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Review Article

The Current Perspectives in Clinical Research: Computer-Assisted Drug Designing, Ethics, and Good Clinical Practice

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Abstract

In the era of emerging microbial and non-communicable diseases and re-emerging microbial infections, the medical fraternity and the public are plagued by under-preparedness. It is evident by the severity of the Coronavirus disease (COVID-19) pandemic that novel microbial diseases are a challenge and are challenging to control. This is mainly attributed to the lack of complete knowledge of the novel microbe's biology and pathogenesis and the unavailability of therapeutic drugs and vaccines to treat and control the disease. Clinical research is the only answer utilizing which can handle most of these circumstances. In this review, we highlight the importance of computer-assisted drug designing (CADD) and the aspects of molecular docking, molecular superimposition, 3D-pharmacophore technology, ethics, and good clinical practice (GCP) for the development of therapeutic drugs, devices, and vaccines.

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INTRODUCTION

The world is still fighting the Coronavirus Disease (COVID-19) pandemic, which practically challenged humankind on every front. It has become necessary for pharmaceutical companies to constantly develop new drugs targeting prevalent diseases and emerging and re-emerging ones[1-3]. Drug designing can be broadly classified into two categories: structure-based and ligand-based drug designing. The structure-based method considers the structures of both target and the ligand. At the same time, the ligand-based approach utilizes only the structure and target of the ligands[4,5]. Once the designing method is finalized, the new drug undergoes four phases before entering the consumer usage market. The drug development involves four phases, including phase 1, 2, 3, and 4[6].

Phase 1, also termed the drug development phase, evaluates humans' drug dosage and toxicity. A minimal amount of the drug is given to healthy and physiologically sound male volunteers. In this phase, the dosage with the first sign of toxicity is noted[7]. Phase 2 is considered a pre-clinical phase where the trial drug is assessed for its efficacy against a specific disease. In this phase, a small amount of the new drug is given to the patient volunteers, who are followed up on a timely basis. This phase decides the optimum dosage for patient use[8]. Phase 3 is called the clinical development phase, and wherein many patients are recruited to evaluate and confirm the results obtained in the previous two phases. The drug is compared with

the current treatments or uses a placebo, and its efficiency is identified. The complete data on the efficacy and safety of the drug is collected and placed before the international and national regulatory agencies like the Food and Drugs Administration (FDA), the United States of America (USA), and the Central Drugs Standard Control Organization (CDSCO), India for final approval of marketing[9]. Phase 4 involves post-marketing studies, which are also called pharmacovigilance. During this phase, the long-term safety and efficacy of the drug are assessed in a larger population group[10].

Various techniques to discover drugs have evolved from finding a natural substance to treat diseases and using computer-assisted drug designing (CADD) for manufacturing the drugs (**Figure 1**). The latest addition to this array of technology is molecular docking and artificial intelligence[11,12]. The molecular docking process consists of two main stages: ligand conformation and positioning of the ligand within the target sites[13]. In the current review, we comprehensively discuss the nuances of clinical research, which include CADD, discovery, molecular docking, molecular superimposition, 3D pharmacophore technology, ethics, and good clinical practice (GCP).

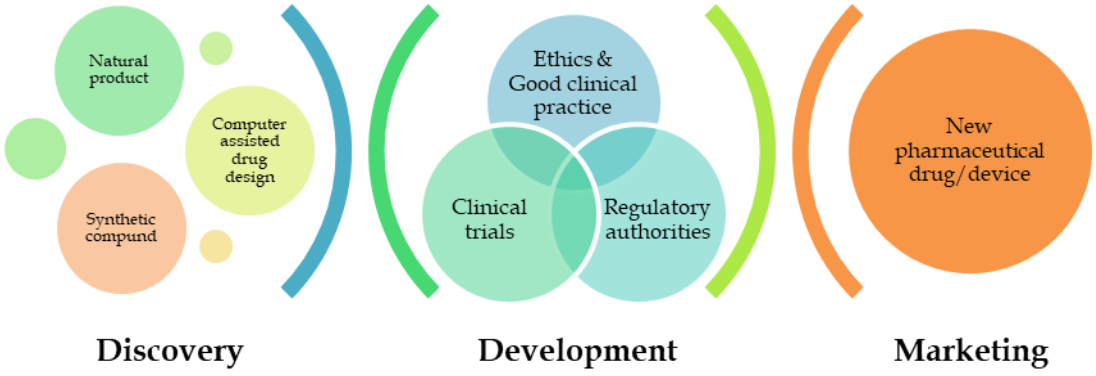

Figure 1. The process of new pharmaceutical drug/device discovery, development, and marketing

THE NUANCES OF DRUG DESIGN AND DISCOVERY

Drug design and discovery involve a complex process. Given the improved scientific and technological advances, the drug discovery process has shifted from the traditional processes to the more synthetic approaches. Drug design has transformed from when the drugs were discovered from the purification and alteration of a known natural substance to the novel technique of producing the drugs from chemicals. Improved knowledge of the disease, from physiological to molecular and atomic levels, and the availability of advanced technologies have significantly influenced the drug design and the discovery process[14]. The drug design and discovery process can be depicted in stages that include identifying the problem/disease, finalizing the compound, and conducting the phase-wise trials (phase 0, phase 1, phase 2, phase 3, and phase 4). After clearly understanding the process involved in drug design and discovery, we move towards developing and manufacturing the drug. An increased understanding of the disease/problem and the genetic basis of the disease enables the identification of the target protein that cures the disease[15] (**Figure 2**).

Since several diseases like Alzheimer's, Parkinson's, and malignancies have different contributing factors, identification of those factors and finding/discovering the modulating compounds using molecular and computer-assisted approaches are considered multidimensional approaches to drug discovery[16]. Although technological advancement proves to be a boon to drug design and discovery, there will still be issues identifying the appropriate drug target for a particular disease and the rational approaches to its discovery[17,18]. The essential components of drug design and discovery include the identification of a problem/disease/target. The case here could be when a satisfactory treatment is unavailable, or there is not yet any therapeutic drug available to treat. Once a target is identified, a search for any natural substance with known therapeutic value is searched and further analyzed for the hit compound, which is further purified and evaluated through clinical trials[19].

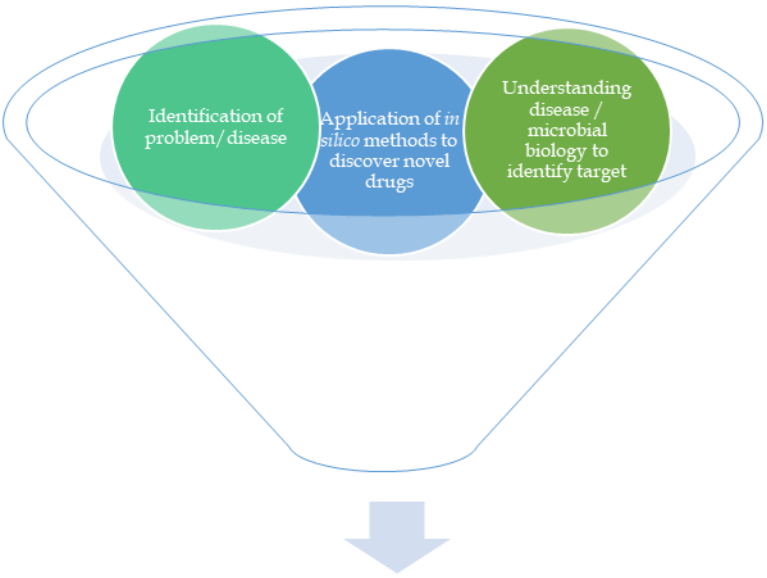

Figure 2. The process of drug design and discovery

The hit molecule is purified using medicinal chemistry studies. The pre-clinical studies are performed to assess the biological activities and toxicological characteristics of the cell cultures and experimental animals before being evaluated in humans in different phases of clinical research. The compound can be synthesized synthetically from chemicals or by modifying a known compound[20]. The CADD, also called the '*in silico* method,' has been instrumental in studying and analyzing the compound in recent times. Even with the increased technological advances, the process of drug design and discovery is a lengthy (time-consuming), costly, complex, and highly unpredictable process[21]. Several avenues require therapeutic interventions to prevent and cure various diseases that include and are not limited to tumors, microbial infectious diseases like malaria, infectious diseases by antibiotic-resistant microorganisms, and other non-infectious conditions, as noted from previous reports[22-24].

Recently, some resolute researchers have discovered a novel Computational Analysis of Novel Drug Opportunities (CANDO), used to fight Ebola using the repurposed therapeutic CANDO Platform[25]. The automatic computer software is currently available to virtually screen and identifies the naturally available products with medicinal value as potential drug candidates[14]. The available technologies have been instrumental in analyzing naturally available bioactive compounds for their anticancer properties, as noted in a recent research report. In this study, the plants of Origanum species were found to produce bioactive oils (carvacrol) that have potential anti-tumor properties, as observed from the experimental animal studies[26]. The availability and accessibility of advanced computational methods in drug design and discovery have increased the productivity and success of developing newer drugs. It has helped screen several naturally available and known natural compounds for their therapeutic value[27]. Recently a public-private partnership (PPP) has been initiated to collaborate and produce newer anti-tubercular drugs in a project called more medicines for tuberculosis (MM4TB)[28].

MOLECULAR DOCKING: A CLUE TO DRUG DESIGN AND DISCOVERY

After identifying the target and finding the desired compound/hit, the most critical drug design and discovery process is to validate the compounds' complementarity with the molecular docking technique. Molecular docking studies enable researchers to find the best confirmation between the protein target and the ligand[13]. Molecular docking identifies the configuration where the protein-ligand complex shows maximum interaction with the least energy. It also finds different protein targets and inhibitors of the target proteins and designs appropriate molecules or ligands to bind to them. This

process is influenced by several factors, including intramolecular (bond length, bond angle) and intermolecular forces (electrostatic, van der Waals forces, and others). The docking type includes protein-protein, protein-ligand, lock-key, and fitting and flexible docking[29,30]. Molecular docking is a computational methodology where the target protein and ligand interactions are carefully studied regarding their best sites of attachments/interactions. The molecular docking studies use computer programs to analyze various ligand-protein binding confirmations and rank these confirmations, which forms an essential aspect of pharmaceutical research[31]. The discovery of whole human genome sequencing has improved the understanding of various disease processes and has been instrumental in identifying better drug targets and binding sites. Molecular docking also helps study the small molecule binding affinities to the target protein and the biochemical processes involved in the ligand-protein bindings[32].

Of all the newer *in silico* techniques available for drug discovery, molecular docking is considered a key concept for successful drug discovery using structure-based drug design (SBDD)[33]. Identification of newer molecular entities/blockbuster drugs is a tedious and costly affair that the newer molecular docking technology can overcome[34]. Using molecular docking, the novel binding site for the drug (HIV-1 integrase) for combating human immunodeficiency virus (HIV) infection was discovered[35]. In recent times, the molecular docking mechanism has been used to study the molecular and quantum mechanics of the proteins, using these studies to discover newer antimicrobial therapeutic agents and assess the role of larger protein-protein complex interactions in developing drugs[36]. In the SBDD, the ligand/protein binding capacity with the receptor is analyzed for the strengths of the bond, stability, and affinities using various scoring parameters[37]. There are now ligand libraries available, and it is effortless to virtually screen the ligand compatibility with a protein or a receptor target[38]. The molecular docking technique enables high throughput screening of multiple ligands and their complementarity with the potential receptors (**Figure 3**)[39].

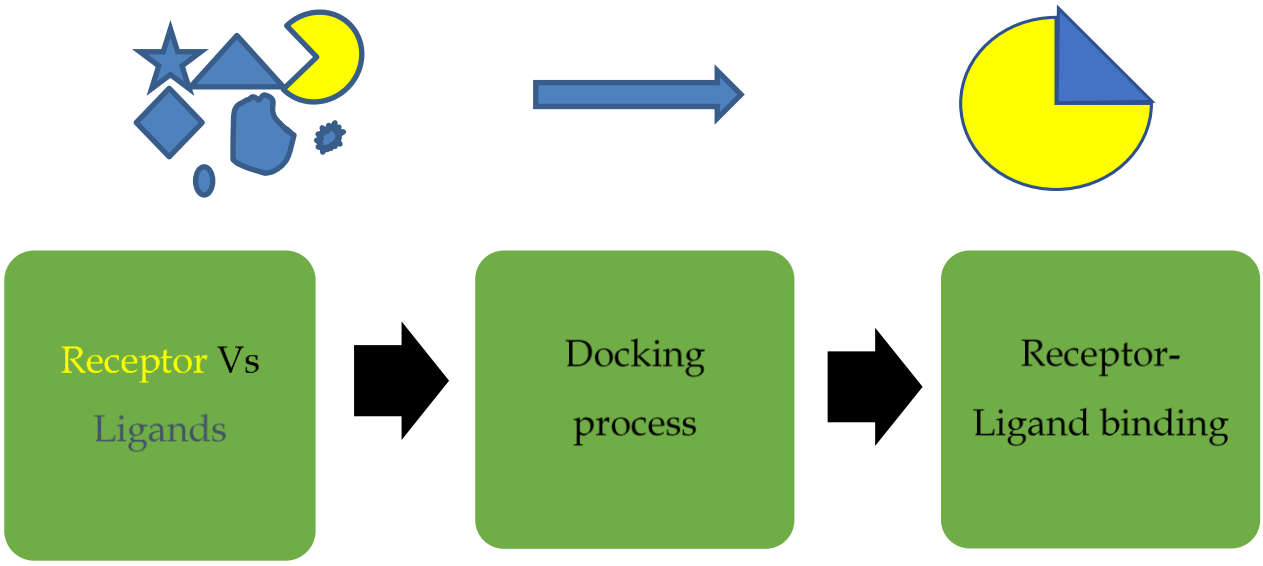

Figure 3. Molecular docking process to assess multiple ligands and their complementarity with the receptors

SYNTHESIS OF PHARMACOPHORE ELEMENTS USING CADD

The most significant part of a drug design and discovery is the synthesis of three-dimensional ligands, also called 3D-pharmacophore elements. The CADD enables the development of pharmacophore elements and to study of the spatial arrangements and the electrochemical properties of the ligands[40]. The 3D-pharmacophore ligands help understand the ligand's binding abilities to the protein/enzyme. The pharmacophores are the carrier molecules/ligands which help bind the drug/protein. Pharmacophores are the molecules that bind to the target proteins and bring about the needed biological

response (treatment). The activities of the pharmacophore elements depend on the hydrogen bond donor/acceptor, positively/negatively charged, aromatic/aliphatic rings or moieties, and hydrophobicity[41,42].

X-ray crystallographic studies are used to study the molecular structure/confirmations of the ligand (spatial arrangements and electrochemical properties) and the receptor. High-affinity ligands are more suitable for attachment to the receptors and show no steric repulsions with receptors. The pharmacophore technology assists in studying the ligand's binding sites (high affinity/low affinity), modifying the binding site/molecular structures to improve the binding capabilities of the ligand with the receptor/protein (**Figure 4**)[43]. Pharmacophore-based ligand synthesis methods will help identify the suitable biological target, as noted from a recent study that found hepatocyte growth factor receptor (c-Met) as a suitable target for new compounds[44]. The quantitative structure-activity relationship (QSAR) and three-dimensional ligand-based pharmacophore models are frequently used to identify the target binding sites on the ligand, as noted from the research studies on Alzheimer's disease[45].

In CADD, synthesizing pharmacophore elements is crucial for designing and discovering a new drug. Recent research elaborated on using a pharmacophore model to synthesize new quinolone derivatives for their antioxidant activities[46]. Pharmacophore modeling was used to synthesize a ligand-based pharmacophore model to synthesize the serotonin receptor antagonist, which has a therapeutic application in managing various clinical conditions, including anxiety and others[47]. Because CXCR2 is an essential receptor in the development and metastasis of cancerous conditions, the ligand-based pharmacophore model was prepared using the computational method (virtual screening) to synthesize the CXCR2 antagonists[48].

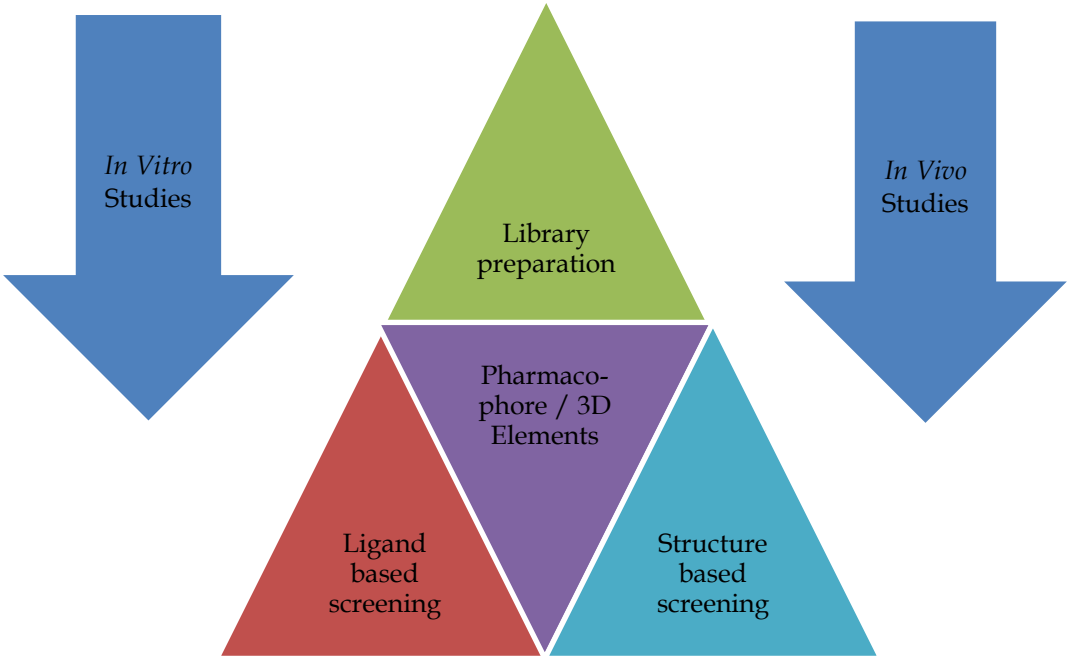

Figure 4. Pharmacophore based ligand screening

THERMODYNAMICS OF DRUG DESIGN AND DISCOVERY

The success of the drug design and the discovery depends on the thermodynamics of the ligand-receptor complexes. This concept discusses the conformational modes of the ligand and its multiple binding sites to the protein/receptor. It also elaborates on the two important mechanisms of assessing the binding affinities of the ligands to the protein/receptor molecules: free energy perturbation (FEP) and thermodynamic integration (TI)[49]. The nature of the receptors includes those without the endogenous ligand (enzymes, ion channels, proteins, and nucleic acids) and those with the endogenous

regulatory ligands (hormones, auto acids, neurotransmitters, growth factors, and cytokines). By using the CADD, the conformational properties of the ligand-receptor/protein complex may be studied/understood using the quantum chemical methods that include the Schrödinger equation. In this equation, the molecule is considered a collection of positively charged nuclei and negatively charged electrons moving under the influence of Coulombic potentials[50].

The ligand and the receptor interactions will decide the complex's stability and the drug delivery potential. The protein-ligand of the ligand-receptor interactions depends on the complexes' enthalpy and entropy[51]. The bioactive conformational energies of the ligand-receptor/protein complexes assume greater significance because the higher the affinity, the greater the complexes' stability. The affinities depend on the free energy difference (ΔG) between the bound ligand-protein complex and the unbound protein and the ligand[52]. The water affinities and the hydrophobicity associated with the stable ligand-receptor complexes depend on the protein's polar, non-polar, and topographical complex concavities, as noted in a previous study[53].

Drug design and discovery is a complex process involving several versatile research areas. The ligand-binding ability of the receptor (drug-target complex) is checked using thermodynamic studies, and those ligands which are faulty can be eliminated, and those with improved binding capacity can be selected for further research. The thermodynamic studies include the assessment of the free energies (ΔG) of the ligands, their enthalpies (ΔH), and the entropies (ΔS)[54]. Thermodynamics is the study of the heat change that occurs when two molecules interact. It is used to identify inhibitors and antagonists to minimize antimicrobial drug resistance due to mutations, reduce side-effects caused by non-specific attachments, and water solubility to increase bioactivity, as noted from the available research findings[55]. The lead optimization studies apply thermodynamics considering three essential aspects that include the presence of appropriate enthalpy in the hydrogen bonds, there is favorable entropy in hydrophobic interactions, and conformational changes that are entropically unfavorable[56].

MOLECULAR SUPERIMPOSITION AND MOLECULAR MECHANICS INVOLVED IN DRUG DESIGN

Among the most significant advantages of CADD, the technique of molecular superimposition assumes great significance. Understanding the process of molecular superimposition and molecular mechanisms involved in drug design and discovery is essential. After preparing a 3D-pharmacophore element, the molecular superimposition helps to compare different molecules for their conformational properties and ability to bind or fit into the model. The molecular superimposition may be done using either the atoms/fragments or the molecules. Molecular superimposition can be rigid or flexible[57]. The computer method QUASIMODI is used to perform superimposition and the Patterson-density-based similarity index, and the electron-density derived similarity is applied to optimize the confirmations. The FLEXS, FLASHFLOOD, SUPERFLEX-SIM, and the FLASH methods are applied to perform a flexible alignment. The semiflexible approach can be applied using the computer program, the SUPERPOSE, and the CATALYST[58]. However, molecular superimposition ensures that various atoms and molecules are checked for their confirmations, and binding abilities, the stability of a 3D-pharmacophore element also depends on the molecular mechanics of the molecule that is assessed. The molecules are a combination of atoms, and the stability of the complex depends on the bond lengths, bond angles, torsional angles, and the non-bonded distances between atoms of the molecule[59].

Clathrin is a protein present on the cell membranes of eukaryotes with various functionalities that include the uptake of bacteria, membrane-bound proteins, and others. A recent study reported using a flexible docking mechanism to identify the confirmations on the clathrin for its binding ability to the Bolinaquinone to inhibit its activities[53]. Most synthetic drugs are synthesized by using organic molecules containing carbon atoms. Therefore, medicinal chemists play an active role in drug design and discovery. Molecular mechanics involve synthesis, alteration, and representation of 3D structures of the molecules. Molecular mechanics include applying computational technologies to study the molecular and biological properties of various protein/receptors/targets using theoretical and experimental data. The molecular mechanics involve

X-ray crystallographic studies to understand the 3D conformation of the molecule and the ability of the molecule to bind to the target/receptor. Molecular mechanics are inexpensive and easy to manage and are used to reproduce molecular confirmations matching and adjusting the bond lengths, bond angles, and torsion angles to equilibrium values to the one it has been designed to bind/attach[60]. The QSAR study is a technique that quantifies the anatomical and biological properties of the molecules/ligands/proteins. The physicochemical properties include hydrophobicity, structural, ion-ion interactions, and steric effects. A recent study attempted to combine the molecular docking technique with the QSAR method to find the binding sites on the transforming growth factor-β (TGF-β) necessary to stop invasion and tumor metastasis[61].

3D-PHARMACOPHORE ELEMENTS IN DRUG DESIGN AND DISCOVERY

The 3D-pharmacophore and the typical feature of the pharmacophore include hydrogen-bond donors and acceptors, positively and negatively charged ions, and hydrophobicity. The pharmacophore elements form the basis/core of medicinal chemistry. The pharmacophores are synthesized by using the active molecules in such a way that they retain the biological activity, and a slight change in the configuration of the molecules may influence the biological activities. The pharmacophore technology is to synthesize the ligand and receptor antagonists, as noted in the case of dopamine antagonist receptors and the serotonin (5-hydroxy tryptophan) receptors. The 3D-pharmacophore elements are prepared using the atoms and the molecules bound by various bonds/forces like the hydrogen bonds, electrostatic forces, and the van der Waals forces. Also, the pharmacophore elements may contain the heteroatoms such as oxygen, nitrogen, and polar functional groups such as carboxylic acids, amides, and hydroxy groups[62].

There are two types of pharmacophore elements, structure-based (X-ray) and ligand-based (derived from active compounds) pharmacophore elements[63]. Since not all protein structures have been elucidated, the ligand-based pharmacophore synthesis is most opted by the researchers. The software used in the molecular modeling pharmacophores includes the MOE and Phase[64]. Pharmacophore technology is essential in drug design when the structural data on a target receptor is unavailable. The pharmacophore method is used to perform lead discovery, lead optimization, and to assess the similarity and variations in the structural confirmations of the ligand and the receptor[65]. According to the international union of pure and applied chemistry (IUPAC), the pharmacophore is defined as the interactions of molecular structures to their molecular target by the steric and electric features and defining a specific biological property. The pharmacophore technique uses molecular interaction to define a ligand's binding ability to the receptor, including features such as hydrogen bond donors, hydrogen bond acceptors, positive and negative charged ion groups, and hydrophobic regions[66].

HUMAN PARTICIPANTS IN CLINICAL TRIALS

Clinical research is usually undertaken to solve a current medical/public health problem. The problem in most instances would be the patients suffering from various diseases that include both infectious (microbial infections) and non-infectious conditions. The solution looked for is to find a treatment for a disease that has neither a therapeutic intervention available nor a vaccine present, and when the current treatment is plagued with complications/severe adverse effects. Although the pharmaceutical substances are designed based on CADD and other *in silico* methodologies, they are tested on healthy and diseased people to assess their safety and efficacy before being approved by the regulatory authorities for prescription purposes. The regulatory bodies stress the need for human subjects' protection, informed consent, and support for the families of trial participants during clinical trials[67,68]. It was recommended to provide aids and tools consisting of detailed information about the trial to potential volunteers and facilitate better decision-making[69,70]. The regulatory agencies in France have enforced 'Jardé law,' an improved clinical trial directive that enhances the protection of the rights of trial participants[71]. Clinical trials involve special population groups like the children, pregnant women, and elderly aged, among other vulnerable groups, which may potentially pose ethical and legal obligations (**Figure 5**)[72-76].

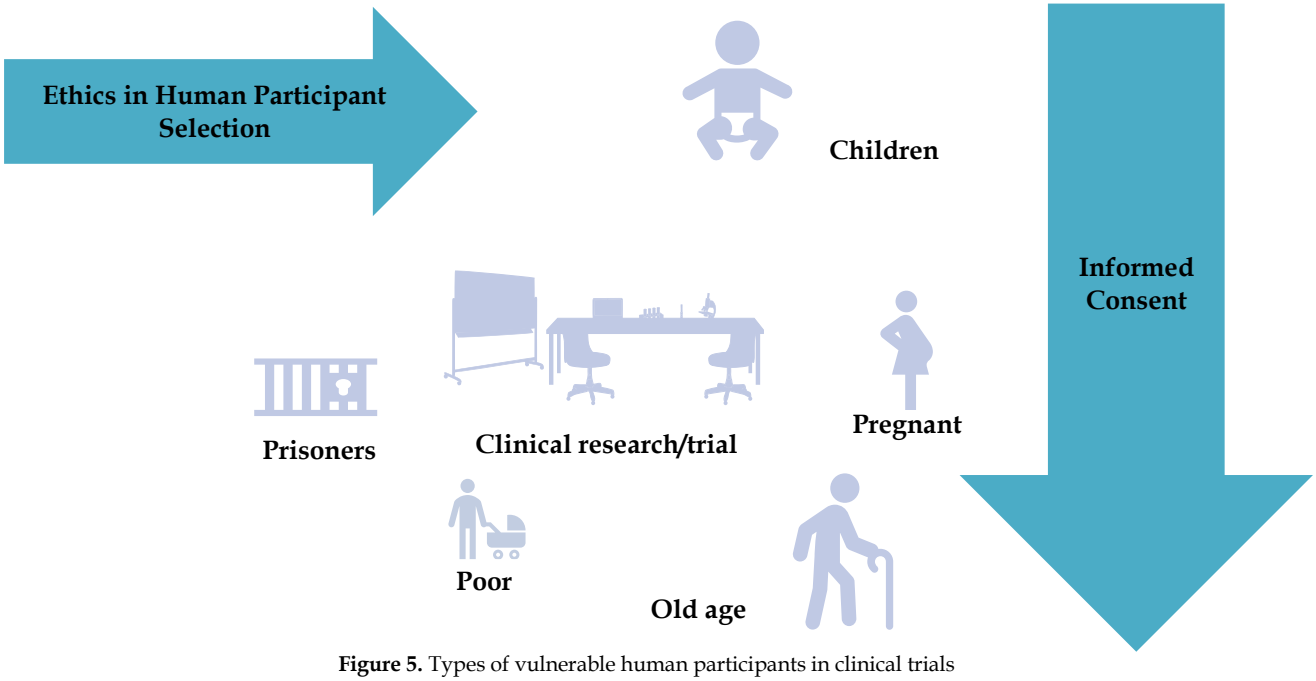

Figure 5. Types of vulnerable human participants in clinical trials

ETHICS IN CLINICAL RESEARCH: PROTECTION OF HUMAN RIGHTS

Although clinical research is conducted for the welfare of the people, the ethical concerns of the subjects participating in the research must be satisfied. This concept delineates the policies that protect the human rights of the subjects taking part in the clinical research. The institutional review boards (IRBs) play vital roles and responsibilities in regulating the conduction of clinical research. The IRBs emphasize the functional regulations and ethical considerations during cooperation and collaborating research that should strictly be followed by the institute that engages (also the institute which do not engage in human subject research) in research involving the human subject. Clinical research involving human subjects is critical in protecting human rights concerning the humans participating in the research. In most instances, it applies to the risk and burdens that a human subject participating in clinical research is exposed to during clinical research. The first such regulation regarding ethics in clinical research involving human subjects was the Nuremberg code, followed by the 1964 Helsinki declaration by the World Health Organization (WHO). It was later followed by the Belmont report by the United States of America[77].

With the international guidelines as a parameter, national guidelines for protecting human rights were implemented by the respective countries, including India's Indian Council for Medical Research's (ICMR) Ethical Guidelines for Biomedical Research on Human Subjects in the later years[78]. The ethical code of conduct during clinical research involving human subjects has gained significance due to the infamous human experiments during World War I and II. Also, the Tuskegee Syphilis human research that led to unethical practices involving a particular group of humans, including the prisoners and mentally ill people, was instrumental in framing ethical code in clinical research involving humans[79]. Clinical research becomes ethical by satisfying seven requirements that include research to enhance further understanding of a disease/condition, scientific methodology used while conducting the research, including appropriate participants after following scientific procedures, and favorable risk-benefit ratios. An independent review board approves the study protocol, informed consent is taken without any influence, and respect for privacy protects the well-being[80].

Since clinical research is conducted for a good social cause and the improvement of human health, such research must satisfy ethical concerns and justify the research concerning its social value requirement (SVR). The SVR is justified in all cases of clinical research, which satisfy eight ethical concerns that include safeguarding the rights of participants who cannot give consent, respect for autonomy, investigator integrity (not exposing subjects to undue risks), deceiving participants

(promising undue advantages/incentives), not exploiting the participants, stewardship of public resources (spending for a social cause), imparting public trust (benefiting public), compensating any deviations for the above rules (make sure the competent adults are recruited for research on the non-social cause, only expose to no more than moderate risks, compensate the undue risk with benefits, preserving privacy, and not use public funds)[81].

ETHICS IN CLINICAL RESEARCH: INFORMED CONSENT

Informed consent is the process of obtaining the approval and voluntary acceptance by the individual participating in the clinical research. Also, the informed consent acts as a bridge between the investigators and the participants as to how the research work is conducted (research flow), the interventions, the risks involved to the benefits, and the necessary precautions in case of any adverse events. It would sum up the process of gaining confidence and satisfaction to the effect that all ethical concerns are/will be appropriately addressed. In clinical research or any other research, informed consent assumes tremendous significance from an ethics perspective if humans are involved. The institutional review boards play a key role in ensuring the contents/elements of the informed consent form and the process of obtaining it from the participants. Clinical researchers must understand the process and elements of informed consent while obtaining the consent from the specially-abled group participating in the research following the council for the international organization of medical sciences regulations (CIOMS). In emergency circumstances, the informed consent and all other issues related to the informed consent become an exception[82].

Informed consent should not only be considered a formality but a legal compulsion/obligation, as observed by a previous report from India[83]. The challenges of the informed consent obtaining process were elaborated in previous research that noted that the informed consent process might be influenced by religious sentiments, patient perceptions, specially-abled groups/vulnerable populations (children, pregnant women), and the general local, social, and cultural characteristics of the population[84]. Informed consent has many elements, including the fact that the participants are fully aware of the research work, the potential risks, and other aspects of human rights. Informed consent in clinical research should address the elements like when informed consent is required and how the consent is obtained from the participants of a clinical research study. The most significant aspect of informed consent is autonomy (deciding to participate in clinical research and discontinuing at any time). Informed consent is practiced by imparting certain functionalities in the conduction of clinical research that includes protecting privacy, and autonomy, respecting participant values, protecting and promoting the welfare of study participants, preserving trust, satisfying all regulatory requirements, and overall research integrity[85].

GOOD CLINICAL PRACTICE: THE PROCESS OF INVESTIGATIONAL NEW DRUG APPLICATION

Clinical research is conducted following the good clinical practice guidelines laid down by the international conference of harmonization (ICH). These are universally followed throughout the world during the conduction of clinical research involving human participants. All the stakeholders in clinical research, including the principal/investigators and the sponsor, have specified roles and responsibilities. Once a new compound is discovered, an investigational new drug (IND) application must be submitted for the conduction of clinical research. The process of an IND application is generally as per the national and international guidelines/ authorities like the food and drugs administration (FDA), US. The FDA plays a significant role in the process of IND application in case of drugs related to life-threatening illnesses and in the management of imports and exports of the drugs concerning IND[86].

Clinical research is, in most instances, undertaken to identify a new drug. Such a process involves the identification of a problem/disease, identifying a potential molecule/drug, and evaluating the drug through different phases of clinical research. During this process, the first step towards clinical research requires the approval of the IND by appropriate regulatory authorities like the FDA. The INDs are the candidates who have been pre-tested, are found to be

pharmacologically active, and do not pose any risk to humans. The IND is evaluated for its potential toxicity by animal testing even before using it on humans. Only after passing phase 0 the IND proceeds further for an application for its approval through different phases of clinical research where it is evaluated on humans[20]. Depending on its uses, the IND are of various types that include the investigator IND (he/herself initiates the drug trial), the emergency use IND (for treating emergencies by the investigator), and the treatment IND (an experimental drug showing promise is tried as a treatment in cases of serious illness). Also, the IND can be of two types, the commercial and the research IND (**Figure 6**)[87].

The most significant part of clinical research is the implementation of good clinical practice (GCP) guidelines. Once the lead compound is identified and optimized, the next step toward drug discovery is the application for a new drug testing (investigational new drug application-INDA). The potential drug is approved for animal testing (pre-clinical phase to assess for safety and toxicity) and later in humans (clinical research phase 1-4)[88]. While the clinical research is being conducted, the GCP guidelines must be followed at various stages. The GCP guidelines state that regulatory authorities must satisfactorily evaluate the clinical trials like the FDA. The FDA must evaluate each phase of a clinical trial. The GCP guidelines ensure that the clinical trials are approved by the regulatory authorities (IRB), ensuring the trial processes, designing the case report form (CRF), analyzing research planning, and assessing the study reports at regular intervals after completion of the study[89].

Figure 6. Types of Investigational new drug (IND)

GOOD CLINICAL PRACTICE: REGULATORY AUTHORITIES AND CLINICAL TRIAL PROTOCOLS

Among many other procedural processes involved in clinical research, clearance from the regulatory authorities like the FDA is a must before starting clinical research. These authorities monitor the activities before, during, and after the conduction of clinical research. Historically, the GCP guidelines are formulated by the meetings after the Nuremberg code, the declaration of Helsinki, the Belmont Report, recommendations by the respective countries (USA-FDA), and the WHO guidelines. In every step of clinical research, the role played by the regulatory authorities assumes great significance. The

application for an IND is a systematic process that includes three sets of forms, the FDA form 1571 (study protocol), the form 1572, which gives the information about the investigator and the site of investigation, and the FDA form 3674, which contains the clinical trial registration at the respective national agencies[90].

The sponsor and investigators are responsible for updating the modifications/amendments in the study protocol both to the institutional review boards and to the FDA. Also, they are entitled to notify any information amendments (increase/decrease in drug exposure), safety reports (reporting adverse events), and annual reports detailing the status of the study. Protection of human rights, the safety of the participating subjects, and the reliability of the data being generated imply the quality of the clinical research. A rigorous review of the study protocol by the respective institutional review boards and stringent informed consent practices will demonstrate the high scientific standards of a clinical trial study. Continuous monitoring of the trial and regular audits will ensure the quality of a trial[91].

Most clinical trials evaluate the efficacy, safety, and adverse events associated with medical products, including drugs. The clinical trial involves a large group of qualified medical professionals, including the principal investigator, co-investigators, clinical research associates, and the sponsors who fund the trial (**Figure 7**). The clinical trial must follow a protocol (background and purpose of study, trial design, infrastructure required, procedural details, and statistical methods to analyze results), standard operating procedures (SOP), study manuals, and other guidelines, including a well-structured plan of action document. All the deviations in the protocol must be so as not to harm the study participants, and any harm must be addressed and informed to the regulatory authorities[92]. To avoid bias in reporting results, rejection of the results by the sponsor or the regulatory authorities must be appropriately addressed. Although the governments are liberal and encouraging concerning permission for clinical research activities (research and drug manufacturing), unless the GCP guidelines are adhered to, no clinical research will result in positive results[93-95].

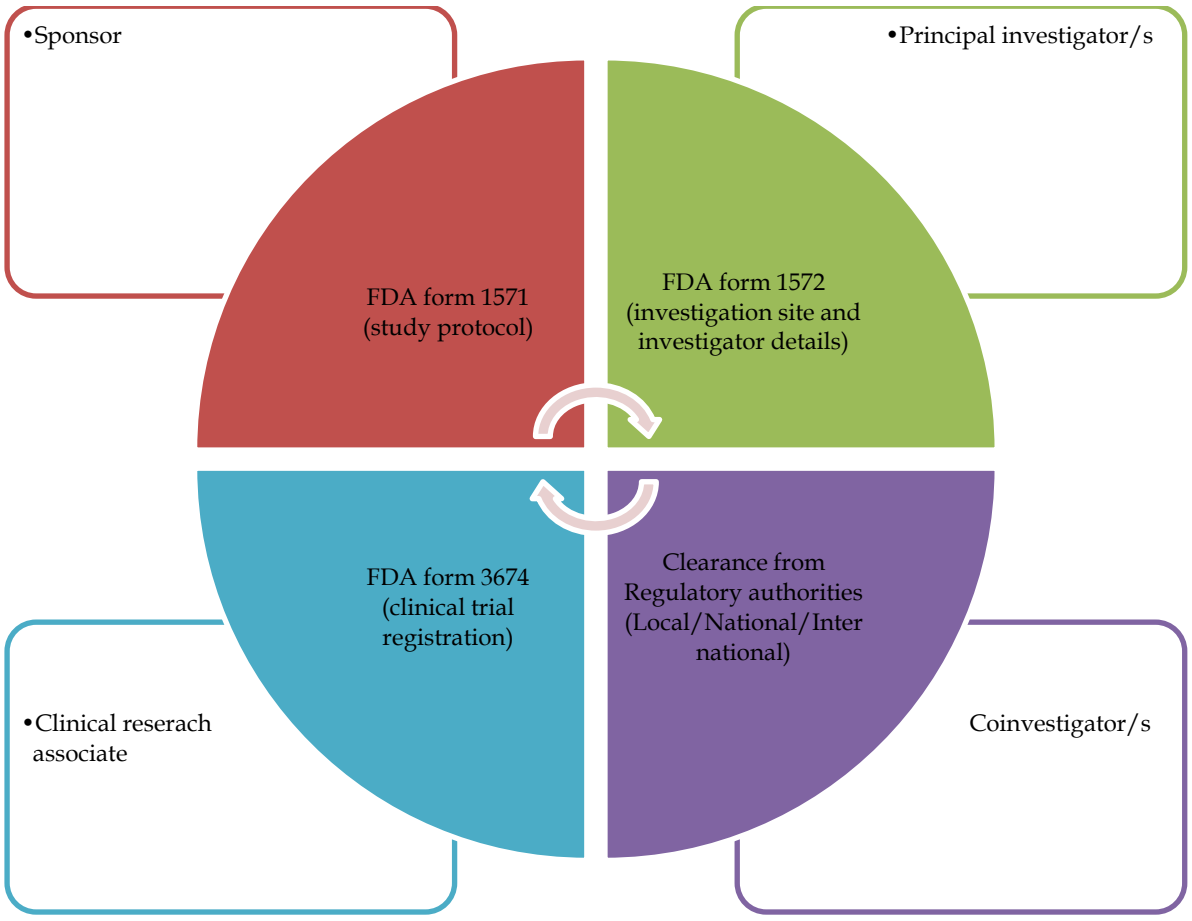

Figure 7. Essential elements of a clinical trial

CONCLUSION

Clinical research is an emerging area with great scope for research. Currently, clinical research aims to find faster solutions to modern, existing, and emerging diseases, including the novel Severe Acute Respiratory Syndrome CoV-2 (SARS-CoV-2) responsible for Coronavirus Disease-19 (COVID-19). The non-availability of a vaccine for HIV, Dengue virus, and no proper treatment for several other microbial infections and tumors, among other life-threatening illnesses, are responsible for the increased focus on clinical research. Several microbial infectious diseases need better antimicrobial therapeutics due to increased antibiotic resistance. Tuberculosis is plagued by multidrug resistance, and therefore, the control of the spread of infection has become a challenge. The *in silico* methodologies discussed in this review may be applied to virtually screen/identify drug candidates and minimize the cost and time taken to develop new drugs. An improved understanding of molecular modeling techniques and *in silico* methods are instrumental in studying the potential drug candidates' pharmacokinetic and pharmacodynamic properties. Adhering to the GCP guidelines on ethics for protecting human/participant's rights and acquiring informed consent from all the participants as prescribed by the regulatory agencies are prerequisites for conducting a successful clinical research/trial.

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AUTHORS' CONTRIBUTION

All authors contribute equally.

DATA AVAILABILITY

Not applicable.

CONFLICT OF INTEREST

There are no conflicts of interest.

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