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DRUG DISCOVERY & DEVELOPMENT: A REVIEW ARTICLE ABOUT GOALS, PHASES, TOOLS OF DRUG DEVELOPMENTAND CHEMICAL COMPOUND LIBRARY

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ABSTRACT

This article provides brief information about the discovery and development. Drug discovery is a long process that may take many years (12-15 years) for designing and developing a few therapeutically effective drugs. It is a very complex, time time-consuming cost-effective process. There are approximately 10,000 compounds are taken for testing in labs 100 compounds are looking for hit molecules from them approx. 10 compounds are found to be lead compounds and only 1 compound is approved as a therapeutically effective drug approved for marketing and use. Drug development and discovery include a number of steps and phases in their process. Nowadays there are various latest tools and technologies used in the development and discovery process. These tools and technologies are easy, less time-consuming accelerated (ADME – Tox) assessments. They can reduce the number of chemical compounds to be evaluated. This review article provides a brief overview and knowledge about the process, phases, tools, and techniques of Drug Discovery and Development process.

KEYWORDS: Drug discovery, Drug development, phases, goals, tools, chemical compound library, FDA approval.

1. Drug Discovery and Development History

The process of locating chemical entities with the potential to serve as medicinal agents is known as drug discovery.[1]

The first pure pharmacologically active molecule to be separated from a plant was **morphine**, which was obtained from the opium produced by cut seed pods of the poppy, **Papaver somniferum**, in 1799 by Friedrich Sertürner, a 21-year-old pharmacist's apprentice. This ushered in a time when drugs derived from plants could be refined, analyzed, and used in exact dosages that did not change depending on the material's origin or age. The discovery of penicillin led to an expansion in pharmaceutical research after World War II, including extensive screening of microbes for novel antibiotics. By 1990, natural compounds or their analogs inspired by them made up around 80% of all drugs. Medicine was revolutionized by the development of antibiotics (such as penicillin, tetracycline, and erythromycin), antiparasitic (such as ivermectin), antimalarial (such as quinine, artemisinin), lipid-controlling drugs (such as lovastatin and analogs), immunosuppressants for organ transplants (such as cyclosporine, rapamycin), and anticancer drugs (such as Taxol).[2]

Throughout the 1960s and 1980s, regulators, academics, and drug developers collaborated to create and improve methods for designing, carrying out, and analyzing randomized controlled clinical trials that could generate the required evidence. This period saw the introduction of numerous significant pharmacological advancements, including cardiovascular remedies, psychiatric drugs, anti-infectives, and cancer treatments. The evidence produced by drug development initiatives was still fairly scarce, nevertheless. As more drug therapies became accessible in the middle of the 1980s and into the 1990s, the FDA and the global regulatory community created the expectation that such data would be gathered throughout the majority of drug development programs. As a result, compared to the norm from 1960 to 1985, modern development programs are often significantly longer, much more detailed, and much more patient-centered.[3]

More drugs than those for any other disease are now being developed to treat cancer. While this has given rise to new drug waves, the downside is that these novel compounds have unique modes of action, drug kinetics and dynamics, response types, and toxicity profiles, which make conventional early clinical trial designs less effective and efficient.[4] Goals include shortening clinical development durations, reducing research and development expenditures, and enhancing judgments to move through the various phases with a higher degree of

assurance in exchange for fewer failedattempts.[5]

2. Drug developmentIntroduction

Drug development refers to all the procedures and actions necessary to take a compound from a drug candidate (the result of the discovery phase) to a finished good that has been given the go-ahead by the relevant regulatory bodies.[6]

Finding a molecule that is therapeutically effective in treating and curing disease is the goal of the drug discovery process. The selection of candidates, synthesis, characterization, validation, optimization, screening, and tests for therapeutic efficacy are all parts of this process.[7]

Drug development may not proceed in a straight line from target identification to drugscreening to optimization to clinical trials.[7]

The process of finding a drug molecule that is therapeutically effective in treating diseaserequires many different steps.[8]

When researchers discover a biological target (such as a receptor, enzyme, protein, gene, etc.) implicated in a biological process through malfunctioning individuals with a disease, they can then begin to design a new drug.[10]

It takes almost 12-15 years to develop a single new drug molecule from the time it is discovered when it is available on market fortreating patients.[8]

In the pipeline for inquiry and development, just one out of every 5,000–10,000 compounds eventually receive approval.[8,13]

The cost of creating a new molecular entity (NME: a small molecule chemical) or new biological entity (NBE: an antibody, protein, gene therapy, or other biological drugs) is unquestionably over $1 billion and, onaverage, has been estimated to be around $2.6billion.[10,11]

3. Goals of drug discoveryand development

One of the main objectives of drug discovery is to promote the recognition of novel molecular entities that might be useful in thetreatment of illnesses that meet the criteria forunmet medical requirements.[9]

The development of the drug has a defined objective to generate the drug in a marketable form and to obtain regulatory approval to commercialize it as soon as possible for usage in specific indications.[8]

The drug development process is designed to "Fail Fast, Fail Early" in order to eliminate important risks before making an expensive large-stage investment, especially at the levelof clinical development.[8]

Emerging models are being developed to reflect this reality and offer greater flexibility, improved collaboration, andincreased preclinical research that may decrease the need for unnecessary human investigations.[12]

4. Phases of Drug Discoveryand Development

Stages of drug discovery anddevelopment include:

- Target identification
- Target validation
- Lead optimization
- Product characterization
- Formulation and development
- Preclinical research
- Investigational new drug
- Clinical trials
- newer drug application
- Approval

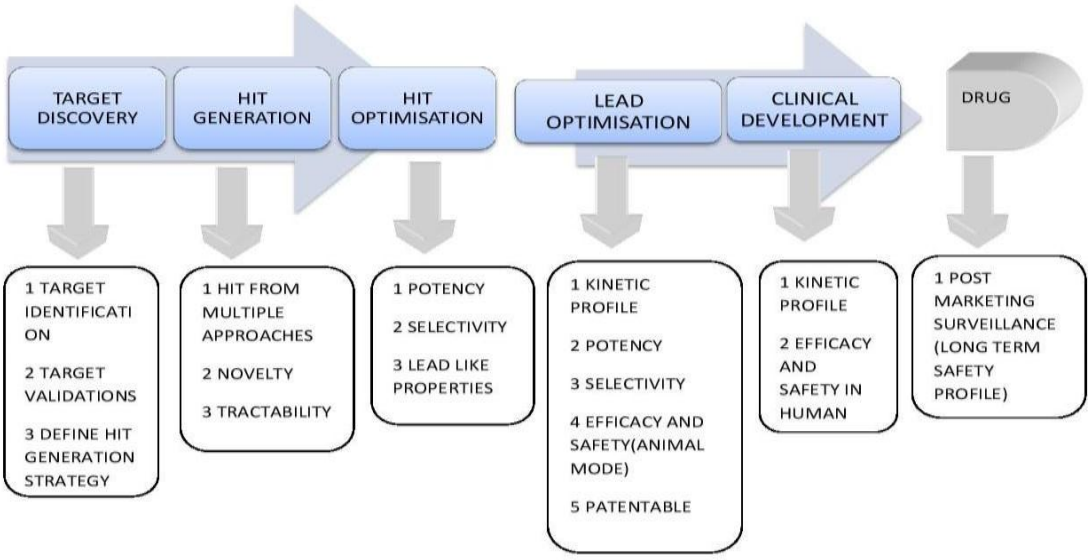

Figure 1: Steps of Drug Discovery & Development.

I. **Target Identification-** Finding the biological cause of an illness and prospective targets for treatment is the first stage in the discovery of a drug.

The molecular mechanisms that the targettargets are then characterized when it has been identified. A good target should be effective, safe, fit clinical and business needs, and be treatable with drugs. Principles from molecular biology, biochemistry, genetics, biophysics, or other fields may form the foundation for target identification strategies.[14,15]

II. **Target Validation –** The process of confirming the intended molecular target, such as a gene, protein, or nucleic acid of a tiny chemical, is known as target validation. Determine the structure-activity relationship (SAR) of small molecule analog, creating a drug-resistant mutant of the putative target knockdown or overexpression, and monitoring the known signaling pathway downstream of the presumed target are all examples of target validation methods. It is the process of proving the functional significance of the chosen target in the manifestation of the disease.[16,17]

Target validation can be broken down into 2 key steps:[18]

1. **Reproducibility:** The first stage is to repeat the experiment to ensure that it can be successfully duplicated after the pharmacological target has been discovered, whether via the use of specialized technology or through a review of the literature. Affinity chromatography, expression cloning,protein microarray, reverse transfected cell microarray, biochemical suppression, siRNA, DNA microarray, system biology, and analysis of currently available drugs are all components of the target validation technique.

2. Introduce variation to the ligand (drug) –target environment –

- Genetic manipulation of target genes (in-vitro) knocking down the gene (shRNA, siRNA, miRNA), knocking out the gene (CRISPR), knocking in the genes (viral transfection of mutantgene)
- Antibodies interact with the target with high affinity and block further interaction
- Chemical genomics chemical approaches against genome encodingprotein.[19,20]

Identification of lead – A chemical lead is described as a synthetically stable, practical, drug-like molecule that exhibits adequate specificity, affinities, and selection for the target receptor in primary and secondary testing. Chemical lead has the following characteristics:

SAR Defined

- Drug ability (preliminary toxicity, HERG)
- Synthetic feasibility
- Select mechanistic assay
- In vitro assessment of drug resistance and efflux potential
- Evidence of in vivo efficacy ofchemical class
- PK/ Toxicity of the chemical class known based on preliminary toxic or in silico studies.[21]

III. **Lead optimization-** After a first leadcompound is identified, a drug candidate is created via the lead optimization procedure. The procedure entails an iterative series ofsynthesis and characterization of a prospective drug to develop a model of the relationship between chemical structure and activity in terms of interactions with targets and metabolism.[22]

IV. **Product Characterization-** The size, shape, strength, weakness, use toxicity, and biological activity of any novel drug molecule that demonstrates a prospectivetherapeutic activity are used to describe the molecule. The earlystages of pharmacological research are useful for defining the compound's mode of action.[23]

V. **Formulation and Development-** To create a bioavailable, stable, and ideal dosage form for a particular administration route, the physicochemical characteristics of active pharmaceutical ingredients (APIs) are characterized during the pharmaceutical formulation stage of drug development.[23]

During Preformulation studies the following parameters are evaluated

- Solubility in different media andsolvents
- Dissolution of active pharmaceutical ingredient (API)
- Accelerated stability services under various conditions
- Solid-state properties (polymorphs, particle size, particle shape, etc.)
- Formulation services and capabilities
- Formulation development of new chemical entity (NCE)
- Optimization of existing formulations
- Process development for selecteddosage forms
- Novel formulations for improveddelivery of existing dosage forms
- Controlled release and sustainedrelease formulations
- Self-emulsifying drug deliverysystems
- Colloidal drug delivery systems
- Sub-micron and nano-emulsions.

VI. **Preclinical Phase (Phase Zero) –** The preclinical phase's goal is to further reduce the pool of therapeutic candidates for later human trials. This is accomplished through in vitroresearch using human cell fractions and cultures, whole animal studies of metabolism, pharmacokinetics, and toxicokinetics, and the creation and use of biomarkers all along the

way to provide earlier signals of efficacy, toxicity, and factors to take into account when developing an acceptable clinical formulation.

- **Phase 1-** This phase's objectives, which are primarily to provide information on acute tolerability and safety, dose-plasma concentration profiles, maximum safe doses and concentrations, routes of metabolism and elimination, and preliminary estimates of the variability associated with these measurements, are carried out in healthy subjects or in somecases patients.[24]
- **Phase 2 -** The evaluation and validation of ineffective treatment concepts (efficacy), the affirmation of acute tolerability, the maximum safe dose, plasma concentration, and the absence of acute safety issues in patients are the main objectives of this phase's initial component (Phase 2A). In the second compartment (Phase 2B), concurrent goals include gathering more proof of effectiveness and investigating dose schedules that will be used in Phase 3 with the general target population.
- **Phase 3 -** studies using a larger patient population in this confirmatory phase are meant to offer documentation of clinical efficacy and safety, a more complicated adverse reaction profile, as well as sources (covariates) and estimates of variability in dose-response related toboth PK and PD.[24]

VII. Investigational New Drug Process

The Investigational New Drug (IND) Process requires drug developers to submit an IND application to the FDA prior to starting clinical trials.[25] Developers must include the following in the IND application:

- Preclinical and toxicity study data
- Drug manufacturing information
- Clinical research protocols for studies to be conducted

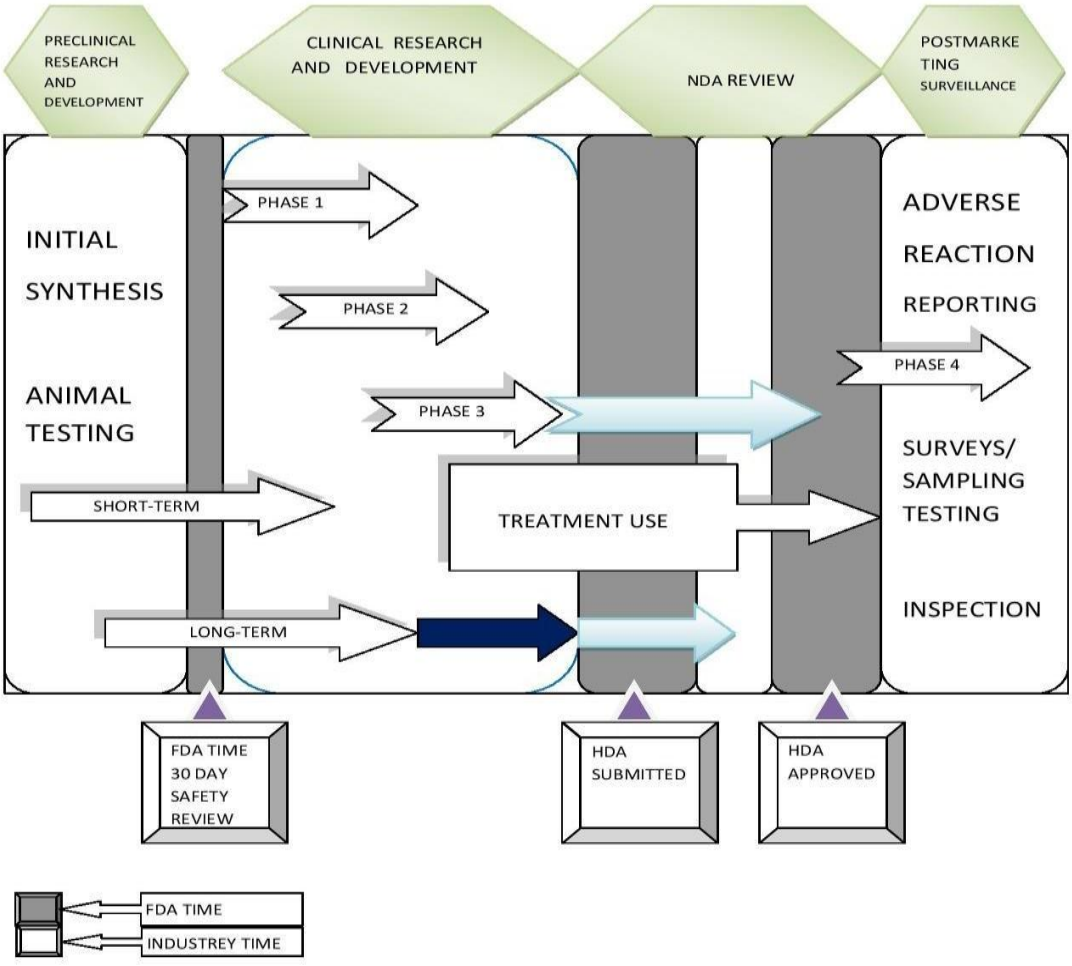

Figure 2: Different Phases in Drug Development.

- Previous clinical research data (if any)
- Information about the investigator/developer.[26]

VIII. New Drug Application

The whole narrative of a therapeutic molecule is expressed in a New DrugApplication (NDA). Its goal is to confirm that the drug is secure and efficient for the investigated individuals. From preclinical data through results from a Phase 3 trial, the NDA for medicine must contain all relevant information. Reports on all studies,

data, and analysis are required from developers.[27] In addition to the results of clinical trials, developers must comprise:

- Proposed labeling
- Safety updates
- Drug abuse information
- Patent information
- Institutional review board complianceinformation
- Directions for us.

IX. Phase 4: Post-Market Drug Safety

Monitoring Phase 4 trials are carried out afterthe FDA has given the drug or device its approval. These studies are also acknowledged as a part of post-approval pharmacovigilance and technical support that involves marketing surveillance. The effectiveness, financial viability, and safety of participants in real-world situations areassessed in Phase 4 trials using a variety of observational methodologies and evaluation patterns. Phase IV studies might be mandatedby regulatory bodies (such as a risk management/minimization action plan change in labeling) or carried out by the sponsoring corporation for other factors, such as competition. Therefore, during the monthsand even years that make up a drug's shelf lifein the market, a genuine depiction of a drug'ssafety is essentially required. FDA reviews reports of complications with prescription and OTC drugs and can decide to add precautions to the dosage or practice information, as well as other events for more serious adverse drug reactions.[28]

5. Tools of Drug Discovery

Preclinical and clinical trials, lead molecule discovery and optimization, target identification and validation, and other traditional drug discovery and development procedures are risky and time-consuming.[29]

Usually, in vivo and in vitro methods are used to investigate the toxicity and side effects of drugs as well as their safety. (ADME-Tox) examinations have been sped up recently thanks to improvements in vitro models suchas organ-on-chip technology.[30]

These methods are nevertheless expensive, labor-intensive, and time-consuming. In order to quickly find pharmacologically active chemical compounds from a huge number of molecules utilizing automated tests, high-throughput screening (HTS) techniques have been developed.[31] Despite the fact that automatic HTS systems lessen the requirement for human intervention, the scope of HTS is still small in comparison to the variety of chemical structures. Additionally, automated toolscontinue to be pricey.

In recent years, computer-aided drug discovery (CADD) methods have gained popularity because they can assist reduce thescale, time, and expense issues thattraditional experimental methods encounter.

In CADD, possible pharmacological targets are computationally identified, massive chemical libraries are virtually screened for promising drug candidates, potential drug candidates are further optimized, and potential drug toxicity is in silico assessed.

By excluding ineffective and harmful chemical compounds from consideration, CADD methods can decrease the number of chemical compounds that must be tested experimentally while raising the success rate.[32]

To increase the precision and effectiveness of CADD procedures, a number of CADD approaches have been created and linked with machine learning strategies.[33]

There are two main methodologies used in CADD: ligand-based drug discovery (LBDD) and structure-based drug discovery (SBDD).[35] The target protein must have structural information, which is often acquired experimentally by nuclear magnetic resonance or X-ray crystallography.[34] When neither is available, the 3D structure of the target protein can be predicted using in silico prediction techniques such as homology modeling[36] or ab initio modeling.[37]

The LBDD methodology is frequently used as an alternative when the structure is unavailable and in silico approaches cannot predict a high-quality structure.

Unless the target is novel, numerous compounds have been found to treat diseases and are compiled in public databases, even though this strategy requires prior knowledge of the known active molecules of the target protein.[38-40] The discipline of CADD is developing quickly, and new approaches and methodologies are being actively developed.The fusion of biological big data and machine learning techniques in recent years has created new opportunities to improve the precision and effectiveness of in silico drugdevelopment.

In silico methods for drug screening Finding small molecules that can alter a target protein's function and, as a result, alterthe phenotype of a disease, is the aim of drug discovery. For many years, the pharmaceutical industry has benefited greatly from in silico drug discovery technology.[41–43] In silico drug discovery primarily offers cost and time savings. Additionally, it can be used at any stage of the drug discovery process, including the preclinical and clinical stages[44], which significantly lowers thelikelihood of failure.

Ligand-based drug screening

To forecast new drug molecules with comparable biological effects, LBDDtechniques use prior knowledge about activemedications, such as their structural,physical, and chemical characteristics.[45] When the target protein's 3D structure isunknown, LBDD is typically used. In the lackof knowledge of the protein structure,techniques like pharmacophore modeling and QSAR provide helpful information on target-ligand interactions.[46] There are a

number of freely accessible compound libraries for virtual chemical compound screening.

Similarity searches

Compound similarity searches are popular and reliable ways to find novel compounds that resemble existing active substances. These techniques are predicated on the notion that molecules with similar physicochemical characteristics are more likely to exhibit similar biological activity.[47,48] A similarity search strategy has recently been used to identify a large number of effective compounds.[49] For instance, this strategy was used to create agonists for the G-protein- coupled receptor GPR30.[50]

Pharmacophore modeling

Sets of electronic and steric characteristics known as pharmacophores are necessary for a drug to be recognized by a protein target.[51] Compound libraries are screened using pharmacophore models as a query to find substances with similar structural characteristics and physicochemical characteristics. The commercial pharmacophore modeling platform (PHASE)[53], 3D-pharmacophore modeling software (HipHop), 3D QSAR pharmacophore generating software (HypoGen), and Ligand Scout[52] are some of the tools available for pharmacophore modeling. More powerful medicinal molecules have been found using pharmacophore modeling.[54–56] By using pharmacophore modeling, for instance, new inhibitors against the type II topoisomerase bacterial DNA gyrase B have been created as powerful antibacterial medications.[57]

Quantitative structure-activityrelationships (QSAR)

The mathematical models created by QSAR techniques relate the structural and physicochemical characteristics of substances to their biological activity. The QSAR method, which was first devised by Hansch and Fujita in 1962[58], is a standard one for finding new drugs. In this approach, QSAR models are trained using molecular descriptors[59] that capture the structural and chemical characteristics of compounds, and the trained models are then used to predict the biological activity of specific chemicals to find novel drug candidates or improve lead molecules.

In order to get around the constraints of the traditional QSAR methods, 3D-QSAR approaches have recently been developed [60]. Comparative molecular field analysis (CoMFA) and comparative molecular similarity indices analysis are two categories of 3D-QSAR methods (CoMSIA). To get over these restrictions, CoMSIA was created. It computes steric and electrostatic grids as well as hydrophobic and hydrogen bonding properties using an exponential functional form derived from the SEAL alignment algorithm.[61] To get over these restrictions, CoMSIA was created. It computes steric and electrostatic grids as well as hydrophobic and hydrogen bonding properties using an exponential functional form derived from the SEAL alignment algorithm.[61]

Structure-based drug discovery

"Corpora non-agunt nisi fixate" refers to the idea that medications do not work unless they are bonded, according to German researcher Paul Ehrlich, who made significant discoveries in pharmacology.[62] Unlike ligand-based drug discovery, SBDD uses the structures of the ligand and the target protein to determine the binding affinity between a ligand and a target protein, specifically a binding pocket.[63] This strategy makes use of molecular docking, fragment-based docking, and molecular dynamics modeling to forecast binding affinity. SBDD methods were effectively used to generate a number of medications that are currently through clinical trials or have received FDA approval.[64]

Target protein structure generation Finding a high-resolution 3D structure of the target protein, which may be available in the Protein Data Bank, is the first stage in SBDD(PDB). If the structure hasn't been determined yet, it can be predicted using data from other structures with related sequences or from scratch.[65]

Binding site prediction

A protein's concave section or tiny pocket is known as a binding site, and it is here that a ligand molecule attaches to create the desired result (activation, inhibition, or modulation). Although these methods can be extremely helpful in detecting potential binding sites, the accuracy of their predictions is affected by a number of variables, including template similarity and pocket-size.[66]

Molecular docking

The next stage is to use molecular docking to find ligands with a high affinity after a target protein's 3D structure has been established. The optimal orientation of a specific ligand within a target protein's binding pocket is predicted by molecular docking algorithms, which also use van der Waals and electrostatic interactions to determine the ligand's affinity. When several compounds are quickly screened during the first virtual screening, this strategy is typically used. The outcomes of rigid docking are improved and optimized using flexible docking techniques.[67-69]

Fragment-based docking

With the use of molecular docking, fragment- based docking has revolutionized the process of drug development. Substructures (fragments) are found in drug compounds. Some of these fragments, like the pharmacophore, are necessary for demonstrating biological effects, whereas others are just employed structurally to put other substructures together. The first fragment-based docking medication, **Zelboaf (PLX4032),** was produced and approved by the FDA.[70] To date, 40 chemical compounds found using this method have entered clinical trials.[71]

Molecular dynamic simulation

In order to get over this restriction, molecular dynamics (MD) simulation was initially developed in the 1970s. In

order to replicate atomic motions and lessen the complexity of the calculation, Newton's equation of motion must be solved.[72,73] In terms of drug discovery, MD simulations offer knowledge of the structural characteristics of proteins and the stability of protein-ligand complexes, which may be used to realistically screen chemical compounds. Additionally, it aids in the discovery of additional druggable binding sites, such as allosteric sites, which in turn facilitates the development of more potent drug molecules. To further enhance MD simulations, a more precise molecular force field is needed to mimic the motions of atoms in target proteins and ligands.[74]

ADME-Tox assessment

The next step after finding potential medication candidates is to evaluate their pharmacokinetic characteristics, such as ADME-Tox. ADME-Tox can also be predicted using computational methods thanks to improvements in machine learning algorithms and gathered datasets.

For ADME-Tox analyses, conventional experimental techniques are still time- consuming and expensive. Lipinski's "rule of five" is a straightforward formula for evaluating a chemical compound's drug- likeness: molecular weight of 500 Da, the lipophilicity of 5, the number of rotatable bonds at 10, hydrogen bond donors at 5, and acceptors at 10. More sophisticated prediction techniques are being utilized more frequently lately to forecast drug-likeness in terms of ADME-Tox characteristics in placeof this straightforward criterion.[75]

6. Chemical CompoundLibraries

Chemical compound libraries and natural product sources are extensively employed in the search for new drugs. These libraries might be huge, generated randomly, or they can be small, specialized libraries created explicitly with an aim in mind. Synthetically created libraries have a few advantages over mixes of natural product extracts, despite the fact that the problem of deconvolution of an active library still exists. The chemicals are usually present at equivalent concentrations. The methods for synthesis and chemical structures are known. And, some structure- activity correlations can be discovered by contrasting active and inactive library members.[76] Many of the earliest combinatorial libraries were primarily composed of peptides, often without regard to the potential for success of these peptides as drugs. Lipinski's now commonly accepted "Rule of Five" provides guidelines for molecular characteristics likely to be associated with poor oral drug absorption(Table 6.1).[77]

The earliest peptide libraries were frequently made up of molecules having all of Lipinski's undesirable traits, making it unlikely that even if a hit was found in a screen, it would be practical for drug development. This is because the larger the peptide, the easier it is to build variety. Further, by constructing libraries with hundreds to thousands of inactive compounds in a single well, along with only one or two active components, the potency of the mixture could be diluted to the point where the active compounds were undetectable. For this reason, many libraries now have fewer compounds per well. Later generations of libraries also have attempted to incorporate the Lipinski rules into their initial design by including more chemical functional groups in the scaffold and/or natural-product backbones. These newer libraries, therefore, are more readily amenable to a wide range of bioassays against soluble acceptors, membrane-bound receptors, microorganisms, differentiation (stem cells), etc.[78]

Table 6.1: Lipinski's Rule of Five

Compounds with two or more of the following characteristics are flagged as likely to have poor oral absorption:

- More than five hydrogen-bond donors
- Molecular weight > 500
- *c* log P (a measure of the partitioning of the compound between octanol and water) >5
- Sum of Ns and Os/ (a rough measure of hydrogen-bond acceptors) > 10

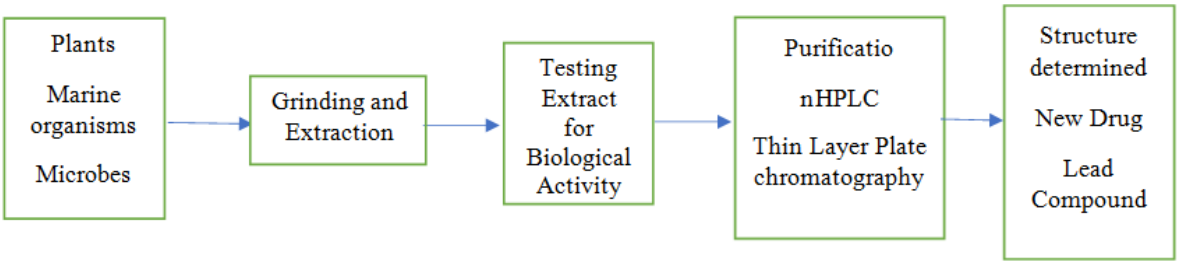

Figure 3: Steps in natural product-derived drug discovery.

CONCLUSIONS

The identification of disease-associated drug targets and therapeutic medicines using in-silico methods has advanced during the last few decades and become more effective and precise.

Because of the quick development of computer techniques and the growth of publicly accessible biological data, in silico drug discovery has recently picked up speed.

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