DRUG DESIGN: A COMPREHENSIVE REVIEW

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Abstract

Drug design and discovery is a multifaceted field within pharmaceutical science that plays a pivotal role in the development of new medications to treat various medical conditions. It involves a systematic and Intricate process of identifying, designing, and optimizing chemical compounds to serve as effective and safe drugs.

Keywords: *Drug Development, QSAR, CADD, Pharmacophore, Docking, ADMET, HTS, Combinatorial chemistry, Clinical trials.*

I. INTRODUCTION

Here's an introduction to the topic: Drug design and discovery starts with the identification of a specific target within the human body, such as a protein or enzyme, which is associated with a disease or medical condition. This target is often a key player in the disease's underlying mechanisms. Researchers then undertake extensive research to understand the three-dimensional structure and function of the target. This involves techniques like X-ray crystallography and computational modeling to gain insights into the target's molecular properties. The next step is to identify or design molecules, known as ligands or drug candidates, that have the potential to interact with the target in a way that either inhibits or enhances its activity. These molecules are often small organic compounds.

Computational tools and techniques, such as molecular modeling and virtual screening, aid in the initial selection of candidate compounds. These tools predict how well a molecule may bind to the target and its potential efficacy.

Once potential drug candidates are identified, they undergo rigorous testing in the laboratory. This includes biochemical assays and in vitro studies to evaluate their interactions with the target and their safety profiles.

Promising candidates then advance to preclinical testing in animal models to assess their effectiveness and safety in a more complex biological environment.

If a compound passes these preclinical tests, it proceeds to clinical trials in humans. These trials involve multiple phases and are conducted to evaluate the compound's safety, efficacy, and dosage.

Throughout this process, medicinal chemists, pharmacologists, and other experts work collaboratively to optimize the chemical structure of the drug candidate, aiming to enhance its potency, selectivity, and overall therapeutic profile while minimizing side effects.

Finally, if a drug successfully completes clinical trials and gains regulatory approval, it can be marketed and made available to patients, providing a new treatment option for the targeted medical condition.

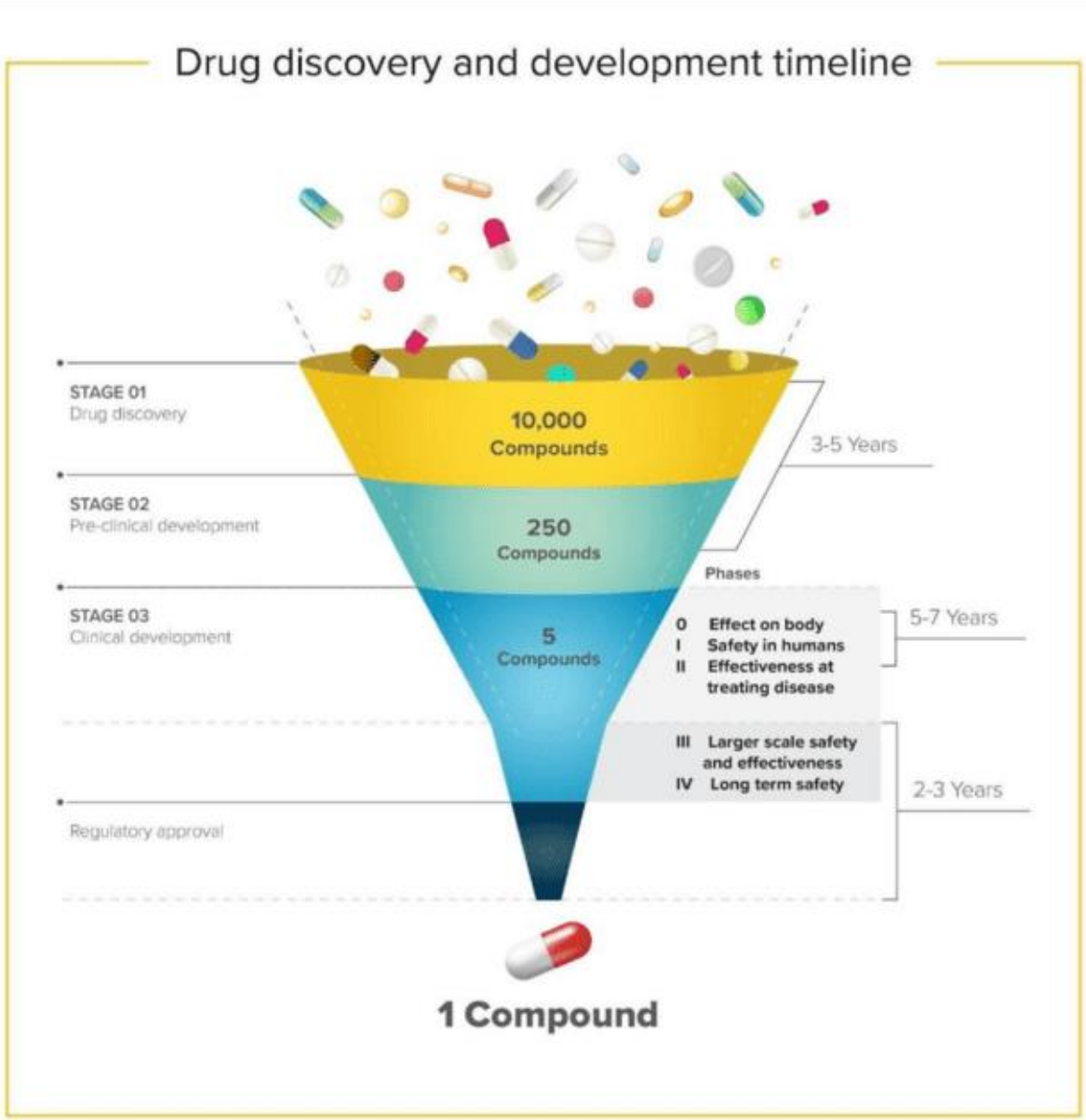

Fig 1: Drug discovery & development timeline

Drug design and discovery is an intricate and time-consuming process that relies on the collaboration of multidisciplinary teams, cutting-edge technology, and a deep understanding of biology and chemistry. It is at the forefront of medical research, continually striving to improve the quality of healthcare by developing innovative medications to address unmet medical needs. [1], [2]

Definition of Drug Design and Discovery:

Drug design and discovery is the scientific process of developing new pharmaceutical compounds or optimizing existing ones with the goal of creating safe and effective drugs to treat various medical conditions. It involves identifying specific molecular targets within the body, designing or discovering molecules (ligands) that interact with these targets, and then rigorously testing and optimizing these compounds to ensure their therapeutic efficacy and safety. [3]

Steps in Drug Design and Discovery:

Fig 2: Drug development process

1. Target Identification: The process begins with the identification of a specific biological target, often a protein or enzyme, that is associated with a particular disease or medical condition. This target plays a crucial role in the disease's mechanism.
2. Target Validation: Researchers validate the chosen target to ensure it is indeed relevant to the disease. This involves studying its function, structure, and potential as a drug target.
3. Lead Discovery**:** The search for potential drug candidates begins. This can involve screening chemical libraries, virtual screening, or designing molecules with the help of computational tools. Promising compounds are identified as "leads."
4. Lead Optimization: Selected lead compounds undergo extensive testing and optimization to enhance their drug-like properties. Medicinal chemists modify the chemical structure to improve factors like potency, selectivity, and pharmacokinetics.
5. Preclinical Testing: Lead compounds are evaluated in laboratory settings and animal models to assess their safety and efficacy. This step helps identify the most promising candidates for human trials.
6. Clinical Trials: Promising candidates progress to clinical trials, which consist of several phases. These trials assess the safety, efficacy, and appropriate dosage of the drug in human subjects.
7. Regulatory Approval: If a drug successfully completes clinical trials and meets regulatory requirements, it can receive approval for marketing and distribution.[5]

II. QUANTITATIVE STRUCTURE-ACTIVITY RELATIONSHIP (QSAR):

A) Definition:

Quantitative Structure-Activity Relationship (QSAR) is a computational technique used in drug design and discovery. It involves establishing a mathematical relationship between the chemical structure of a molecule (quantitative descriptors) and its biological activity or properties. QSAR models help predict the biological activity of new compounds based on their structural characteristics.

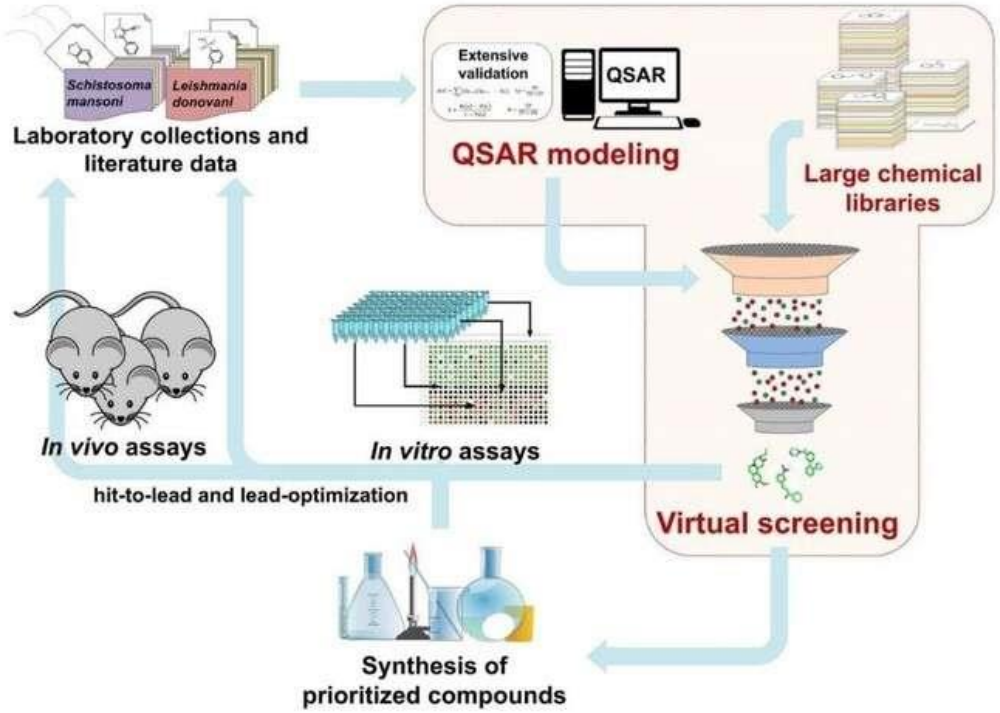

Fig 3: QSAR Process

B) Quantitative Structure-Activity Relationship (QSAR) Process/Steps:

1. Data Collection: QSAR analysis starts with the collection of data on a set of compounds, including their chemical structures and corresponding biological activities or properties.
2. Descriptor Calculation: Descriptors, which are numerical representations of a molecule's structure, are calculated. These descriptors can include molecular weight, charge distribution, and other properties.
3. Model Building: Statistical or mathematical models are constructed to establish relationships between the calculated descriptors and the biological activities. Various modeling techniques, such as regression analysis, are employed.
4. Validation: The QSAR model's predictive accuracy is rigorously validated using a separate dataset not used during model construction. This step ensures that the model can reliably predict the activity of new, unseen compounds.
5. Application: Once validated, the QSAR model can be applied to predict the biological activity of new compounds, aiding in the selection of potential drug candidates for further development.
6. Iterative Optimization: QSAR models can be refined and improved through an iterative process as more data becomes available, leading to more accurate predictions.[7]

In summary, QSAR is a valuable tool in drug design, allowing researchers to make informed decisions about the biological activity of compounds based on their chemical structures, ultimately expediting the drug discovery process.

III. COMPUTER-AIDED DRUG DESIGN (CADD):

A) Definition:

Computer-Aided Drug Design (CADD) is an interdisciplinary field at the intersection of computational chemistry, biology, and informatics. It employs computer-based methods and simulations to accelerate and improve the drug design and discovery process. CADD techniques allow researchers to analyze molecular interactions, predict the properties of potential drug candidates, and optimize compounds with the aim of identifying novel and effective drugs. [4]

B) Process of Drug Design through CADD:

1. Target Selection and Characterization: The CADD process begins with the selection of a molecular target, often a protein associated with a disease. Researchers gather data on the target's structure, function, and binding sites through experimental methods or databases.
2. Virtual Screening: CADD involves virtual screening, where large libraries of chemical compounds are computationally screened to identify potential drug candidates that could interact with the target. This screening relies on molecular docking simulations, which predict how well a compound binds to the target's active site.
3. Lead Identification: Promising compounds from virtual screening are selected as potential leads. These compounds are further analyzed for factors like binding affinity, selectivity, and pharmacokinetic properties.
4. Lead Optimization: CADD tools help medicinal chemists optimize the chemical structures of lead compounds. Molecular modeling techniques, such as quantitative structure-activity relationship (QSAR) and molecular dynamics simulations, assist in modifying compounds to enhance their efficacy and safety profiles.
5. ADME-Tox Assessment: CADD also includes the prediction of Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADME-Tox) properties of drug candidates. Computational models estimate how well a compound is absorbed, distributed, metabolized, excreted, and whether it has potential toxic effects.
6. Structure-Based Design: In structure-based drug design, the three-dimensional structure of the target protein is used to guide the modification of lead compounds. This approach allows for the design of molecules that fit precisely into the target's active site.
7. Ligand-Based Design: Alternatively, ligand-based drug design relies on the analysis of known ligands that interact with the target. CADD techniques help identify common structural features among active compounds, aiding in the design of new molecules.
8. Iterative Optimization: The drug design process through CADD is often iterative. Researchers continually refine and test new compounds based on computational predictions and experimental data until they identify a lead candidate with the desired therapeutic properties.
9. Experimental Validation: Finally, promising drug candidates identified through CADD are synthesized and subjected to laboratory testing. Their interactions with the target and biological activity are experimentally validated in vitro and in vivo.

Computer-Aided Drug Design plays a crucial role in streamlining the drug discovery process, reducing costs, and increasing the likelihood of identifying successful drug candidates. It combines computational power with scientific knowledge to expedite the development of innovative medications for various diseases and conditions. [8]

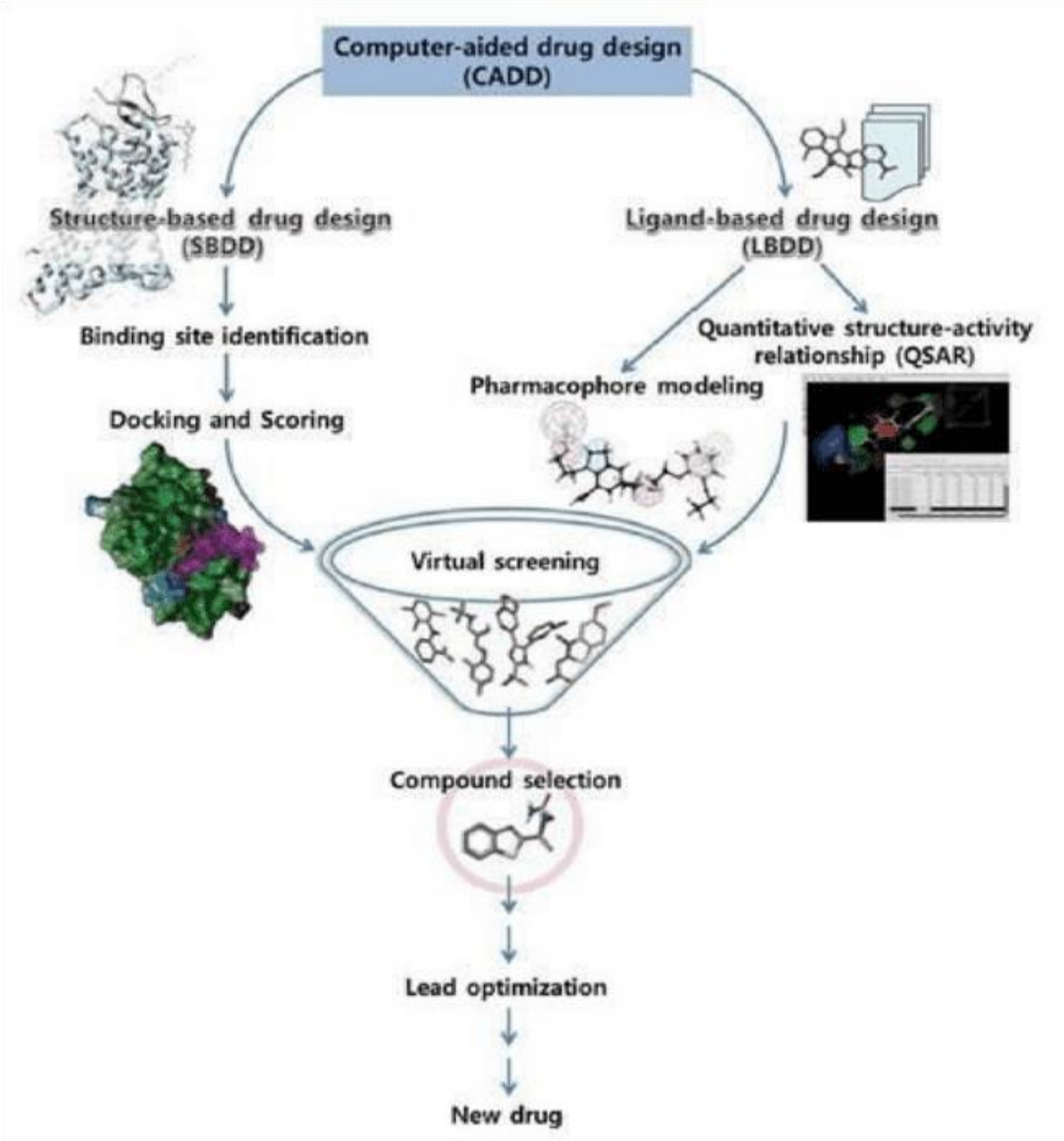

Fig 4: CADD Process

IV. CHEMICAL STRUCTURE REPRESENTATION:

Molecular Formulas: Molecular formulas are used to represent chemical compounds by indicating the types and quantities of atoms present. For example, H_2O represents water, consisting of two hydrogen (H) atoms and one oxygen (O) atom.

Structural Formulas: Structural formulas provide a detailed representation of a molecule's arrangement, showing how atoms are connected and bonded together. Bond types, such as single, double, or triple bonds, are often depicted.

Skeletal Structures: Skeletal structures simplify complex molecules by highlighting the carbon backbone while implying the presence of hydrogen atoms and heteroatoms (e.g., nitrogen, oxygen) at specific locations. [11]

V. DRAWING TOOLS IN CADD:

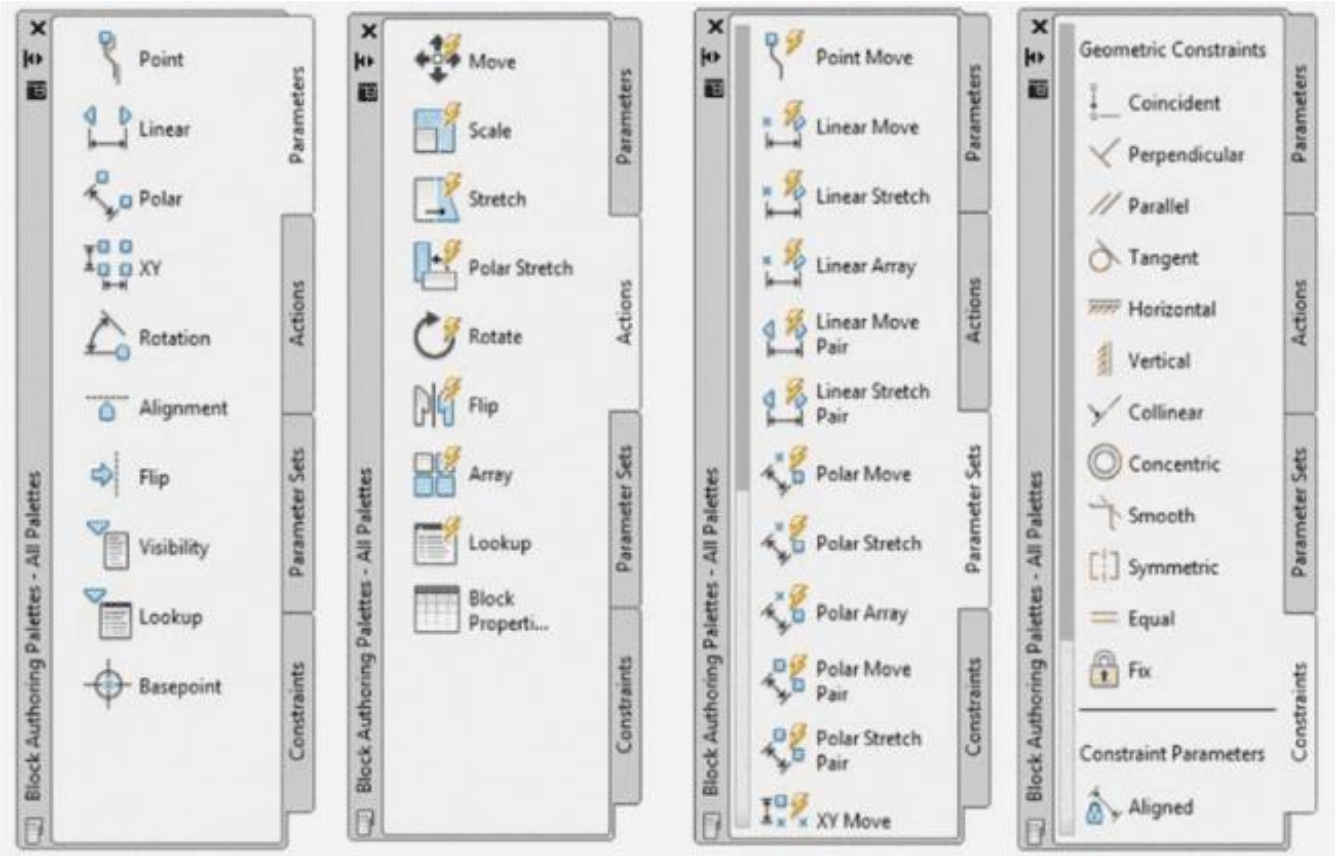

Fig 4: Drawing tool's in CADD

1. Chemical Drawing Software: Specialized software tools in CADD enable researchers to draw and visualize chemical structures accurately. These tools support the creation of 2D and 3D representations.

2. 2D Depiction: 2D representations are commonly used for clarity. Researchers sketch molecules on a flat plane, representing atoms and bonds in a 2D format, which is suitable for many purposes.

3. 3D Depiction: In CADD, 3D representations become essential for understanding spatial arrangements. They are crucial for studying how molecules interact with target proteins or enzymes in a three-dimensional space. [12]

VI. PRESENTATION IN CADD:

1. Visualization: Visualization is central to CADD for analyzing molecular interactions. It helps researchers examine how a drug candidate binds to a target protein or identify potential binding sites.

2. Docking Studies: In molecular docking simulations, 3D visualizations illustrate how a ligand fits into a target protein's binding site. Visualization aids in assessing binding affinity and interactions.

3. Quantitative Structure-Activity Relationship (QSAR): CADD researchers use graphical representations to depict structure-activity relationships, showing how changes in a compound's structure relate to changes in its biological activity.

4. Communication: Effective communication of CADD findings is crucial. Researchers create visually informative presentations and reports to convey complex structural and functional insights to colleagues and stakeholders.

5. Publication: Valuable CADD research findings are often published in scientific journals. These publications include clear and informative structural illustrations and diagrams to communicate discoveries to the scientific community.

In conclusion, chemical structure representation, drawing, and presentation are fundamental aspects of CADD. They enable researchers to visualize and analyze molecular interactions, understand the relationship between chemical structure and biological activity, and effectively communicate their findings in the drug discovery process. Chemical database search is a critical aspect of Computer-Aided Drug Design (CADD) and

plays a pivotal role in identifying and evaluating potential drug candidates. Here's an overview of chemical database search in CADD:

1. Database Selection: The process begins with the selection of chemical databases. These databases contain information about a vast array of chemical compounds, including their structures, properties, and biological activities. Commonly used chemical databases include PubChem, ChemSpider, ChEMBL, and proprietary databases maintained by pharmaceutical companies.

2. Data Retrieval: CADD researchers access these databases to retrieve relevant chemical information. This information can include the 2D and 3D structures of compounds, physicochemical properties, toxicity data, and known biological activities.

3. Virtual Screening: Chemical database search is often employed in virtual screening, where large libraries of compounds are computationally screened to identify molecules that have the potential to interact with a specific target of interest, such as a protein associated with a disease.

4. Similarity Search: One common approach in chemical database search is similarity searching. In this method, a query molecule (e.g., a known drug or lead compound) is used to search the database for molecules with similar chemical structures. This helps identify compounds that may have similar biological activities.

5. Pharmacophore Search: Pharmacophore-based searching involves defining the essential features or functional groups of a molecule that are crucial for its biological activity. The database is then searched for compounds that match these pharmacophoric features.

6. Filtering and Prioritization: After retrieving potential hits from the chemical database search, researchers employ various filters and criteria to prioritize compounds for further investigation. These filters can include considerations like drug-likeness, synthetic accessibility, and predicted binding affinity.

7. Lead Identification: Promising compounds identified through database searching are often considered as leads. These leads undergo further evaluation through molecular docking, QSAR analysis, and other CADD techniques to assess their potential as drug candidates.

8. Data Integration: Researchers combine data from various sources, including experimental data and computational predictions, to make informed decisions about which compounds to pursue for experimental testing.

9. Iterative Process: Chemical database search is typically an iterative process. Researchers refine their search criteria, evaluate new compounds, and update their database as more information becomes available during the drug discovery process. [13]

In summary, chemical database search is a crucial component of CADD that enables researchers to efficiently identify and prioritize potential drug candidates. By leveraging vast repositories of chemical information and computational techniques, CADD accelerates the initial stages of drug discovery and aids in the selection of compounds with the highest likelihood of success in experimental testing and development.

VII. **PHARMACOPHORE:**

1. Definition: A pharmacophore is a molecular framework or arrangement of specific chemical features within a molecule that is essential for its interaction with a biological target, such as a protein or enzyme. These features include hydrogen bond donors/acceptors, aromatic rings, and hydrophobic regions. Pharmacophores serve as 3D models or patterns that help in the design and identification of potential drug candidates. [9]

2. Process: The creation of a pharmacophore involves identifying key interactions between a ligand (e.g., a drug or potential drug candidate) and its target. This typically includes analyzing crystallographic or computational data to determine which chemical features are critical for binding and activity. Pharmacophore modeling software is then used to generate a 3D representation of these features. Once a pharmacophore is established, it can be used to search chemical databases for compounds that fit the pharmacophoric pattern, aiding in lead compound identification and optimization. [10]

VIII. DOCKING:

Definition: Molecular docking is a computational technique used in CADD to predict how a ligand (usually a small molecule or drug candidate) interacts with a target receptor, typically a protein. It simulates the binding process by calculating the energetically favorable orientation and conformation of the ligand within the receptor's binding site.

Process: Molecular docking involves the following steps:

1. Preparation: The target protein structure and ligand are prepared, including the removal of water molecules and the addition of hydrogen atoms.
2. Scoring: Different scoring functions are applied to evaluate the binding affinity and energy of various ligand poses within the binding site.
3. Sampling: Docking software explores various orientations and conformations of the ligand to find the most energetically favorable binding pose.
4. Analysis: Docking results are analyzed to identify the ligand's binding mode, interactions with the target, and binding affinity. [14]

IX. DOCKING ANALYSIS:

Definition: Docking analysis refers to the examination and interpretation of the results generated by molecular docking simulations. It involves assessing the binding modes, interactions, and energetics of ligand-receptor complexes to gain insights into their potential as drug candidates. [16]

Process: Docking analysis includes the following aspects:

1. Binding Mode: Determining how the ligand binds within the active site of the target protein, including its orientation and interactions with specific amino acids.
2. Scoring: Evaluating the docking scores to estimate the binding affinity; lower scores indicate stronger binding.
3. Interaction Analysis: Identifying specific molecular interactions, such as hydrogen bonds, hydrophobic interactions, and electrostatic interactions, between the ligand and the protein.
4. Binding Free Energy: Estimating the binding free energy to predict the thermodynamic stability of the complex.
5. Pose Clustering: Clustering similar ligand poses to identify the most representative binding mode. [17]

X. ADMET:

Definition: ADMET is an acronym that stands for Absorption, Distribution, Metabolism, Excretion, and Toxicity. It represents a set of critical properties and processes that influence a drug's fate within the body. Assessing ADMET properties is essential in drug design and development to ensure a candidate's safety and efficacy. [18]

1. Absorption: Examining how well a drug is absorbed into the bloodstream, considering factors like solubility and permeability.
2. Distribution: Studying how a drug is distributed to different tissues and organs in the body, which impacts its bioavailability.
3. Metabolism: Investigating how the drug is metabolized, often in the liver, to assess its metabolic stability and the potential formation of active or toxic metabolites.
4. Excretion: Analyzing the routes and efficiency of drug elimination from the body, primarily through urine and feces.

5. Toxicity: Assessing the potential toxic effects of the drug on various organs and systems, including hepatotoxicity (liver toxicity), cardiotoxicity (heart toxicity), and more.

ADMET evaluation guides medicinal chemists and researchers in selecting compounds with desirable pharmacokinetic and safety profiles for further development. It plays a crucial role in reducing the attrition rate of drug candidates during the drug development process. [19]

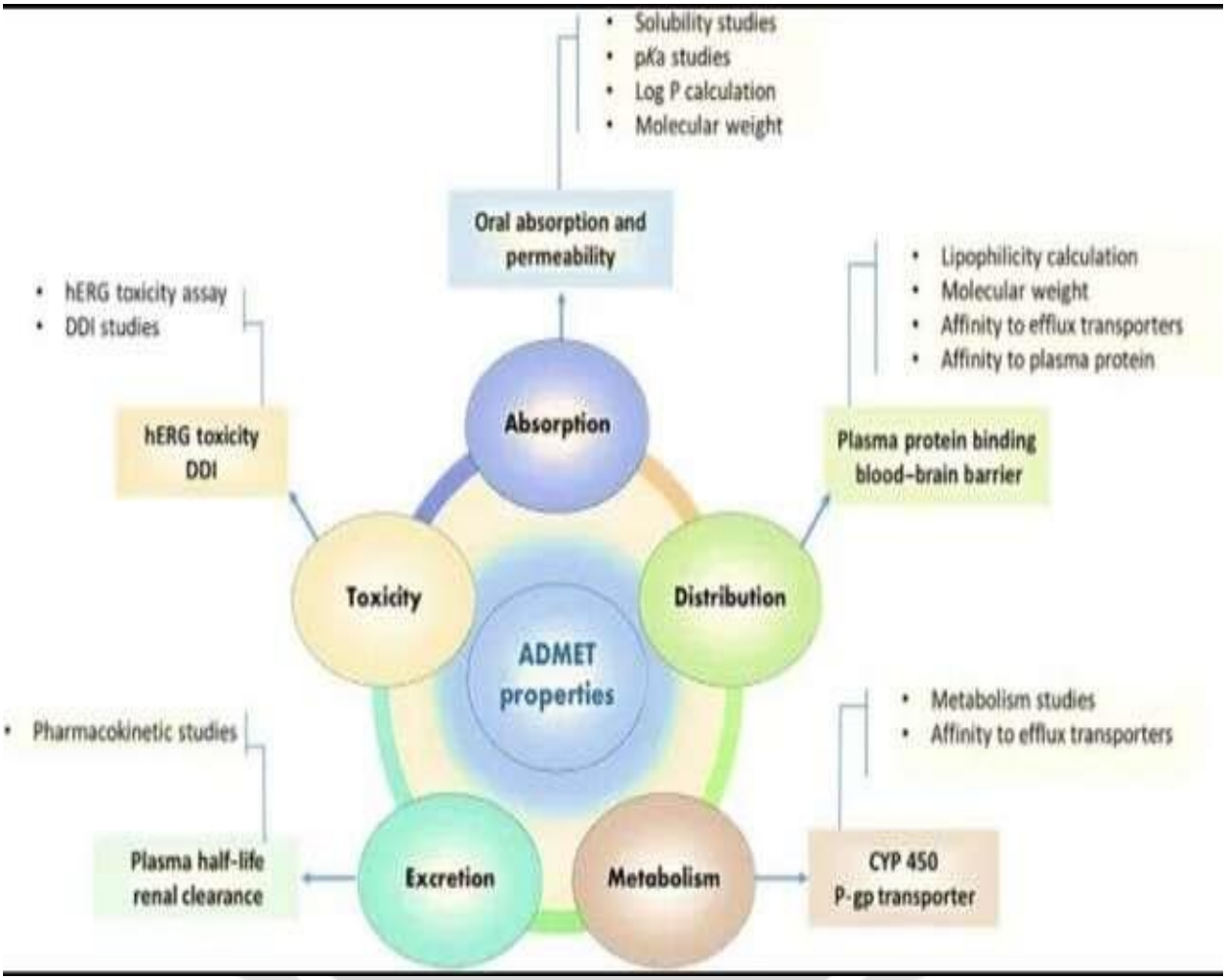

Fig 5: ADMET

XI. COMBINATORIAL CHEMISTRY:

Definition: Combinatorial chemistry is a technique used in drug discovery and material science that involves the systematic synthesis of a large number of diverse chemical compounds simultaneously or in a highly parallel fashion. This approach aims to create libraries of compounds with variations in their chemical structures, allowing for the efficient screening of potential drug candidates. [20]

Process: The process of combinatorial chemistry includes the following steps:

1. Design of Compound Libraries: Researchers design libraries by selecting building blocks and chemical reactions that will generate a diverse set of compounds.
2. Parallel Synthesis: Multiple reactions are conducted in parallel, often using automation and robotics, to create a wide array of chemical compounds simultaneously.
3. Quality Control: Each compound is analyzed for purity and identity to ensure the library's quality.
4. Screening: The combinatorial library is then subjected to biological or biochemical assays to identify compounds with desired properties, such as activity against a specific target. [22]

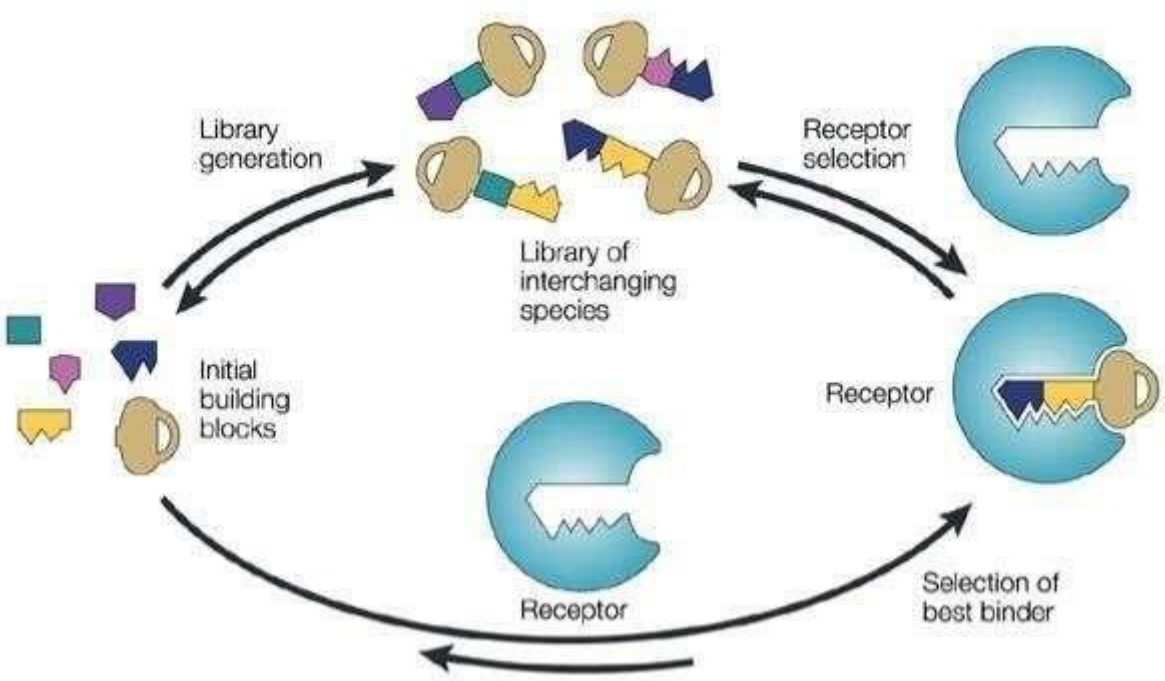

Fig 6: Process of Combinatorial Chemistry

Applications: Combinatorial chemistry is valuable in lead generation and optimization. It accelerates the process of identifying potential drug candidates by providing a broad pool of compounds for screening. Additionally, it can lead to the discovery of new chemical entities with improved properties. [21]

XII. HIGH-THROUGHPUT SCREENING (HTS):

Definition: High-Throughput Screening (HTS) is a technique used in drug discovery that involves the rapid testing of a large number of compounds for their biological activity. It is typically used to assess the interaction of compounds with specific biological targets, such as proteins or enzymes. [23]

Process: The process of HTS includes the following steps:

1. Compound Library: A diverse library of chemical compounds is prepared, often including natural products, synthetic molecules, or compounds from combinatorial chemistry.
2. Assay Development: Researchers design and optimize assays that measure the activity or binding of compounds to the target of interest. These assays are typically conducted in microtiter plates.
3. Automation: HTS often involves automation to handle and test thousands of compounds quickly. Robots are used to dispense compounds, perform assays, and collect data.
4. Data Analysis: The results of the assays are analyzed using computational methods to identify compounds that exhibit the desired activity. [24]

Applications: HTS is a crucial tool in the early stages of drug discovery. It allows researchers to rapidly test the biological activity of a vast number of compounds, helping to identify potential lead compounds for further optimization. HTS is used in various areas of drug discovery, including target-based screening, phenotypic screening, and fragmentbased screening.

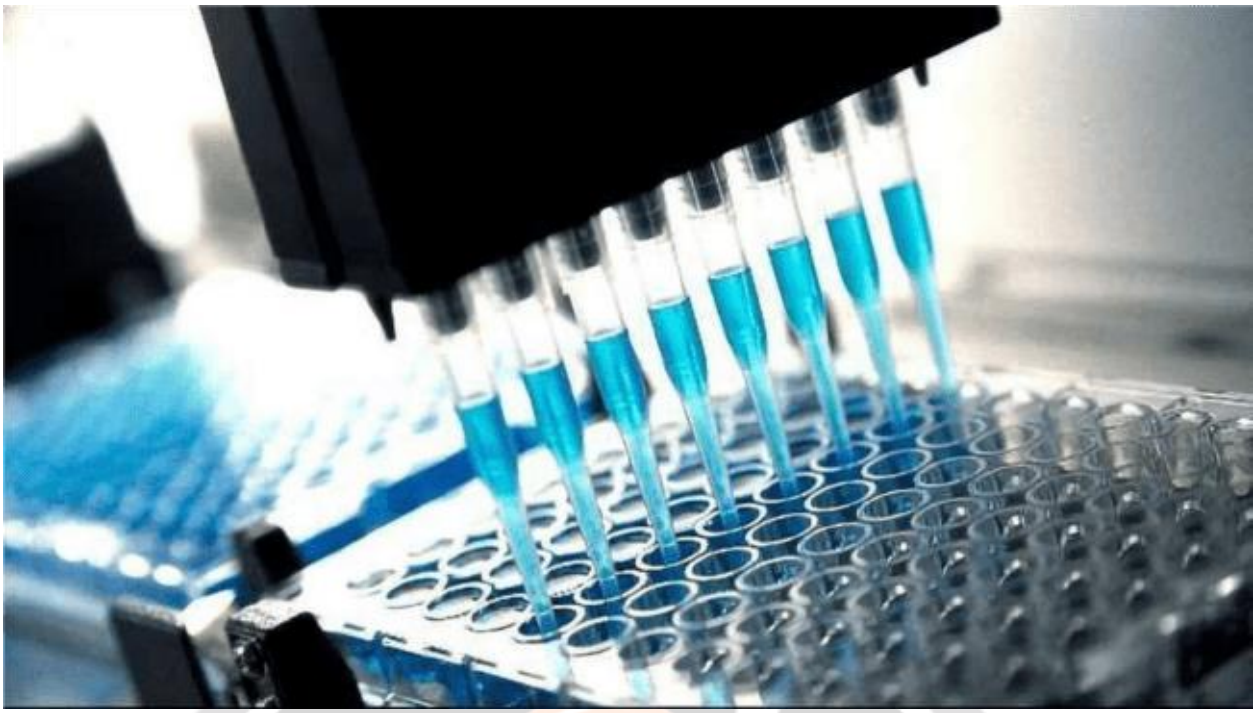

Fig 7: High-Throughput Screening

Together, combinatorial chemistry and HTS significantly accelerate the drug discovery process by generating diverse compound libraries and rapidly screening them for biological activity. These techniques have played a pivotal role in the identification of potential drug candidates and the development of new therapies for various diseases. [24]

"Drugs from natural sources designed through drug design" refers to the process of discovering and developing pharmaceutical compounds derived from natural substances, such as plants, microorganisms, or marine organisms, through the application of modern drug design and discovery techniques. Here's an overview of how this process works: [26]

XIII. DISCOVERY OF NATURAL COMPOUND:

1. Collection and Screening: The process begins with the collection of natural samples, which can include plant extracts, microbial cultures, or marine organisms. These samples are then screened for potential pharmacologically active compounds. [27]
2. Isolation and Purification: Once a promising source is identified, the active compounds are isolated and purified using various techniques, such as chromatography. This step results in the isolation of individual chemical entities. [25]

XIV. MODERN DRUG DESIGN TECHNIQUES:

1. Structural Analysis: The isolated natural compounds are subjected to structural analysis, which may involve techniques like nuclear magnetic resonance (NMR) and mass spectrometry. These analyses provide information about the compound's chemical structure.
2. Pharmacophore Modeling: Computational techniques, such as pharmacophore modeling, are used to identify the key structural features and functional groups responsible for the compound's biological activity. This information guides further drug design efforts.
3. Virtual Screening: Natural compounds and their derivatives can be subjected to virtual screening against specific drug targets using molecular docking simulations. This helps predict how well they might interact with the target.
4. Chemical Modification: Medicinal chemists may undertake structural modifications of the natural compound to enhance its pharmacological properties, such as improving its potency, selectivity, or bioavailability. These modifications are often guided by insights from computational modeling. [29]

XV. OPTIMIZATION AND DEVELOPEMENT:

1. Lead Optimization: The modified natural compound, now considered a lead compound, undergoes optimization to fine-tune its chemical structure and improve its drug-like properties. This process aims to strike a balance between efficacy, safety, and manufacturability.
2. Preclinical Testing: The lead compound is subjected to preclinical studies, including in vitro assays and animal testing, to assess its safety and efficacy. This stage helps identify potential issues and provides data for regulatory submissions. [28], [30]

XVI. CLINICAL TRIALS AND BEYOND:

1. Clinical Trials: If the lead compound successfully passes preclinical testing, it proceeds to clinical trials in humans. These trials evaluate the compound's safety, efficacy, and dosage in various phases, with the ultimate goal of gaining regulatory approval.
2. Market Entry: Once regulatory approval is obtained, the natural compoundderived drug is marketed and made available to patients, providing a new therapeutic option for specific medical conditions. [31], [32]

In summary, the process of developing drugs from natural sources using modern drug design techniques involves the initial discovery and isolation of active compounds from nature, followed by structural analysis, computational modeling, chemical modification, and optimization. This integrated approach combines the benefits of traditional herbal medicine and natural products with the precision and efficiency of contemporary drug discovery, resulting in new medications with therapeutic potential.

Conclusion :

In conclusion, drug design and development represent a crucial and intricate process in modern healthcare. Through the integration of computational techniques, structural biology, pharmacology, and medicinal chemistry, scientists can identify potential drug targets, design novel compounds, optimize their properties, and ultimately bring safe and effective medications to market. This multidisciplinary approach not only accelerates the drug discovery timeline but also enhances drug efficacy, safety profiles, and patient outcomes. As technology continues to advance, we can expect further innovations in drug design methodologies, leading to the development of more targeted and personalized therapeutics for various diseases and medical conditions.

XVII. REFERENCES

[1]Dr CHANDAN R.S. and Dr. Mrs. ALPANA J ASNANI textbook of Medicinal chemistry3(Introduction to drug design and development) page No. 12.1 and 12.37

[2]Drews J. Drug discovery: a historical perspective. Science;2000,287 287(5460):1960-4.

[3]Doytchinova, I. Drug design–past, present, future. Molecules 2022, 27, 1496.

[4]Daina A, Blatter MC, Baillie Gerritsen V, Palagi PM, Marek D, Xenarios I, et al. Drug Design Workshop: A Web-Based Educational Tool To Introduce ComputerAided Drug Design to the General Public. Journal of Chemical Education. 2017; 94(3):335-44.

[5]Amol B. Deore, Jayprabha R. Dhumane, Hrushikesh V wagh, Rushikesh B. Sonawane,The stages of Drug Discovery and Development Process. Asian Journal of Pharmaceutical Research and Development. 2019; 7: 62-67

[6]Muhammad U, Uzairu A, Arthur DE. Review on: quantitative structure activity relationship (QSAR) modeling. J Anal Pharm Res. 2018;7(2):240-242.

[7]Sanket B. Bhatshankar , Amit S. Tapkir , Quantitative Structure-Activity Relationship And Group-Based Quantitative Structure-Activity Relationship: A Review IJPSR ;2023 ;14(3): 1142-1143

[8]Pratik Swarup Das , Puja Saha , A Review on Computer Aided Drug Design In Drug Discovery, World Journal of Pharmacy And Pharmaceutical Sciences ;2017; 6: 279280

[9]Wilson G.L., Lill M.A. Integrating structure-based and ligand-based approaches for computational drug design. Future Med. Chem. 2011;3:735–750.

[10]JP Hughes, S Rees, SB Kalindjian, KL Philpot. Principles of early drug discovery. British Journal of Pharmacology. 2011; 162: 1239-1249

[11]Kalyaanamoorthy S., Chen Y.P. Structure-based drug design to augment hit discovery. Drug Discovery Today, 2011;16:831–839.

[12]Jimish R. Patel, Hirak V. Joshi, Ujashkumar A. Shah, A Review on Computational Software Tools for Drug Design and Discovery. Indo Global Journal of Pharmaceutical Sciences,2022;12: 53-81

[13]Barrawaz Aateka Y, Shahajan S Baig, Bawazir Abubakar Salam, COMPUTER AIDED DRUG DESIGN: A MINI-REVIEW. Journal of Medical Pharmaceutical and Allied Sciences, 2020;9:2584-2591

[14]Wermuth C., Ganellin C., Lindberg P., Mitscher L. Glossary of terms used in medicinal chemistry (IUPAC Recommendations 1998) Pure Appl. Chem. 1998;70:1129–1143.

[15]Sunita Pandey , BK Singh, Current advances and new mindset in computer-aided drug design: A review. The Pharma Innovation Journal; 2017; 6(8) :72-76

[16]Grinter SZ, Zou X. Challenges, applications, and recent advances of protein-ligand docking in structure-based drug design. Molecules. 2014;19: 10150-76

[17]Muneeza Maqsood , Yusra Karim, Eman Fatima, Computer Aided Drug Designing (CAAD): Tools used for structure-based drug designing. Biomedical Letters. 2020; 6(2) :149-163

[18]Nishant Nandkhile, Sachin Vanpure, Prathmesh Khetmalis, Rahul Bhondwe. Spectroscopic Analysis and ADME Studies of Phytochemicals in Methanolic Leaves Extract of Sonneratia apetala Buch.-Ham. Research Journal of Pharmacognosy and Phytochemistry 2022; 155-162.

[19]Jannatul Ferdows , Tamanna Tasnim and Shayeda Shanjeeda Akter .Drug Discovery and development. International Journal of Current Research. 2018; 10: 73682-73684.

[20]Shaikh SM, Nalawade, Shete AS, A Review on Combinatorial Chemistry. Research & Review: Journal of Chemistry, 2017;6(2) :14-26

[21]AK Mishra, A Gupta, AK Singh, Combinatorial Chemistry and it's application- a review. International Journal of Chemical and Analytical Science, 2010; 1(5): 100105

[22]Akkimi Padma, Basu Venkateswara Reddy, S. Meena, REVIEW ON COMBINATORIAL CHEMISTRY. World Journal of Current, Med. Pharm. Research, 2019; 1(1):39-43

[23]Robert P Hertzberg, Andrew J Pope, High-throughput screening :new technology for the 21st century. ELSEVIER, 2000; 4(4): 445-451

[24]Martis E.A. , Radhakrishnan R. , Badve R.R ,High-Throughput Screening: The Hits and Leads of Drug Discovery-An Overview, Journal of Applied Pharmaceutical Science, 2011;01(01): 02-10

[25]Mahidol C, Ruchirawat S, Prawat H, Pisutjaroenpong S, Engprasert S, Chumsri P, et al. Biodiversity and natural product drug discovery. Pure Appl Chem. 1998;70:2065–72.

[26]Arun Gupta, Satyajyoti Kanjilal, Shefali Katiyar, Drug discovery from plant sources: An integrated approach, An International Quarterly Journal of Research in Ayurveda, 2012; 33(1): 10-19.

[27]Li Zhang, Junke Song, Linglei Kong, The strategies and techniques of drug discovery from natural products. ELSEVIER (Science Direct), 2020;216: 107686.

[28]Tansaz M., Tajadini H. Comparison of leiomyoma of modern medicine and traditional Persian medicine. J. Evid.-Based Complement. Altern. Med. 2016;21:160–163.

[29]Feroz Khan, Dharmendra Kumar Yadav, Anupam Maurya, Modern Methods & Web Resources in Drug Design & Discovery. Letters in Drug Design & Discovery, 2011; 8: 469-490.

[30]Gedeck P, Kramer C, Ertl P. 4 – Computational Analysis of Structure-Activity Relationships. In: Lawton G, Witty DR, editors. Progress in Medicinal Chemistry. Elsevier; 2010. Pp. 113–160.

[31]Kandi V, Vadakedath S., Clinical research: an overview of study types, designs, and their implications in the public health perspective. American Journal of Clinical Medicine Research, 2021;9: 36-42.

[32]Venkataramana Kandi, Sabitha Vadakedath, Clinical Trials and Clinical Research: A Comprehensive Review. Cureus Journal of Medical Science, 2023; 15(2): e35077.