

Review Article

A new era of pharmacognosy – “Molecular Pharmacognosy”

Himesh Soni*, Priyanka Narwani, A. K. Singhai

Lakshmi Narain College of Pharmacy, Bhopal, Madhya Pradesh, India.

*Corresponding Author. Tel.: +91 9826386065, E-mail address: himeshsoni@rediffmail.com

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ABSTRACT

At the edge between Pharmacognosy and molecular biology, molecular Pharmacognosy has developed as a new intermediate branch. This article reviews the methods, relevance and scene of molecular pharmacognosy. The main background focus in this manuscript including the molecular identification of medicinal raw materials, phylogenetic evolution of medicinal plants/animals, evaluation and preservation of germplasm resources for medicinal plants, etiology of endangered medicinal plants species, biosynthesis and bio-regulation of alleopathic substances. A recent advancement in herbal drug discovery involves a comprehensive approach including molecular techniques.

INTRODUCTION

Plants have been appropriate source of medicines for past era. These medicines primarily took the form of crude drugs. Eventually data concerning medicinal plants was recorded in herbals literatures. In the early 19th century the use of isolated active compounds utilized and screened for various therapeutic activity. The isolation and characterization of pharmacologically active compounds from medicinal plants persist today. In modern era, various molecular techniques have been applied to the standardization of herbal medicines, to elucidate analytical marker compounds[1]. Medicinal raw materials are derived from natural sources, including plants, animals and minerals sources which are intended for applications in disease treatment, health-care or the production of medicines [2]. The study of these crude drugs (organized or unorganized) is come under Pharmacognosy. The term Pharmacognosy was first introduced between 1811 and 1815, and formerly referred to “materia medica”, the acquaintance of drug materials or pharmacology. It is derived from two Greek words, *pharmakon* (a drug) and *gignosko* (to acquire knowledge of) [3]. Afterward, pharmacognosy became limited to that branch of pharmacy investigating medicinal substances from the plant, animal and mineral kingdoms in their natural, crude, or unprepared state, or in the form of such primary derivatives as oils, waxes, gums, and resins [4].

At present, at the beginning of the 21st century, pharmacognosy teaching and research is pursued passionately by its disciples in academic departments of pharmacy globally. Although the name pharmacognosy may be substituted in certain countries by terms such as phytochemistry or pharmaceutical biology, natural products research which include aspects of analytical chemistry, bioactive compound discovery, bioassay method development, biocatalysis, biosynthesis, biotechnology, cell biology, chemotaxonomy, clinical studies, cultivation of medicinal plants, ethnobotany, genetics, marine chemistry, microbial biotransformation, molecular biology, organic synthesis, pharmacology, phytochemistry, phytotherapy, the standardization of traditional medicines, taxonomy, tissue culture, and zoopharmacognosy [5]. Recently, Pharmacognosy and natural products research area are elaborated in molecular level. *Molecular pharmacognosy* is a discipline that studies the classification, identification, cultivation and conservation of medicinal raw materials, as well as the production of their active components at a molecular level [6]. The theory of “molecular pharmacognosy” was first introduced by HUANG *et al.* [7] in Prospects for Application of Molecular Bio-techniques to Pharmacognosy in 1995. In June 2000, The Press of Beijing Medical University published Molecular Pharmacognosy [8]. The second edition of the book edition was published in 2006 [9].

This article enlightens the basic background, development and significance of Molecular Pharmacognosy.

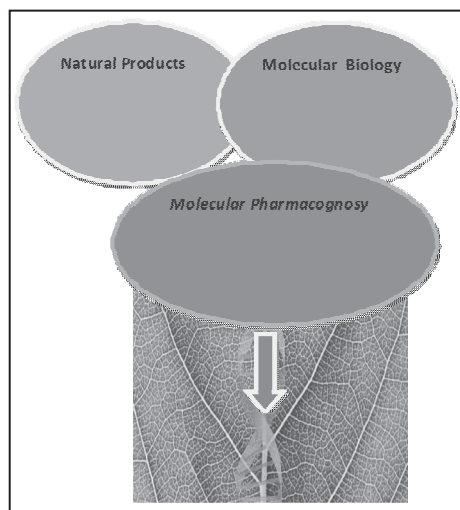


Fig. 1. Emerging trend of Molecular Pharmacognosy

Molecular pharmacognosy is a rising discipline combining molecular biology and pharmacognosy, and its development depends on systems biology with reference to genomics, proteomics and metabolomics and also involved methods of modern biotechnology. Molecular biology has become vital to drug discovery from medicinal plant, through the determination and accomplishment of appropriate screening assays directed towards physiologically relevant molecular targets.

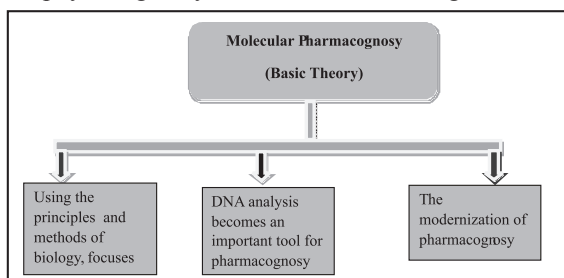


Fig. 2. Backbone of Molecular Pharmacognosy

1. PHARMACOGNOSY AT THE MOLECULAR LEVEL

With the development in science and technology, especially in biology and their related disciplines, there is significantly accelerated the evolution of pharmacognosy at the current scenario. At 21st century there are significant expand of pharmacognosy research, the research content was blown up and new techniques and methods were developed. From these advances various difficulties have emerged as well. The following questions are typical examples. How might the qualitative variability observed in medicinal raw materials be defined? How do high-quality medicinal materials (especially top-geoherbs) form, and what are the molecular basis and the environmental mechanism for such formation? What is the biological mechanism of active-components accumulation in

medicinal raw materials, and what are the factors influencing these mechanisms? How to increase the content of active components? What are the characteristics of the germplasm resources of medicinal raw materials, and what are the differences between the germplasm resources of medicinal raw materials and the plants as crops? [10]. To resolving these query, molecular biology has become necessary tools to medicinal plant drug discovery through the determination and implementation of suitable screening assays directed towards physiologically significant molecular targets. Pharmacognosy encapsulates all of these fields into a diverse interdisciplinary science.

2. DEVELOPMENT OF MOLECULAR PHARMACOGNOSY

The main motto of research in pharmacognosy are to attain the identification and quality assessment of plants (individual/populations), or provide scientific basis for the production and sustainable use of medicinal raw materials resources. Such studies are conducted at the cellular levels. By contrast with the task of pharmacognosy, molecular pharmacognosy aims to identify particular molecules in medicinal raw materials, study the background of their origin, reveal the molecular mechanisms of secondary metabolite accumulation, understand the principles governing the biosynthesis of secondary metabolites, and provide scientific bases for high-quality production and conservation of medicinal raw materials [11].

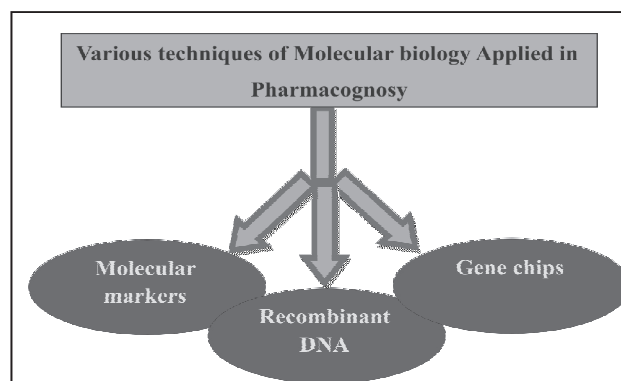


Fig. 3. Techniques of molecular biology applied to pharmacognosy

These techniques have provided significant support for DNA polymorphism detection in molecular pharmacognosy.

2.1 Molecular markers in herbal drug technology

Herbal drug technology is used for transformation of botanical materials into medicines, where standardization and quality control with proper assimilation of modern scientific techniques and traditional knowledge is important. Previously, pharmacognosy mostly addresses quality-related issues using custom botanical and organoleptic parameters of crude drugs, and chemo-profiling assisted characterization with chromatographic and spectroscopic techniques. The modern pharmacognosy includes all the aspects of drug designing and discovery, where molecular biology and biotechnology-driven applications play a vital role.

Molecular markers generally refer to biochemical constituents, including primary and secondary metabolites and other macromolecules such as nucleic acids. Secondary metabolites as markers have been extensively used in quality control and standardization of botanical drugs. Molecular marker such as DNA markers, which have several merits over typical phenotype markers. DNA markers are reliable tools as the genetic composition is unique for each species and is not affected by exogenous factors [12]. Various DNA-based methods are employed for species characterization and adulteration detection in medicinal plants.

2.1.1 RAPD analysis for plant genetic study

RAPD is a rapid and sensitive method and is able to provide reproducible and characteristic fingerprints of composite genomes without prior sequence information. The use of short primers of arbitrary sequence during PCR results in amplification of different segments of genomic DNA, which after gel electrophoresis gives characteristic band patterns. Most informative DNA bands on RAPD are usually of the 300- 3000bp range. RAPD provides a cost-effective method for the precise and schedule evaluation of variability. It may also be used to identify areas of maximum diversity. Thus molecular technique provides a powerful tool for the study of plant population genetics [13].

Other molecular markers used in Plant Genome Analysis are as follows [14]:

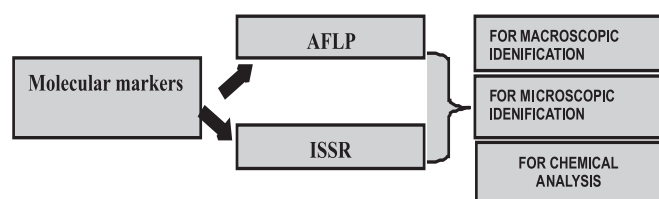


Fig. 4. Molecular markers

2.1.2 Quantitative estimation of DNA from different parts of same species

Modern approaches for develop a simple, efficient, reliable and cost-effective method for isolation and estimation of total genomic DNA from various parts of the same species. With reference to this, previously studied were carried out by *Soni et al.*, 2012 modified CTAB method gave good quality of DNA. This method was determined to be the best method for *Coleus aromaticus* DNA isolation from stem and leaves. The differences in quality and quantity of isolated DNA observed by gel electrophoresis. The size of isolated DNA was about ± 1200 bp. In leaves and stem explants portion of plant A_{260}/A_{280} ratio of ranges 1.6 to 1.9 (Average about 1.8) indicating the level of purity of DNA. The DNA obtained was unshared, showing little or no RNA contamination. UV absorbance ratio for protein contamination ($A_{260/280}$) and carbohydrate contamination ($A_{260/230}$). For a good and clean preparation of nucleic acid, the $A_{260/280}$ ratio, which represent protein contamination, should be between 1.8 to 2.0 while the $A_{260/230}$ ratio, which represent carbohydrate contamination, should

be more than 2.0. The quantization of the obtained DNA from leaves and stem were found to be 3.7 & 0.40 $\mu\text{g/ml}$ respectively. Poor stem DNA quantity could be due to certain reasons like mixing of RNA or protein, improper expression of transcription factor or secondary metabolite interferences. *C. aromaticus* plant which is the source of natural products or bioactive substances produced a large amount of secondary metabolites and substances of medicinal importance. The cells of the plant are known to contain high concentrations of polysaccharides in addition to the active metabolites, complicating the problem of DNA isolation [15].

2.1.3. Emerging of Recombinant DNA technology for improvement in genetic variation

Recombinant DNA technology provides a powerful tool that enables scientists to engineer DNA sequences and thereby produced genetically improved strain.

2.1.4 Gene chip technique

For determination of gene expression profiles, analyses of polymorphisms, construction of genomic library, analysis of mapping, and sequencing by hybridization Gene chip technique could be employed.

2.1.5 Biotransformation

This technique is generally used in studies about the biosynthesis and accumulation of secondary metabolites derived from plant sources [16]. Biotransformation is the chemical transformation mediated by microorganism /plant cell or animal cell. The microorganism or plant cell act as the catalyst. These involve simple chemically defined reaction catalyzed by enzyme present in the cell. The cell may be microbial, plant or animal. Microbial cell have advantage over plant and animal cell due to their high surface volume ratio, rapid growth and high rate of metabolism for efficient transformation. Biotransformation carried out with plant cell successfully gives noble compound like cardiac glycoside, digoxin, benzoquinoline etc. Enzyme catalyst is superior to chemical catalyst because of their chemical specificity, regio- specificity, reaction specificity. mild condition required and lowering of activation energy.

2.1.6. Elicitor

Elicitors are compounds stimulating any type of plant defense. Elicitor includes both substances of pathogen origin (exogenous elicitors) and compounds released from plants by the action of the pathogen (endogenous elicitors). Elicitors could be used as increase of plant secondary-metabolite synthesis and could participate an important role in biosynthetic pathways to enhanced production of commercially important phyto-constituents. Elicitors are triggered defense response and thereby enhanced releases of the secondary metabolites [17].

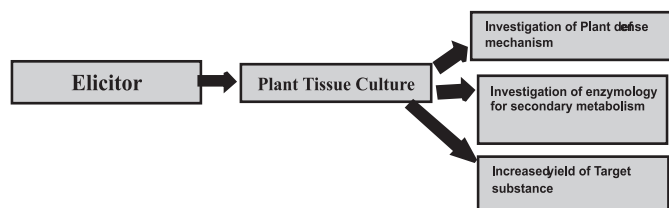


Fig. 5. Utilization of Elicitation in various areas

3. HEART OF RESEARCH IN MOLECULAR PHARMACOGENOSY

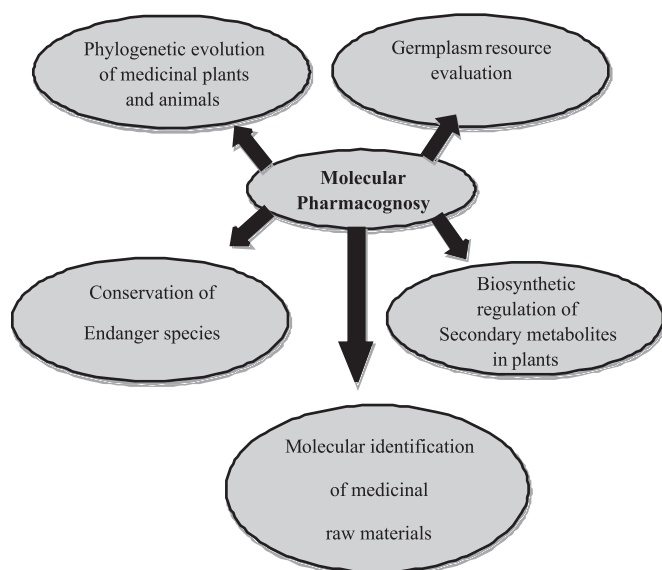


Fig. 6. Central core of molecular pharmacogenosy

Above areas of research are the central core of Molecular Pharmacogenosy with contract to Pharmacogenosy which leads reorganization and identification of the origins of medicinal raw materials, investigations and documentation searches of resources of medicinal raw materials, concern of quality-control standards and quality assessment of medicinal raw materials [18-19].

4. CURRENT SCENARIO FOR ADVANCEMENT IN MOLECULAR PHARMACOGENOSY

4.1 Combinatorial biosynthesis

The general concept of combinatorial biosynthesis is to unite metabolic pathway in different organism at genetic level, where genes from different microorganism are combined for the production of novel plant phyto-constituents. Recent achievements with the polyketides biosynthesis from microorganism (*Streptomyces*), proven the prospective of combinatorial biosynthesis. With reference to the pharmaceutical Podophyllotoxin and Paclitaxel biosynthesis (cell culture) are examples of combinatorial biosynthesis [20].

4.2 Clinical pharmacogenosy

Molecular techniques and tools provides correct authentication of plant raw material and thereby aid in herbal drug discovery. This new intermediate discipline may broaden the scope of clinical aspects of pharmacogenosy and play a progressive task in the safe, rational and efficient use of traditional and herbal medicine. There are several unproven therapeutic benefits and hidden toxicities and difficulties in standardizing natural treatments. Clinical pharmacogenosy is a link between botanicals and clinical research knowledge providing clinical and pharmaceutical researchers, physicians and other healthcare professionals with the key information they need to assist the progress of herbal and traditional medicines [21].

4.3 Reverse pharmacogenosy

Introduction of new concept in pharmacogenosy is “Reverse pharmacogenosy”, which deals with the finding new biological targets from structurally similar chemicals and finally finding the natural sources of the biologically active natural compound which contain them [22]. Various steps involve in Reverse Pharmacogenosy are as follows:

Structural database for natural compounds

Lead compounds that were already isolated found in commercial databases. The structure database also called Virtual Chemical Database (VCDB). Example; CONCORD which contains more than 100,000 natural lead moiety structures, along with their 3D coordinates. Virtual screening of the compounds was carried out on the basis of chemical diversity.

Structure determination of Target Enzyme: There are two methods for determination of target enzyme structures [23]:

Experimental Methods: Like X-ray crystallography, NMR spectroscopy etc.

Homology modeling: Fast and useful method, where sequence similarities between template and the target enzyme is used to model the 3-D structure of the target enzyme. Various software for Homology modeling are commercially available such as Raptor X, Mod Pipe, Biskit, TASSER-Lite, Pro Model, LOMETS, etc.

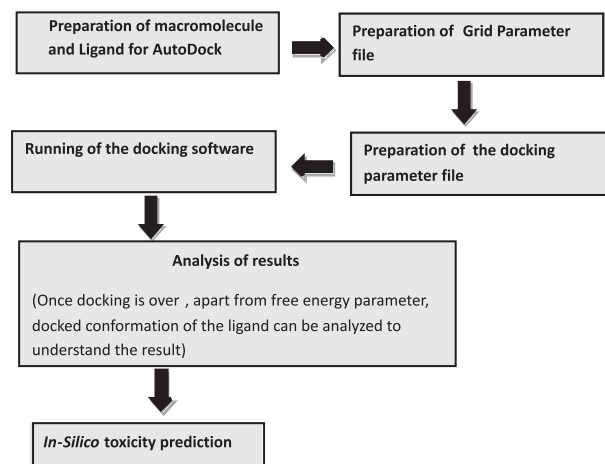


Fig. 7. Docking study of macromolecules

Design of Inhibitor Molecules: There are two approaches for virtual screening : screening based on ligand properties, i.e physicochemical properties (one-dimensional data) and pharmacophores (3D data) which are techniques of quantitative structure-activity relationship (QSAR).

Docking: Docking and molecular modeling are performed by various softwares such as AutoDock, DOCK, DOT ,FADE,etc. Docking involved following steps:

A recent advancement in reverse pharmacognosy opens the gateway of new trend of research, which includes development of the various computer aided software which contains databases of herbal drug alongwith their taxonomical, phylogeny, phytochemical profile of the bioactive compound. Example; Ethnopharmacological database (ETPHDB) which contains information about Family, genus, species, common names and synonyms of the plants. Development of such software accelerates the drug discovery of herbals. With reference to molecular docking *Soni et.,al* was investigate the docking of Rutin(Flavone) with COX-2.

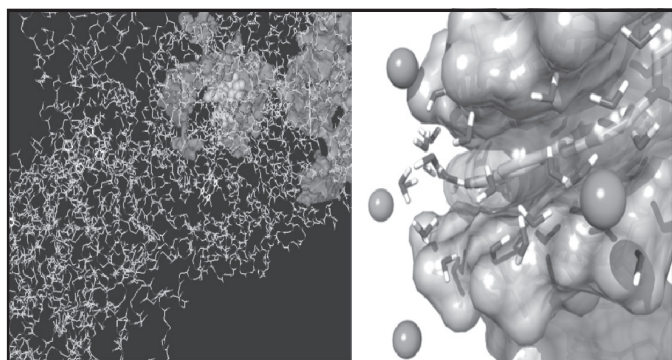


Fig. 8. Cavity structure (Golden color-Rutin, Green Color-Cavity)

Docking studies confirmed that the main interaction of COX-2 inhibitors with rutin is Hydrogen bond and Vander wall interaction. Above studied of natural plant flavonoid known as rutin has been identified as ligand and its COX-2 inhibitory activity has been checked *in-silico* with the help of docking facility [24].

4.4 DNA barcoding

It helps in identification of the species of the raw materials. A gene region of about 600 base pairs is sequenced and used as barcode [25].

4.5 Biosynthesis and regulation of bioactive compounds

Secondary metabolites are accumulated from the plant having therapeutic efficacy. Therefore, the quality of a medicinal raw material chiefly based on the presence and amounts of secondary metabolites. Molecular pharmacognosy research focus on the systematic study of the gene/genome which are responsible for production as well regulation of the phyto-constituents. It also includes the application of genetic engineering for the enhanced the level of bioactive components [26]. Previously, molecular basis of regulation of inorganic nutrients is not known but due to development of molecular pharmacognosy it has proven that

regulation of inorganic nutrients also effect the physiological regulation of secondary metabolism production eg: Manganese limitation accelerates vitamin C production in *Aspergillus niger* [27].

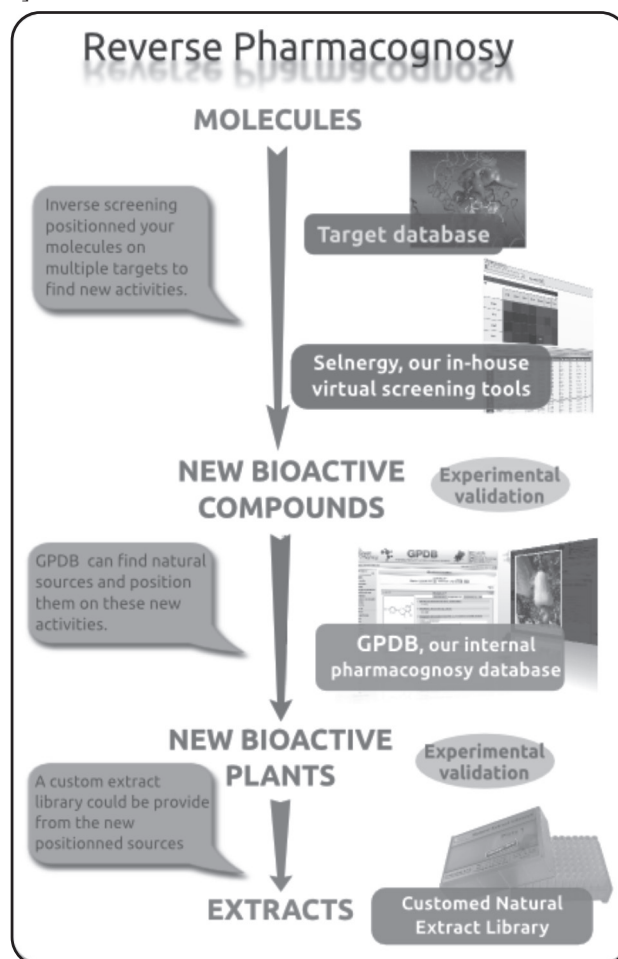


Fig. 9. Scheme representation of Reverse Pharmacognosy

4.6 Preservation of germplasm resources

Germplasm resources also known as genetic resources. A Germplasm resource contains various genetic materials produced artificially from propagative materials. These resources are further used in future for the selection and propagation of new plant species having high yield of secondary metabolites. The collection, grouping, conservation and evaluation of germplasm resources are essential elements of the study of germplasm resources of medicinal plants and animals [28].

4.7 Natural product biosynthesis diversity

The research on plant natural product biosynthetic pathways at the molecular level opens the gateway of new drug discovery. The recent reviewed studies revealed the how biosynthetic diversity is generated using relatively conserved enzymatic mechanisms. This promising knowledge will offer the bridge to the next era of natural product gene discovery utilizing functional genomics. Characterization of Chalcone synthase(plant natural product polyketide synthase) was carried out at the molecular level [29].

4.8 Genomics, Proteomics and Metabolomics

The study of the structure and function of the genome is comes under genomics. Further, elaborated in sub-class like structural, functional and comparative genomics. The study of the proteome i.e. full complement of proteins made by cell. The use of genome sequence analysis to determine the capability of cell, tissue or organism to synthesize small molecules is come under metabolomics [30]. It is also defined as “Systematic study of the distinctive chemical fingerprints that specific cellular processes leave behind. Metabolomics with reference to natural product is one of the important bases for studying the relation between the composition of complex and variable mixtures of plant derived remedies as well as their biological effects. Plant metabolomics starts with the analysis of as many as probable detectable individual bioactive moiety that is present in the material. It also helps to study the secretion, percentage and composition of individual herbal marker compound, eg; studied of metabolites in *Ginkgo biloba* leaves and effect of harvesting time (sunrise and sunset) on their flavonoids contents [31].

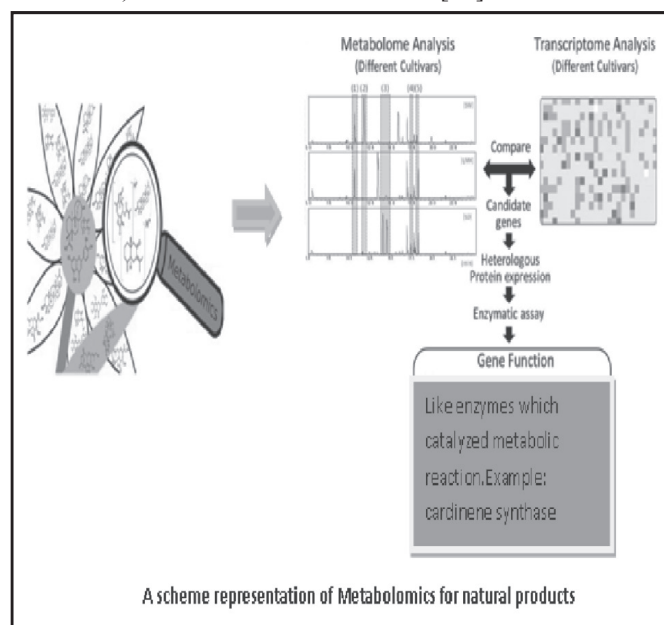


Fig. 10. Metabolomics for natural products

5. APPLICATIONS OF MOLECULAR PHARMACOGENOSY

Pharmacognosy is a focus emerging from practice while the study of molecular mechanisms is theory basis of molecular pharmacognosy. Molecular pharmacognosy is an area of research which will unquestionably undergo intensive development in close proximity to future. Molecular pharmacognosy has developed as a novel intermediate discipline. With the help of the method and technology of molecular pharmacognosy, a wide range of challenging troubles were resolved, such as the identification of medicinal raw materials, etiology and protection of endangered plant species. Therefore, molecular pharmacognosy will provide the new methods and insight for modernization of pharmacognosy.

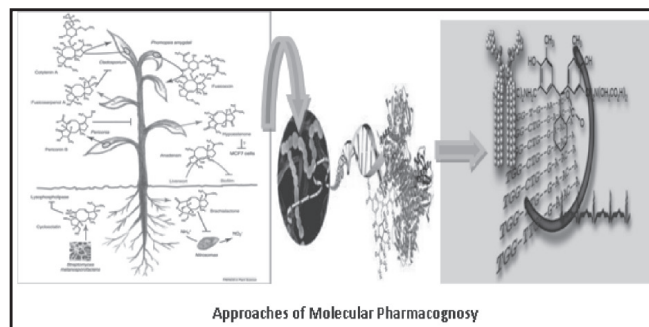


Fig. 11. Approaches of Molecular Pharmacognosy

CONCLUSION

As we enter the new millennium of the 21st century and, it may be assert that attention in pharmacognosy as a discipline and natural products in general is at an all time high. The past decade has proven use of herbalism. This phenomenon has been imitated by an increasing consideration to herbal remedies (phyto-medicines) as a form of unconventional therapy by the health professions inclusive of pharmacy and medicine. A recent innovation in field of pharmacognosy is the molecular pharmacognosy. It is rising up with the development of molecular biology. The techniques of molecular biology have developed rapidly in modern era, and by the used of this techniques and principle there has been greatly evolution on identification, formation mechanism, quality evaluation, resource defense and production of active compounds in crude drugs. Nevertheless, each method has certain restrictions, which includes accuracy, validation of process and cost. Therefore constraint needed to be overcome. Furthermore, the enormous advance of molecular pharmacognosy could be predictable in DNA fingerprint analysis, DNA identification of the plant raw material, studying the phylogenetic relationship and saving the endangered plant resources for future uses. This new discipline of science is merged of pharmacognosy with various branches of sciences such as molecular biology, biotechnology, chemical biology, structural biology, proteomic, genomic, metabolomics and bioinformatics.

REFERENCES

- [1] Marcy, J.B.; Douglas A. Drug discovery from medicinal plants. *Life Sciences*.2005,78, 431-41.
- [2] Huang, L. Q. Molecular Pharmacognosy; Beijing: Press of Beijing Medical University,2006; 2,1-2.
- [3] Hocking, G.M. *A Dictionary of Natural Products*. Plexus Publishing, Inc., Medford,1994;1,3.
- [4] Trease, G.E.; Evans, M.D. A text book of Pharmacognosy; Baillier, Tindal and Caussel, London, 13th Edn, 144 -148.
- [5] Douglas King horn, A. Pharmacognosy in the 21st century, *Journal of Pharmacy and Pharmacology*. 2001, 53, 135–148.
- [6] Huang, L.Q.; Xiao, P.G; Molecular Pharmacognosy. Beijing: China Press of Traditional Chinese Medicine 2008; 1,189.
- [7] Huang, L.Q. Prospects for application of molecular biotechnique to pharmacognosy. *China. J. Chin. Mat. Med.* 1995, 20, 634.

- [8] Huang, L. Q. *Molecular Pharmacognosy*; Beijing: Press of Beijing Medical University, 2000,1,375.
- [9] Huang, L. Q. *Molecular Pharmacognosy*; Beijing: Press of Beijing Medical University 2006; 2,678.
- [10] Huang, L. Q.; Xiao, P.G.; Lan, P.; Gao, Wen.Yuan. *Molecular pharmacognosy. Science China. Life Sci.* 2010, 53, 6, 643-652.
- [11] Xie, Z .W. Evaluation of molecular pharmacognosy. *China. J Chin. Mater. Med.* 2001, 26,216.
- [12] Joshi, K.; Chavan, P.; Warude, D.; Patwardhan, B. Molecular markers in herbal drug technology. *Current Sci.* 2007, 87,2, 159-160.
- [13] Cheema, S.K.; Pant, M.R. RAPD Analysis of the Seven Cultivated Varieties of *Capsicum annum* L. *Journal of Pharmacognosy and Photochemistry.* 2013, 2,1,152.
- [14] Sharma, A.; Namdeo, A.; Mahadik, K.R. Molecular Markers: New Prospects in Plant Genome Analysis. *PHCOG. REV.* 2008, S 2,3,28.
- [15] Soni, H.; Singhai, A.K.; Sharma, S. Quantitative estimation of DNA isolated from leaves and stems of *Coleus aromaticus*. *Int. J. Pharm.* 2012, 2,1, 84-89.
- [16] Zhang, C. H.; Chen, Y. W.; Zheng, Y. Study on the chemical components of transformation outcome of microbial transformation by *Aspergillus niger*. *Nat. Pro. Res. Dev.* 2008, 20, 585–588.
- [17] Radman, R.; Sacz, T.; Bucke, C.; Keshvartz, T. *Biotechnol. Appl. Biochem.* 2003, 37,91-10.
- [18] Cai, S.Q. *Pharmacognosy*; People’s Medical Publishing House. Beijing, 2007, 2 .
- [19] Huang, L. Q.; Xiao, P. G. *Molecular Pharmacognosy*; China Press of Traditional Chinese Medicine Beijing, 2008, 3, 2–3.
- [20] Khan, M.Y.; Aliabbas, S.; Kumar, V.; Rajkumari, S. Recent advance in medicinal plant biotechnology. *Indian Journal of Biotechnology.* 2009, 8, 10-11.
- [21] Kazemi, M.; Eshraghi, A.; Yegdaneh, A.; Ghannadi, A. Clinical pharmacognosy- A new interesting era of pharmacy in the third millennium. *DARU Journal of Pharmaceutical Sciences.* 2012, 20, 18.
- [22] Khan, M.d. Yaseen.; Kumar, V.; Gajjar, A.; Vyas, N.; Panchal, S.; Butani, A. Reverse Pharmacognosy In New Drug Discovery. *Current Pharma Research Journal.* 2007,1,5, 31-36.
- [23] Jones, G.; Willett, P.; Glen, R.C.; Leach, A.R.; Taylor, R. Development and validation of a genetic algorithm for flexible docking. *J. Mol. Biol.* 1997, 267, 3, 728-748.
- [24] Soni, H.; Singhai, A.K.; *In-vivo* and *In-silico* Design of Anti-inflammatory Activity of Rutin. *Int.J. of Environmental. Sci. and tech.* 2014, 2,1, 44-48.
- [25] Herbert, Paul. D. N.; Stoeckle, M. Y.; Tyler, S.; Charles, M. Francis. Identification of Birds through DNA Barcodes. *PLoS. Biol.* 2004, 2,10, 312.
- [26] Huang, L.Q.; Xiao, P.G.; Gao, Wenyuan. Molecular pharmacognosy. *Science China. Life Sci.* 2010, 53, 6, 647.
- [27] Kubicek, C. P.; Rohr, M. Novel Trends in physiology and technology of citric acid production. In *overproduction of Microbial Products*, Academic Press London, first edition, 1982; 42.
- [28] Huang, L. Q. *Molecular Pharmacognosy*; Beijing: Press of Beijing Medical University, 2000; 1,217.
- [29] Richard, A.; Dixo. Plant natural products: the molecular genetic basis of biosynthetic diversity. *Current Opinion in Biotechnology.* 1999, 10, 192.
- [30] Primrose, S. B.; Twyman, R. M. *Principles of Genome analysis and Genomics*, Blackwell publishing company, Berlin Germany, Third edition; 2003, 9.
- [31] Wang, M.; Robert Jan A.; Henrie, J.K.; Joop H.J.; Van, N.; Renger, F.W.; Rob, H.; Peter J.V.; Louis M H.; Rob, V.; Janvander, G. *Metabolomics in the Context of Systems Biology: Bridging Traditional Chinese Medicine and Molecular Pharmacology. Phytother. Res.* 2005,19, 175.