The Antiseptic

Estd.1904

Indexed in IndMED

A MONTHLY JOURNAL OF MEDICINE AND SURGERY

Email: admin@theantiseptic.in

www.theantiseptic.in

Vol. 113 • No. 12 DECEMBER 2016 ISSN 003-5998 • ₹ 100

Nutraceuticals-Old wine in new bottle

SANJAY AGRAWAL

Introduction

With the increase in lifestyle diseases, nutraceuticals have emerged not only as a necessity but also as an alternative for prevention and treatment for various chronic diseases. In 2010, the US nutraceutical market was US $ 50.4 Billion making it the largest nutraceutical market in the world. European nutraceutical industry was valued at US $ 35 Billion and Indian market US $ 2 Billion in 2010. The dietary supplements segment in the US was growing at roughly 3.1 percent while the functional food and beverages segment was growing at 5.6 percent[1-2]. In Australia, vitamins and dietary supplements grew by 7% in 2011 to be valued at USD$1.43 billion. Health and wellness trends in Australian society have encouraged consumers to take greater care of their health and maintain optimal nutritional condition. This trend has been coupled with increased awareness and marketing activities conducted by the dietary supplement industry promoting that some grocery food products consumed in Australia do not provide all the necessary vitamins and minerals. Companies in the US and Europe are looking to diversify these products by leaning more and more towards natural nutraceutical ingredients and believe that product and ingredient innovation is the way forward for the nutraceutical industry. There is also a trend to incorporate traditional herbal ingredients (usually Ayurvedic) into the nutraceutical portfolio. Key example is the Chyawanprash supplements market in India, which stood at US $74.5 Million in 2010.

There is confusion over the terms nutraceuticals, dietary supplements, food supplements and pharmaceuticals[3]. The term 'nutraceutical' was coined from nutrition and pharmaceutical in 1989 by Stephen Defelice as any substance that is a food or a part of food and provides medical or health benefits, including the prevention and treatment of disease. Such products may range from isolated nutrients, dietary supplements and specific diets to genetically engineered designer foods and herbal products. A dietary supplement is a product consumed through mouth that contains ingredients intended to provide health ingredients such as vitamins, minerals, enzymes, etc. They can also be herbal extracts or concentrates and may be found in many forms such as tablets, capsules, liquids or powders. Functional foods are also foods that have components or ingredients added to give it a specific medical or physiological benefit in addition to a purely nutritional effect. In India, the practice of 'Ayurveda' lays emphasis on food and the Ayurvedic preparations are herbal products with health benefits and they are classified as pharmaceuticals. Thus there exists a very thin margin between 'Nutraceuticals and Pharmaceuticals; Dietary Supplements and Functional Foods[4]. Hippocrates, the father of Western Medicine highlighted, around 2000 year ago quoted 'Let food be your medicine and medicine be your food'. The Indians, Egyptians, Chinese, and Sumerians are just a few civilizations that have used food as medicine. In contrast to the natural herbs, spices and folk medicines have been used for centuries throughout Asia and the nutraceutical industry has grown alongside the expansion and exploration of modern technology. In fact many of the drugs have been derived after being isolated from the plant like digoxin, aspirin, metformin, etc. Thus the growth of 'Nutraceuticals' appears to be like presenting old wine in new bottle.

Differences between Nutraceuticals and Pharmaceuticals

Pharmaceuticals are normally considered as chemicals that affects physiological functions. While the chemicals derived from plants, or proteins and vaccines derived from animal sources may have distinction of being called as nutraceuticals. The major difference one may claim is that pharmaceuticals are designed specifically for medical use under a physician's supervision, and are subject to Food and Drugs Administration approval. Health supplements (including nutraceutics, food or dietary supplements) may not need medical supervision, or Food and Drugs Control Administration approval. Canada divides nutraceuticals between 'functional food' and 'nutraceutical health products'. A functional food is similar in appearance to (or may be) a conventional food that is consumed as part of a usual diet, and is demonstrated to have physiological benefits and/or reduce the risk of chronic disease beyond basic nutritional functions, i.e. they contain bioactive compounds. A natural health product is a product isolated or purified from foods that is generally sold in medicinal

Dr. Sanjay Agrawal,
Leading Pharmaceutical Consultant and Inventor,
Editor-in Chief of IJMToday
6/146, Malviya Nagar, Jaipur-302017, Rajasthan.

Specially Contributed to "The Antiseptic"
Vol. 113 No. 12 & P : 08 - 11

forms not usually associated with foods. A natural health product is demonstrated to have a physiological benefit or provide protection against chronic disease.

There has been a debate all over the world on the regulation of traditional medicines from other systems of medicines like 'Ayurved, Unani, Siddha and Homeopathy, Chinese', all of which have herbal or natural source of origin. In USA, dietary supplements do not require to be approved by the USFDA before marketing, but companies must register their manufacturing facilities with the FDA[5]. In Japan, all functional foods are required to be present in their naturally-occurring form and not capsule, tablet, or powder and expected to be consumed in the diet regulating biological process with a hope to prevent or control diseases[6]. In Europe, as such there is no regulatory framework for 'functional foods' or 'nutraceuticals'. The rules to be applied are however, numerous and depend on the nature of the food stuff. The rules of the General Food Law Regulations, including responsibility for food safety, traceability, recall and notifications, definitely are applicable to all foods. In Australia there is a separate 'Complementary Healthcare Council of Australia' for nutraceuticals and it is a part of the Therapeutic Goods Administration regulating medicines and medical devices.

In general, pharmaceuticals as per the rules of FDA need a prescription or recommendation from a certified medical practitioner for purchase. The choice of a health supplements is up to the individual. Health supplements are sold without restrictions at health food stores, grocery stores, drug stores, national discount chains, mail-order and Internet. It is claimed that pharmaceuticals works on symptoms on the particular part or whole body, giving immediate effect or results at the cost of side effects, whereas, nutraceuticals are claimed to work on the root cause, not on symptoms and take their natural time as the products are natural based.

Going back to the era of Ancient systems of the Medicines

Utilization of the ancient knowledge of Ayurveda with other traditional practices of medicine such that it is scientifically acceptable has remained a great challenge. In spite of large amount of money spent by the Governmental funding agencies and pharmaceutical companies for research on herbal research, the return on investment is significantly less than anticipated. Conventional drug development is slow and expensive, taking 12 to 15 years and $1500m $1800m to develop a new drug. Despite these massive and very expensive efforts worldwide, the industry R & D pipeline is relatively dry and the attrition rate of new drug entities is very high. The number of new drug approvals is on decline. The life of a new drug in the market is short. There have been several safety problems with respect to new drugs. Despite very stringent and demanding regulatory processes, there has been several post approval or post marketing withdrawals of new drugs including some of the major blockbusters.

Recently, some of the leading visionaries and scientists have promoted the concept of 'Reverse Pharmacology' in India for the research strategies in Ayurvedic drugs[7]. The process of development of natural medicine through Reverse Pharmacology approach has provided a number of phytoconstituents leads and hits. As a result 'Reverse Pharmacology' proved successful in development of formulations of 1) Mucuna pruriens for Parkinson's disease 2) Arogyawardhani, the Picrorrhiza kurroa for hepatitis; 3) Commiphora mukul in Phase I trial in volunteers; 4) Rubia cordifolia for eczema; 5) Saraca indica for dysfunctional uterine bleeding; 6) Curcuma longa for cancer prevention and urticaria; 7) Commiphora mukul for rheumatoid arthritis; 8) Panchvalkal (5 plants combination) for burns and infected wounds; and 9) Volatile essential oils of spices for antimicrobial activity and many more. A systematic phytopharmacology research correlating kinetics and the dynamics of the natural products is now been adequately pursued[8]. The strategy of Reverse Pharmacology seems to have been accepted internationally. Willcox et al[9] have reviewed the development of anti-malarial drugs using Reverse Pharmacology approach from herbal sources.

Modern Approach for the New Drug Discovery from Herbals

In recent years Translational research has appeared as a paradigm for research alternatives to the dichotomy of basic research and applied research. It is often applied in the domain of medicine but has more general applicability, as a distinct research approach[9]. It is also applied in practice with the approaches of participative science and participative action. Translational Research can be seen as the key missing component. Translational research has proven to be a powerful process that drives the clinical research engine. The extensive research work carried out in herbal drugs in India has resulted in a large number of phytoconstituents. It is therefore, essential that it must be translated into practical applications. Translational research on single formulation offers a great scope for phytopharmacology.

The active phytoconstituents are useful not only for quality control parameters but also to provide a lead for the development of novel therapeutic agents based on their dynamic and kinetic profile. The target's affinity alone does not create a new drug. Sufficient bioavailability and biological half life, negligible side effects and a lack of toxicity are mandatory properties. Over the period, "Small molecule" natural products (SMNPs) have been proved as a source of most successful development of new drugs. The naturally occurring yohimbine alkaloid reserpine, as an antihypertensive and tranquilizing agent and galanthamine, originally isolated from Galanthus nivalis approved for the treatment of Alzheimer's disease are examples of successful natural products. Almost 74% of anticancer agents approved between 1981 and 2002 were natural products, natural product-derived, or natural product inspired. Thus, a sizable phytopharmacology assured a translational success. Another example is of the statins, the inhibitors of the HMG CoA reductase enzyme. They are one of the leading groups of compounds widely prescribed as anti-hypercholesteremic agents, with long-term cardiovascular benefits. Mevastatin and lovastatin are natural products isolated from Penicillium brevicompactin and Aspergillus terreus, respectively. Atorvastatin is one of the most commercially successful drugs ever used. However, the development of atorvastatin was an inspiration from the parent compounds lovastatin and mevastatin. Despite the great successes already achieved in natural products chemistry and drug development, we in India have barely begun to tap the potential of our molecular diversity.

There are several reasons why the interest in finding bioactive natural products has generally declined at several major pharmaceutical companies. The reasons quoted are that the research in this field is time-consuming, highly complex and often ineffective. Further there is a problem of patents and protection of Intellectual Property rights (IPR). On one side Ayurvedic herbal products offer a huge potential, growing at a considerably faster rate than allopathic drugs, on other side, the patent laws are not well-structured in this segment. To prevent multinational corporations from 'bio-piracy' and patenting traditional medicinal herbs, India has declared that about 200,000 traditional treatments are 'public property'. The TRIPs agreement made IP an international obligation and has extended IP claims to traditional knowledge also. Article 27 of TRIPS mandates patents to be made available for inventions, whether products or processes, in all fields of 'emphasis added technology' provided the said inventions are new, inventive and capable of industrial application. This includes the purification or characterization of active drugs and/or the development or the modification of molecules based on traditional knowledge.

Isolation, purification and structure elucidation of a new chemical entity from a medicinal plant; discovery and characterization of novel, unobvious and useful biological properties, synthesis of useful new analogues or derivatives, and formulation for a combination of herbal medicine in new dosage form with higher therapeutic efficacy are patent eligible subject matters. Further, new indications, extraction and separation of active ingredients from herbal drugs used in the production of pharmaceutical substances, preparation and processing techniques of standardized extracts are also patentable.

Harnessing potential IP is necessary for the economic development of a country. Integration of IP aspects with issues related to benefit sharing is important for adequate market development[11]. The protection and maintenance of IPR on drugs based on traditional knowledge has gained momentum in many developing nations in the last decade. In 2001, there were more than 50,000 patent publications on traditional medicine throughout the world. China had approximately 20,000 Traditional Chinese Medicine (TCM) patent publications by the end of 2002. There has been an increasing trend for filing the patents by Indian research institutes and companies on herbal drugs. The Indian herbal drug sector is beginning to be an important economic indicator for the nation. It has been observed that there is a gradual increase in patent filing through the years.

In the light of withdrawals of several major blockbuster drugs, there is a need for a new paradigm in drug discovery and development. Method of rational drug design involves the design and synthesis of compounds based on the known structure of either a specific target or one of its natural ligands. A more rational and economic search for new lead structures from nature must therefore be a priority in order to overcome these problems. It is desirable that the knowledge of phytoconstituents, leads and hits identified especially with the reverse pharmacology approach may be extended for the development of new drug entities on the fast track through translational phytopharmacology. Traditionally the new drug discovery starts with identification of new "drug targets" i.e. investigation of naturally existing cellular or

molecular structure involved in the pathology of a disease where a drug-in-development is meant to act on. There is a plethora of drug targets available especially with the publication of Human Genome project. Contrastingly, in the old times, even up to mid 20th century, herbal drug discovery never employed the drug targets studies. Based on the documented evidence of efficacy of herbal drugs, documented clinical studies through reverse pharmacology approach, it is possible that instead of identifying new targets or validation of new target, they should be utilized for the development of new drug entities. Under the translational phytopharmacology a 'Hit' will be a primary active compound with non-promiscuous binding behavior, exceeding a certain value of threshold in a given assay. It can be a compound isolated from a plant and characterized for chemical structure, having a possibility of being specifically present in that plant or in other plants showing similar activity or the chemical structure possesses characteristics of compounds having similar activity. The Hits can be re-tested using different pharmacological and biochemical/ biotechnological tools followed by dose response curve generation, synthesis feasibility and intellectual property evaluation to confirm 'Hit' compounds. The structures are quickly checked in specialized databases to define patentability. One can do 'Hit ranking and clustering': Confirmed hit compounds are then taken for molecular modeling, (QSAR and docking studies). Analogs can be quickly selected. Medicinal chemists will also start synthesizing related compounds using different methods such as combinatorial chemistry, high-throughput chemistry or more classical organic chemistry synthesis. This phase can be followed by Lead optimization phase where in lead compounds, new analogs with improved potency, are synthesized and physiochemical/metabolic properties suggestive of reasonable in vivo pharmacokinetics is investigated.

With the above mentioned methodology, we have been making an attempts to take herbal medicines like ginger (Zingiber officinale), Indian gooseberry (Amla Embelica officinale) and Enicostemma littorale from nutraceuticals to pharmaceuticals.

Conclusions:

Although, there is a growing market for nutraceuticals worldwide, there are regulatory concerns for the safety and efficacy for the products. This situation is not different than what existed and is currently going on for the pharmaceuticals. The origin of drugs by and large from herbal sources, as the history reveals, cannot be undermined. With the increase in new clinical applications nutraceuticals are likely to fall within the novel foods and ingredients regulations but their purity, dosage requirements and clinical consequences exceed those of most healthy foods. Further, the fact the effects obtained from nutraceuticals are due to complex mixtures or due to one or more individual substrates are making the situation more complex. Thus, nutraceuticals will play an important role in future disease management. However. Their success will be governed by control of purity, safety and efficacy without inhibiting innovation. The application of pharmaceutical standards, standardization of formulations, dosage forms and production controls are likely to be a challenge and present a threat that could paralyze the industry.

REFERENCES:

1. Indian Nutraceuticals Market Forecast to 2017, December 2012, Indian Business News Agency, http://www.researchandmarkets.com/reports/2359101/
2. Nutraceuticals: A Global Strategic Business Report, Global Industry Analysts, July 2012
3. De Felice L Stephen. The nutraceutical revolution, its impact on food industry. Tr Food Sci Tech 1995: 6; 59-61
4. Adelaja Adesoji O, Schilling Brian J. Nutraceutical:blurring the line between food and drugs in the twenty-first century. The Magazine of Food, Farm and Resource Issues 1999: 14; 35-40.
5. http://www.fda.gov/food/dietarysupplements/ucm109764.htm Accessed April 3. 2014
6. Patel D, Dufour Y, Domigan N. Functional Food and Nutraceutical Registration Process in Japan and China: Similarities and Differences. J Pharm Pharmaceut Sci 2008: 11(4); 1-11.
7. Patwardhan B,.Vaidya ADB, Chorghade M, Joshi SP. Reverse Pharmacology and Systems Approaches for Drug Discovery and Development. Current Bioactive Compounds 2008: 4; 1-12.
8. Patwardhan B,.Vaidya ADB, Chorghade M. Ayurveda and natural products drug discovery. Current Science, 2004: 86; 789-99.
9. Anger GJ Piquette-Miller M. Translational Pharmacology: Harnessing Increased Specialization of Research Within the Basic Biological Sciences. Clini Pharmac. Therapeu.2008: 83; 797-801
10. Willcox ML, Graz G, Falquet J Diakite C, Giani S, Diallo D. A "reverse pharmacology" approach for developing an anti-malarial phytomedicine. Malaria Journal 2011: 10; S8
11. Soejartoa DD, Fonga HS, Tana GT, et al Ethnobotany/ethnopharmacology and mass bioprospecting: J Ethnopharm 2005: 100 ;15–22.

The smooth muscle relaxant drugs tamsulosin (an α-adrenoceptor antagonist) and nifedipine (a calcium channel stabilizer) are possible agents, their use being termed medical expulsive therapy (MET).- **The Lancet**