# Computer-aided Drug Design

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## ABSTRACT

Omnipresent pathogens which are responsible for severe infectious diseases till today and their threat is still alive due to undiscovered pathogens and the mutants of the existing ones. Moreover, chronic diseases/syndromes do pose a big challenge to the survival of humanity. Worldwide medicinal researchers are working to develop effective medicine while considering the various therapeutic strategies. The present review presents significance of computer aided drug design for the development of new drugs.

**KEYWORDS**: Computer-Aided Drug Design, *in-silico* studies

## INTRODUCTION & DISCUSSION:

Origin of drug used and discovered in the early history by the mankind has been missing due to unscripted historical evidences. The knowledge of plants use in sustaining human health and well being of mankind has traversed from generation to generations. Animal products and minerals along plants have also been optional materials to be used in form of drugs. Chinese Medicine, Ayurveda and Greek Medicine, the ancient medicine systems have conceptualised imbalancing in body constituents as responsible parameter for the ailments; similarly, restoration of these components in their natural proportion by the means of medicines has been established as therapy. In the modern scenario, various other factors like infection by the foreign particles and inborn or acquired defect in the genetic material have also been comprehended in the cause of disorder/disease.

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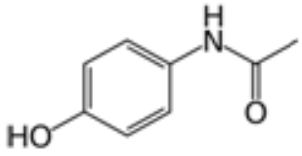
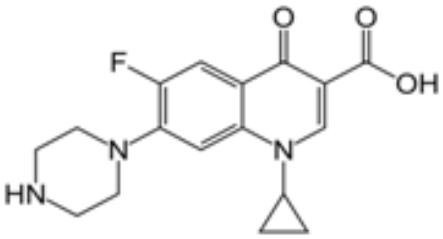
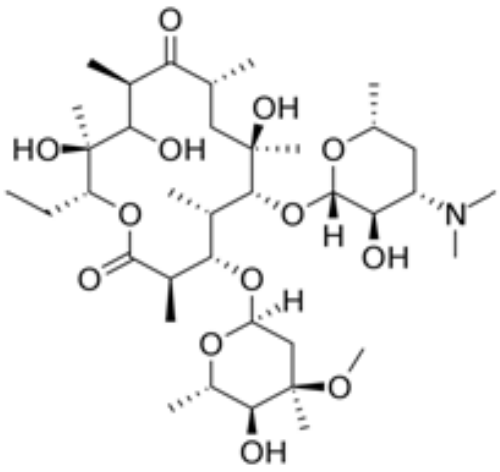


Paracetamol



Ciprofloxacin



Erythromycin

This physiological condition (disease or disorder) causes fatal and non-fatal discomfort depending upon responsible factor. Chronologically developed therapeutic strategy uses a chemical molecule (drug) which when administered in the body brings soothing physiological changes in response to a disorder/infection (Figure-1).

**SOURCES OF DRUG**:

The knowledge that has travelled through the generation indicates towards natural products as the primary source of material that was used as therapeutics. In the general perception it was thought that the natural product that has some structural similarity with any body organ may show some biological potency to that part of the body although that is not true in the modern concept. As revealed earlier that due to unscripted history of drug origin the information effective in real sense has been documented with the growth of civilization which is still in use. It has been seen that various parts of flora and fauna have

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got pharmaceutical ability for the treatment of various disorder e.g. the bark of cinchona tree has been used in the treatment of malaria. Similarly, whole plant of Neem (*Azadirachtaindica*) has been used as an effective antimicrobial material in the Indian civilization.

With the development of Chemistry, isolation and synthesis of main essence responsible for the treatment of ailment of plant product was the aim of study and research as well. Thus, the active components were tried to obtain from the natural product for the precise use of the natural material and better results e.g. quinine was the isolated active antimalarial component of bark of the cinochona tree. In this progression, synthetic medicinal chemistry, another head of chemistry lead to development of synthetic products as new age medicinal agents because of their more paced potency and stern activity e.g. chloroquine was a synthetic and more effective antimalarial agent as compared to isolated quinine and cinchona bark as well.

**DRUG ACTION:**

Drug after its introduction inthe body passes through biological barriers (digestion and drug metabolism) reaches the site of action which may be a receptor on cell or in the cell leading to the formation of drug-receptor complex (**Figure-2**). Drug –receptor complex brings out the pharmacological action either by enzyme inhibition or interaction with bio-product responsible for the disease.

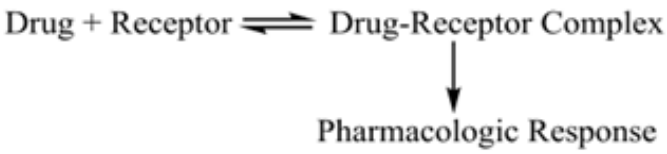


**Figure-2**

**DRUG DISTRIBUTION:**

There are three main ways to administer drug to the body viz. oral, intramuscular and intravenous mode. In the oral mode of drug administration, drug is ingested that undergoes through the digestion process to reach the blood (systemic circulation) after assimilation. This systemic circulation delivers the drug to the site of action in the body. Intramuscular administration of drug involves the delivery of drug in the muscular region of the body or beneath the skin from where it directly goes to the systemic circulation. The third mode of drug introduction in the body is direct

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injection of drug in the blood stream which is the fastest mode of drug delivery to the site of action. Though the both later methods are fast in their drug distribution mechanism but are painful moreover it is not necessary and possible to administer by these two ways.

## COMPUTER-AIDED DRUG DESIGN:

Conventional drug design is based on a prototypical molecule, which can be a natural product or a structurally modified natural product.In recent times, drug design involves understanding the etiology of the disease and the structure of the receptor where the drug will bind (**FIGURE-3**).Computational drug design method includes structural correlation of compounds with receptor site of biological activity in terms of its binding ability. Computational methods calculate molecular properties like molecular mass, molecular structure with requisite structural parameter for binding ability and reversible nature of the substrate, which are very important to generate pharmacophore hypotheses. After compilation of pharmacophoric hypothesis, *in silico* screening of chosen chemical database is carried out to deduce drug-receptor interactions (Molecular Docking) in order to identify the potential lead compounds (Hits). Lead compounds are further synthesisedand subjected to *in vitro* (in test tube/ petri dish) screening to check their preliminary biological potency.Successful *In vitro* results directs the potent compounds to *in vivo* (organism)testing for its activity in a living

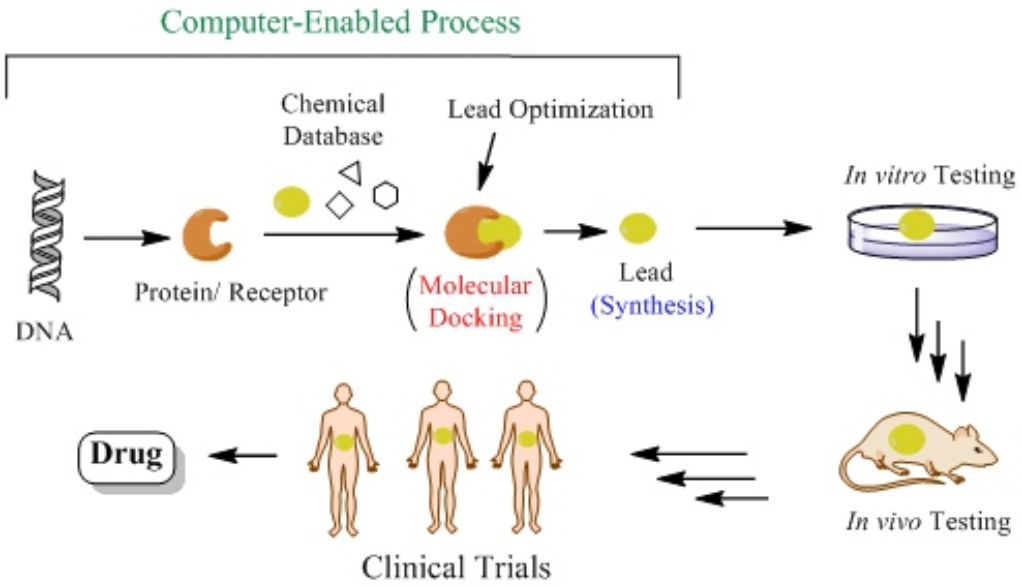


**FIGURE-3** Schematic Presentation of Computer-Aided Drug Design

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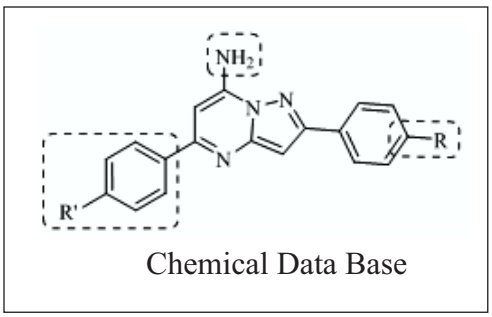
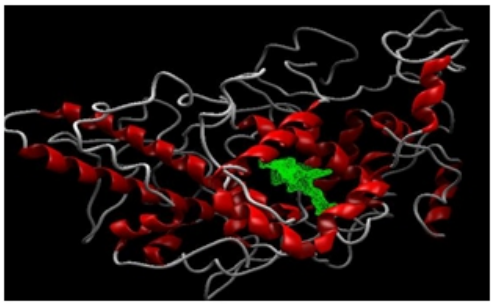
system in order to check its viability in the living system. Further, ADME (Absorption, Distribution, Metabolism and Excretion) studies of the potential compound are carried out to find out its drug suitability. In the next step, the drug candidate enters into Clinical trial stage in order to determine toxicity and side effects on the prolonged usage where the fruitful results of clinical trial of the drug candidate enables it to be approved by competent authorities like Food and Drug Administration (FDA).

## LEAD EXPLORATION BY MOLECULAR DOCKING:

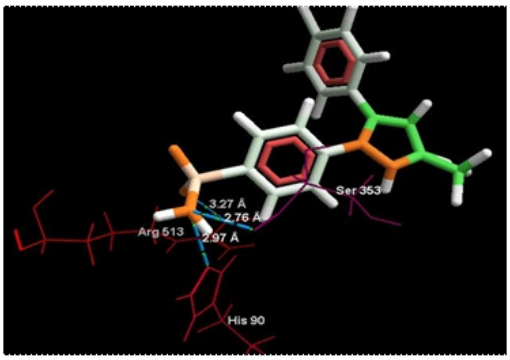
Molecular docking is an important structure-based drug design where the ability of binding conformation of molecules (Chemical Data Base) to the appropriate target binding site is explored with the help of computer simulation (**FIGURE-4**). Study of the binding behaviour of the molecule with the receptor site plays an important role in rational design of drugs. Structural features of the target binding site (enzymes) are obtained due to enzymatic ability to get crystallized where X-ray crystallography of this crystallized structure reveals the size and binding option available in the receptor molecule.

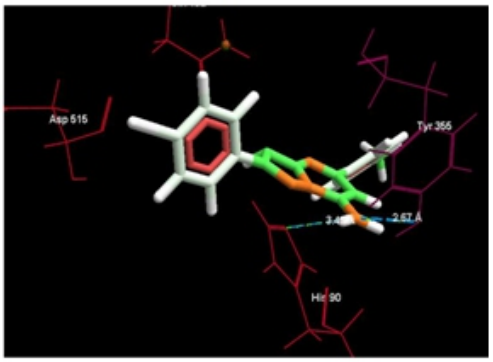



Chemical Data Base



Receptor Site (Green in colour) in Enzyme




Binding Interaction of Lead with receptor Site by Computer Simulation (Molecular Docking)

**FIGURE-4**

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Thus, the known vacant receptor size and binding options helps in designing of a requisite chemical database, which may act as the best fit. A good fitment score (binding score) shifts the molecular database to their synthetic process where the library of molecules is synthesised by following an effective structural variation.

***IN VITRO / IN VIVO TESTING*:**

All the synthesized chemical compounds with a good binding score are subjected to *In vitro* or *In vivo* testing to explore the required biologically important trait. The preliminary remarkable competency of compound library shifts the best of those to administration methods exploration and rigorous biochemical analysis (ADME) in order to introduce a new clinical trial. Successful trials pave the pathway of clinical trials to be disclosed as a drug.

**CONCLUSION:**

Computer aided drug design has expedite the process of drug development as the *in-silico* modelling explores the receptor ligand interaction in the three dimensions which mimics the biochemical pathways in real to a significant extent. Moreover, the close proximity of the *in-silico* result with the in-vitro results proves the prime importance of the strategy.

**REFERENCES:**

1. Mukherjee, P. K., Harwansh, R. K., Bahadur, S., Banerjee, S., Kar, A., Chanda, J., & Katiyar, C. K. (2017). Development of Ayurveda–tradition to trend. *Journal of ethnopharmacology*, *197*, 10-24.
2. Islas, J. F., Acosta, E., Zuca, G., Delgado-Gallegos, J. L., Moreno-Treviño, M. G., Escalante, B., & Moreno-Cuevas, J. E. (2020). An overview of Neem (Azadirachta indica) and its potential impact on health. *Journal of Functional Foods*, *74*, 104171.
3. Christensen, S. B. (2021). Natural products that changed society. *Biomedicines*, *9*(5), 472.
4. Meshnick, S. R., & Dobson, M. J. (2001). The history of antimalarial drugs. *Antimalarial chemotherapy: mechanisms of action, resistance, and new directions in drug discovery*, 15-25.
5. Beale, J. M., Block, J., & Hill, R. (2010). *Organic medicinal and pharmaceutical chemistry*. Philadelphia: Lippincott Williams & Wilkins.
6. Aggarwal, R., Singh, G., Kaushik, P., Kaushik, D., Paliwal, D., & Kumar, A. (2015). Molecular docking design and one-pot expeditious synthesis of novel 2, 5-diarylpyrazolo [1, 5-a] pyrimidin-7-amines as anti-inflammatory agents. *European Journal of Medicinal Chemistry*, *101*, 326-333.

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