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The Nutraceutical Revolution - Revisited

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Abstract:
Some 80% of the world's populations still rely upon plants for primary health care; even today in Western medicine, and despite progress in synthetic chemistry, some 25% of prescription medicines are still derived either directly or indirectly from plants or food. Nutraceuticals is a food or part of a food that allegedly provides medicinal or health benefits, including the prevention and treatment of disease. The nutraceutical revolution is in full Swing and will dramatically change the nature of the food industry. It will lead us into a new era of medicine and health, in which a food industry will become research-oriented similar to pharmaceutical industry. Novel developments in plant biotechnology and molecular biology add further dimensions to the use of plants in the production of Phytochemicalsas therapeutic agents."Phytochemicals" means plant chemicals. In spite of the advances of synthetic chemistry and its contribution to pharmaceuticals discovery and development during the later part of the 20thcentury, the use of herbal remedies and plant-derived drugs remains substantial. Ayurveda, the traditional Indian medicine (TIM) and traditional Chinese medicine (TCM) remain the most ancient yet living traditions. The resurgence of TIM and TCM and growing awareness of health-care world over has resulted in increased use of nutraceuticals. The use of nutraceuticals, as an attempt to accomplish desirable therapeutic outcomes with reduced side effects, as compared with other therapeutic agents has met with great monetary success. In this article a detailed study was carried out to understand nutraceuticals and its future.

Key words:
Nutraceuticals, Phytochemistry, Ayurveda, Traditional Indian Medicine.

Introduction:
The nutraceutical revolution is in full Swing and will dramatically change the nature of the food industry. It will lead us into a new era of medicine and health, in which a food industry will become research-oriented similar to pharmaceutical industry.

The revolution began in the early 1980s, when the actual or potential clinical benefits of calcium, fiber and fish oil were supported by clinical studies published in distinguished medical journals, and when physicians began to educate their colleagues and consumers about thesesubstances via the mass media. A continuous stream of published clinical studies followed, defining the potential benefits of a growing range of products on a rapidly expanding array of specific disease processes. Examples include the use of β-carotene to prevent certain types of lung cancer, niacin to prevent recurrent heart attacks, pyridoxine to treat and prevent depression, vitamin A to treat measles, magnesium to treat hypertension, garlic to reduce atherosclerosis, fish oil for hypertension, cranberry juice to prevent urinary tractinfections, antioxidants to reduce damage from heartattack and countless others. For the first time physicians - convinced by the published clinical data-joined consumers in their broad belief that foods or parts of food have medical value. This marked the entry of nutraceuticals into the mainstream of clinical practice, giving rise to an increasingly urgent need torationalize the Scientific and medical development of these products, their commercial availability and thecommunication of information about them to the primarydual audience of physicians and consumers. Nutritionists, armed with more clinical as well as preclinical data, will play a more critical role in bringing about an effective physician-consumer interface. The promise of nutraceuticals, should be considered in two ways - potential nutraceuticals and established nutraceuticals. A potential nutraceutical is one that holds a promise of a particular health or medical benefit; such a potential nutraceutical only becomes an established one after there are sufficient clinical data to demonstrate such a benefit. Thus, folic acid was a potential nutraceutical until sufficient clinical evidence for its role in the prevention of neural tube defects was generated to make it an established one, whereas ginseng tea remains a potential nutraceutical because of a lack of sufficient clinical evidence for anyindications (l). The food industry is presently comfortable with basic research but almost totally ignorant of the clinical research process.

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The basic ingredients of any innovative or discovery processes are: first, having an idea and second, testing it. The innovative process in assessing a nutraceutical, however, is considerable more difficult. It involves the identification of the nutraceutical substance (the idea), and its clinical evaluation (testing it). In order to join the nutraceutical revolution, the food industry must take a giant step into an unknown area - the clinical evaluation of its products formedical and health benefits and look for plant kingdom as agreat treasure.

1. Treasure hunt in plant kingdom

Plants have long been a source of therapeutic agents used by man. Some 80% of the world's populations still rely upon plants for primary health care; even today in Western medicine, and despite progress in synthetic chemistry, some 25% of prescription medicines are still derived either directly or indirectly from plants. The use of plants in medicines ranges from crude preparations or extracts, to refined extracts and single molecular species. In terms of categories of use this encompasses food supplements, herbal medicines, botanical drugs and prescription medicines. Increased interest in plants as a source of novel pharmacophores recognizes their chemical diversity and versatility, not matched by synthetic chemistry libraries. In spite of the surge of activity in synthetic chemistry over the last 30 years or so, almost half the some 850 small moleculesintroduced as drugs were derived from plant sources. Over 100 small molecules derived either directly or indirectly from plants are currently at some point in the clinical trials process. It is argued that the present use of plant derived drugs and remedies only scratches the surface of what is a major reservoir of untapped potential, the level of biological and chemical diversity possessed by plants having much to offer in the drive fornovel therapeutic agents in the fight against disease.

2. Novel development

Novel developments in plant biotechnology and molecular biology add further dimensions to the use ofplants in the production of therapeutic agents. Society ofChemical Industry for Millennia has utilized theproperties of plants not just for food and shelter but alsofor health and well-being. Herbal extracts andpreparations, for a long time the mainstay of the healer and physician's 'tool kit', still comprise the major part of primary health care for some 75-90% of the world's rural population; even in relation to Western medicine, plants still provide the basic raw materials for some 25% ofprescription drugs (2-3).

After the ascendancy ofsynthetic chemistry over natural product drug discovery and development during the latter part of the 20th century there are signs of a reawakening of interest in the sector, with the pharmaceutical industry once again beginning to look at the plant kingdom as a source of chemical scaffolds for drug synthesis, often coupled tohighly innovative molecular approaches seen in many ofthe small biopharmaceutical companies (4). Coupled tothe sometimes stunning advances in molecular biology and genetic engineering, plants are also increasingly seenas potential "factories' for the production of a wide rangeof high-value therapeutic agents. It is the purpose of this chapter something of the nature of these developments and thepossible renaissance of the triangle: plants, medicines and human beings.

3. Plants to Phytochemicals

"Phytochemicals" means plant chemicals. Plantshave the ability to synthesize mixtures of structurally diverse bioactive compounds with multiple and mutually potential therapeutic effects. The plants have the capacity ofmanufacturing the secondary products. Phytochemicals withantioxidant properties tend to be brightly colored becausethey contain chromophores, a series of alternating single-bonded and double-bonded carbons. Isoprene is often thebuilding block of such units. The darkest green vegetablescontain the most chlorophyll, and vegetables with the mostchlorophyll require the most antioxidants. Green will maskthe other colors, when othercolored antioxidantPhytochemicals are present. Hundreds of Phytochemicals arecurrently being studied. Many are believed to have a majorpositive impact on human health (5). Important plantsecondary metabolites have been isolated over a period oftime from natural Sources. The phytochemical may belong tothe following categories: terpenoids, phenolic compounds, alkaloids, glycosides, carbohydrates, lipids, proteins, nucleic acids, etc. Some of the phytochemical from the plants are listed in Table 1 (5).

4. Herbs through ages

50000 years ago the body of a Neanderthal man was laid to rest in a cave (the Shanidar Cave) on the border of northern Iraq and Iran. Around the body were placed eight different species of herbs, all of which we now know to possess medicinal properties. Of those eight herbs, seven are still found growing in the same locality today, and one of them, Ephedra, gave us the potent bronchodilator "ephedrine'.

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Today, this medicine isproduced through chemical synthesis. The discovery of the grave with its herbal treasures has provided one of the earliest indications of the importance of plants to man as a source of therapeutic remedies. Down the millennia the use of a wide variety of plants by humans to satisfy a range of therapeutic needs grew. Recorded history provides reference to the use of medicinal plants from many parts of the world, as far apart as China, Greece, India, Rome and the Middle East. The use of medicinal plants was particularly well developed in China. One of the earliest known Chinese herbalists, Shen Nung, who lived around 2800 BC,described some 350 medicinal or herbal plants.

Table 1: List of some of the Phytochemicals with the name of the plants

Class	Compound	Scientific Name
Alkaloid	Piperine	Piper nigrum
Alkaloid	Cocaine	Elythroxylum coca
Alkaloid	Colchicines	Gloriosa superba
Alkaloid	Berberine, hydrastine	Hydrastis canadensis
Complex mixture	Latex	Aloe vera
Flavonoid	Catechin	Camellia sinensis
Monosaccharide	Fructose	Vaccinium spp.
Organic acid	b-Resercyclic acid	Cannabis sativa
Polyphenol	Tannin	Eucalyptus globules
Phenolics	Gallic acid	Lawsonia inermis
Phenolic acid	Lupulone, humulone	Humulus lupulus
Sulfoxide	Allicin, ajoene	Allium sativum
Terpenoid	Essential oil	Aegle marmelos
Terpenoids	Essential oils	Ocimum basilicum
Terpenoids	Essential oils	Laurus nobilis
Terpenoid	Terebinthone	Schinus terebinthifolius
Terpenoid	Essential oil	Barosma setulina
Terpenoid	Essential oil	Anethum graveolens
Terpenoid	Asiatocoside	Celltella asiatica
Terpene	Trichorabdal A	Rabdosia trichocarpa
Thinoin	Fabatin	Vcia faba

Sumerian ideograms from around 2500 BC provide a detailed account of a wide range of herbs used for their medicinal properties, and are noteworthy for mention of the opium poppy, still the source of one of the most powerful analgesics in the pharmaceutical armamentarium today, but at that time called the 'plant of joy', indicating perhaps rather different use. A particularly detailed and extensive record was produced under the direction of Hammurabi, King of Babylonia from 1728 to 1686 B.C. known as the Code of Hammurabi.

The records contained many herbal remedies that we recognize today, and are remarkable for their details. That there was an early trade in medicinal plants is to be seen from the descriptions of medicinal plants from Syria in the temples of Karnak in Egypt dating from around 1500 B.C. Descriptions of the use of medicinal plants inIndia were often to be found alongside poetry and verse,particularly in the Vedas of 4500 BC. There is evidence of extensive use of medicinal plants by the indigenouspeoples of North and South America. Europe also had a foundation of Celtic herbal medicine, largely lost in the mists of time. Throughout the Middle Ages and well into the 19thcentury within Europe, as in other parts of the world, herbal medicines provided the mainstay of primary health care. Single-entity prescription medicines which dominate Western primary health care today began to appear in the later part of the 18" century. While the 19th century marked a complete transition from complexmixtures and extracts to single-substance prescriptionmedicines. Plant extracts and botanically derived drugs continued to provide the mainstay of the generalphysician's armamentarium well into the 20 century (6).

5. A forgotten chapter

The transition from herbal preparations to defined, single chemical entity prescription medicines is well illustrated and marked by the discovery of the cardiac glycoside digitalis from the foxglove, Digitalis purpurea. The use of the foxglove in the British Isles and elsewhere goes back well before recorded history, to Celtic times, perhaps 2000 years ago and possibly derived from earlier Druidical influence. The earliest known detailed written record of use goes back to the Physicians of Myddfai, herbal doctors who lived in South Wales as we know it today and who certainly administered to the Princes of Wales for well over a thousand years. Sometime in the 12" or 13" century these Physicians of Myddfai were persuaded to write down much of their herbal medicine knowledge.

These ancient records were translated into English during the 1860s and are available for all to see, from the original Welsh texts to the English translations. In those early records or "pharmacopoeia' foxglove is described as being used for paralysis or hemiplegia. The 'modem" story is to be picked up from about 1770, when a young Edinburgh-trained physician named William Wittering, then practising in Birmingham, fell in love with and married one of his patients who he was treatingfor dropsy, a painful circulatory condition.

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His wife told him of an old woman who lived in the county ofShropshire, close to where the Physicians of Myddfai hadbeen active, and who used herbs to treat the condition. He visited the old herbalist, found that she used an extract of foxglove and gained the recipe from her. Wittering then set about refining the preparation, finding that there were great variations in the content of the active component in the foxglove tissues and that great care was needed to make a standard preparation which was not only efficacious but also possessed a non-lethal dose level, extracts of foxglove being quite toxic to humans if not carefully controlled and administered. (It is often forgotten that plants produce some of the most potent toxins known to man, ranking with those such as snake venoms in potency and speed of action. Following Wittering's work and that of others the active components of foxglove, digitoxin (β -methyl form) and digoxin were isolated and have since been used as the primary treatment for dropsy and a range of heart conditions.Mode of action is exclusively through action on cardiacmuscle.

From Wittering's time and the identification of β methyl digitoxin as the prime active constituent offoxglove, identification of the active component of anumber of other medicinal herbs followed, including forexample ephedrine from Ehpedim, the analgesicacetylsalicylic acid (aspirin) from willow, and the potentanalgesics morphine and codeine from the opium poppy,Papaver somniferum, Advances in synthetic chemistry were to take the process one stage further with the use ofchemical synthesis to produce such drugs rather than have them derived from plant material. Such an approachavoided the vagaries of supply and quality and has nowbeen applied to a number of previously plant-derived drugs (6).

6. 20th century scenario

In spite of the advances of synthetic chemistry and its contribution to pharmaceuticals discovery and development during the later part of the 20thcentury, the use of herbal remedies and plant-derived drugs remains substantial. According to recent trade statistics, it is apparently growing. From a classical study in the 1970s Farnsworth and his colleagues estimated that some25% of all prescription medicines in the USA were plant derived at some level. Similar figures have also beenmentioned anecdotally in relation to use in the EuropeanUnion (3). In the beginning of 21stcentury the WHO estimated that 11% of basic and essential drugs were 'exclusively' of flowering plant origin.

This corresponds to 28 major drugs. Other recent estimates suggest that 89-120 drugs are derived from plants for use in Western nations, this in turn would correspond to roughly 5-10%of the total (7). The market in plant-derived drugs was estimated to be US $20 billion in 2002, with a roughly equal split between prescription medicines and over-the-counter (OTC) preparations. An indication of the current levels of growth being achieved for key groups of plant-derived chemical families which contribute the major part of thedrugs (please see Table 1). The major increase seen in the use of terpenoids is probably largely due to increased use of taxol, a majoranti cancer agent, and its derivatives. Such increases as outlined in Table 2 are also to be seen inthe trade levels in the raw materials for herbal medicines.

Table 2: World trade figures for key plant-based drug components (billions of US dollars)(9)

Chemical family	1997	2002
Terpenoids	7.6	12.4
Glycosides	7.3	9.2
Alkaloids	3.6	4.0

The interest in natural products as a source of novel pharmacologically active pharmacophores was generated during the two decades from 1960 to 1980 (7). Following that period the balance swung heavily towards synthetic chemistry libraries, which provided many of the major drugs entering prescription use in the later part of the 20th century (4). A further factor was also the impact of high-throughput screening, together with the then perceived promise of combinatorial chemistry. In spite of massive investment by the pharmaceutical industry in these new technologies, the numbers of new drug leads anticipated are not there to be seen, and indeed there is increasing concern throughout the industry at the lack of druggable leads in company pipelines. Against this background there is evidence of a gradually growing renewal of interest in natural products and in particular plant sources. Such renewal of interestis based on four overlapping factors:

» Indications that large pharmaceutical companies are showing interest in natural products as a source of chemical scaffolds and pharmacophore leads as their synthetic pipelines become restricted and the promise of combinatorial chemistry appears less than once anticipated (4).

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» Increased consumer interest in herbal preparations fascination with 'traditional' medicine.
» A coming together, to a degree, of Eastern and Western medical traditions, and a recognition on the part of Western pharmaceutical companies. The traditional medicines of China, India, and elsewhere have much to offer to Western medicine through identification of novel therapeutic agents which have been used for millennia.
» Vastly improved technology relating to extraction systems for plant material, chemical characterization, rationalization and standardization of complex plant mixtures, coupled with improved quality, availability and reproducibility/consistency of source material (6).

7. Resurgence of Ayurveda

Ayurveda, the traditional Indian medicine (TIM) and traditional Chinese medicine (TCM) remain the most ancient yet living traditions. These are the two 'great traditions' with sound philosophical, experiential and experimental basis. Increased side effects, lack of curative treatment for several chronic diseases, high cost of new drugs, microbial resistance and emerging diseases are some reasons for renewed public interest in complementary and alternativemedicines.

» Use of indigenous drugs of natural origin forms a major part of alternative therapies
» More than 1500 herbals are sold as dietary supplements or ethnic traditional medicines.
» Pharmaceutical companies have renewed their strategies in favor of natural product drug development and discovery.
» In Europe, Analyticon Discovery has stressed on drug discovery based on natural product chemistry.
» In the Asia-Pacific region, MerLion Pharmaceuticals in Singapore has comprehensive structures and capabilities necessary for natural product based drug discovery.
» China has successfully promoted its own therapies over the globe with a science-based approach.
» Growing popularity of TCM can be evidenced by the rapid increase in number of licensed Chinese medicine providers in the United States.
» The Chinese government has pledged to create several export-oriented TCM giants in the coming years.
» Continuous efforts in promotion of the indigenous therapies by China have put TCM in a commendable position.
» Global acceptance of Ayurveda is gearing up and there has been a steep rise in the demand for medicinal plants from India.
» The Pharmaceutical Research and Development Committee report of Ministry of Chemicals, Government of India also underscores the importance of traditional knowledge.
» The increasing use of traditional therapies demands more scientifically sound evidence for the principles behind therapies and for effectiveness of medicines.
» Recent advancements in the analytical and biological sciences, along with innovations in genomics andproteomics can play an important role in validation ofthese therapies.
» Western scientific community views traditionalmedicines cautiously and stress the concerns related toresearch, development and quality (7).

8. Nutraceuticals - the only alternative

The resurgence of TIM and TCM and growing awareness of health-care world over has resulted inincreased use of nutraceuticals. The use of nutraceuticals, as an attempt to accomplish desirable therapeutic outcomes with reduced side effects, as compared with other therapeutic agents has met with great monetary success. The preference for the discovery and production of nutraceuticals over Pharmaceuticals is well seen in pharmaceutical and biotechnology companies. Some of thepharmaceutical and biotechnology companies, whichcommit major resources to the discovery of nutraceuticals include Monsanto (St Louis, MO), American Home Products (Madison, NJ), DuPont (Wilmington, DE), Abbott Laboratories (Abbott Park, IL), Warner-Lambert (Morris Plains, NJ), Johnson & Johnson (New Brunswick, NJ), Novartis (Basel, Switzerland), Metabolex (Hay-ward, CA), Genzyme Transgenic, PPL Therapeutics, Interneuron(Lexington, KY), Sami Labs (Bangalore, India).

9. Global Markets, Regulations and Acceptance

The global pharmaceutical market was worth US $550 billion in 2004. The herbal industry shares about US $62 billion with good growth potential. The World Bank reports trade in medicinal plants, botanical drug products andraw materials is growing at an annual growth rate between 5and 15% (8). Within the European community, botanical medicine represents an important share of the pharmaceutical market (9) The nutraceuticals sector is also growing rapidly. In 2001, US $17.8 billion was spent in the United States ondietary supplements, US $4.2 billion of it for botanicalremedies (10).

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In India the value of botanicals related trade isabout US $10 billion per annum with annual export of US1.1 billion (ll) while, China's annual herbal drugproduction is worth US 48 billion with export of US $3.6billion (12). Presently, the United States is the largest market for Indian botanical products accounting for about 50% ofthe total exports. Japan, Hong Kong, Korea and Singaporeare the major importer of TCM taking 66% share of China'sbotanical drugs export. Globally, there have been concerted efforts tomonitor quality and regulate the growing business of herbaldrugs and traditional medicine. Health authorities andgovernments of various nations have taken an active interestin providing standardized botanical medications. UnitedStates Congress has fuelled rapid growth in the nutraceuticals market with passage of the Dietary Supplement Health andEducation Act in 1994. US Food and Drug Administration (FDA) has recently published Harmonization guidanceCommon Technical Document addressing concerns related to quality of medicines that also includes herbs.

The national Center forComplementary and Alternative-Medicine has been inaugurated as the United States FederalGovernment's lead agency for scientific research in this arena of medicine. Its mission is to explore complementaryand alternative healing practices in the context of rigorousscience, support sophisticated research, train researchers,disseminate information to the public on the modalitics thatWork and explain the scientific rationale underlying,discoveries. The center is committed to explore and fund all such therapies for which there is sufficient preliminary data, compelling public health need and ethical justifications (13,l4). World Health Organization (WHO) is keen regarding traditional medicine that has been active in creating strategies, guidelines and standoff botanicalmedicines. The global scenario uses vividly both promise and challenges presented by the westernmedicines. Indianeeds to identify the extent to Ayurvedic therapeutics is safeand effective so that it widget wide global acceptance.

10. Summary

The vastness of the potential nutraceutical market willbe substantially more persuasive for much-needed changethan the failed common sense and historical precedenceapproach. I am fairlysure that once this vastness isadequately understood and believed - in one way or another- nutraceutical research will begin to flourish mightilyowing to the energy and creativity of corporate capitalism.

The resurgence of corporate capitalism has madenumerous drugs to enter the international market through exploration of ethno pharmacology and traditional medicine,Progress in genomics and proteomics has opened new gateways in therapeutics and drug discovery and development, Better understanding of the human genome has helped inunderstanding scientific basis of individual variation. Drugtargets have evolved during the last decade, but the industry remains target-rich and lead-poor trapped in the old mindset and strategies. TIM although scientific studies have been done on a large number of Indian botanicals, a considerably smaller number of marketable drugs or phytochemical entities have entered the evidence-based therapeutics. China has successfully promoted its own therapies and drugs likeginseng, ma huang and gingko with scientific evidencesacceptable for the global community. Approach ofintegrative medicine by selective incorporation of elementsof TCM alongside the modem methods of diagnosis hasachieved a great success in China.

India needs a clear policy for such integrationwithout compromise on the strategies that are science-based.Efforts are needed to establish and validatepharmacoepidemiological evidence regarding safety and practice of Ayurvedic medicines. Pharmacoeconomic studies on TIM and TCM are rare, but can help in understandingcost-effectiveness and cost benefit of traditional medicine. In all such attempts, TCM examples would help India at various levels including policies, quality standards, integration practices, research models and the complementary integration where public health is kept at the central position. Both TIM and TCM are great traditions with strong philosophical basis and could play an importantrole in new therapies, drug discovery and developmentprocesses.

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