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A Comprehensive Review on Tools Used in Drug Discovery

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ABSTRACT
Its long, costly, complicated method for drug development involves identifying novel therapeutic compounds and assessing their safety and effectiveness. Traditional procedures is lengthy as well as unsuccessful because of lower effectiveness.Modern tools including computational methodologies, artificial intelligent (AI), studies in vitro, in vivo studies, omics technologies, and advanced imaging techniques have substantially increased the rate and accuracy of drug discovery. In silico technologies that predict drug-target interactions before clinical trials, such as molecule docking, QSAR, molecular dynamics, virtual screening, as pharmacophore modeling, can save time and money. High-throughput screening, cell-based assays, as well as in vitro models such as organisms may provide more accurate biological information. Animal studies, such as transgenic zebrafish systems, contribute to our understanding of medication risk and disease pathways without upholding the moral 3Rs. Omics-based technologies (transcriptomics, metabolomics, proteomics, and genomes) provide better target identification and personalized therapy. Imaging techniques such as molecular imaging, X-ray crystallization, nuclear medicine, or cryo-electron microscopy may be utilized to determine the shape of proteins and monitor therapeutic effects. AI, CRISPR, and digital twin technology together represent the future of faster, more precise, and personalized medicine development.

KEYWORDS:- Drug discovery, In-silico Tools, Molecular Docking, QSAR, AI (Artificial Intelligent), high-Throughput Screening (HTS), organoids, zebrafish model, omics technologies, molecular imaging, CRISPR, digital twins, In-Vivo, In-Vitro

I. INTRODUCTION

Finding and developing novel medications is an exhausting and time-consuming procedure that usually involves labor-intensive equipment, techniques such high-throughput screening, or trial-and-error analysis.[1,2] These methods are often inaccurate, costly, and time-consuming.[2] With its enhanced speed, accuracy, and efficacy, artificial intelligence (AI) presents an opportunity to fundamentally alter the drug discovery process. [3] It is possible to speed up the development of new medications and enhance the entire drug discovery process by combining AI's predictive power with the expertise and experience of human researchers. [1,4] Most of the drugs that are now in utilize come from the environment, while organic compounds are a crucial source of novel ideas for drug development.[5,6]Conventional methods for medication design and discovery are costly and time-consuming.[7]When conventional methods for medication discovery and development are highly likely to not be successful, researchers have adopted computer-aided drugs development, and CADD.[8] The use of computational techniques to identify substances with potential medical applications has grown in importance.[9]Current AI methodologies prioritize the utilization of pattern recognition on extensive data sets pertinent to the whole drug discovery process, hence reducing barriers in clinical and preclinical studies.[10]The binding strength between receptor–protein interactions and structural changes in the receptor are evaluated bystructure-based drug development methods.[11,12] It is increasingly essential to incorporate computerized, scientific, and AI-based technologies that improve efficiency and effectiveness in finding possible therapeutic molecules in order to expedite and accelerate the development of novel medications.[10]

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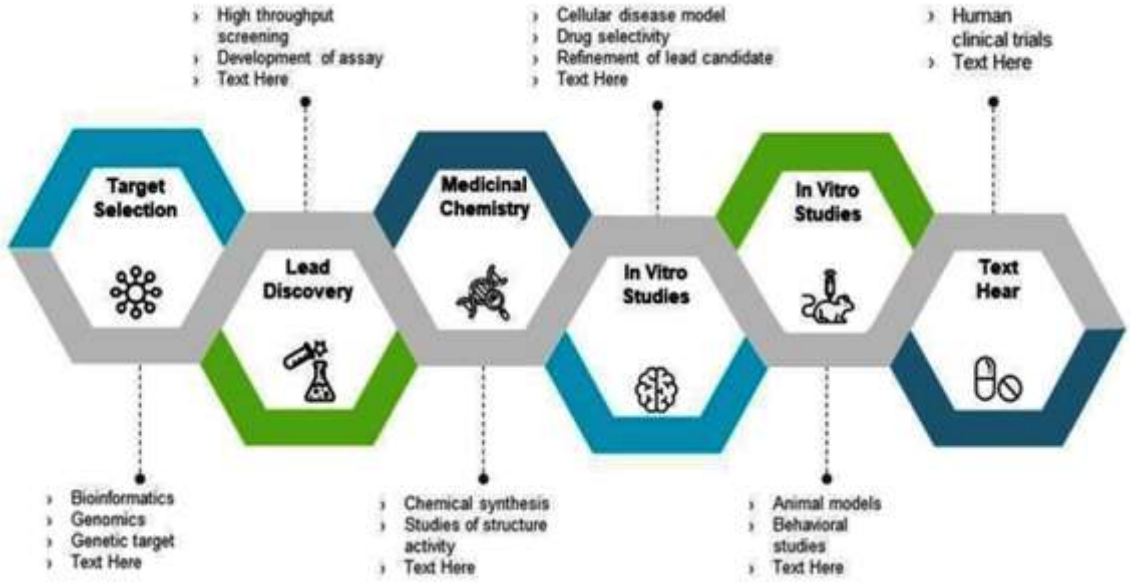

Figure 1:- Drug Discovery and Development Process

TOOLS IN DRUG DISCOVERY

IN-SILICO TOOLS (COMPUTATIONAL APPROACHES)

These In-silico methods include digital screening, three-dimensional QSAR, molecular docking investigations, molecular dynamics simulations, using ADMET property forecasts.Computational techniques based on ligands and structures are very useful for discovering novel compounds with unique biological characteristics that function against a certain target.[13]

A) Molecular docking

Molecular docking is, in fact, essential to modern drug development and discovery.[14]Within simulations of specific molecules, this enables researchers to study molecular reactions, such as potential drug complexes.[15] Researchers can find potential drug candidates more efficiently than with traditional experimental methods by virtually screening large collections of chemicals.[16,17] The process involves predicting a ligand's desired shape and sequence when it binds to a receptor and assessing binding affinities, which aid in the selection and improvement of possible drugs.[18,19]Docking algorithms can be broadly classified as either stiff or flexible.[20,21] The approach to searching that the method of assessment have both variables that define the quality with pairing technology.[22]It is possible to identify potential molecules, forecast ligand-protein interactions, and explain structure-activity connections.[23] The accuracy of estimates for bonds and the discovery of novel compounds is increased when AI and ML are combined.[24]

B) QSAR (Quantitative Structure–Activity Relationship)

Through the use of computational models, QSAR enables the prediction of biological action for substances depending on its physiological and physical characteristics.In ligand-based drug design methods, QSAR is an essential component.[25]One important application of this technique is to drug discovery, in which it is possible to predict the attraction of a recently discovered drug candidate.[26] In Chemometric techniques are used to develop a QSAR model by linking observed activity with descriptors, and various chemical descriptors are used to explain the compounds' chemical structure.When new substances have been adequately described, QSAR techniques may accurately forecast their actions.[25]When advanced artificial intelligence methods are used, QSAR prediction accuracy increases.[27]

C) Molecular dynamics

Molecular dynamics simulations are being more frequently used in the modern drug development process.MD simulations provide important information on the dynamic nature of the target that is essential to drug design.[28]For analyzing the range of ligand-binding pocket configurations, atomistic MD simulations developed as valuable tools.[29]MD simulations are now helpful tools for verifying previously docked

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positions.[30] It is expected that MD will play a much larger part by the medicine formulation procedure when greater or better Molecular Dynamics techniques advance.[28]

D)Virtual screening & AI/ML-based prediction

Online screening has emerged as a cost-effective substitute for experimental evaluation, choosing low-molecular-weight molecules using computational methods.[36] The precision with which computer docked estimates both the position and binding strength is a key factor in the success of virtual screening.[37] When binding estimates are underway, testing across ultra-large chemical databases is made possible by active learning methodologies.[37] AI has significantly enhanced virtual screening by integrating various sources of information and improving score methods.[38] Graph neural networks are effective in determining smaller compounds' interactions affinity also produce results that are easy to understand.[39] The identification of interesting chemicals from incredibly huge chemical databases is accelerated by artificial intelligence, diffusion procedures, as well as computational methods.[40]

E)Pharmacophores Modeling

The molecular functional properties needed for an atom to bind to specific receptors are identified using pharmacophore approaches.[31]The combination of chemical and electronic characteristics required to guarantee the best interactions between molecules to a biological target is known as a pharmacophore.There are two methods for creating pharmacophore models: ligand-based and structure-based pharmacophore modeling.[31]Understanding a framework of a ligand-protein combination allows for better pharmacophore characteristic creation and selection.[32]"ROC curves, Fischer's method, GH scoring, and mimic group testing can be used to verify pharmacophores.[33]Wide drug databases can be effectively screened using pharmacophore models to find new or recognized compounds that have the required chemical characteristics for activity.[34]

i)Structure based

The structure-based approach uses the structural data of target proteins, including enzymes or receptors, to identify chemicals that could be applied as medications. [31]Understanding a framework of a ligand-protein combination enables better pharmacophore properties creation and selection. [32]

ii) Ligand based

The ligand-based technique entails building three-dimensional pharmacological model with depends only to the physical properties identified substances to developing drugs.[31]Finding medications that bind to a single proteins receptors in this manner allows the discovery of related chemicals resulting in the creation of new drugs.[35]

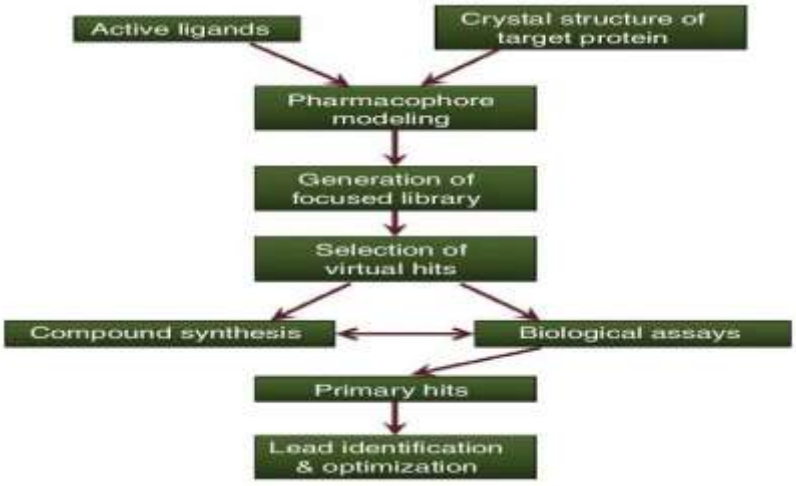

Figure2:-The creation of the pharmacophore system, virtual hit identification, chemical manufacturing, biological testing, along with improvement of initial results into potential targets are all depicted by this pharmacophore-based drug development process.

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IN-VITRO TOOLS

A) High Throughput Screening(HTS):

High-throughput screening (HTS) provides the first chemical material needed to create a novel drug. Finding compounds that change the actions of biological targets often proteins associated with disease is the aim of HTS programs.The uniformity, small size, and stability and accuracy optimization of biochemical assays make them perfect with machines.Current high-throughput screening activities are aided by chemical handling machines, specific identification methods, reduced size, or the application for data analysis to handle and understand big databases.[41]

B)Cell based Assay

Assays that use cells make more environmentally acceptable platforms than chemically identifications.Cell-specific assays are used to assess movement, toxicities, or development, and also to look at morphological changes along with cell signaling pathways to identify the most promising medication selection.However, due to their inability to adequately represent the biological basis of cells, two-dimensional cell culture simulations often fail to predict a given in-vivo drug reaction.The rapid advancement of three-dimensional cell culture methods in cell-based studies more closely mimics the physiological functions of living organisms.[42]

C) Biochemical Assay

The consistency, small size, and stability and durability optimization of biochemical tests make them perfect for machines.[43]Several assays for targeted interaction to organisms as well as separated proteins are being discovered. These techniques monitor changes in the weight variation, equilibrium, structure, or transparency of protein and its ligand interactions [44]

D)Organoid and lab on chip technology

Organoids are tiny, extremely natural copies of organ capable of properly capture their multiple roles.Organoid technology provides an essential connection between conventional cells and in-vivo systems.AI, nanotechnology, and organoid technologies have significantly enhanced large-scale, rapid, and cost-effective drug safety and effectiveness testing.[45]The goal of a microbiological system, sometimes referred by the term an organ-on-a-chip, is to simulate the primary body functions.Organ-on-a-chip microfluidic technology enables the specific modification of cellular surroundings to investigate complex interactions between different organs.[46]Organoids-on-a-chip, a more advanced system has been created to take into consideration all of these components.[47]

IN-VIVO TOOLS

A)Animal model in drug discovery

Animal models have an ability to mimic human sickness or therapy.When a medicine or ingredient is found, its dosage, adverse reactions, and chemical tests are evaluated in vivo for possible future usage in patients.Animal models are more important in biomedical research since therapeutic efficacy and safety of drugs are essential criteria for allowing a medication or surgical instrument for use by humans.For early-stage pharmacokinetic research, including safety, toxicity, and effectiveness, animal models are essential before translating to patients.[48]

B)Transgenic and knockout model

An animal that is having its genome modified to include genes from another species and to create specific features is known to be transgenic animal.Many types of transgenic animals have been developed for the purpose of researching human diseases, assessing experimental medications, and gathering human biological data.[49]CRISPR/Cas9 genome-editing technologies have revolutionized conditionally and knock-in/knock-out animal models, enabling specific genetic modification for disease modeling.[50]

C) Ethical Considerations & 3Rs (Replacement, Reduction, Refinement)

The three Rs-Reduction, Refinement, and Replacement-serve as an structure for animal experiments.[56] Reduction makes sure that as few animal experiments are utilized as possible to achieve accurate results.[57] Refinement enhances the health of experimental animals by decreasing their anesthesia, trauma, and anxiety.[58] Methods which maybe totally or almost skip using experimental animals are known as methods of replacement.[59] For optimizing living conditions while developing computational methods to evaluate emotion, mental state, and detecting pain, responsible advances the health of animals.[60]

D)Zebrafish model

The zebrafish model and also humans share 70% of the same DNA, and more than 80% of genes linked to disease are remaining.[51]Diseases may be modeled and

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recorded in never before seen molecular details because of effective modifying genes and current high-quality scanning.[52] Because of their human-like animal anatomy, ease of upkeep, excellent potential for reproduction, tiny size, rapid development, and transparency in the earliest phases of life, zebrafish are commonly used in toxicity research.[53,54] Zebrafish models provide a rapid, inexpensive, and highly visual means of examining the development of diseases and screening drugs in vivo.[55]

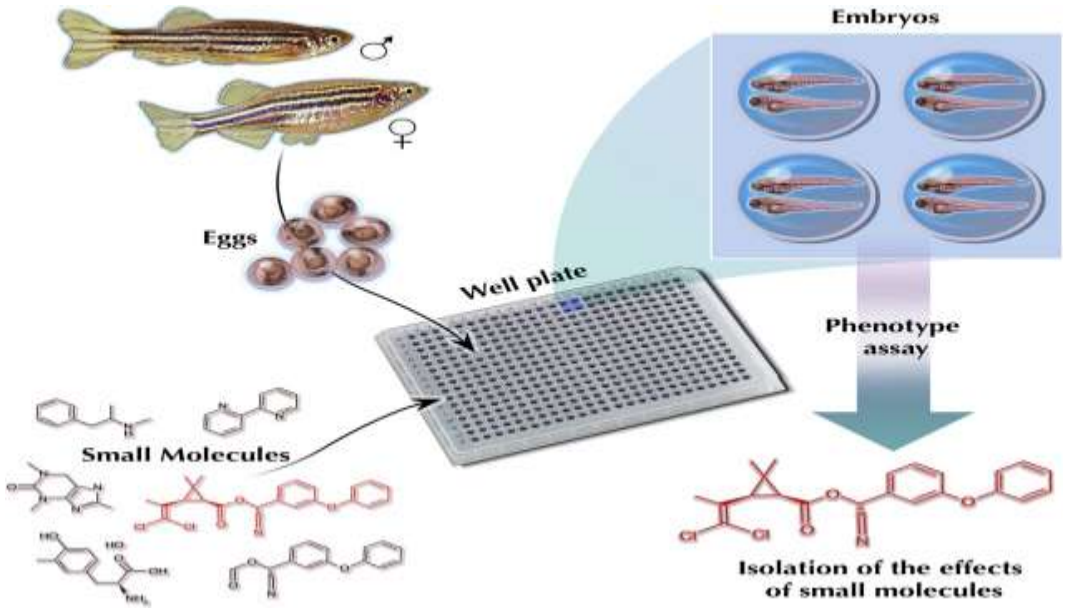

Figure 3:-An example of a drug screening procedure useszebra fish. Several tiny chemicals have been applied to implanted zebrafish eggs into an empty dish. Phenotype tests follow to examine the embryos in order to determine the active chemicals or investigate their biochemical impacts.

OMICS BASED TOOLS

A)Genomics

The development of genomics is having an important effect for the drugs discovery company.[61] Genome-wide associations (GWAS) performed a major role in finding variations in genes related to a range of medical conditions.[62] The combination of genomic data, providing a solid foundation in genetics knowledge and enables practical understanding of disease pathways, has transformed drug discovery.[61]The probability of developing and approval of medications with a goal regulation is supported by GWAS data is increasing.[63]Genetic data will be used to determine the process and possible source of action of the disease's interaction.[64]

B)Proteomic

The in-depth investigation of the way proteins work in order to identify a living thing's species is known as proteomics.Qualitative proteomics has the ability to provide comprehensive knowledge into disease pathways, cell-level functioning, or protein identification.For analyzing the proteins in physiological fluids such urine, plasma, inhaled breath, and spinal fluid, proteomics may identify or monitor signals.[65]By providing a complete image of protein interactions connected to systems suspected in the evolution of disease, proteomics will help in the discovery of new drugs.[66]

C)Metabolomics

Metabolomics provides an in-depth overview of the metabolic all systems of living things.Metabolomics improves a medication discovery procedure given that it determines pharmacokinetics, pharmacodynamics, or therapeutic efficacy.Investigating medication repurposes or drug-drug interactions, but also developing specific therapies are made simpler by metabolomics.Metabolomics is a useful technique for analyzing the toxicity of medication prospects to both liver and kidneys, according to almost 150 researches.Combination with other omics, like as transcription, lipidomics, proteomics, microbiome,

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and genetics, can provide a comprehensive understanding of pharmacological modes action or disorders.[67]

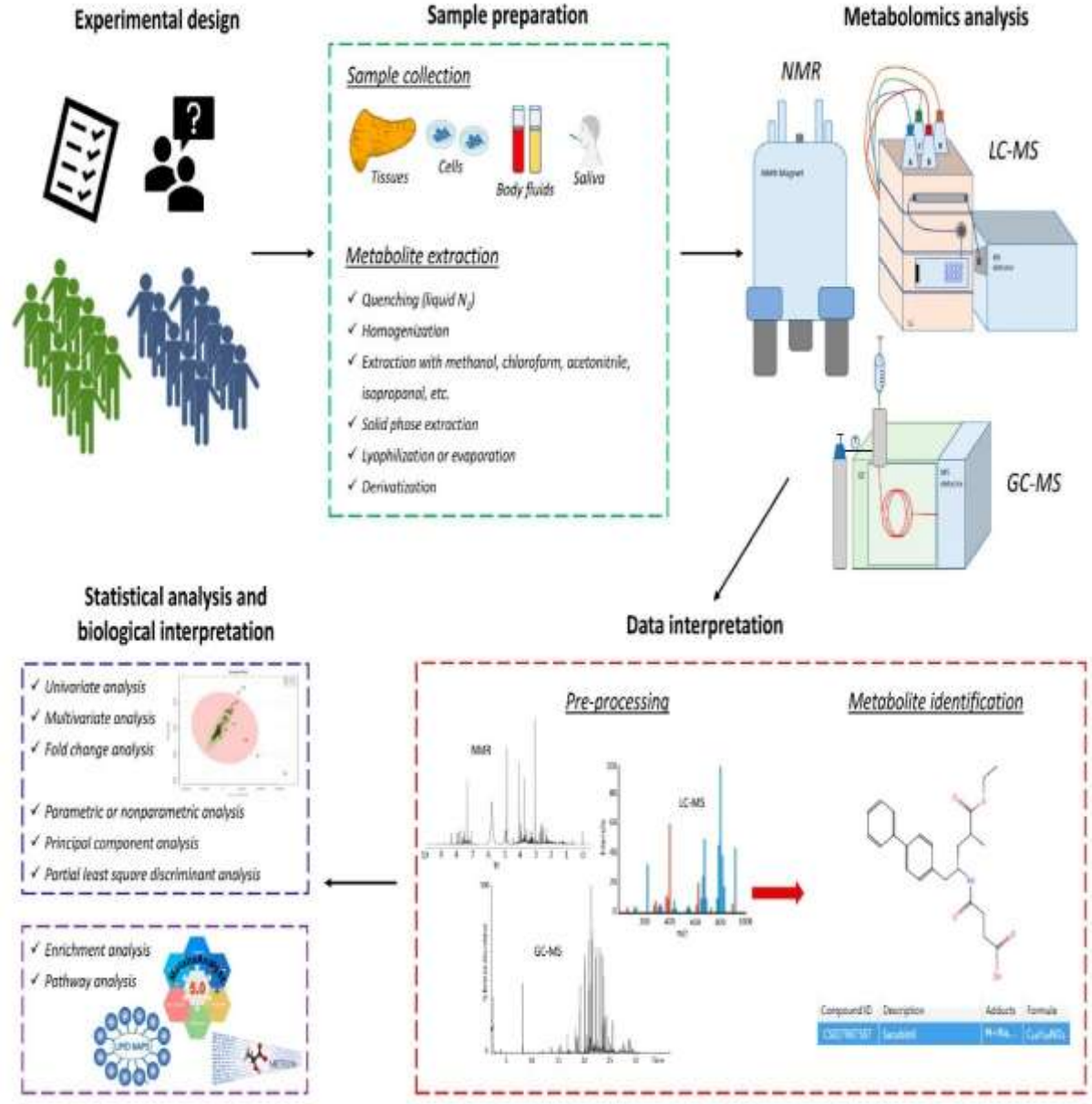

Figure 4:-An overview of the metabolomics procedure, including sample extraction and collection, data processing, NMR/LC-MS/GC-MS analysis, and also final metabolite identification.

D)Transcriptomic

The term "transcriptome" refers to the whole set of all RNA molecules generated bycertain cells or tissue types during a specific condition or developmental stage.Drug testing and biomarker detection have made use of high-throughput sequencing ofRNA due to its high throughput, immediate identification speed, and low cost.[68] Thedegree of transcription in genes, genetic behaviors, molecular basis of sickness, andthe pathways affected by drug treatment are all shown by transcriptomics.[69] RNA-seqcan be used to design drugstargeted and investigate the biological mechanismsresponsible for lots of disorders.Particular information about the mechanismscausing cancer and target therapy selection can be obtained through single-cell RNAsequencing.[68]

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IMAGING AND BIOPHYSICAL TOOLS

A)X-ray Crystallography

X-ray crystallography continues to be an essential source for structural organism data for drug discovery.[70] Structure-Based Drug develop uses the 3-D structure of the target to develop drugs with tiny molecules.[71]Crystallography is particularly helpful for identifying modifications that could enhance purity and for optimizing particles.[72]Generally speaking, X-ray structures having greater clarity and can generate better simulations of how small and large molecules interact.[70] X-ray crystallography will remain a crucial method for medication research and discovery as advances in technology.[70]

B)NMR Spectroscopy

NMR spectroscopy is a standard method for studying the atomic-level framework, interactions, and movement of molecules.NMR spectroscopy can provide detailed information on interactions and structural movements within time.The method of choice for atomic-level protein structure investigation in complicated and natural conditions is in-cell NMR.Solid-phase nuclear magnetic resonance [NMR] has a highly efficient strategy to examine the shape of protein membranes in lipid bilayers.[73]

C)Cryo-Electron Microscopy (Cryo-EM)

A resolution improvement has given cryo electron microscopy [EM] a competitive alternative with structure-oriented Medicinal Design.Cryo-EM allows samples to be examined in nearly biological situations by preserving the molecules in their native state.While this may be used to a wide range of pharmacological targets with different mechanisms of actions, cryo-EM provides an effective method in drug development.By using cryo-EM in the drug design process, there is a great deal of possible for faster the development of improved drugs.[74]

D)Mass Spectrometry

When developing new drugs, mass spectrometry is crucial for both complete mass determinations with structures of therapeutic molecules.MS is now a helpful complement of various physiological methods including EM, NMR, and X-ray crystallography.[75]Characterizing biomolecules in their original folded state is made possible by native MS.[76]Native MS provides essential details about binding equilibrium as well capacity, enabling the investigation to antibody connections to compounds such as receptors, including other molecules.[75]

E)Molecular Imaging

Molecular imaging techniques are essential for observation, therapy analysis, testing, diagnosis, and also discovery.PET's high ability of detecting basic physical target-ligand relationships has made it the accepted for molecules.[77]Functional molecular imaging shows modifications to signals throughout both space and time, providing a unique viewpoint on disease.[78]High-contrast soft tissue imagery or multimodal function and metabolic data are provided by hybrid PET/MR systems with no extra doses of radiation.[77]PET imaging is ideal for researching radiation therapy injections and generating medication treatments.[78]

ARTIFICIAL INTELLIGENCE AND MACHINE LEARNING TOOLS

A)Role of AI in Drug Repurposing

Discovering new applications for current drugs out of original applications, called "drug repurposing," has a variety of advantages, such as reduced research periods and also expense.[80]AI technology is now having an adverse effect on healthcare.[80] Information like clinical databases, biological journals, digital medical records, and genetic information will all be integrated and analyzed using AI techniques.[81]AI and medication repurpose having the potential to deal with the urgent therapeutic needs of patients with uncommon diseases.[82]AI can employ information graphs, research-based graph techniques, and high-throughput screening to estimate, verify, and rate potential medications for novel purposes.[80]

B)Predictive model for ADMET

A complete and efficient system to evaluate associated with ADMET metrics, physical features, and therapeutic aspects is provided by ADMETlab 3.0. Computer-based predictive models have significantly advanced in result for rapid growth of technology with ADMET research results.The DMPNN-drivenADMET prediction models performed exceptionally well generally for the two classification goals.In the area of in vitro methods of drug development, ADMET lab 3.0 is a significant innovation that provides a broad, reliable, and accurate service.[83]

C)Generative AI for Novel Drug Design

The use of generative AI in pharmaceutical study and discovery produces positive results. [84]Generative AI methods are

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capable of producing completely new molecules with specific required properties.[85] These uses of GAI models provide potential for improved methods to develop novel medicinal molecules with begin.G-AI is used by Chemistryto produce novel, small, drug-like compounds that are specifically designed for particular properties. [84] In the search for novel chemicals that mimic pharmaceuticals, variational encoders [VAEs] are usually used.[86] GANs have the ability to generate novel, physically acceptable compounds, expanding the chemical space available for possible therapeutic options.When it comes with drug studies, diffuse probabilities work very effectively.Message-passing techniques are used by neural networks that graph to learn and generate molecular graphs.[84]

II. CHALLENGE AND LIMITATIONS

1. Computational tools limitations

Ensuring digital representations were accurate has a major difficulty in CADD.[87]For its precision, it is necessary to take steps to minimize chances of inaccuracies or rejections.The data used for instruction computer-aided design tools affects their quality, and a recurring issue is the dearth of properly chosen, high-quality datasets.[88]Over-reliance on CADD projections without additional experimental validation could lead to incorrect attempts.[89]Modern CADD methods require an important quantity of processing speed.[90]Properly recording cellular adaptability may have a significant impact on CADD study findings.[91]Prediction understanding is made more challenging by a variety of systems produced with machine learning and artificial intelligence.In CADD, maintaining data privacy and addressing moral dilemmas pertaining to the use of medical records is essential.[88]

2. Translation gap between in vitro and in vivo

The mortality rate of clinical trials for novel molecular entities is significantly increased by low efficacy in humans.[92]Almost every suggested treatment target that has been demonstrated to affect how a disease progresses in humans is also known to affect condition-specific in vitro systems or animal models.[93] Knowing the barriers and range of translation of animal models into human health situations helps with deciding during the medication creation procedure.[92]Considerable material variation among the patients was revealed by clinical investigation, and these could affect the course of treatments.[94]

3. Ethical issues with animal models

Much scientific advancementwas made possible by animal research, but discussions on empathy or moral practices were initially triggered by ethical concerns about using animals in tests.To reduce animal suffering, researchers should give priority to replacement, reduction, and refinement.[95]

4. Data integration challenges in omics

The increased complexity, variability, and incidence of values that are absent among varieties of data made integrating information from various omics challenging."[96]High computing demands, limited interpretability, and the requirement for large datasets for model training are challenges for deep learning-based multi-omics integration.[96]One of the biggest challenges establishes data collecting and processing methods across various omics layer and research institutes.[97] To really enhance healthcare, multi-omics have to be properly validated along with easily incorporated in medical systems.[97]

III. FUTURE PROSPECTIVE

1. Personalised/precision medicine

Personalized healthcare is undergoing a revolution thanks to the integration of proteins, metabolism, and genetics.This combination allows for a comprehensive assessment of each person's health from testing of biological, molecular, or biochemical profiles.[98] It is now simpler to examine genetic data and identify biomarkers for a range of diseases because to technological advancements including NGS (next-generation sequencing) andbioinformatics.[99] Personalized medicine, which employs genomic insights to modify treatments based on each patient's own molecular history, changed cancer treatment.[100]

2. Integration AI, Omics and CRISPR

AI models were used to develop RNA guides (gRNAs) to CRISPR-Cas systems.[101]AI is now crucial for analyzing medical data due to recent advancements in multi-omics technology.[102]AI analyzes patient genetic data to identify changes, variations, and biomarkers related to a variety of diseases, including Alzheimer's, diabetes, and cancer.[101]CRISPR technology, AI, and also omics-based data integration enable

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predictive, preventative, and highly tailored therapeutic approaches.[103]

3. Digital twins and predictive stimulation

With regard to management, service delivery, illness prevention, treatment, and general wellbeing, the digital twin of health (DT4H) idea has a chance to transform the healthcare system.With modeling, artificial intelligence (AI), or reasoning, the digital twin can give predicted information as well as replicate an operational system on the moment.Digital twins have been utilized to simulate, predict, and enhance procedures in healthcare in everything from drug testing and hospitals with virtual clinical studies to customized therapy design.[104]

IV. CONCLUSION

The total study demonstrates that combining of different cutting-edge research methods made new drug development quicker, safer, in addition to economical. In the past, traditional lab tests and trial-and-error were the primary methods used to find new medicines. These methods were costly and time-consuming. Molecular docking, QSAR-based structural dynamics, virtual screening, or pharmacophore modeling are examples of in-silico methods that are currently assisting researchers in finding viable drug candidates prior to laboratory testing. Additionally, in-vitro instruments including lab-on-a-chip systems, organoids, cell-based assays, or HTS provide more reliable biological data. Zebrafish, transgenic animals, or knockout tools are examples of in-vivo tools that enable researchers to investigate medication security with progression of diseases in organisms without adhering to these three Rs together with ethical standards.

The knowledge of disease mechanisms at the cellular level is being significantly enhanced by omics technology (genomics, proteomics, metabolomics, and transcriptomics) along with imaging methods such as X-ray crystallography, cryo-EM, nuclear magnetic resonance (NMR), or molecular imaging. Drug repurposing, ADMET property prediction, and the creation of whole novel medicinal compounds have all been made possible through artificial intelligence & machine learning. Even though there are difficulties like data integration, ethics, computing constraints, and language gaps, these are being reduced by ongoing technology improvements.

AI, multi-omics, CRISPR, and also digital twin technology will be integrated in the future to increase the prevalence of personalized and precision medicine. These developments will enable safer, effective, as well as patient-specific medications to be created based on each patient's own genetic and biological profile. All things considered, the fusion of conventional and contemporary methods has produced a strong and effective framework for the creation of medications of the future.

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