WWW.IJRPR.COM

International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

Drug Discovery and Development Process

Mr. Gahininath Thansing Jadhav [a], Mr. Rahul Bhavlal Jadhav [b]

[a] Department of Chemistry, B. K. Birla College (Autonomous), Kalyan-421304
[b] Aditya Institute of Pharmacy, Derabardi, Dhule road, Chalisgaon-424101
DOI: https://doi.org/10.55248/gengpi.5.0124.0225

A B S T R A C T

Drug discovery and development follows following sequence:

Target identification --> Validation --> Lead identification --> Lead optimization --> Product characterization --> Formulation and development --> Preclinical research --> Investigational New Drug --> Clinical trials --> New Drug Application --> Approval

Conversion of a particular organic compound to drug requires huge amount of money and time. So, any type of failure at any stage causes great loss. In this review, we have come across various methods which are used currently in the field of Drug discovery from literature. Now though we have computational advances which leaded in more and more rationale in silico designing, still industry is depending on in vitro experimental studies. Bioprinting technology shows great applications in drug screening, checking toxicity and so on. AI-Artificial Intelligent, nowadays gaining weightage in drug discovery process, which cut down the research and development cost. In India, we have great history of traditional medicine. Currently serious efforts are taken to develop traditional medicine into future ready drug. There are various advantages of modelling and simulation at pre-clinical stage of drug development. In recent years, Halogen bond catches the attention for hit-to-lead-to-candidate optimization which leads to improve drug-target binding affinity. Drug discovery based on Ayurveda follows a 'Reverse Pharmacology' path from Clinics to Laboratories

Keywords: Drug Discovery, Drug Candidate, Bioprinting, AI, Computational, Reverse Pharmacology

Conversion of a particular organic compound to drug requires huge amount of money and time. So, any type of failure at any stage causes great loss. Now though we have computational advances which leaded in more and more rationale in silico designing, still industry is depending on in vitro experimental studies. Hence in vitro-in vivo correlations improving day by day. In this regards 3D (three-dimensional) tissue model are very helpful as compared to traditional 2D (two-dimensional) models. Bioprinting technology shows great applications in drug screening, checking toxicity and so on. [1]

New drug candidate's in vivo metabolism are estimated and predicted by in vitro methods. By using such method, we can study metabolic stability and harm of drug-drug interactions of new drug candidate. In current time, many pharmaceutical companies study in vitro and in silico drug metabolism predictor software and latest technology. By analyzing available data, it is clear that in vitro methods are very useful for identification and elimination of new drug candidate which is not showing appreciated metabolic properties. [2]

To treat or cure any disease, we need drug which is identified by drug discovery process. The drug discovery process contains following steps, identification of candidate, its synthesis, characterization, validation, optimization, screening and assays for therapeutic efficacy. After these steps, if a compound shows its significance, then the process of drug development earlier to clinical trial starts. The journey of a compound from its discovery to marketable drug takes around 12 – 15 years and requires about US $1 billion investment. On an average, from million molecules screened only a single goes in clinical trials and which is getting finally recognized as a drug. Drug discovery and development follows following sequence:

Target identification --> Validation --> Lead identification --> Lead optimization --> Product characterization --> Formulation and development --> Preclinical research --> Investigational New Drug --> Clinical trials --> New Drug Application --> Approval. [3]

Various studying methods consists of in silico models , iDEATM help in optimizing chemical synthesis as the fraction absorbed can be predicted depends only on structural characteristics . The prediction can be made more accurate by feeding the iDEATM model with Caco-2 permeability data and solubility data at various pH's. Another trust worthy technique is in situ rat intestinal perfusion which is used to investigate drug absorption potential in combination with intestinal metabolism. The bioavailability with respect to role of the liver, evaluated by portal vein sampling experiments in dogs. [4]

In silico methods of drug discovery studied with reference to identification of drug targets wherein genes or proteins are associated with specific diseases. [5]

With advances in computer technology, we can understand biological system , for example : cells, tissue etc. By virtue of which drug's interaction with active sites can be understanding as well as prediction goes well. Thus companies explore these to improve the chances of converting targets into therapies. [6]

AI-Artificial Intelligent, nowadays gaining weightage in drug discovery process, which cut down the research and development cost. [7]

In India, we have great history of traditional medicine. Currently serious efforts are taken to develop traditional medicine into future ready drug. [8]

There are various advantages of modelling and simulation at pre-clinical stage of drug development. Such data of combination of physiologically based pharmacokinetic (PBPK) having pharmacokinetic–pharmacodynamic relationship (PK/PD) models provides the basis for quantitative outputs allowing comparisons across compounds and resulting in improved decision-making during the selection process. [9]

Computational systems biology is an emerging field in biological simulation that attempts to model or simulate intra- and intercellular events using data gathered from genomic, proteomic or metabolomic experiments. ODEs, Stochastic differential equations, S-system formalism or power law equations, PDE or molecular dynamics, CA or DCA, ABM, Pi calculus are different methods used in computational system biology.

[10]

At the time of drug discovery and development, solubility and permeability plays key role. In the discovery setting 'the rule of 5' predicts that poor absorption or permeation is more likely when there are more than 5 H-bond donors, 10 H-bond acceptors, the molecular weight (MWT) is greater than 500 and the calculated Log P (CLogP) is greater than 5 (or MlogP >4.15). [12]

In recent years, Halogen bond catches the attention for hit-to-lead-to-candidate optimization which leads to improve drug-target binding affinity. Heavy organohalogens (i.e., rganochlorines, organobromines, and organoiodines) are capable of forming halogen bonds. [13]

When there is lack of structural data of the target receptor, pharmacophore mapping is used. [14]

Indian traditional knowledge of Ayurveda gives us advantage of having phytochemicals as anti-microbial agents. Drug discovery based on Ayurveda follows a 'Reverse Pharmacology' path from Clinics to Laboratories. [15]

In recent years, use of traditional medicine for primary health care have increased. Nowadays pharmaceuticals are derived from plants. [16]

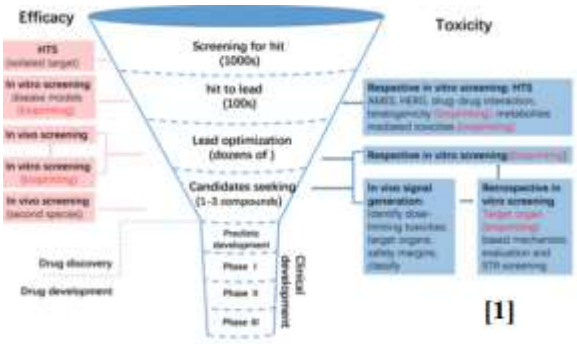
BLAST (Basic Local Alignment Search Tool), FASTA (Fast Alignment) Tool , EMBOSS (European Molecular Biology Open Software Suite) , BioEdit (Biological Editor) , ClustalW , RasMol (Raster Molecule) tool , PyMOL , Swiss-PDB Viewer , Discovery Studio , Swiss-Modeller , Modeller , PHYRE , PubMed, DDBJ (DNA Data Bank of Japan) , NCBI Genbank , PDB (Protein Data Bank) , KEGG (Kyoto Encyclopedia of Genes and Genomes) are Bioinformatics tools and databases commonly employed in DD process. ISIS Draw , ChemDraw , ACD Chemsketch , MarvinSketch , JME Molecular Editor , ISIS/Base , ACD Chemfolder , Chemspider , PubChem , CSD (Cambridge Structural Database) , ChEMBL are Chemiinformatics tools and databases commonly employed in DD process. [18]

New models for drug discovery are developed to have the lack of modern and effective drugs used for neglected diseases.

Indian medicinal plant may be used in post-genomic era to develop drug candidate.. [20]

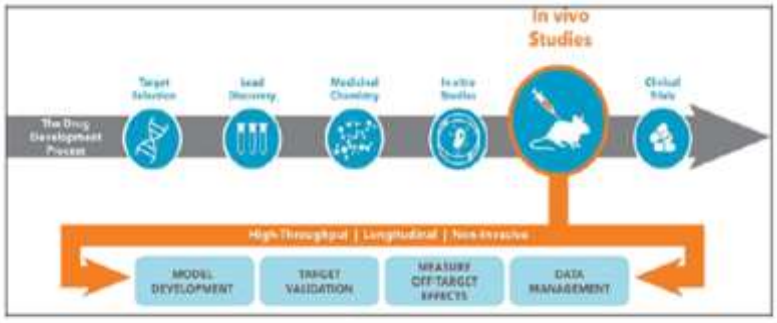
In India, more than 70% of the population depends on Ayurveda. New methods are used and develop by using medicinal plants. Ayurvedic Pharmacoepidemiology, Observational therapeutics and Reverse Pharmacology paths have led to significant hits, leads and drug candidates for several diseases. The approach of Reverse Pharmacology has been adopted globally by several groups. [21]

The challenges, recent development and new thinking on drug R&D for neglected diseases through public–private partnerships are discussed. [22]

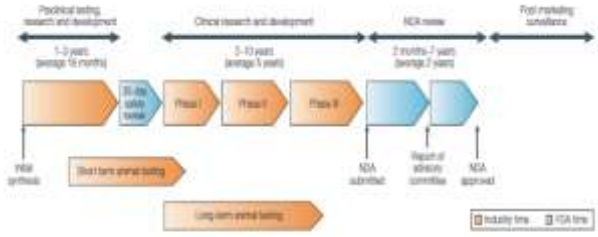


[1]

[1]

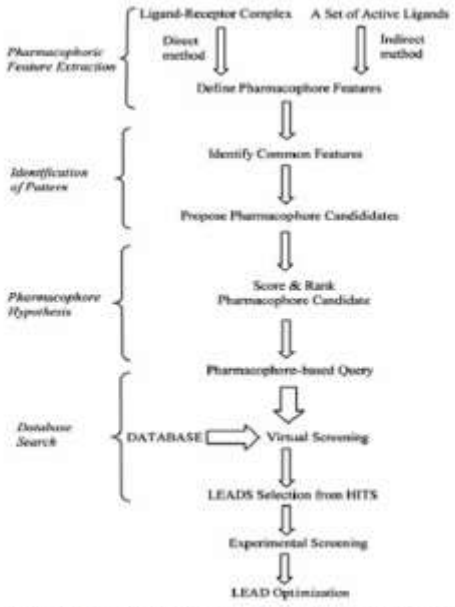


Stages of drug discovery and development process [3]

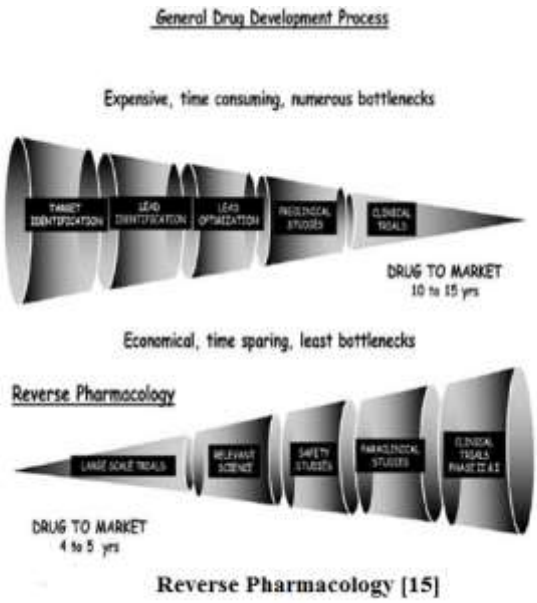


The drug approval process in the United States.

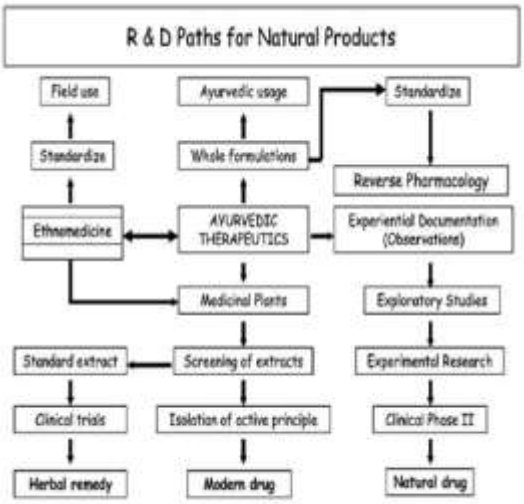
[11]



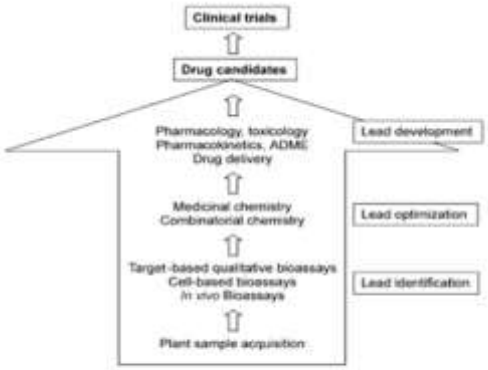
Flow chart of virtual screening using pharmacophore method [14]



Reverse Pharmacology [15]



R & D Paths for Natural Products [15]



Drug discovery process from plants [17]

REFERENCES

[1] Weijie Peng, Pallab Datta, Bugra Ayan, Veli Ozbolat, Donna Sosnoski and Ibrahim T. Ozbolat, '3D Bioprinting for Drug Discovery and Development 1 in Pharmaceutics', Sciencedirect, https://www.sciencedirect.com/science/article/pii/S1742706117303069

[2] Pawe Baranczewski, Andrzej Stañczak, Kathrin Sundberg, Richard Svensson, Asa Wallin, Jenny Jansson, Per Garberg, Hans Postlind, 'Introduction to in vitro estimation of metabolic stability and drug interactions of new chemical entities in drug discovery and development' Review, Pharmacological Reports 2006, 58, 453–472 , ISSN 1734-1140

[3] Deore, AB, Dhumane JR, Wagh HV, Sonawane RB, The Stages of Drug Discovery and Development Process. Asian Journal of Pharmaceutical Research and Development. 2019; 7(6):62-67, DOI: http://dx.doi.org/10.22270/ajprd.v7i6.616

[4] Hilde Bohets, Pieter Annaert, Geert Mannens, Ludy van Beijsterveldt, Katelijne Anciaux, Peter Verboven, Willem Meuldermans and Karel Lavrijsen, 'Strategies for Absorption Screening in Drug Discovery and Development', Current Topics in Medicinal Chemistry 2001, 1, 367-383, https://www.researchgate.net/publication/11464979

[5] V. Srinivasa Rao and K. Srinivas, 'Modern drug discovery process: An in silico approach', Review, Journal of Bioinformatics and Sequence Analysis Vol. 2(5), pp. 89-94, June 2011, http://www.academicjournals.org/JBSA

[6] Neil Kumar, Bart S. Hendriks, Kevin A. Janes, David de Graaf and Douglas A. Lauffenburger, 'Applying computational modeling to drug discovery and development', Reviews, Drug Discovery Today _ Volume 11, Numbers 17/18 _ September 2006

[7] Agrawal P (2018) Artificial Intelligence in Drug Discovery and Development. J Pharmacovigil 6: e173. doi:10.4172/2329-6887.1000e173

[8] Tanjore Balganesh, Tapas K. Kundu, Tushar Kanti Chakraborty, and Siddhartha Roy, 'Drug Discovery Research in India: Current State and Future Prospects', ACS Medicinal Chemistry Letters, pubs.acs.org/acsmedchemlett, dx.doi.org/10.1021/ml500183c | ACS Med. Chem. Lett. 2014, 5, 724−726 (2014)

[9] T. LAVE, N. PARROTT, H. P. GRIMM, A. FLEURY, & M. REDDY, 'Challenges and opportunities with modelling and simulation in drug discovery and drug development', Xenobiotica, October–November 2007; 37(10–11): 1295–1310, DOI: 10.1080/00498250701534885, (2007)

[10] Wayne Materi and David S. Wishart, 'Computational systems biology in drug discovery and development: methods and applications' , REVIEWS, Drug Discovery Today _ Volume 12, Numbers 7/8 _ April 2007, Elsevier, doi:10.1016/j.drudis.2007.02.013

[11] Michael Dickson and Jean Paul Gagnon, 'KEY FACTORS IN THE RISING COST OF NEW DRUG DISCOVERY AND DEVELOPMENT', R E V I E W S, Nature Reviews Drug Discovery · June 2004 DOI: 10.1038/nrd1382 · Source: PubMed, https://www.researchgate.net/publication/8568742, (2004)

[12] Christopher A. Lipinski, Franco Lombardo, Beryl W. Dominy, Paul J. Feeney, 'Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings' , ELSEVIER, Advanced Drug Delivery Reviews 23 (1997) 3-25

[13] Zhijian Xu, Zhuo Yang, Yingtao Liu, Yunxiang Lu, Kaixian Chen, and Weiliang Zhu, 'Halogen Bond: Its Role beyond Drug−Target Binding Affinity for Drug Discovery and Development', dx.doi.org/10.1021/ci400539q | J. Chem. Inf. Model. 2014, 54, 69−78,

[14] Santosh A. Khedkar, Alpeshkumar K. Malde, Evans C. Coutinho and Sudha Srivastava, 'Pharmacophore Modeling in Drug Discovery and Development: An Overview', Medicinal Chemistry, 2007, 3, 187-197, DOI: 10.2174/157340607780059521

[15] Bhushan Patwardhan, Ashok D. B. Vaidya, Mukund Chorghade and Swati P. Joshi, 'Reverse Pharmacology and Systems Approaches for Drug Discovery and Development', Current Bioactive Compounds 2008, 4, 201-212

[16] Ramar Perumal Samy and Ponnampalam Gopalakrishnakone, 'Therapeutic Potential of Plants as Anti-microbials for Drug Discovery', Review, Advance Access Publication 24 June 2008 eCAM 2010;7(3)283–294 , Doi:10.1093/ecam/nen036

[17] Sanjay M. Jachak and Arvind Saklani, 'Challenges and opportunities in drug discovery from plants', REVIEW, CURRENT SCIENCE, VOL. 92, NO. 9, 10 MAY 2007

[18] V. UMASHANKAR1, S. GURUNATHAN, ' DRUG DISCOVERY: AN APPRAISAL', Review,

International Journal of Pharmacy and Pharmaceutical Sciences , Int J Pharm Pharm Sci, Vol 7, Issue 4, 59-66, ISSN- 0975-1491

[19] Eric Chatelain & Jean-Robert Ioset (2011) Drug discovery and development for neglected diseases: the DNDi model, Drug Design, Development and Therapy, , 175-181, DOI: 10.2147/DDDT.S16381

[20] Satendra Singh, Dev Bukhsh Singh, Shivani Singh, Rohit Shukla, Pramod W. Ramteke, Krishna Misra, 'Exploring Medicinal Plant Legacy for Drug Discovery in Postgenomic Era', REVIEW, Proc. Natl. Acad. Sci., India, Sect. B Biol. Sci. https://doi.org/10.1007/s40011-018-1013-x 2018

[21] Ashok D.B. Vaidya, 'Reverse Pharmacology-A Paradigm Shift for Drug Discovery and Development', Current Research in Drug Discovery, Ashok D.B. Vaidya / Current Research in Drug Discovery 2014, 1 (2): 39.44 , DOI: 10.3844/crddsp.2014.39.44

[22]Solomon Nwaka and Robert G. Ridley, 'Virtual drug discovery and development for neglected diseases through public–private partnerships', NATURE REVIEWS | DRUG DISCOVERY VOLUME 2 | NOVEMBER 2003