

# DOCKING A TOOL FOR EVIDENCE BASED HERBAL FORMULATION DEVELOPMENT: A REVIEW

## Abstract

Now a days every day in market new herbal formulations based on ethno information are getting introduced. In these marketed new preparations use of number of different types of herbs is done. No attempt is made to provide any kind of authentic information about the due to what and how the preparation show a specific pharmacological activity or the exact way by which it shows a specific mechanisms of action. The problem is the speed with which new formulations are introduced, they are becoming obsolete and getting vanished from market. This has been observed during covid time.

First case there is need of detail study in the form of identification of phyto constituents from the herbs or plant material that is used. Scientific correlation of pharmacological activity with presence of specific phyto constituent or group of constituents is need of hour. Application of docking or virtual screening can be a tool in design and development new herbal formulations with authenticity.

If mechanism by which the developed formulation shows pharmacological activity is identified the chances of success of formulation in market is going to increase many folds. In present review any attempt has been done to show how molecular docking or virtual screening of active constituents from various plant sources may be done on selected targets, by which of probable mechanism of action by which formulation shows desirable pharmacology activity can identification which can help in increasing authenticity/Clams related to specific herbal formulation.

## Authors

### **Sachin Pishawikar**

Department of Pharmaceutical Chemistry and Pharmacognosy

New College of Pharmacy

Uchgaon, Kolhapur, India.

### **Ravindra Kumbhar**

Department of Pharmaceutical Chemistry and Pharmacognosy

New College of Pharmacy

Uchgaon, Kolhapur, India.

### **Piyusha Nejdar**

Department of Pharmaceutical Chemistry and Pharmacognosy

New College of Pharmacy

Uchgaon, Kolhapur, India

## I. INTRODUCTION

Research has become a part and parcel for pharmaceutical industry. After introduction of drug design concept, it was expected that success of drug discovery of new drugs would increase many fold. Application of molecular modeling feature will help in design and discovery of new compounds having drug like characteristics. Molecular modeling was supposed to be a one of experimental and greater tools to carry out study about binding of specific structural chemical entity with a specific selected target as well as will play a significant role in study of structure-activity relationships. This kind of study would be responsible for establishing or knowing exact mechanism of action of new chemical entities. [1] Each and every individual is born with different body physiology, as the study of physiological factors affecting drug action could not be done to that extent expected success has not been reached. One of the main reason for failure was identified was insufficient study related to pharmacodynamics properties like potency, affinity, efficacy, selectivity and pharmacokinetic properties like absorption, distribution, metabolism, excretion and toxicity. The advancement in discovery and sophistication has lead to use of analytical instruments like X-ray crystallography, infrared spectroscopy, nuclear magnetic resonance (NMR) in resolution of large number of three-dimensional structural aspects of protein biomolecular which can be used as targets for design and discovery of new drug [2, 3]. The information obtained using these tools needs efforts and understanding for storing, organizing and exploring the intricate aspects of intermolecular structural features as well as structural features of target and then using it for describing probable mechanism with which a specific pharmacological activity is shown by chemical entity[4]. With this structure-based drug design (i.e., the use of three-dimensional structural information gathered from biological targets) has become predominant or main component as well as feature of modern medicinal chemistry [5]. The modern drug-receptor concept and its in depth study has made molecular docking, structure-based virtual screening and molecular dynamics major components for study of structure base designing of drugs. The analysis of molecular recognition and events such as binding energetics, molecular interactions and induced conformational changes has become possible due to use of these instrumental tools.[6]. In drug design use of PDB(Protein Data Base) and libraries of bioactive molecule is done to get the idea about what space generated due to structural diversity is occupied by ligands as known interaction with a specific target. The information has lead to development of ligand based drug design methods like Ligand-based virtual screening (LBVS), similarity or drug likeness searching, QSAR modeling and pharmacophore hit structure generation [7, 8]. It is felt that if application of SBDD and LBDD approaches is done for phyto constituents too then it can turn out to be a major guiding or tools for drug discovery research activity carried out by academia and industry institutions. [9] The integrated approaches can successfully be employed in a number structural investigation of phyto constituents, their chemical and biological properties where by development of authentic herbal formulations having authentic information about the pharmacological activity shown by that formulation can be done whereby discovery of drug like chemical entity with more safety and efficacy can be done. [10,11].

The information related to biologically active compounds isolated or extracted from different plant sources has become one of the important feature of research related to finding new promising structural components and further using it in development/ discovery of new drugs. Virtual screening methods are direct and rational approaches for the searching new promising phytoconstituents, as well as for the discovery of drugs and formulations that will have advantage of low cost, low side effects and with high efficacy (Lavecchia and Di

Giovanni, 2013; Tripathi and Misra, 2017). Molecular docking has emerged as the most prospective method of new drug discovery due to its ability of carrying the study of the affinity of a particular substance in relation to a certain specific biological target (Klebe, 2006; Ma et al., 2013; Schomburg et al., 2014; Scior et al., 2012; Shoichet, 2004; Vyas et al., 2008). The mentioned aspect has led to use of virtual screening as one of the promising and useful method in designing and development of new herbal medicines to satisfy the numerous clinical needs.

The advancement related to combinatorial chemistry had emerged as new hope of higher success rates for the discovery of new chemical entities (NCEs), it has failed to achieve the expected success rate in new drug discovery. This has led to prompting researchers to come out with a novel approach of integrating drug discovery, where Ayurvedic knowledge can be used as synergistic feature for drug discovery from plant sources. The natural products obtained from various plant material have become sources of many of the new drugs and active ingredients of medicines. The starting point of research for plant-based new drug discovery would be identification of the right plant candidate using knowledge of Ayurvedic, study of traditional documented medicinal use, tribal non-documented use, and thero literature search.

Six classes of sources are there for NCEs. The four classes out of six are botanical, fungi, bacterial and marine sources while the modern pharmaceutical chemistry adds two more categories of sources that are synthetic chemistry and combinatorial chemistry. The natural and botanical sources do have specific importance in the context of present review.

The botanical sources provide following classes of NCEs during new drug discovery processes.

1. Bioactive/Phyto chemical entities ready to be used directly as drug, e.g. digoxin.
2. Bioactive/Phyto chemical entities which themselves can act as lead structure and modified chemically to get more potent compounds, e.g. paclitaxel from *Taxus* species.
3. The novel chemical entities which may be converted into drug like compounds with or without carrying out any chemical reaction or modification.
4. Isolation of pure phyto constituents that can be used as marker compounds in standardization of crude plant material or extract.
5. Pure phyto constituent that can be used as pharmacologically active components or tools.
6. Herbal extracts directly as drugs of botanical or biological origin, e.g. green tea extract.

## II. STRUCTURE-BASED DRUG DESIGN (SBDD)

Structure-Based Drug Design constitutes study of interaction of small organic molecules /chemical entities known as ligands with macromolecules which are going to act as receptors for showing a specific pharmacological activity is of great importance as well as significance in pharmaceutical research and development [12]. SBDD leads to systematic use of structural data (e.g., macromolecular targets, also called receptors), generally obtained experimentally or via computational homology modeling [13]. The purpose is to find out ligands with specific electrostatic and stereochemical features to achieve high receptor binding affinity so that with more efficacy pharmacological action can be observed. This feature may be useful in identification of mechanism of action of phytoconstituents and in development of authentic phyto formulation.

### **III. MOLECULAR DOCKING**

For structure based drug design (SBDD) study, molecular docking has turned out to be a commonest tool due to its capability to predict, with a substantial degree of accuracy, the structural conformation or features needed in small-molecule/chemical entity or ligands to get bind to the selected target with specific binding site. With its first use as molecular modeling algorithms in 1980s, it has found its place as one of the essential tool to be used related to drug discovery and for predicting the exact mechanism by which chemical entities as well as phyto constituents may be showing the expected pharmacological activity.[22].

### **IV. DOCKING (MOLECULAR INTERACTIONS)**

For the interaction of a drug with specific receptor there is involvement of number of forces like, hydrophobic, dispersion, or van der Waals, hydrogen bonding, and electrostatic determination of which makes docking study complex. The major force responsible for proper binding to appears is hydrophobic interactions, but the specificity of the binding appears to be controlled by hydrogen bonding and electrostatic interactions. Identifying and modeling the intermolecular interactions occurring between ligand-protein complex is difficult because there is involvement of so many degrees of freedom and insufficient knowledge of the effect of solvent on the binding association.

By carrying out docking of ligand to a binding site, it is considered to be natural course of how and with what intensity the ligand is going to bind to its receptor. The positive fruitful interaction is necessary for showing specific pharmacological activity with minimal use of energy. There are simple methods for docking rigid ligands with rigid receptors like concept of lock and key model as well as a flexible ligands can also be docked with rigid receptors.

Even though the active phytochemical constituents of individual plants are being well established with detail phytochemical investigation their present is in minute quantity and are insufficient to achieve the desirable therapeutic effects. There is always a need to carry out investigation as whether individual phyto component or combination of components is needed to get phenomenon of positive herb-herb interaction in the form of synergism. Certain pharmacological actions of active constituents of phyto components are significant only when potentiated by presence of other plants or plant constituents. On the other hand if use isolated or singly may not be that active. All these kind of studies are needed to be done and recorded where by authentic herbal formulation can be developed.

### **V. USE FOR DOCKING IN DEVELOPMENT OF AUTHENTIC FORMULATION**

It is consideration or expectation form the herbal based pharmaceutical formulations (PHFs) that it will result in lesser side effects compared to that of allopathic formulations used for same type of disease condition. Though for modern allopathic drugs at most care now a days has been taken in designing them in such a way that they show efficacious therapeutic results with lesser side effects on administration. As the body physiology is different for different individuals, though care is taken still most of them cause unwanted side-effects, like insomnia, vomiting, fatigue, dryness of mouth, diarrhea, impotency, confusion, hair loss, specific organ toxicity and in some cases may become fetal. Patients suffering from Rheumatoid arthritis (RA ) invariably are prescribed to use non-steroidal anti-

inflammatory drugs. A side effects many patients experience GIT discomfort, renal side effects, leading to dyspepsia, gastric irritation and ulceration in some cases salt and fluid retention leading to hypertension.

For majority of diseases treated with allopathic formulations, herbal formulations are available. But in case of herbal formulations as they are going to contain number of phyto components together, each constituent is definitely going to have some kind of activity hence there is need of preliminary investigation. If a use of modern tools like molecular modeling is done scientific validation of herbs can be done. As the herbal formulations will be showing less side effect. Due to scientific study and generation of scientific data even allopathic doctors can be convinced for the use of herbal formulations.

In present study as example how use of modern features of drug design can be used for authentication for herbal formulation can be done is being put forward. The spices used in day to day life as well as many species of plants have proved their efficacy of lipid lowering activity. By carrying out authentic scientific study different spices may be combined together in the form of extract or as such in formulation and prescribed for lipid lowering activity.

The major problems linked with this type of herbal formulations is there is no well defines related to the main active ingredients or constituents. There fore it becomes one of the important feature of knowing the active component and their molecular interaction, which will be helpful in analyzing therapeutic efficacy of the product and also to standardize the product. Efforts are now being made to investigate mechanism of action of some of these plant constituents using modern model systems. which are generally used for designing of allopathic formulations.

## **VI. NEED OF FINDING MECHANISM OF ACTION OF PHYTO CONSTITUENTS**

The term mechanism of action (MoA) is used to describe specific biological interaction by which it is expected that a drug produces its specific pharmacological effect or action. A mechanism of action usually includes mention of the specific molecular targets to which the drug binds, such as an enzyme or receptor. Receptor sites have pockets generated due to complex structural features of biomolecules from which they are formed and have specific affinities for structural components present in drug structure.

Drug design concept was introduced way back in 1990's, but the amount of success expected has not been achieved. Major reason is physiological factors that governs toxicity related issues are not addressed. Hence in present days again focus has shifted to discovery of specific phyto constituent responsible for showing pharmacological activity. Study on only various extracts for pharmacological action is losing significance as no scientific justification can be given about probable mechanism by which a specific pharmacological action is shown by phyto constituent. To overcome this drawback, isolation of probable specific chemical constituents can be done form extract by selective extraction process and confirmation of pharmacological activity can be done by carrying out docking study. Knowledge about specific compounds from various herbal (plant) parts makes the experimental studies easier and helps to focus on better understanding the mechanism of action and future therapeutic potential.

In present work we have made an attempt to identify mechanism of action of few known phyto constituents present in spices which show lipid lowering activity.

Please insert the information about PDB's Used in docking study of following constituents of spices

**Table 1**

| Molecule                        | VDW  | Hydrophobic  | H-bond             | Charge             | Pi-stacking | Binding-energy |
|---------------------------------|--|--|--------------------|--------------------|-------------|----------------|
| 6-<br>GINGEROL_opt<br>t_C27_LP9 | LYS1969A<br>SER1972A<br>PHE1973A<br>ASP1976A<br>HIS1720B<br>ARG1741B<br>GLN1744B<br>HIS2141B   | LYS1969A<br>SER1972A<br>PHE1973A<br>ASP1976A<br>ARG1741B<br>LEU1742B                         | HIS1720B           | ARG174B            |             | -24.159893     |
| 6-<br>SHOGAOL_opt<br>_C13_LP5   | ARG1741A<br>GLN1744A<br>ALA1933A<br>ASN1937A<br>PHE1973A<br>ASP1976A<br>ALA1977A<br>VAL1979A<br>ASP1980A<br>ARG1717B<br>HIS1720B<br>ASN1815B<br>PHE1973B<br>ASP1976B | ASP1976A<br>VAL1979A<br>ASP1980A<br>HIS1720B<br>ASN1815B<br>SER1972B<br>PHE1973B<br>LYS2137B | ASN193A<br>ASN181B | ARG174A<br>ARG171B |             | -17.427404     |
| AJOENE_opt_<br>C34_LP3          | HIS1720A<br>ASP1976A<br>VAL1979A<br>ASP1980A<br>SER1716B<br>ARG1717B<br>HIS1720B<br>ASP1976B   | ASP1976A<br>VAL1979A<br>ASP1980A<br>ARG1717B<br>HIS1720B                                     | SER171B            |                    |             | -35.712700     |
| ALLICIN_opt_<br>C16_LP2         | ASP1976A<br>VAL1979A<br>ASP1980A<br>HIS1720B   | ASP1976A<br>VAL1979A<br>ASP1980A   |                    |                    |             | -23.690526     |
| Molecule                        | VDW  | Hydrophobic  | H-bond             | Charge             | Pi-stacking | Binding-energy |
| CAPSAICIN_o<br>pt_C1_LP5        | TYR1719A<br>HIS1720A<br>PHE1930A<br>GLN1934A<br>ASN1937A   | GLN1934A   | LYS1982B           |                    |             | -37.505326     |

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|  |  |  |                                |                     |                         |                            |
|--|--|--|--------------------------------|---------------------|-------------------------|----------------------------|
|  | HIS1720B<br>ASN1937B<br>PHE1973B<br>ASP1980B<br>LYS1982B<br>HIS1720B<br>ARG1814B<br>ASP1976B<br>LYS1982B                                     |  |                                |                     |                         |                            |
| CINNAMIC<br>ACID_opt_C27<br>_LP7         | SER1716A<br>ARG1717A<br>HIS1720A<br>ASP1980A<br>HIS1720B<br>ASP1976B<br>VAL1979B<br>ASP1980B   | ASP1976B<br>VAL1979B<br>ASP1980B                                     |                                |                     |                         | -27.308252                 |
| CURCUMIN<br>ENOL<br>FORM_opt_C9<br>5_P25 | HIS1720A<br>GLN1934A<br>ASN1937A<br>ASP1980A<br>ARG1612B<br>ARG1717B<br>HIS1720B<br>ASN1937B<br>PHE1973B<br>ASP1980B                         | ASN1937A<br>ARG1717B   | HIS1720A<br>ARG161B            | ARG161B<br>ARG171B  |                         | -41.826328                 |
| CURCUMIN<br>KETO<br>FORM_opt_C5<br>3_LP7 | ARG1741A<br>GLN1934A<br>HIS1720B<br>LYS1969B<br>SER1972B<br>PHE1973B<br>ASP1976B<br>ASP1980B   | ARG1741A<br>LEU1742A<br>LYS1969B<br>SER1972B<br>PHE1973B             | ARG174A<br>GLN193A<br>HIS1720B | ARG174A<br>LYS1982B |                         | -42.936680                 |
| <b>Molecule</b>                          | <b>VDW</b>   | <b>Hydrophobic</b>   | <b>H-bond</b>                  | <b>Charge</b>       | <b>Pi-<br/>stacking</b> | <b>Binding-<br/>energy</b> |
| DIHYDROCAP<br>SAICIN_opt_C<br>14_LP7     | TYR1719A<br>HIS1720A<br>ARG1741A<br>GLN1744A<br>PHE1930A<br>GLN1934A<br>HIS1720B<br>ASP1721B<br>ASN1937B<br>PHE1973B<br>ASP1976B<br>ASP1980B | GLN1934A<br>HIS1720B<br>ASP1721B<br>ARG1814B<br>ASP1976B<br>ASP1980B | GLN193A                        | LYS1982B            |                         | -33.586331                 |
| EUGENOL_opt<br>_C5_LP5                   | ARG1717A<br>HIS1720A<br>ASP1980B   | HIS1720A<br>ASP1976B<br>ASP1980B                                     |                                |                     |                         | -31.342243                 |

|                               |  |                                  |  |  |  |            |
|-------------------------------|--|----------------------------------|--|--|--|------------|
| THIACREMO<br>NONE_opt_LP<br>2 | ASP1976A<br>VAL1979A<br>ASP1980A<br>HIS1720B | ASP1976A<br>VAL1979A<br>ASP1980A |  |  |  | -22.051328 |
|-------------------------------|--|----------------------------------|--|--|--|------------|

In above table represents the docking study of active constituents obtained from various traditional spices which are used commonly. The constituents are gingerol, shogaols from ginger, ajoene, allicin and thiacremonone from garlic, capsaicin and dihydrocapsaicin from capsicum, cinnamic acid and eugenol in cinnamon, curcumin from turmeric in enol and keto form. On the basis of this study an attempt in developing following type of authentic herbal formulation can be done.

## VII. DEVELOPING PHYTO FORMULATION

Docking study Able us in getting idea about how the active constituent present from selected spices can be responsible of showing its specific pharmacological activity as well as to what probably extent the activity can be associated. On the basis of efficacy of docking shown by active constituent the decision may be taken about in how much quantity of each spices has to be used along with excipients and diluents in developing poly herbal formulation.

The following table shows on the basis of the docking study, different spices can be used in following quantities along with excipients and diluents where by a formulation with known mechanism of action can be developed. The develop formulation has to be screened in animal models for confirmation of lipid lowering activity. it has been decided that

| Name of Constituent             | Amount in mg |
|---------------------------------|--------------|
| Ginger                          | 30           |
| Capsicum                        | 10           |
| Turmeric                        | 30           |
| Cinnamon                        | 20           |
| Garlic                          | 10           |
| <b>Other constituents</b>       |              |
| Binder(Starch)                  | 10%          |
| Diluent( lactose)               | 20%          |
| Lubricant ( Magnesium Stearate) | 0.5-1%       |

## VIII. CONCLUSION

Docking study has become an important tool in drug development process. It can also play an important role in identification of mechanism of action of various herbal constituent and can help in development of authentic herbal formulations based on ethno information. This type of study can be considered as tool for future formulation development.



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