General Introduction

Drug discovery from natural products: The future, not so far
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Natural products: herbal origin

No doubt that divine creator created Mother Nature, (herbal plants) saving millions of lives unknowing of their importance and its value for decades. Herbalism or Botanical Medicine or Ethnomedicine, is the term given for usage of herbal plants for their therapeutic or medicinal value. Throughout the history of mankind, the traditional medicine comprising medicinal plant, mineral and organic matters etc., practiced by traditional practitioners and herbalists played a vital part. The ancient record is evidencing their usage by Indian, Chinese, Egyptian, Greek, Roman and Syrian dating back to about 5000 BC. About 500 plants with medicinal use are mentioned in ancient texts and around 800 plants have been used in indigenous systems of medicine.

From a "scientific" perspective, many herbal treatments are considered experimental. The reality is, however, the herbal medicine has a long and a respected history. Many familiar medications of the twentieth century were developed from ancient healing traditions that treated health problems with specific plants (Billore et al., 2004).

The current accepted modern medicine or allopathy has gradually developed over the years by scientific and observational efforts of scientists. However, the basis of its development remains rooted in traditional medicine and therapies. The history of medicine includes many ludicrous therapies. Nevertheless, ancient wisdom has been the basis of modern medicine and will remain as one of the important source of future medicine and therapeutics. The future of natural products drug discovery will be more holistic, personalized and involve wise use of ancient and modern therapeutic skills in a complementary manner, so that maximum benefits can be acquired to the patients and the community (Bhushan patwardhan et al., 2004).
Ethnopharmacology is a highly diversified approach to drug discovery involving the observation, description, and experimental investigation of indigenous drugs and their biologic activities. It is based on botany, chemistry, biochemistry, pharmacology, and many other disciplines (anthropology, archaeology, history, and linguistics) that contribute to the discovery of natural products with biological activity. As evident from the above discussion, nature is the best combinatorial chemist and till now natural product compounds discovered from medicinal plants (and their analogues thereof) have provided numerous clinically useful drugs. In spite of the various challenges encountered in the medicinal plant based drug discovery, natural products isolated from plants will still remain an essential component in the search for new medicines.

Today, science has isolated the medicinal properties of a large number of botanicals, and their healing components have been extracted and analyzed. Many plant components are now synthesized in large laboratories for use in pharmaceutical preparations. For example, vincristine (an antitumor drug), digitalis (a heart regulator), and ephedrine (a bronchodilator used to decrease respiratory congestion) were all originally discovered through research on plants (Perumal Samy and Gopal Krishna kone, 2007).

In this modern era, the health organizations and pharmaceutical industries developed this hypothesis on herbs into limelight by developing as a miracle medicinal drugs. Emergence of the modern pharmaceutical industry is an outcome of all these different activities that developed potent single molecules with highly selective activity for a wide variety of ailments.

Proper utilization of these resources and tools in bioprospecting will certainly help in discovering novel lead molecules from plants by employing modern drug discovery techniques and the coordinated efforts of various disciplines. The key factors to remain competitive with the modern system of medicine includes, continual improvements in the speed of dereplication, isolation, structure elucidation, and compound supply processes and prudent selection of drug targets for the screening of Natural Product libraries (Alan Harvey, 2008).
Pharmaceutical research took a major leap along with it natural products chemistry, pharmacologists, microbiologists and biochemists began to unravel the chemistry of natural processes in human, animals, plants and microorganisms. Advances in synthetic organic chemistry lead to the identification of many key chemical molecules that offered more opportunities to develop novel compounds. Many new drugs emerged by this route, particularly those now being used to treat infections, infestations, cancers, ulcers, and blood pressure conditions. Many drugs were developed through random screening of thousands of chemicals synthesized as dye-stuffs and the like; many others resulted from serendipity (happy chance) arising from sharp-eyed observations of physicians and scientists. Examples of such drugs include sulphonamides, isoniazid, anti-psychotics, anti-histamines and penicillin.

Emergence of the modern pharmaceutical industry is an outcome of all these different activities that developed potent single molecules with highly selective activity for a wide variety of ailments. The drugs produced in many cases improved on nature, viz. a new range of local anaesthetics from cocaine avoided its dangerous effects on blood pressure; chloroquine is much less toxic than quinine. These successes and many more like them resulted in reduced interest in natural products drug discovery and many major drug companies almost neglected such divisions. Work on developing new drugs for the treatment of the world’s major diseases, malaria, trypanosomiasis, filariasis, tuberculosis, schistosomiasis, leshmaniasis and amoebiasis came almost to a standstill. In addition, although botanical medications continued to be produced in every country, the clinical efficacy of these was usually not evaluated and the composition of these complex mixtures was only crudely analysed. Thus, herbal medicines became the domain of ‘old wives’ tales’ and quack medicine, exploitation of the sick, the desperate and the gullible (Bhushan Patwardhan et al., 2004).

**Drug discovery from natural products – The History behind**

Traditional knowledge served as a powerful search engine and most importantly, greatly facilitated intentional, focused and safe natural products research to rediscover the drug discovery process (Bhushan Patwardhan et al., 2004).
Over 200 years ago, a 21-year-old pharmacist’s apprentice named Friedrich Sertürner isolated the first pharmacologically active pure compound from a plant: morphine from opium produced by cut seed pods of the poppy, *Papaver somniferum*. This initiated an era wherein drugs from plants could be purified, studied, and administered in precise dosages which did not vary with the source or age of the material. Pharmaceutical research expanded after the Second World War to include massive screening of microorganisms for new antibiotics because of the discovery of penicillin (Jesse Li and John Vederas, 2009).

A number of scientific investigations have been highlighted the importance and the contribution of many plant families i.e. Asteraceae, Liliaceae, Apocynaceae, Solanaceae, Caesalpinaceae, Rutaceae, Piperaceae, Sapotaceae used as medicinal plants. Medicinal plants play a vital role for the development of new drugs (export and import diverse parts or bioactive compounds in the current market) by (Perumal Samy and Gopal Krishna kone, 2007)

The value of natural products in this regard can be assessed using 3 criteria:

- The rate of introduction of new chemical entities of wide structural diversity, including serving as templates for semisynthetic and total synthetic modification
- The number of diseases treated or prevented by these substances, and
- Their frequency of use in the treatment of disease (Young won chin et al., 2006).

An analysis of the origin of drugs greatly developed between 1981 and 2002 which proved that natural products or natural product derived drugs comprised 28% of all new chemical entities (NCEs) launched in the market. In addition, 24% of these NCEs were synthetic or natural mimic compounds, based on the study of pharmacophores related to natural products. This combined percentage (52% of all NCEs) suggests that natural products are important sources for new drugs and are also good lead compounds suitable for further modification during drug development. The large proportion of natural products in drug discovery has
stemmed from the diverse structures and the intricate carbon skeletons of natural products (Ashok Tiwari and Madhusudana Rao, 2002).

Since secondary metabolites from natural sources have been elaborated within living systems, they are often perceived as showing more “drug-likeness and biological friendliness than totally synthetic molecules,” making them good candidates for further drug development. Scrutiny of medical indications by source of compounds has demonstrated that natural products and related drugs are used to treat 87% of all categorized human diseases, including as antibacterial, anticancer, anti diabetic anticoagulant, antiparasitic, and immunosuppressant agents, among others. There was no introduction of any natural products or related drugs for 7 drug categories (anesthetic, antianginal, anti histamine, anxiolytic, chelator and antidote, diuretic, and hypnotic) during 1981 to 2002. The 90 drugs of that type has became commercially available in the United States or were approved worldwide from 1982 to 2002, ~79% can be traced to a natural product origin.

By 1990, about 80% of drugs were either natural products or analogs inspired by them. Antibiotics (e.g., Penicillin, Tetracycline, Erythromycin), antiparasitcs (e.g., Avermectin), antimalarials (e.g., Quinine, Artemisinin), lipid control agents (e.g., Lovastatin and Analogs), immunosuppressants for organ transplants (e.g., Cyclosporine, Rapamycins) and anticancer drugs (e.g., Taxol, Doxorubicin) revolutionized medicine (Jesse Li and John Vederas, 2009).

Of these some of the below mentioned are plant derived natural products which turned to be drugs (Table 1)
**Table 1 Plant derived ethanotherapeutics and traditional modern medicine**

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Drug</th>
<th>Basic investigation</th>
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<tbody>
<tr>
<td>1.</td>
<td>Codeine, morphine</td>
<td>Opium the latex of <em>Papaver somniferum</em> used by ancient Sumarians, Egyptians and Greeks for the treatment of headaches, arthritis and inducing sleep.</td>
</tr>
<tr>
<td>2</td>
<td>Atropine, hyoscyamine</td>
<td><em>Atropa belladona, Hyoscyamus niger</em> etc., were important drugs in Babylonian folklore.</td>
</tr>
<tr>
<td>3</td>
<td>Ephedrine</td>
<td>Crude drug (astringent yellow) derived from <em>Ephedra sinica</em> had been used by Chinese for respiratory ailments since 2700 BC.</td>
</tr>
<tr>
<td>4</td>
<td>Quinine</td>
<td><em>Cinchona spp</em> were used by Peruvian Indians for the treatment of fevers</td>
</tr>
<tr>
<td>5</td>
<td>Emetine</td>
<td>Brazilian Indians and several others South American tribes used root and rhizomes of <em>Cephaelis spp</em> to induce vomiting and cure dysentery.</td>
</tr>
<tr>
<td>6</td>
<td>Colchicine</td>
<td>Use of Colchicum in the treatment of gout has been known in Europe since 78 AD.</td>
</tr>
<tr>
<td>7</td>
<td>Digoxin</td>
<td>Digitalis leaves were being used in heart therapy in Europe during 18th century</td>
</tr>
</tbody>
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Frequency of use of natural products in the treatment and/or prevention of disease can be measured by the number and/or economic value of prescriptions, from which the extent of preference and/or effectiveness of drugs can be estimated indirectly. According to a study by Grifo and colleagues, 884 representatives with 150 prescription drugs in the United States fell into the category of natural products and related drugs. They were prescribed predominantly as anti-allergy/pulmonary/respiratory agents, analgesics, cardiovascular drugs, and for infectious diseases. Another study found that natural products or related substances accounted for 40%, 24%, and 26%, respectively, of the top 35 worldwide ethical drug sales from 2000, 2001, and 2002 (Young won chin et al., 2006).
Modern technology helps for successful herbal medicine

Natural product substances have historically served as the most significant source of new leads for pharmaceutical development. New approaches to improve and accelerate the joint drug discovery and development process which are expected to take place mainly from innovation in drug target elucidation and lead structure discovery. However, powerful new technologies with the advent of robotics, bioinformatics, high throughput screening (HTS), molecular biology-biotechnology, combinatorial chemistry, in silico (molecular modeling) and other methodologies are revolutionizing drug discovery. Traditional knowledge will serve as a powerful search engine and most importantly, it will greatly facilitate intentional, focused and safe natural products research to rediscover the drug discovery process (Newman et al., 2003).

Currently, there is substantial decline in new drug approvals and impending loss of patent protection for important medicines. However, untapped biological resources, “smart screening” methods, robotic separation with structural analysis, metabolic engineering, and synthetic biology offer exciting technologies for new natural product drug discovery.

Advances in rapid genetic sequencing, coupled with manipulation of biosynthetic pathways, may provide a vast resource for the future discovery of pharmaceutical agents (Jesse Li and John Vederas 2009).

Several interlocking phases of exploration of natural sources can be considered: access to the biological resource, appropriate screening of resources to locate a useful activity, analysis of the structure of the key compound, generation of analogs for optimal activity, and production of the target drug.

Challenges in Drug Discovery from Herbal Plants

In spite of the evident successes of drug discovery from medicinal plants, future endeavors face many challenges. Pharmacognosists, phytochemists, and other natural product scientists will improve the quality and quantity of compounds that
enter the drug development phase to keep pace with other drug discovery efforts (Butler, 2004) and the drug should reach the market.

**Herbal drug development or Ethnopharmacological assessment: A need for Future hope**

Herbal drug development includes various steps, starting from a passport data on raw materials, correct identification, pharmacognostic and chemical quality standardization, safety and preclinical pharmacology, clinical pharmacology and randomized, controlled clinical trials. Addressing standardization is vital and needs broader consideration. Recently, many international authorities and agencies, including the World Health Organization, European Agency for the Evaluation of Medicinal Products and European Scientific Cooperation of Phytomedicine, US Agency for Health Care Policy and Research, European Pharmacopoeia Commission, Department of Indian System of Medicine have started creating new mechanisms to induce and regulate quality control and standardization of botanical medicine. Organic compounds from terrestrial and marine organisms have extensive past and present use in the treatment of many diseases such as diabetes and serve as compounds of interest both in their natural form and as templates for synthetic modification.

For example, the approved drugs such as Exenatide 65, Byetta, is a synthetic analog of exenadin-4, which was originally isolated as a 39 amino acid peptide from the saliva of the Gila monster (*Heloderma suspectum*), and the first insulin mimetic found to improve glycemic control. Subcutaneous exenatide was launched in the United States for use in patients with Type 2 diabetes who have failed in glycemic control by treatment with metformin and/or a sulfonylurea.

In 1991, WHO developed guidelines for the assessment of herbal medicine, and the 6th International Conference of Drug Regulatory Authorities held at Ottawa in the same year ratified the same.
The salient features of WHO guidelines are:

- Quality assessment: Crude plant materials or extract plant preparation and finished product.
- Stability: Shelf life.
- Safety assessment: Documentation of safety based on experience and toxicological studies.
- Assessment of efficacy: Documented evidence of traditional use and activity determination (Animals and human)

In conclusion, opportunities for multidisciplinary research that joins the forces of natural products chemistry, molecular and cellular biology, synthetic and analytical chemistry, biochemistry and pharmacology to exploit the vast diversity of chemical structures and biological activities of natural products. It seemed to be a golden triangle consisting of traditional knowledge, modern medicine and modern science with systems orientation will converge to form an innovative discovery engine for newer, safer, affordable and effective therapies (Butler, 2004). Efforts in these directions are underway to establish pharmaco epidemiological and experimental evidence base for new chemical/molecular entities and development of standardized herbal formulations under the Council for Scientific and Industrial Research (CSIR) and Government of India’s New Millennium Indian technology leadership initiative.

Above all, life expectancy in most of the world has lengthened from about 40 years early in the 20th century to more than 77 years today (Jesse and John 2009) which stands as a result of success of herbal medicine in drug discovery.

**Genesis of the Project**

Diabetes is defined as a state in which homeostasis of carbohydrate and lipid metabolism is improperly regulated by insulin. This results primarily in elevated fasting and postprandial blood glucose levels. If this imbalanced homeostasis does not return to normalcy and continues for a protracted period of time, it leads to hyperglycemia that in due course turns into a syndrome called diabetes mellitus.
Diabetes mellitus is a metabolic disorder characterized by a predisposition to developing significantly raised blood glucose. The first recorded description of diabetes mellitus dates back to the Ebers papyrus in Egypt around 1500 BC. It has been noted in almost all ancient cultures with a tradition of written language such as Vedic, Chinese, Arabic, and Mediterranean. Diabetes is a major public health problem affecting a significant minority of all populations and people with it suffer more ill health and die younger.

The Ebers Papyrus written in approximately 1550 BC provides the earliest documentation about the use of plants in the treatment of conditions associated with diabetes. In India, the early Ayurvedic texts such as the Sushruta Samhita and the Charaka Samhita written in the 4th to 5th century BC describe the use of about 760 and 500 species of medicinal plants, respectively, including those prescribed for conditions such as glycosuria, polyphagia, and polyuria associated with diabetes (Inder et al., 2005). In China, Ben Jing, written in about 104 B.C., contains detailed descriptions of 252 species with reference to those used to treat diabetes. It is easier to track the traditional and modern uses of species in the treatment of diabetes in cultures with a strong written culture like those in India, China, and the Middle East than it is in South America and Africa, where much less documentation is available to the researcher.

Despite their long tradition of use in most parts of the world, very few of these species have been exposed to modern, large-scale, clinical-type trials to test their efficacy. Some species used in the ancient civilizations of India and China have been used for hundreds of years and some people would suggest that they are effective. However, it is clear that more research needs to be undertaken on these species because, in most cases, the active compounds and their mode of action still remain unclear. For example, hundreds of species are used in Chinese medicine for treating diabetes, but only seven multiple-species antidiabetic products have been approved for clinical use in China (Shaodang Chen et al., 2013).
It was thought worthwhile to explore extensively the potential usage of medicinal plants with traditional claims to be having activity against diabetes and subject them to systematic phytochemical and pharmacological studies. Diabetes mellitus is a metabolic disorder, which also occurs as a outcome of obesity, hyperlipidemia, nephropathy, neuropathy, retinopathy and Non alcoholic fatty liver disease (NAFLD). In all these, NAFLD is still remaining untreated due to lack of medicines. Hence we would be giving a detail focus on diabetes associated with NAFLD in upcoming chapters.