Review Article

Boon of Plants to Human Health in 21st century

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ABSTRACT

One of the most pressing challenges for the next 50 years is to reduce the impact of chronic disease. The concept of growing crops for health rather than for food or fiber is slowly changing plant biotechnology and medicine. Rediscovery of the connection between plants and health is responsible for launching a new generation of botanical therapeutics that include plant-derived pharmaceuticals, multicomponent botanical drugs, dietary supplements, functional foods and plant-produced recombinant proteins. Many of these products will soon give conventional pharmaceuticals in the treatment, prevention and diagnosis of diseases, while at the same time adding value to agriculture. Such given conventional products can be accelerated by developing better tools for the efficient exploration of diverse and mutually interacting ways of phytochemicals and for the manipulation of the plant's ability to synthesize natural products and complex protein.

INTRODUCTION

In past centuries people have used plants for healing. Plant products – as parts of foods or botanical potions and powders – have been used with varying success to cure and prevent diseases. There are many written records about medicinal plants date back at least 5000 years[1]. The strong historic bond between plants and human health began to unwind in 1897, when Friedrich Bayer and Co. introduced synthetic acetyl salicylic acid (aspirin) to the world. Aspirin is a safer synthetic analogue of salicylic acid, an active ingredient of willow bark, and was discovered independently by residents of both the New and Old worlds as a remedy for aches and fevers[2]. The twentieth century became a triumph for the synthetic-chemistry-dominated pharmaceutical industry, which replaced natural extracts with synthetic molecules that often had no connection to natural products. This rise of the pharmaceutical industry had a tremendous impact on disease treatment and prevention, saved countless lives and became one of the outstanding achievements of the twentieth century. It is easy to overlook the fact that human medicines still contain phytochemicals – valued at US$22 608 million in 1997. The Pharmaceutical industry in India is the world's third-largest in terms of volume and stands 14th in terms of value.[3]According to Department of Pharmaceuticals, Ministry of Chemicals and Fertilizers, the total turnover of India's pharmaceuticals industry between 2008 and September 2009 was US$21.04 billion.[4]While the domestic market was worth US$12.26 billion. Sale of all types of medicines in the country is expected to reach around US$19.22 billion by 2012.The pharmaceutical industry By providing a 'pill option diminished the historical connection between food and the treatment of disease. 'An apple a day keeps the doctor away' is the advice one usually gets from a mother, not from a professional health organization. Although plants are slowly making a comeback in several areas of human health (i.e. functional foods, dietary supplements and recombinant protein manufacturing), they are still losing importance in areas such as the traditional drug discovery process. Exports of pharmaceuticals products from India increased from US$6.23 billion in 2006-07 to US$8.7 billion in 2008-09 a combined annual growth rate of 21.25%.[2] According to PricewaterhouseCoopers (PWC) in 2010, India joined among the league of top 10 global pharmaceuticals markets in terms of sales by 2020 with value reaching US$50 billion [4]. Some of the major pharmaceutical firms including Sun Pharmaceutical, Cadila Healthcare and Piramal Healthcare.[3]

Single-ingredient drugs

Until recently, plants were an important source for the discovery of novel pharmacologically active compounds, with many blockbuster drugs being derived directly or indirectly from plants[5][6]. During the twentieth century, the emphasis gradually shifted from extracting medicinal compounds from plants to making these compounds or their analogues synthetically. Natural products were widely viewed as templates for designed to make perfect new drugs, referred to by industry as new chemical entities (NCEs). The contribution of plants to disease treatment and prevention is still enormous. In the 1970s, 25%

of all drugs dispensed in the USA contained compounds derived from flowering Plants [7] , with an even greater proportion of phytochemicals used as drugs worldwide[8]. In the twenty-first century, 11% of the 252 drugs considered as basic and essential by the World Health Organization were exclusively of flowering plant origin[9].The greatest recent impact of plant-derived drugs was probably felt in the antitumor area, where taxol, vinblastine, vincristine and camptothecin have dramatically improved the effectiveness of chemotherapy against some of the deadliest cancers. The most important pharmaceuticals still derived from plants – directly or as precursors. This is particularly true for phytochemicals that are well documented for their pharmacological activity, such as alkaloids[10] Phenylpropanoids[11] and terpenoids[12][13]. whose levels often increase by two to three orders of magnitude following stress or elicitation[13][14]. Thus, elicitation-induced, reproducible increases in bioactive molecules, which might otherwise be undetected in screens, should significantly improve reliability and efficiency of plant extracts in drug discovery while at the same time preserving wild species and their habitats.

Botanical drugs

Food and Drug Administration (FDA) recently published guidance for standardized multifunctional and multicomponent plant extracts, referred to as botanical drugs, thus making it possible to market these products under the New Drug Application (NDA) Approval Process[15]. In response to the public demand for trustworthy and effective alternatives to NCE pharmaceuticals, the agency proposed abbreviated preclinical and clinical testing protocols for botanical drugs derived from plants with a safe history of human use. This has enabled indian industrial and academic scientists to become involved in botanical drug R&D efforts. Interaction between different molecular components can be also required for an optimal therapeutic effect of plant extracts. The root extract of a *Tripterygium wilfordii* Hook F has been used historically as a traditional Chinese medicine to treat rheumatoid arthritis, an observation recently supported by a Phase I/II doubleblind, placebo-controlled trial in the USA[16][17].

Botanical drugs are fully accepted and widely prescribed in China, Japan, India and other Asian and African countries. In addition, some countries in Europe, such as Germany, allow physicians prescribe botanical drugs. The NCE paradigm of the twentieth century attempts to treat complex diseases with a 'single golden molecular bullet'. The first flaw in this paradigm appeared relatively recently when problems of resistance to antimicrobial and anticancer drugs became apparent. The multifactorial nature of many complex diseases, such as diabetes, heart disease, cancer and psychiatric disorders, is also an important consideration. Most of these diseases cannot be ascribed to a single genetic or environmental change but arise from a combination of genetic, environmental or behavioral factors[18] Unlike the Western NCE paradigm, traditional medicinal systems of the East always believed that complex diseases are best treated with complex combinations of botanical and non-botanical remedies that should be further adjusted to the individual patient and to the specific stage of the disease. This approach, best articulated and developed in traditional Chinese and Ayurvedic medicinal systems, emphasizes the mutually potentiating effect of different components of complex medicinal mixtures. plants have adapted a similar strategy in their biochemical warfare with pathogens, which are the main causes of plant disease and death. Relying on a single antibiotic to stop pathogens would probably be evolutionarily suicidal for plants because a resistance would develop. Although poorly studied, the ability of plants to produce families of structurally and functionally diverse antimicrobial compounds that act together to prevent the development of resistance has been documented. The future of botanical drugs depends on two factors: sustaining a favorable regulatory environment and developing technologies for the efficient discovery, development and manufacture of botanical drugs. At present, a majority of botanical drugs under development are derived from ethnobotanical sources and traditional medicinal uses. Common strategies involve upgrading well-known botanical dietary supplements. In addition to the creative and innovative

technologies needed for new botanical drug discovery, manufacturing botanical drugs presents a challenge not encountered by the modern pharmaceutical industry. As stated above, environmental and genetic factors might dramatically affect the biochemical compositions of plant extracts. Therefore, production of botanical drugs will require genetically uniformed monocultures of source plants grown in fully standardized conditions to assure biochemical consistency and to optimize safety and efficacy in every crop. It is unlikely that field-grown plants can meet the quality standards for botanical drugs. Fully controlled greenhouse-based cultivation

systemsdeveloped for high quality year-products passage of the Dietary Supplement and Health. Although the general public often considers botanical supplements natural and safe alternatives to conventional synthetic pharmaceuticals, there is relatively little scientific evidence behind this belief. The demand for dietary supplements is driven by a variety of factors that include an aging population with substantial disposable income, a growing trend to self-medicate, mistrust in the conventional medical establishment, and the perception that natural is healthy and that plant products are safe. These trends suggest the growing demand for supplements and functional foods, providing that quality standards and efficacious new products are introduced.

Functional and medicinal foods

This is probably the best-known and best-reviewed area of botanical therapeutics because of its connection to the mainstream of plant biotechnology and molecular biology. As with other botanical therapeutics, the precise definition of functional foods is vague. This review considers only those crops engineered or selected to deliver certain health benefits. Botanical functional foods produced by fortification, such as orange juice with calcium, or advertised for their innate health benefits, such as cereals with high fiber, In the area of engineered functional foods, much attention was given to the development of golden rice, healthy plant oils from modified oil crops, edible vaccines and plants with increased levels of essential vitamins and nutrients. Golden rice was engineered with two plant genes from *Narcissus pseudonarcissus* and one bacterial gene from *Erwinia uredovora* to synthesize carotene, a precursor of vitamin A, at quantities sufficient to reduce vitamin-A deficiency [19] , Plant oils have many historical uses in food and industrial applications. The current health-related goals of plant oilseed engineering is to increase the content of healthy fatty acids and reduce unhealthy fatty acids in the four most important oilseed crops, which in descending order are, soybean, oil palm, rapeseed and sunflower[20] . For example, genetic engineering was successful in reducing levels of *trans*-unsaturated fatty acids and the ratiobetween omega-6 and omega-3 unsaturated fatty acids in some vegetable oils[21] thus reducing the risk of heart disease[22], Proposed in the early 1990s, the idea of engineering tomatoes, bananas or potatoes to express a vaccine generated a lot of excitement as a simple way to distribute vaccines to developing countries[23][24]. Plant-produced oral vaccines were recently shown to be highly effective as boosters that have increased the immunity of mice to measles[25] , and humans to hepatitis B[26] . Concerns about safety and correct dosing associated with direct consumption of vaccine-producing crops might ultimately result in a more traditional approach, whereby plants are used to biomanufacture edible vaccines that are at least partially purified and delivered in a more conventional and properly dosed form such as a solution, powder or pill. Other recent advances in functional plant foods include increasing vitamin E content in plants following initial demonstrations in *Arabidopsis*[27]; selecting high lycopene or vitamin C tomatoes[28] , metabolic engineering of legumes and tomatoes for high content of bioflavonoids, known for their antioxidant, anticancer and estrogenic properties; and possible uses of thioredoxin to decrease allergenicity of foods[29] . Functional foods selected, advertised for high content of therapeutically active molecules such as vitamins (A, C and E), isoflavones, antioxidants, leaving the determination of their true medical benefit to the consumer. However, none of the genetically engineered, plant-derived functional foods on the market today are advertised and labeled as such. In India, the Departments of Agriculture will most probably regulate genetically engineered functional foods, requiring thorough clinical validation, safety testing and strict quality control. A major constraint in engineering secondary metabolites in functional foods is the scarce information about their biosynthetic genes and pathways the future of plant-based functional foods seems bright and, as a result, grocery and drugs stores might eventually look more alike. Functional foods with clear and direct health benefits for the consumer should lead to greater acceptance of crop genetic engineering, now almost exclusively, and controversially, used for crop protection.

Recombinant proteins

Recombinant proteins, such as antibodies, vaccines, regulatory proteins and enzymes, represent one of the most rapidly growing segments of the pharmaceutical industry. With dozens of proteins in clinical development today there is a substantial shortage of industrial capacity to manufacture future recombinant drugs[30] . During the past decade, plants have emerged as promising biopharming systems for commercial production of pharmaceutical proteins. Tobacco was the first plant to express a recombinant antibody in 1988[31], with further

confirmation in 1989[32] .Advantages offered by plants include low cost of cultivation and high biomass production, relatively fast 'gene to protein' time, low capital and operating costs, excellent scalability, eucaryotic post-translational modifications (i.e. glycosylation, folding and multimeric assembly), low risk of human pathogens and endotoxins and a relatively high protein yield. These advantages are potentiated by the ease of plant transformation through particle bombardment, electroporation, *Agrobacterium*-mediated transformation, or infection with modified viral vectors[33]. Plants are generally considered to be low-cost, safe and relatively fast alternatives to many existing manufacturing systems, particularly when large quantities of multimeric recombinant proteins (i.e. antibodies) are required. Most major groups of human pharmaceutical proteins have been produced successfully in a diverse variety of crops and model systems (e.g. maize, rice, wheat, soybean, tomato, potato, mustard, oilseed rape, turnip, alfalfa, banana, tobacco and *Arabidopsis*) using stable nuclear and plastid transformations, as well as transient expression systems such as viruses. Plants can successfully perform the posttranslational modifications required by the majority of pharmaceutical proteins under development. Heterologous proteins requiring these modifications are usually retained in the endoplasmic reticulum (ER) using the C-terminal ER retention sequence or targeted into the protein secretion modification pathway that delivers the recombinant proteins into the intercellular spaces (apoplast) via the ER and Golgi apparatus. Both strategies significantly enhance protein expression[34,35.] The highest yield of recombinant protein in plants is achieved by chloroplast expression or possibly by transient viral expression[42]. Downstream protein purification is often as expensive as the biomanufacturing and should never be overlooked in the total 'cost of goods' equation. At least two approaches have been used successfully to lower the cost of downstream purification of plant-produced proteins: oleosin-fusion technology for heterologous proteins produced in oilseeds[36,37] , and rhizo- and phyllo-secretion platforms based on continuous, non-destructive recovery of a target protein from plant exudates[38,39] . The latter also offers the advantage of continuous protein production that integrates the biosynthetic potential of a plant over its lifetime and might lead to higher protein yields than single harvest and extraction methods. It is likely that no single ideal system will ever emerge for the manufacturing of every recombinant protein, each system having distinct advantages and disadvantages[40][41]. Empirical analysis of several recombinant production systems might be required before the most efficient system is identified.

CONCLUSIONS

Plants are arguably poised for a comeback as sources of human health products. The hopes for this comeback are rooted in the unique and newly appreciated properties of phytochemicals conventional NCE-based pharmaceuticals and are based on the: (1) enormous propensity of plants to synthesize mixtures of structurally diverse bioactive compounds with multiple and mutually potentiating therapeutic effects; (2) low-cost and highly scalable protein and secondary metabolite biomanufacturing capacity of plants; (3) diminishing return of the single NCE approach to drug discovery and disease treatment and prevention; (4) cost limitation on the prevention and treatment of complex diseases chemical synthesis of complex bioactive molecules. Similarly, an important challenge is the development of discovery, validation and manufacturing technologies that are compatible with multifunctional phytochemical mixtures. However, plants plays very important role , it is harder to make predictions for the area of functional/medicinal foods. The increasing cost of energy and chemical raw materials, combined with the environmental concerns associated with conventional pharmaceutical manufacturing, will make plants even more compatible in the future. Crops that will benefit the most include tobacco and corn as the major recombinant protein manufacturing crops and many minor crops and medicinal plants that will become sources of future botanical therapeutics. Farmers that adapt to growing crops for health, rather than calories, will profit from greater margins and higher values enjoyed by the health industry and, as a result, the planet could become greener and more healthy.

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