Through the bioinformatics study we can identify the biologically active entity, activity of the constituents, target organ and storage as well. It is very necessary to identify and study the drug target for the final development of the new discovered drug.[2,14,15] From bioinformatics we can determine the human genome sequence, by determining the human genome sequence the characteristics of gene and coding of target protein can be identified, which will help in the development of a new drug. More and more biological targets can be identified and analyzed from bioinformatics and it is having a great potential in future in drug development and it will be beneficial for the pharmaceutical companies also.[16,17,18]

Validation: To store and manage available drug target information Bioinformatics is very useful it also provides different algorithm and Strategies for the prediction of new drug targets. After the successful discovery of potential drug targets it's very important to establish a strong relation between a putative target and a disease of interest.[19,20] The establishment of this kind of relation is very important to justify the drug development process. Bioinformatics is playing a significant role in the process name in target validation. Drug target validation is very essential for the clinical testing and approval phases of the drug.[21,22,23]

Reduction of cost: Drug discovery, development to bring that particular drug into the market is very costly procedure.Pharmaceutical companies invests lots of money into these. Sometimes it may not give positive result also; on such cases pharmaceutical companies face a huge loss. For which some of the companies do not pay any interest in development a new drug in future.[5,24,25] So pharmaceutical companies wants more productivity along with less investment. In such cases bioinformatics plays a key role in new drug discovery, development. It helps to reduce the failure rate. Basically bioinformatics accelerates the whole process from discovery, development to clinical trials. It helps to select drug target identification, validation, assay development to virtual-high-throughput screening (v-HTS). In this way bioinformatics reduces the cost in discovery, development of a new drug.[21,27]

Promote new drug and novel drug development:

There are so many subsequent costs that can disturb the pharmaceutical industry including commercialization cost, litigation and drug recall cost, general cost to society etc. Per approved drugs the commercialization costs would be to 250 million dollars; this is a high one because most of the new drugs are the replicas of the existing drugs.[1,3] Commercialization is very important to gain attraction of both physician and patients to reuse the copycat drugs. Bioinformatics act as interface and provides so many approaches and opportunities to the pharmaceutical companies to discover the new drug targets and develop novel drugs. If the Novel Drug can be developed then the cost of the drugs will be lower than the expected because there will be no such competition with the existing drug.[28]

Barriers of bioinformatics in new drug development:

Bioinformatics could not make any perfect changes in the drug Discovery and development process because the practice is new and has a limited access. And till now the Bioinformatics could not make any considerable impact on the cost of the drugs the cost of the drugs is continuing to rise. Many pharmaceutical industries are facing drug Discovery and development related challenges and it has been observed very clearly; including high cost of the drug discovery to the length of the drug development process the risky trials and the approval process as well. But sometime the the approved drugs and the marketing procedure and innovation gap could be the the main problem of drug development process. These problems are remaining unsolved despite having a good bioinformatic investment. So this is an indication of a larger problem in the future. So we have to solve the problems and use bioinformatics for the betterment of the pharmaceutical industries.[29]

Different bioinformatics tools and databases:[30]

Bioinformatic tools	Databases
STRING	Molecular interaction
SMART	Functional information of proteins
MINT	Functional interactions of different biological molecules
Path BLAST	Used to search molecular interaction
Potential Drug Target Database	Information about drug target
Graemlin	Multiple network alignment
CFinder	Finding of nodes
IntAct	Data analysis of molecular

	interaction
MOLPHY /PAML	Phylogenetic analysis tool
PharmGKB	Detects drug-gene interaction
SuperTarget	Drug-target database
STITCH	Metabolic pathways database
scRNASeqDB	Database on gene expression as per RNA sequences
Virus Finder	Used to find viruses and their interactions

PHARMACOGENOMICS IN DRUG DISCOVERY AND DEVELOPMENT:

Pharmacogenomics can be defined as the study of genes and how the drugs can affect the individual responses. It's new branch including both the Pharmacology and the genomics for the development of effective doses and medications. Human Genome Project is helping to learn the relation between the genes and its effect on the body responses to medications. Different genetic makeup provides different effectiveness of medication and their adverse drug reactions for every individuals. After all these advancements pharmacogenomics is lagging behind till the date. The use of pharmacogenomics is limited nowadays but there is a high chance of this approach in near future to treat the widespread health problem like cardiovascular disorders, HIV, cancer etc. and it will help the mankind.[30,31]

Personalized medicine:

Recent advances in pharmacogenomics helps to recognize the different reactions of a drug. With the elevation of Genomics, pharmaceutical technology, pharmaceutical biotechnology, microscopy, advance technology make personalized medicine more available nowadays. Basic concept of personalized medicine is the link between Health and gene. In personalized medicine, patient's family health histories has been documented and from this documents genetic sources of the particular disease or disorder has been identified.[32,33,14] The drug of personalized medicine recommend based on an individual genomics. Molecular interaction, microRNA profiling helps to recognize the disease mechanism. Not only that genetic sequencing, haplotype mapping, SNP genotyping also plays an important role to identify risks and vulnerability of that particular disease or disorder.[34,35] Implementation of personalized medicine therapy reduces the risk of toxicity and other adverse effects as well as it will improve the outcome of treatment. The trial and error approach will be replaced by a better understanding of the individual variations and their effects on toxicity, drug metabolism and excretion. For a few medications only the evidence of the clinical utility of pharmacogenetic testing is available and FDA only requires pharmacogenetic testing for a small number of drugs.[36,37]

Restoration of orphan drugs:

Pharmaceutical companies mainly focus on the major drugs which are prescribed for the diseases affecting 20 million people or more. These are called as blockbuster drugs. As a result we can see there is a loss of drug which are developed to cure the diseases which affect a small number of people. These drugs are called as potential drugs or abandoned drugs or orphan drugs. So if pharmacogenetic genomic strategy could be adapted this will develop and revive the orphan drugs and help in demonstrating their potential beneficiaries.[38] As a business point of view of pharmaceutical companies, they will help in developing the orphan drugs to encourage the the reduction in the size of a population to be treated and this is the only way they could give up the blockbuster drugs and encourage the orphan drugs.[39,40]

Nowadays various international food and drug authorities have recognized the Pharmacogenomics and encouraged their approaches for drug discovery and development. But there are some resistance to use these approaches. The reason behind this kind of resistance is some perception that the use of pharmacogenomics strategy will lead to some significant loss of revenue of the drug market. But such perception is completely rejected and considered as MYTH by some of the workers and they have reported that the use of these pharmacogenomic strategies will increase the drug market size and they have the potential for the future.[41]

Limitations of Pharmagenomics Progress in Drug Designing and Development:

Pharmacogenomics study is based on the genomic variations specifically the coding regions. But practically it is very difficult to predict the gene variations and the coding regions. For the drug response single nucleotide polymorphism (SNP) plays an important role in this drug response. SNPs occur every 100 to 300 bases amongst the 3 billion base Human Genome. So millions of SNPs should be identified and analyzed to determine the involvement of the genomics in drug response.[42]One of the main limiting factors of this pharmacogenomics based drug delivery is the limited awareness and knowledge of the relationship between gene variations and variable drug response. There is an another limiting factor for this process that it is a very time consuming and complicated process and which may not be possible in near future because many genes are likely to influence responses so it will make a big process to select the specific genes amongst. For this genomic process each and every doctor, physician need a better understanding of genetics and they need to execute an extra step to determine which drug is the best for each patient and the treatment should be different for each patients as well. The economic factors should also be kept in mind for the future.[43,44,45]

CONCLUSION:

Drug designing and development is a very expensive and time consuming process. It's is a very complex one as well. To overcome the cost and time related problems bioinformatics and pharmacogenomics work as a frontier. Bioinformatics provide a wide range of drug related data bases and software; pharmacogenomics provide the genome level information; both the informations are very important for pharmaceutical companies to design a new drug.

Though bioinformatics and pharmacogenomics are still in the initial phases and facing some limitations but they have the potential to become a front liner in the drug development process in the future.

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