Role of reverse pharmacognosy in finding lead molecules from nature

Diptanu Biswas,*
Creative educational society's college of pharmacy, NH-7 Chinnatekur, Kurnool, Andhra Pradesh-518218
***Corresponding author: E.mail: diptanu69@gmail.com**

ABSTRACT

Alternative systems of medicine viz. Ayurveda, Siddha and traditional system of Medicine have become more popular in recent years and have proven their significance in medical sciences [1]. Combining the strength of knowledge based on traditional systems such as Ayurveda with the dramatic power of combinatorial sciences and high-throughput screening (HTS) will help in the generation of structure activity libraries. The three main hurdles in the drug development to provide new functional leads are time, money and toxicity which can be reduced by traditional knowledge and experimental database [3]. High-throughput screening (HTS) for biological testing and combinatorial chemistry to generate potential hits are the various efforts to accelerate and rationalize drug discovery, but these techniques have not able to increase the discovery of new herbal molecules that are active in vivo [4]. Pharmacognosy, ethno pharmacology and phytochemistry are various branches which have contributed to the discovery of new biologically active natural entities [5]. Many studies have been done which favor integrating traditional knowledge into user friendly databases help the early drug discovery stages [6]. The review will focus on the technique used in reverse Pharmacognosy along with its importance in natural drug discovery to finding out a lead molecule from the natural source.

Key words: Reverse Pharmacognosy, Lead molecule, Traditional system of medicine.

INTRODUCTION

Pharmacognosy as the study of the physical, chemical, biochemical and biological properties of drugs, drug substances or potential drugs or drug substances of natural origin as well as the search for new drugs from natural sources. It is also defined as the study of crude drugs treated scientifically. Pharmacognosy is an important link between pharmacology and medicinal chemistry. As result of rapid development of phytochemistry and pharmacological testing methods in recent years, new plant drugs are finding their way into medicine as purified phytochemicals, rather than in the form of traditional preparations. The knowledge of pharmacology is essential for understanding action of drugs on animals and the human system. Pharmacognosy is the infrastructure on which depends evolution of novel medicines, as it is seen that several crude drugs are utilized for preparation of galanicals or as sources of therapeutically significant substances that cannot be synthesized economically. Further, the crude drugs also provide essential intermediates for final synthesis of active compounds. Phytopharmaceuticals or synthetic drugs derived from phytochemicals have to be ultimately incorporated in suitable dosage form which involves the knowledge of dispensing and preparative pharmacy, pharmaceutical technology and analysis [8]. Reverse Pharmacognosy is defined as the science of integrating documented clinical experiences and experiential observations into leads by trans disciplinary exploratory studies and further developing these into drug candidates or formulations through robust preclinical and clinical research [9,10]. The traditional knowledge inspired reverse pharmacology described here relates to reversing the routine laboratory to clinic progress of discovery pipeline to clinics to laboratories [11].

STEPS INVOLVED IN PHARMACOGNOSY

Selection of plants: Plants are selected on Ethno pharmacological knowledge when specific therapeutic area is desired for treatment. Using knowledge from different cultures increases the probability and ability to identify effective materials that correspond to the therapeutic area. One important consideration is the availability for sufficient quantities of samples for testing and subsequent development [12].

Extraction: Extraction can be defined as a process of removal of soluble materials from an insoluble residue, either liquid or solid, by treatment with a liquid solvent. Extraction is generally done by solvents of different polarity [13].

Biological evaluation: When the estimation of potency of crude drug or its preparation is done by means of its effect on living organisms like bacteria, fungal growth or entire animal, it is known as bioassay. Herbal drugs are screened for their activity by bioassay [14].

Characterization: Isolation of active compounds from the extract is an important step; it is generally done by chromatographic techniques like TLC, HPTLC and HPLC. Main constituents of the drug are studied with the aid of HPTLC and modern spectroscopic techniques, using HPLC-coupled spectroscopic techniques such as HPLC-UV, HPLC-MS as well as HPLC-NMR [15].

Various parts of reverse pharmacognosy: Reverse Pharmacognosy is a new concept of finding new biological targets from structurally similar chemicals and finally finding the natural sources of the biologically active natural compound which contain them

Structural database for natural compound: Natural compounds that appear in the published literature and compounds found in commercial databases forms the structural database also called Virtual Chemical Database (VCDB). The sources of these compounds are available, and frequently the method applied for their extraction is also described. Chemical diversity of the compound is the final criterion for the selection of compounds for virtual screening.

Target database: The target database is composed of 3D protein structures, determined by X-ray crystallography or by homology modeling. The majority of the structures are from humans, although it also contains proteins from other sources (e.g. viruses, bacteria). Protein/ligands pair interaction energy is obtained and involves retrieval of active ligands from a set of 100 non active compounds; method is explained in detailed by Greenpharma [16].

Virtual screening tools: The basic goal of virtual screening is the reduction of the enormous virtual chemical space of small organic molecules, to synthesize and screen against a specific target protein, to a manageable number of compounds that exhibit the highest chance to lead to a drug candidate. There are two methods for virtual screening: screening based on ligand properties, i.e. physicochemical properties (one-dimensional data), fragmental description (two-dimensional data) and pharmacophores (3D data) which are techniques of quantitative structure-activity relationship (QSAR) [17] and screening based on target properties, which requires knowledge of the 3D structure of the target and the ligand which are techniques of de novo design and docking, which involves generating new ligands or adjusting ligands in the active site of the target respectively.

Ethno pharmacological database (ETPHDB): In order to develop botanical data, natural chemical structures, biological testing of extracts and compounds, ETPHDB has been developed. Family, Genus, Species, Common names and Synonyms of the plants are included in this database. The database accelerates the discovery of bioactive ingredients e.g. anti-inflammatory compounds [18]. The ETPHDB contains botanical information on plants and their traditional uses, and phyto chemistry data associated with biological activity of plants, database allows being a link between plants, molecule and activity. The experimental validation process consists of internal biological tests and/or data gathered from scientific literature. Real hits or real inactive candidates enable the validation of the target models. The starting material for Pharmacognosy is raw plants selected by considering their traditional uses or by biodiversity[19]. Extracts are made from the plants and screened on biological assays to find active ones. The active compound(s) are characterized by an iterative bio-guided fractionation. So Pharmacognosy starts with plants and ends with molecules. Reverse Pharmacognosy may be undertaken with or without a virtual component. Molecules are selected by chemical diversity. They are screened on several biological assays. Then with the help of compound source database, plants containing bioactive molecules can be determined. Docking and inverse-docking software can be introduced prior to the biological screenings. Reverse Pharmacognosy begins with molecules to get bioactive plants with their biological activity characterized at the molecular level [20].

Pharmacophore programs: Can be either ligand-based (LB), or target-based (TB) (the latter being superior/preferable); pre-requisite(s) for use. 3D structures of known ligands to be chosen as targets or known 3D structures of target protein, and ideally known 3D structure(s) of known complex are known in this class [21].

Docking programs: Pre-requisites known 3D structure of target proteins; use to dock potential small molecule ligands into protein active sites, optimizing their topographical and chemical component and their interaction was consider for the study [22].

Pattern recognition: Multi-purpose programs for post-screening analyses algorithms employed (for the purposes of dimensionality reduction) include: principle components analysis, multi-dimensional scaling, self-organising maps, and various forms of cluster analysis.

Proteomics and/or genomics data visualization and analysis: Application specific programs for statistical processing and visualization of data output from DNA micro-array experiments, proteomics experiments etc.

Novelty: Reverse Pharmacognosy is used to find new biological targets for natural compounds by virtual or real screening and identify natural resources that contain the active molecules. Reverse Pharmacognosy and its inverse docking component cannot only be integrated into a program for new lead discovery but is also a useful approach to find new applications for identified compounds.

Application: The aim of reverse Pharmacognosy is to find new biological targets for natural compounds by virtual or real screening and identify natural resources that contain the active molecules. Cosmetic industry prefers to use plant extracts as active ingredients. For

pharmaceutical domain, compounds are favored. And knowing different sources that contains particular molecules is also of inter. It shows a successful collaboration between scientist of biological and physical sciences disciplines. It plays a major role in originating meaningful screening and testing models and in the overall evaluation of new agents. It helps in tremendous research efforts in Pharmaceutical sciences. It provide a basis for development of new approach to combat new human diseases.

Table.1.Plant Derived Drugs used as medicine

Year	Trade name	Lead compound	Disease area	Class
2000	*Artemotil*	Artemisinin	Anti-malarial	Semi-synthetic, NP
2002	Orfadin	Leptospermum	Antityrosinaemia	NP derived
2002	Reminyl	Galantamine	Alzheimer's disease	Alkaloid, NP
2004	Apokyn	Morphine	Parkinson's disease	Semi-synthetic, NP
2004	Spiriva	Atropine	CPOD	Alkaloid, NP
2005	Sativex	Dronabinol/cannnabidol	Pain	Cannabinoids, NP
2007	Vyvanse	Amphetamine	Hyperactivitydisorder	Amine, NP-derived
2008	Relistor	Naltrexone	Pain	Alkaloid, NPderived
2009	Qutenza	Capsaicin	Pain	Vaniloid, NP
2013	Crofelemer	Oligomeric proanthocyanadin	Anti-diarrheal agents	Polyphenolic,NP

Table.2.Lead compound from natural source and their use

Name of the plant	Lead compound	Activity
Ammit vinsega	Khelluin	Bronchdialator
Berberis species	Berberine	Antidiarrhoeal
Cammelia sinesis	Caffeine	CNS stimulant
Catheranthus roseus	Vincristine	Anti-cancer
Cassia angistifolia	Sennoside	Laxative
Cephaelis ipecacuanha	Emeine	Anti-amoebic
Claviceps purpurae	Ergometrine, Ergotamine Ergotoxine	Oxytoxic, Vasoconstrictor Vasodialator
Cinchona species	Quinidine, Quinine	Anti-malarial, Anti arrhythmic
Datura species, Hyoscyamus species and Atropa belladonna	Hyoscyamine, Hyoscine Atropine	Para sympatholytic
Dioscorea species	Diosgenin	Anti-inflammatory
Ephedra species	Ephedrine	Sympathomimetic
Erythroxylum coca	Cocaine	Local anaesthetic
Glycorrhiza glabra	Glycyrrhetinic acid	Anti-inflammatory
Lobelia inflanta	Lobelline	Anti-asthmatic
Papaver sominiferum	Morphine, Codeine, Papaverine	Analgesic and sedative
Pilocarpus jaborandi	Pilocarpine	Parasympathomimetic
Plantago ovato	Psyllium mucilage	Laxative
Podophyllum species	Podophyllotoxin	Anti-cancer
Rauwolfia serpentina	Reserpine	Hypotensive, Vasodialator
Solanum species	Solasidine	Harmonal

CONCLUSION

The concept of research is directed to search for the new chemical entities for the treatment of life threatening diseases. The current review is an attempt made to utilize the principles of reverse pharmacology in conjugation with Ayurveda, siddha and traditional other systems of medicine to develop newer strategies for the drug discovery which will offer newer chemical entities with potential biological activities. India has moved forwards in advocating global usefulness of Ayurveda in the scenario of health care through global networks. As a result many foreign countries have began looking at India for understanding Ayurveda and incorporating it through education, research and practice to meet the overwhelming desire of consumers

to access Complementary & Alternative Medicine. So in such an arena reverse Pharmacognosy, by making use of it virtual screening tool and important databases can play important role in reducing the time and wealth. It can accelerate the drug discovery to a considerable extent.

REFERENCES

1. Patwardhan and M. Hooper, Ayurveda and future drug development, Int. J. Alternative Complement. Med. 10, 1992, 9–11
2. R. Lahana, How many leads from HTS?, Drug Discovery Today, 4(10), 1999, 447-448
3. P.L. Myers, Will combinatorial chemistry deliver real medicines, Current Opinions on Biotechnology, 8(6), 1997, 701-707
4. R. Anton, Plantes Therapeutiques, Lavoisier, Cachan, France, 1999
5. G. Massiot, How far can one go in the field of structural elucidation of natural products, J. Ethnopharmacology, 32(1-3), 1999, 103-110
6. Shah BN and Sheth AK, Text book Pharmacognosy and phyto chemistry, Edn. Elsevier publication, 2010: 2-8
7. Wallis T E, Text book of Pharmacognosy, 5th edn. CBS publishers &distributors, New Delhi,.1985, 1-6
8. P. Tiew, J.R. Loser, U. Kokpol, W. Chavasiri and K. Hostettmann, Antifunagal, antioxidant and larvicidal activities of compounds isolated from the heartwood of Mansonia gagei, Phytother. Res., 17(2), 2003,190-193
9. Josang, H.E. Bitar, V.C. Pham and T. Sevenet, Daphcalycine, a novel heptacycle fused ring system alkaloid obtained from Daphniphyllum Calycinum, J. Org. Chem., 68(2), 2003, 300-304
10. X. Yan, J. Zhou and Z. Xu, Concept Design of Computer-aided study on tradional Chinese drugs, J. Chem. Inf. Compt. Sci., 39(1), 1999, 86-89
11. P. Bernard, T. Scior, B. Didier, M. Hibert and J.Y. Berthon, Ethnopharmacology and bioinformatics combination for lead discovery: Application to phospholipase A2 inhibitors, Phytochemistry, 58(6), 2001, 865-874
12. Vaidya A D & Devasagayam T P, Current Status of Herbal Drugs in India: An Overview, J Clin Biochem Nutr, 2007, 41
13. Vaidya A D B, Reverse pharmacological correlates of ayurvedic drug actions, Indian J Pharmacol, 4, 2006, 38:
14. Ramalingaswami V, Satyavati G V, Sir Ram Nath Chopra, Indian J Med Res, Suppl:V-VI, 1982, 76,
15. Sen G & Bose, K C, Rauwolfia serpentina, a new Indian drug for insanity and high blood pressure, Ind Med World, 2, 1931.
16. Satyavati G V, Gum guggul (Commiphora mukul) the success story of an ancient insight leading to a modern discovery, Indian J Med Res, 87, 1988: 327.
17. B. Natarajan, B.S. Paulsen and P. Pushpangadan, An Ethnopharmacological Study from the Coimbatore District, Tamil Nadu, India: Traditional Knowledge Compared With Modern Biological Science, Pharmaceutical Biology, 37(5), 2001, 378–390
18. C.K. Kokate, A.P. Purohit and S.B. Gokhle, Analytical Pharmacognosy, 15, 2002, 123-130
19. Q.T. Do and P. Bernard, Pharmacognosy and Reverse Pharmacognosy: a new concept for accelerating natural drug discovery, I. Drugs., 7(11), 2004, 1017- 1027
20. Y.C. Martin, M.G. Bures, E.A. Danaher, J. De Lazzer and I. Lico, A fast new approach to pharmacophore mapping and its application to dopaminergic and benzodiazepine agonists, J. Comput. Aided. Mol., 7(1), 1993, 83- 102
21. N. Baurin, E. Vangrevelinghe, L. Morin-Allory, J.Y. Merour, P. Renard, M. Payard, G. Guillaumet, C. Marot, 3D-SAR CoFA study on imidazolinergic I_2 ligands : A significant model through a combined exploration of structural diversity and methodology, J. Med. Chem., 43(6), 2000; 1109-1122
22. H.J. Bohm, The computer program LUDI: A new method for the de novo design of enzyme inhibitors, J. Compt. Aided. Mol. Des., 6(1), 1992, 61-78
23. G. Jones, P. Willett, R.C. Glen, A.R. Leach and R. Taylor, Development and validation of a genetic algorithm for flexible docking, J. Mol. Biol., 267(3), 1997, 728-748