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Insilico Molecular Docking - A tool to understand the action of *Rasaushadhis*

Shrilata A.P,[1] Chandramouli HM,[2] Medikeri Surekha S,[3] Hiremath Shobha G.[4]

[1]Post Graduate Scholar, [2]Professor, [3]Professor & HOD, [4]Emeritus Professor, Department of Rasashastra and Bhaishajya Kalpana, Government Ayurvedic Medical College, Bengaluru, Karnataka, India.

ABSTRACT

Rasashastra, a branch of *Ayurveda* consists of many metallo-mineral preparations which are explained as highly efficacious in smaller doses and even in shorter duration. We know the functions of *Rasaushadhis* (herbo-mineral preparations), but we are lacking the knowledge of their Pharmacodynamics which may benefit us in understanding the exact site where, how and which active principle work and at what rate a drug will interact with its target biomolecule. The advent of new Sciences like Bioinformatics has made drug discovery faster and economical. Bioinformatics research focuses on biology at a molecular level by identifying the effect of drugs at the level of individual genes, DNA, RNA and proteins. It utilizes existing information to model disease pathways and identifies precise targets of the drug. The unclearly answered questions can be clarified by understanding and adopting the concept of 'Insilico Molecular Docking', means a computational study of binding of Ligand to specific Receptor. The action between the receptor and ligand is by selectivity and affinity; Lock and Key concept. It encompasses all theoretical methods and computational techniques to model and the behavior of molecules and by scoring function we can come to know the best suitable receptor for particular ligand. The working methodology includes preparation of Ligand, Receptor, Docking and inspection by X-Ray Crystallography, NMR techniques. The process of standardization is needed in *Rasashastra* but, there are some difficulties. One can overcome this by understanding the mode of action of *Rasaushadhis -Rasabhasmas* through molecular Docking which helps in drug discovery and development, optimisation of action and inhibition of harmful effects.

Key words: *Molecular Docking, Rasaushadhis, X-Rray crystallography, NMR techniques.*

INTRODUCTION

Ayurveda, an ancient science inherents huge treasure in it, which is being practiced since ages. It includes many of the Herbs, Poisonous drugs, Metallo-Mineral preparations which are found to be effective in curing various ailments. A metal which is incinerated in different organic media is found to exhibit different action which is been proven.[1]

But, with the rapid progress in medical science, the authenticity and safety of Ayurvedic drugs are being questioned. This is mainly due to the lack of Objective data, Research documentations that is acceptable to international regulatory and scientific community.[2]

The action of any drug is studied by the method of invitro or invivo experimentations, but knowing which particular component or the principle of the drug is providing that particular action would help in cut shortening both time and cost and such a complete analysis provides the basis for both the rational therapeutic use of a drug and the design of new and superior therapeutic agents. Basic research in Pharmacodynamics also provides the fundamental

Address for correspondence:
Dr. Shrilata A. P.
Post Graduate Scholar, Department of Rasashastra and Bhaishajya Kalpana, Government Ayurvedic Medical College, Bengaluru, Karnataka, India.
E-mail: apshrilata95@gmail.com

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insights into biochemical and physiological regulations.[3]

These can be studied, proved, documented through the concept of Insilico Molecular Docking i.e. studying which particular part of the drug (Ligand) is binding to particular part of the body system (Receptor) with the help of computer and various technologies like X-Ray crystallography, NMR etc. which would definitely help to prove the target action efficacy safety of *Rasoushadhis* and other Ayurvedic drugs to the world.

Understanding Insilico Molecular Docking

The action of any drug studied commonly by the methods like Invitro, Invivo[4] studies.

- **Invitro study:** Is a method of study where in the cell / tissue is cultured outside the living system and the study is carried out. Ex: Study on the endothelium of blood vessels. Study on bone marrow. Study on the blastocytes derived from embryonic stem cell lines.

- **Invivo study:** Is the method of study where in the study is carried out on living system. It may be on human beings (clinical study) or other animals (preclinical study). But the duration and cost will be more and the result will not be satisfactory.

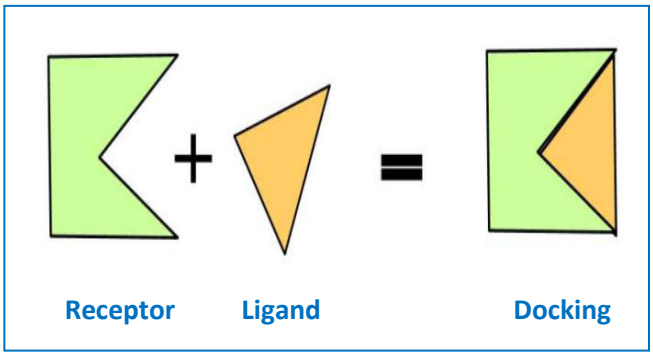
To get the clear results and to cut down the research timeline and cost by reducing wet lab experimentations and on living system new technology which is getting appreciation today in the modern world is Insilico Molecular Docking study.

What is Insilico Molecular Docking?

The word Insilico[5] is derived from the Latin word '*Insilicon'*. Is an expression used to mean performed on computer or via computer simulation. Insilico research in medicine is thought to have the potential to speed up the rate of Discovery while reducing need for expensive lab work, clinical trials.

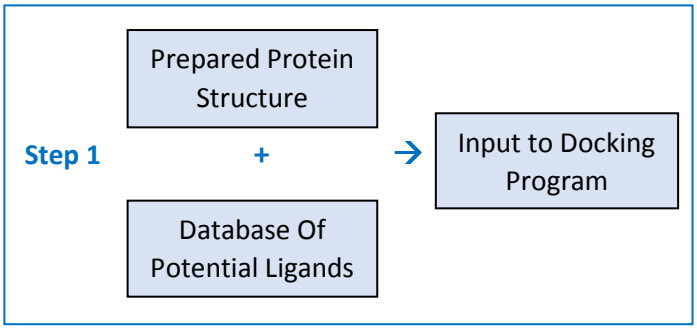
This can be achieved by producing and screening the drug candidate more effectively and the drug candidate is nothing but the 'Ligand' in technical terms. A 'Ligand' is any molecule which attaches selectively to a particular site and the site is known as receptor. A 'Receptor'[6] is a macromolecule or a binding site located on the surface or inside the effecter cell that serves to recognize the signal molecule/drug/ligand and initiate response to it.

In total the process by which the molecular modelling software fits a Ligand into the target binding Receptor is 'Insilico Molecular Docking'.



Molecular docking is used for finding the binding modes of Protein (Receptor) with Ligands. Molecular modeling is a general term used to describe the use of computers to construct molecules and perform variety of bindings possible. It encompasses all theoretical methods and computational techniques used to find out the structure of particular molecule. Molecular docking is frequently used to know/ study whether the two molecules interact with each other, if so orientation (translations, rotations, internal changes) that maximizes the interaction, minimizes the total energy of the complex. Docking is the key to rational drug design.

The process of Docking[7]



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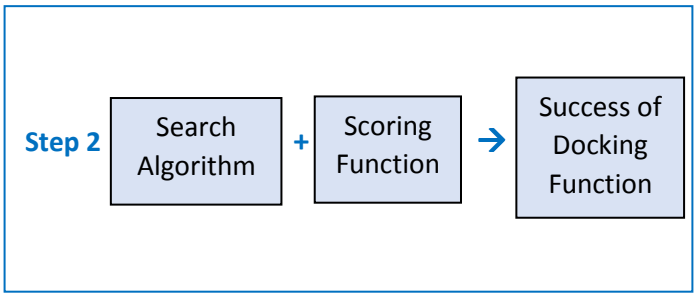

1. Deriving the 3D structure of Ligand by the techniques like x Ray crystallography, NMR and other techniques.
2. Receptor modelling- identifying the 3D structure of the Receptor
3. Docking - The database of potential Ligands and Receptor structure are put into the computer software programs like Autodock, Dock, Linux Gold etc.
4. Calculation of energy by - a) Search algorith, b) Scoring function. Through search algorithm all the possible optimal confirmation for the given Ligand- Receptor complex is determined.

   By scoring function the strength of intermolecular interaction between the Receptor and Ligand is predicted and estimated the energy of pose.
5. Different docking will be ranked.
6. The best one having highest energy and bound properly is selected.

Docking with *Rasaushadhis*

The *Rasaushadhis* are the mixture of herbal, mineral/metallic components and thus form a complex molecule, so it is difficult to understand their Pharmacodynamics inside the body. This complexity can be solved by the utility of recent technology, viz. Insilico Molecular Docking.

1. In the production of new drug [8]

In traditional method the production of new drug entity and releasing it into market is a time consuming tedious procedure. It includes following steps;

Target discovery (2-3 years)
↓
Screening (1 year)
↓
Lead optimization (1- 3 years)
↓
Preclinical studies (1-2 years)
↓
Clinical studies (5-6 years)
↓
Licensing (1-2 years)
↓
Releasing to market

But with the help of Insilico Molecular Docking we can cut short the time duration required for the production to release of drug and can find the better drug too.

Compound identification (1-1.5 years)
↓
Compound aquision (0-1.5 years)
↓
Preclinical development (0-1 year)
↓
Clinical trial (1-6 years)
↓
Licensing (1-2 years)
↓
Releasing to market

2. Multi targeting action of the Drug[9]

It can be revealed by molecular interaction studies. In the classics of *Ayurveda* there are many formulations having indication for more than one condition.

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Eg: the herbo-mineral formulation *Arogyavardhini Vati*[10] - having ingredients like *Parada, Gandhaka, Loha, Abhraka, Tamra, Shilajatu Katuki, Chitraka* etc. and the formulation is indicated for *Jwaraadi* 15 diseases. How this could be possible!! This we can understand by the knowledge of molecular interactions. The single formulation *Arogyavardhini Vati* might be having multiple ligands in it and particular ligand that binds to specific receptor would give the related action. i.e.

- The ligand concerned with Copper[11] along with Iron, Sulphur, Zinc, Tin, Lead, Aluminium may bind to particular receptor → Oxidation of Cysteine → Cysteine catabolised in GIT and Blood plasma → It influences Glutathione, which is useful in DNA synthesis, influences immune nervous GI system.
- Ligand concerned with the Liver function may binds to particular receptor and reduces toxic effect of alcohol, prevents Liver damage.
- Ligand related with the Cardiac function might be acting on Cholinoreceptors regeneration of heart by improving Cardiomyocyte structure and Antihyperlipidemic action.

3. Lead Optimization[12]

Clinical efficacy of particular *Bhasma* depends on the media with which it is purified and incinerated may be due to its chemical composition and structure; this can be understood by Insilico Molecular Docking technology. Eg: For *Abhraka* (Mica) many medias have been explained.[13]

4. Drug discovery and development

In the treasure of *Rasashastra* there are various drugs and formulations indicated in many dreadful diseases like Cancer, but it is very expensive and time consuming to evaluate its effect clinically. In such conditions the Insilico Molecular Docking is a boon. Eg: *Vajra Bhasma*[14] is indicated in Cancer, Infertility. *Heeravedhyorasa* in *Sannipataja Moorcha* (altered consciousness).

5. To understand the mode of action of the drug

Eg: *Swarna Bhasma* in *Amavata, Vatavyadhi*[15].

6. To compare between the two drugs and selection of the best one in particular disease is possible through the Insilico Molecular Docking study.

Discussion

The process of standardization in all aspects of human endeavor is necessary but difficult. In *Rasashastra* the process of standardization is particularly difficult as it deals with complex molecules always.

So by adopting recent technology - Insilico Molecular Docking one can better understand our science and widening the boundaries of knowledge.

To achieve the best results one should be very cautious in

- The selection of proper 3D structures of Ligand and Receptor from the database.
- Selection of suitable Docking software program.
- Observation and selection of the best docked drug with minimum energy and angulation.

Conclussion

Knowledge of molecular association aids in understanding a variety of pathways, taking place in the living structure and knowing the possible pharmacological targets. There are many formulations in *Rasashastra* which are widely practiced but their mode of action is unclear and many of them contain poisonous and costly drugs like Gold, Diamond etc. For such formulations it becomes difficult to carry out animal or clinical studies because of problem related to resources and ethical clearance, in such conditions Insilico Molecular Docking study can be conducted to get quick and better information and exact result.

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