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

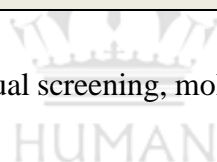
**Sachin A. Pishawikar, Aarti A. Varne, Kajal K. Mohite**

*Anandi Pharmacy College, Kalambe Tarf Kale, Dist. Kolhapur, India*

### **ABSTRACT**

Markets are getting flooded with numerous herbal formulations based on ethno information. Major problem with these formulations is extensive use of herbs is done but there is lack of information related to their probable mechanisms of action. Virtual screening methods can play significant role in design and development of authentic new herbal formulations to satisfy the numerous clinical needs with known mechanism of action. The aim of the present review is, how molecular docking of active constituents identified in the studied herbs can be done on selected targets, by which identification of probable mechanism of action by which they show desirable pharmacology activity can be done. If mechanism is known naturally authenticity of herbal formulation is going to increase.

**Keywords:** Herbal formulations, Virtual screening, molecular docking, pharmacology activity



## **INTRODUCTION**

The research-based pharmaceutical industry has increasingly seen applicability of modern medicinal chemistry methods, including molecular modeling, as powerful tools to study the structure-activity relationships (SAR) and with that finding exact mechanism of action of established entities as well as new chemical entities [1]. In addition to pharmacodynamics data (e.g., potency, affinity, efficacy, selectivity), pharmacokinetic properties (ADMET: absorption, distribution, metabolism, excretion and toxicity) have also been studied through the application of these methodologies [2]. The field has progressed hand-in-hand with advances in biomolecular spectroscopic methods such as X-ray crystallography and nuclear magnetic resonance (NMR), which have enabled striking progress in molecular and structural biology. These techniques have allowed the resolution of more than 100,000 three-dimensional protein structures, providing vital structural information about key macromolecular drug targets [3]. Efforts in storing, organizing and exploring such information have generated a growing demand for robust and sophisticated computational tools. Based on this perspective, the accurate integration of in silico and experimental methods has provided the up-to-date understanding of the intricate aspects of intermolecular recognition [4]. Within this framework, structure-based drug design (SBDD) methods (i.e., the use of three-dimensional structural information gathered from biological targets) are a prominent component of modern medicinal chemistry [5]. Molecular docking, structure-based virtual screening (SBVS) and molecular dynamics (MD) are most frequently used SBDD strategies due to their wide range of applications in the analysis of molecular recognition events such as binding energetics, molecular interactions and induced conformational changes [6]. A distinct approach in drug design comprises the use of bioactive small-molecule libraries. The unique chemical diversity available in these libraries represents the space occupied by ligands known to interact with a specific target. This type of information is used in ligand-based drug design (LBDD) methods [7]. Ligand-based virtual screening (LBVS), similarity searching, QSAR modeling and pharmacophore generation are some of the most useful LBDD methods [8]. SBDD and LBDD approaches have been applied as valuable drug discovery tools both in academia and industry [9], owing to their versatility and synergistic character. The integration of these approaches has been successfully employed in a number of investigations of structural, chemical and biological data [10,11].

In recent world information about biologically active compounds is important in search of new promising substances and for the further development of new drugs. Now a days scientists

describe virtual screening methods as the direct and rational approaches for the search of new promising substances, as well as for the discovery of drugs, whose advantages are low cost and high efficiency (Lavecchia and Di Giovanni, 2013; Tripathi and Misra, 2017). Hence the virtual screening method is often used by scientists and pharmaceutical companies engaged in development and implementation of new medicines (Cheng et al., 2012; Lionta et al., 2014; Pitt et al., 2013). Method of molecular docking is considered to be the most prospective due to its ability for the study of the affinity of a particular substance in relation to a certain 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 promising and useful method in designing new herbal remedies to satisfy the numerous clinical needs.

New drug discovery is facing serious challenges due to reduction in number of new drug approvals coupled with exorbitant rising cost. Advent of combinatorial chemistry had provided a new hope of higher success rates for discovery of new chemical entities (NCEs). But even this scientific development has failed to improve the success rate in new drug discovery. This scenario has prompted researchers to come out with a novel approach of integrated drug discovery, where Ayurvedic wisdom can synergize with drug discovery from plant sources. The sources of many of the new drugs and active ingredients of medicines are derived from natural products. The starting point for plant-based new drug discovery is identification of the right candidate plants by applying knowledge of Ayurvedic, traditional documented use, tribal non-documented use, and exhaustive literature search.

Frequency analysis of the ingredients of the ancient documented formulations and analysis of their Ayurvedic attributes also provide an in-depth idea of the predominance of particular Ayurvedic characteristics based on which appropriate candidate plants may be selected for bioactivity-based fractionation.

In general, there are six classes of sources for NCEs. The four classes are botanical sources, fungi, bacteria, and marine sources. In addition to these four classes, modern pharmaceutical chemistry added two categories of man-made substances, i.e. synthetic chemistry and combinatorial chemistry. Of these natural sources, botanical sources are of specific importance in the context of this review. The botanical sources are known to provide the following classes of NCEs for drug discovery processes.

- Bioactive compounds for direct use as drug, e.g. digoxin.
- Bioactive compounds with structures which themselves may act as lead compounds for more potent compounds, e.g. paclitaxel from *Taxus* species.

- The novel chemophore which may be converted into druggable compounds with/without chemical analoging.
- Pure phytochemicals for use as marker compounds for standardization of crude plant material or extract.
- Pure phytochemicals which can be used as pharmacological tools.
- Herbal extracts as botanical drugs, e.g. green tea extract.

## **2. Structure-Based Drug Design (SBDD)**

Studying the principles by which small-molecule ligands recognize and interact with macromolecules is having a great importance in pharmaceutical research and development (R & D) [12]. SBDD refers to the systematic use of structural data (e.g., macromolecular targets, also called receptors), which are usually obtained experimentally or through computational homology modeling [13]. The purpose is to conceive ligands with specific electrostatic and stereochemical attributes to achieve high receptor binding affinity. This feature may be useful in identification of mechanism of action of phytoconstituents and in development of authentic phyto formulation.

## **3. Molecular Docking**

Molecular docking is one of the most frequently used methods in SBDD because of its ability to predict, with a substantial degree of accuracy, the conformation of small-molecule ligands within the appropriate target binding site. Following the development of the first algorithms in the 1980s, molecular docking has become an essential tool in drug discovery as well as it can be used in determination of exact mechanism of phyto constituents.[22].

### **Docking (Molecular Interactions)**

Modeling the interaction of a drug with its receptor is a complex problem. Many forces are involved in the intermolecular association: hydrophobic, dispersion, or van der Waals, hydrogen bonding, and electrostatic. The major force for binding appears to be hydrophobic interactions, but the specificity of the binding appears to be controlled by hydrogen bonding and electrostatic interactions. Modeling the intermolecular interactions in a ligand-protein complex is difficult because there are so many degrees of freedom and insufficient knowledge of the effect of solvent on the binding association.

The process of docking a ligand to a binding site tries to mimic the natural course of interaction of the ligand and its receptor via a lowest energy pathway. There are simple methods for

docking rigid ligands with rigid receptors and flexible ligands with rigid receptors, but general methods of docking conformationally flexible ligands and receptors are problematic.

Even though the active phytochemical constituents of individual plants have been well established, they usually present in minute amount and always, they are insufficient to achieve the desirable therapeutic effects. For this, scientific studies have revealed that these plants of varying potency when combined may theoretically produce a greater result, as compared to individual use of the plant and also the sum of their individual effect. This phenomenon of positive herb-herb interaction is known as synergism. Certain pharmacological actions of active constituents of herbals are significant only when potentiated by that of other plants, but not evident when used alone.

#### **Use for docking in development of authentic formulation:**

Often, pharmaceutical herbal formulations (PHFs) result in fewer side effects as compared to allopathic drugs. Although modern allopathic drugs are designed for efficacious therapeutic results, administration of most of them come with unwanted side-effects, such as insomnia, vomiting, fatigue, dry mouth, diarrhea, seizures, impotency, confusion, hair loss, organ toxicities and even death! Patients prescribed with non-steroidal anti-inflammatory drugs for rheumatoid arthritis (RA) treatment may experience mainly gastrointestinal and renal side effects, including dyspepsia, gastric ulceration, salt and fluid retention, as well as hypertension. The above-mentioned formulations have been considered for their possible hypoglycaemic actions and the researchers have carried out some preliminary investigations. Scientific validation of several Indian plant species has proved the efficacy of the botanicals in showing lipid lowering activity. Thus many different spices have been used individually or in combination in the form of extract or as such have been used for lowering lipid content. Some have been converted into formulations.

One of the major problems with these types of herbal formulations is that the active ingredients are not well defined. It is important to know 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 model systems.

#### **Need of finding mechanism of action of phyto constituents**

As per pharmacology, the term mechanism of action (MOA) represents the specific biochemical interaction through which a drug substance produces its pharmacological effect. 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 specific affinities for drugs based on the chemical structure of the drug, as well as the specific action that occurs there.

In present day modern science, concoctions or crude extract-based studies are losing their significance and the focus has, for the better, shifted towards discovery and exploitation of specific compounds for their therapeutic actions. 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.

### **Target**

#### **HMG-CoA reductase**

HMG-CoA reductase inhibitors (also known as statins) lower LDL cholesterol in the blood by blocking hepatic HMG Co-A reductase, the rate-limiting enzyme in cholesterol biosynthesis. This action depletes the intracellular cholesterol pool, leading to an up-regulation of LDL receptors and a decrease in serum cholesterol.

There are different PDB ID for HMG-Co-A reductase

<b>PDB ID</b>	<b>Enzyme name</b>
1hwj	Complex of the catalytic portion of human HMG-Co-A reductase with cerivastatin
1HW1	The FADR-DNA complex: transcriptional control of fatty acid metabolism in Escherichia coli
1HW9	Complex of the catalytic portion of human HMG-COA Reductase with simvastatin

**Table No. 1 : Docking interactions of different Constituents of Spices on PDB – 1HW9**

Molecule	VDW	Hydrophobic	H-bond	Charge	Pi-stacking	Binding-energy
6-GINGEROL_opt_C27_LP9	LYS1969A SER1972A PHE1973A ASP1976A HIS1720B ARG1741B GLN1744B HIS2141B	LYS1969A SER1972A PHE1973A ASP1976A ARG1741B LEU1742B	HIS1720B	ARG174B		-24.159893
6-SHOGAOL_opt_C13_LP5	ARG1741A GLN1744A ALA1933A ASN1937A PHE1973A ASP1976A ALA1977A VAL1979A ASP1980A ARG1717B HIS1720B ASN1815B PHE1973B ASP1976B	ASP1976A VAL1979A ASP1980A HIS1720B ASN1815B SER1972B PHE1973B LYS2137B	ASN193A ASN181B	ARG174A ARG171B		-17.427404
AJOENE_opt_C34_LP3	HIS1720A ASP1976A VAL1979A ASP1980A SER1716B ARG1717B HIS1720B ASP1976B	ASP1976A VAL1979A ASP1980A ARG1717B HIS1720B	SER171B			-35.712700
ALLICIN_opt_C16_LP2	ASP1976A VAL1979A ASP1980A HIS1720B	ASP1976A VAL1979A ASP1980A				-23.690526
Molecule	VDW	Hydrophobic	H-bond	Charge	Pi-stacking	Binding-energy
CAPSAICIN_opt_C1_LP5	TYR1719A HIS1720A PHE1930A GLN1934A ASN1937A HIS1720B ASN1937B PHE1973B ASP1980B	GLN1934A	LYS1982 B			-37.505326

	LYS1982B HIS1720B ARG1814B ASP1976B LYS1982B					
CINNAMIC ACID_opt_C27_LP7	SER1716A ARG1717A HIS1720A ASP1980A HIS1720B ASP1976B VAL1979B ASP1980B	ASP1976B VAL1979B ASP1980B				-27.308252
CURCUMIN ENOL FORM_opt_C95_P25	HIS1720A GLN1934A ASN1937A ASP1980A ARG1612B ARG1717B HIS1720B ASN1937B PHE1973B ASP1980B	ASN1937A ARG1717B	HIS1720A ARG161B	ARG161B ARG171B		-41.826328
CURCUMIN KETO FORM_opt_C53_LP7	ARG1741A GLN1934A HIS1720B LYS1969B SER1972B PHE1973B ASP1976B ASP1980B	ARG1741A LEU1742A LYS1969B SER1972B PHE1973B	ARG174A GLN193A HIS1720B	ARG174A LYS1982 B		-42.936680
DIHYDROCAPSAICIN_opt_C14 _LP7	TYR1719A HIS1720A ARG1741A GLN1744A PHE1930A GLN1934A HIS1720B ASP1721B ASN1937B PHE1973B ASP1976B ASP1980B	GLN1934A HIS1720B ASP1721B ARG1814B ASP1976B ASP1980B	GLN193A	LYS1982 B		-33.586331
EUGENOL_opt_C5_LP5	ARG1717A HIS1720A ASP1980B	HIS1720A ASP1976B ASP1980B				-31.342243
THIACREMONONE_opt_LP2	ASP1976A VAL1979A ASP1980A HIS1720B	ASP1976A VAL1979A ASP1980A				-22.051328



In above table the docking study of active constituents from various spices has been represented, like 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.

### **Developing phyto formulation:**

By docking study, we are able to get idea about how the active constituent present in selected spices is going to show its pharmacological activity and to probably what extent. 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

### **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 formulations developed using ethno information. This type of study is going to help in increasing authenticity of herbal formulation.

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