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# Botanical therapeutics: discovery, development and manufacture - prospects and constraints

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### Abstract

Phytochemical and synthetic chemistry based pharmaceutical industry severed the historical connection between food, plants and medicines. Discovering new chemical entity (NCEs) based drugs through high throughput screening methods may reconnect plants and human health at a high level of technological sophistication. Botanical therapeutics with multi-component that comprise functional foods, nutraceuticals, dietary supplements and botanical drugs hold several advantages over conventional drugs that may earn them a more prominent place in the medicine of the next generation. Botanical therapeutics deliver mixtures of multi functional molecules with synergistic and potentiating effects and pleiotropic targeting at a reasonable cost and with some regulatory constraints. They are well suited for long-term disease prevention in an era of genetic testing and increased life expectancy. They also provide additional vehicles for delivering health and wellness. Technologies that address the needs of discovery, development and manufacturing of multi-components botanical therapeutics are emerging, include computational and bioinformatics approaches, cell based gene expression and high-content screening systems. Phytochemical elicitation and unique plant cultivation / extraction methods designed to optimize the production of bioactive, standardized overall extract compositions and assure batch to batch product consistency are needed. Nevertheless, multi-components botanical therapeutics carry risks associated with potential interactions with conventional drugs and adverse reactions, which are difficult to detect and diagnose. Acceptance by medical community and pharmaceutical industry, safety, poor standardization and quality control, and difficulties in identification of active ingredients and determination of their complex mode of action are some of the problems. Solving these problems will accelerate the merger of grocery stores with pharmacies and agriculture with chemical manufacturing and provide physicians and patients with broader and more individualized choices of disease prevention and treatment. Multi-components botanical therapeutics will be useful for next generation.

Key words: herbal health care products, phytochemicals, botanicals, botanical therapeutics, botanical drugs, nutraceuticals, functional foods, dietary supplements, drug discovery, natural products, human health.

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### 1. Single ingredient drugs vs. botanical

The race to develop new chemical entities (NCEs) as components of proprietary drugs led to a revolution in synthetic chemistry and to the development of combinatorial, computational

and high throughput approaches to drug discovery, while a number of drugs are still isolated from the natural sources or prepared by semi-synthesis from a natural precursor, the

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pharmaceutical industry is becoming less interested in plants as sources of new drugs [1]. Researchers who are still using phytochemicals in their drug discovery programs view them as initial leads to be improved through structure activity relationship (SAR) programs and valuable only if a cost effective chemical synthesis route to manufacturing can be established.

The most commonly cited reasons for the diminished interest in phytochemicals as sources of NCEs are:

#### *1.1 Incompatibility of a high throughput format with complex botanical extracts*

Polyphenols, pigments, saponins and other constitutive components of plant extracts often interfere with *in-vitro* protein binding and enzyme activity assays, generating a high number of false positives. So fractionation is required before primary screening. This adds significant costs to the discovery process, while increasing the chances of discovering new leads.

#### *1.2 Reproducibility*

Plants change their biochemical composition depending on the environmental conditions and harvest time. Thus, the same plant species harvested at different times and from different locales may not yield reproducible screening results. These differences may even be expressed during different times of the day, since the transcription of at least some genes involved in plant secondary metabolism, i.e. flavonoids, show diurnal circadian fluctuations [2].

#### *1.3 Price*

High throughput screening technologies require thousands of samples every week. It is prohibitively laborious and expensive to produce enough unique natural product-based extracts

to satisfy the various sample appetite characteristic of modern screening technologies that often emphasize quantity and not quality of samples.

#### *1.4 Difficulty in isolation an active ingredient*

Today's high throughput NCE discovery format requires that active ingredients are characterized rapidly and that the activities associated with previously characterized compound are ignored. This is often difficult to achieve in the time frame of the screen.

#### *1.5 Long resupply time*

Isolation and characterization of actives require gram quantities of the extract that is usually not available at the time of screening. Often resupply must come from exotic plant sources and remote geographical locations. Since fungal and bacterial cultures can be scaled up from the original supply, some natural product-based drug discovery programs such as marine organisms probably constitute the least resuppliable sample sources, unless the lead is produced by the symbiotic microbes commonly associated with these organisms.

#### *1.6 Geopolitical reasons.*

Resources and time necessary to complete legal arrangements and the intrinsic costs of benefit sharing make collections in many regions difficult or impossible [3].

## **2. Multi-component botanical therapeutics: foods or drugs**

These plant-based agents belong to newly defined category of multi-component botanical therapeutics (table 1) that is being developed in academic and industrial laboratories throughout the world [4]. Other botanical therapeutics include single-component drugs originally derived from plants, such as taxol or atropine (table 2).

Botanical drugs and botanical dietary supplements may be derived from a broader variety of plants that normally present in the human diet. Botanical drugs, functional foods and dietary supplements have recently received a boost by the US Food and Drugs Administration in the form of botanical drug guidance and qualified health claims in the labeling of conventional human food and human dietary supplements. The FDA proposed that botanical drugs, representing standardized and partially characterized multi-functional and multi-component plant extracts with a safe history of human use may be developed through abbreviated pre-clinical and clinical protocols. No botanical drugs are currently sold in the US with the possible exception of syrup of ipecac and digitalis extract that were accepted by the US pharmacopoeia long before the introduction of the botanical drug category. Qualified health claims will provide the food and nutraceutical industry with relatively well-defined criteria for claiming health benefits for their products based on scientific evidence.

The new labeling system proposed by the FDA will use a letter-grading system for the strength of scientific evidence behind the claim, with an "A" for those with significant validation, down to a "D" for the weakest. Botanical dietary supplements currently sold in the US are defined by the Dietary Supplement and Health Education Act of 1994 (DSHEA). They also belong to the multi-component botanical therapeutics but are less regulated, standardized, validated and often controversial versions of botanical drugs. In exchange for the absence of disease prevention and treatment claims, DSHEA does not require proof that supplements are safe and effective. Finally, single component botanical therapeutics is basically identical to the conventional drugs of botanical origin, and thus are not the focus of this review.

Multi-component botanical therapeutics may contribute to the future of conventional medicines because of several advantages over conventional pharmaceuticals: they may deliver a complex combination of interacting compounds with pleiotropic effects and, in the case of the functional foods, in doses that exceed those of conventional oral pharmaceuticals. They may also be cheaper and faster to develop and manufacture, resulting in lower costing medicines with a larger emphasis on preventative care. These advantages are further analyzed below.

### **3. Interactive nature of phytochemicals**

In contrast to higher animals, plants synthesize bewildering arrays of organic molecules with functions that have puzzled generations of phytochemists. Major improvements in analytical technology have increased the rate of phytochemical identification every year, but it is widely believed that the great majority of phytochemicals have not been characterized or functionally tested [4, 5]. While some of these compounds, often called secondary metabolites, play defense, communication and internal signaling functions or are biochemical intermediates or catabolites, the functions of many others remain to be determined. It is becoming clear that these compounds may exert their bioactivities by interacting with other molecules, rather than acting alone as probably most of the compounds produced by prokaryotes do. It is possible that the evolutionary significance of a large number of phytochemicals present in each plant lies in their complex mutually potentiating effects that provide protection against diverse pathogenic microbes and herbivores and help to assure more reliable signaling to pollinators and other beneficial organisms. Modern medicine has only recently learned how rapidly pathogens and

cancer cells can develop resistance to single ingredient drugs, necessitating the administration of complex drug cocktails to circumvent or delay the development of resistance. Plants may have learned this strategy very early in their evolution.

For example, *Berberis fremontii* produces both antimicrobial berberine alkaloids and inhibitors of a bacterial multidrug-resistant pump that strongly potentiate the antibacterial activity of berberines [6]. *Coptidis rhizoma*, a medicinal herb with an anti-cancer effect, also contains berberine as major bioactive principle. A recent study showed that the extract of this plant has a more potent antitumor activity than pure berberine and that the effects of the extract and pure berberine on the anticancer genes do not fully overlap [7]. The root extract of a *Tripterygium wilfordii*, used as a traditional Chinese medicine, has a strong anti-inflammatory effect based on blocking the expression of a number of pro-inflammatory genes including those encoding cyclooxygenase-2, inducible nitric oxide synthase and several inflammatory interleukins. A recent phase I/II double-blind, placebo-controlled trial in the US has confirmed that effect [8, 9]. Although the main active ingredient of this extract, suggesting that other unidentified extract components increase its safety and, possibly, efficacy [10]. Similarly, mixtures of plant flavonoids had a synergistic effect on anti-fungal activity greater than the sum of the effects of their purified components [11]. Plants that have mild diuretic properties, such as *Solidago virgaurea* (goldenrod), *Betula* (birch), and *Ononis spinosa* (rest harrow), contain flavonoids, saponins, and volatile oils that in combination are responsible for the overall diuretic effect that cannot be reproduced by a single component [12]. Potentiating phytochemical interactions between the terpene lactones (ginkgolides and bilobalide) that are

platelet activating factors and the flavanoid antioxidants (mostly proanthocyanidins and rutins) and microcirculation enhancers may account for wide range of effects of *Ginkgo biloba* extract [13]. While lycopene in tomatoes has been associated with decreased risk of cancer and cardiovascular diseases in numerous studies [14, 15, 16], whole tomato powder reduced carcinogenesis in rats more than pure lycopene [17].

Negative interferences occur when certain components of the mixture inhibit full biological activity of other components. For example, although tea has higher caffeine content than coffee, its stimulating activity is less marked because of the interaction of caffeine and proanthocyanidins in freshly brewed tea that limit its bioavailability. Similarly, citrus pectins significantly depressed the bioavailability of beta carotene.

Also, the effects of drugs can be altered by commonly consumed phytochemicals. For example, furanocoumarins and to a lesser extent flavonoids present in grapefruit juice substantially alter the pharmacokinetics of calcium blockers and other drugs by suppression of the cytochrome P 450 enzyme CYP3A4 in the small intestine wall in essence increasing their effective dose. Grapefruit juice may also inhibit intestinal P-glycoprotein mediated efflux transport of drugs such as cyclosporine to increase its oral bioavailability [18]. Recently, phytochemicals contained in many botanical dietary substances were shown to modulate effects of many conventional drugs, raising the concerns of doctors and regulators [19].

Multi-component treatment provides better therapy than any single entity for some complex chronic disease. But regulatory requirements make it impractical and somewhat expensive. The realities of an intensely competitive and

regulated pharmaceutical industry dictate that more efforts are placed on the study of negative drug-drug interactions than on the evaluation of potential synergy between existing drugs or drugs and foods. Multi-component botanical therapeutics may become particularly valuable in the long term prevention and treatment of complex diseases requiring extended administration and pleiotropic action.

So why did plants evolve compounds that effectively interact with therapeutic targets in humans? While antimicrobial and selectively cytotoxic compounds protect plants against infectious diseases and herbivory respectively, we can safely assume that most of the other pharmacological activities of phytochemicals are coincidental. Yet, most have evolved to play some function in biological systems and that should make them better therapeutic agents than randomly chosen synthetic chemicals.

#### **4. Emphasis on prevention**

By knowing the sequencing of the human genome, we can predict the risk factor associated with those genes in future generation [20, 21, 22]. For example, easily testable mutations in the tumor suppressor genes BRCA1 and BRCA2 result in a dramatic increase in the risk of breast and ovarian cancer [22]. In families with multiple cancer cases, the estimated lifetime risk of breast cancer is >80% and the lifetime risk of ovarian cancer is 40 to 65% for BRCA1 carriers and 20% for BRCA2 carriers [23]. Study of the gene characteristics and their mutation properties and risks, and then we can assume the risks associated with genes after mutation. For example mutations responsible for increased risks of other cancers, diabetes, and cystic fibrosis, and obesity, autoimmune, psychiatric and neurological diseases are being rapidly catalogued and genetic tests for these mutations developed and transferred to the clinic. Furthermore, new technologies allow the creation of individual

disease risk profiles based on single nucleotide polymorphism (SNP) mapping, gene-expression profiling or proteomics [24, 25].

The advent of genetic testing is impaired by the failure of modern medicine to effectively respond to identified health risks, since treatment and not prevention is still at the core of the health industry. Yet it creates a powerful force for the development of a new generation of preventative therapeutics. Botanical therapeutics and functional foods in particular, may serve as the first, line of defense against genetic risk factors, because of their innate emphases on prevention. For example, about 35 cancer preventive plant-food sources have been identified by the national cancer institute (NCI) including garlic, cruciferous vegetables, ginger, onion, tomatoes and legumes [26-28]. Many phytochemicals associated with foods such as allicin, polyphenols, isoflavones, anthocyanins, omega-3 fatty acids and fiber are implicated in the prevention of cardiovascular diseases [29-31]. However, food companies are often reluctant to expend resources on obtaining qualified health claims on foods because of the inherently genetic nature of this industry and the questionable success of the currently marketed functional foods. On the other hand, doctors are also somewhat reluctant to recommend a functional food because of the limited training they receive in this area. Nevertheless, the accumulation of solid scientific evidence on the benefits of functional foods and some dietary supplements should reverse the slow rate of their acceptance by the medical community.

#### **5. Combinatorial phytochemistry**

As mentioned above, the full health benefits of multi-component botanical therapeutics can rarely be reduced to a single pharmacologically active ingredient. Most foods or botanical extracts contain phytochemicals belonging to several groups of health promoting compounds

that likely interact with each other. In addition, any natural product isolated from a plant is usually a member of a mini-combinatorial library of closely related compounds composed of biochemically related analogues, precursors and catabolites that may have overlapping pharmacological activities. For example, while genestein is the best known soybean isoflavanoid with reported anti-cancer and cardiovascular benefits [32], detailed biochemical analysis of soyabean concentrate revealed the presence of at least 12 structurally similar isoflavones [33] in addition to other multiple biochemical precursors. Many of these compounds were shown to exhibit related pharmacological activities that act together to produce the overall cytotoxic effects of soybean extracts on cancer cells [32, 33].

Mini-combinatorial libraries stored in each plant contain molecules that may be too difficult for a synthetic chemist to make. Complex glycosylation reactions carried out by dozens of glycosyltransferases present in each plant [34, 35] and highly specific hydroxylations carried out by highly diverse plant cytochrome P450 monooxygenases [36] are often too complex for human chemists to perform. In addition, human chemists cannot yet compete with the complex stereochemistry carried out by plant enzymes [37]. It is estimated, however, that natural products, particularly those made by plants, tend to have fewer nitrogen, halogen or sulfur atoms than synthetic pharmaceuticals [38]. Therefore, many structure activity relationship programs experiment with adding halogen or sulfur atoms to natural products in attempts to convert them to synthetic drugs. A hybrid approach that begins with a specific natural product(s) isolated from a plant that is subsequently derivitized through the synthetic combinatorial approaches is now being considered as a valuable NCE discovery strategy for the future [1, 39].

## 6. The power of elicitation

The complexity and unpredictability of the health effects of botanical therapeutics does not end with the pleiotopic and interacting effect of their components. It is well known that different stresses, locations, climates, microenvironments and physical and chemical stimuli (often called elicitors) qualitatively and quantitatively alter the content of bioactive secondary metabolites. This is particularly true for phytochemicals that are well documented for their biological activity, such as alkaloids [40], phenylpropanoids [41] and terpenoids [42, 43], whose levels may increase by 2 to 3 orders of magnitude following stresses or elicitation [44, 45]. Stress-mimicking chemical elicitors also increase the amounts of natural products widely used as pharmaceuticals, such as taxol [46, 47], tropane alkaloids [48], indole alkaloids of *Catharanthus roseus* [49, 50] and salicylates [51]. As a specific example, the genistein content of yellow lupine roots was increased by an order of magnitude by the addition of elicitors to the hydroponics medium supplied to the plant. Similarly, levels of salicylic acid increased dramatically in plants infected by viral or bacterial pathogens. Just as tomatoes from different gardens taste differently and the same grapes produce distinctly flavored wines each year, plants as sources of botanical therapeutics may change their biochemical composition and medicinal properties unless their growing environment is strictly controlled. This simple fact has a significant implication for the discovery and manufacturing of botanical therapeutics that need to be carried out in the conditions that favor the biosynthesis of pharmacologically active compounds.

## 7. Discovery of botanical therapeutics

Today's pharmaceutical discovery is characterized by the dominance of high throughput *in vitro* 'bind and find' approaches and declining interest in phytochemical

bioprospecting. Thus, relatively few efforts are currently being directed to identifying technologies that are better suited for discovering botanical therapeutics.

Ethnobotanical bioprospecting, which takes advantage of traditional medicinal knowledge, and random 'grind and find' bioprospecting have been two methods of choice for phytochemical drug discovery. However, in recent years the development of novel botanical therapeutics from ethnobotanical sources fell short of expectations [52]. It can even be argued that the NCE driven ethnobotanical approaches practiced throughout human history have already identified the most obvious single-component botanical therapeutics. However, this lack of success may also be attributed to relatively simplistic and reductionist approaches practiced by ethnobotanical explorations that emphasized isolation of a single active ingredient. Little care has been taken in re-growing plants in conditions that stimulate the production of bioactives or focusing on the potential interactions of the phytochemicals in producing the overall therapeutic effect. In addition, disproportional effort has been placed on relatively hydrophobic phytochemicals with potential medicinal use. Hopefully, future botanical explorations will be more cognizant of these factors, thus maintaining ethnobotanical bioprospecting as a valid discovery strategy.

One of the approaches we have recently developed as a biorational discovery tool for botanical therapeutics is called Reversed Structural Bioinformatics (RSB). This approach uses computational approaches to uncover phytochemicals that structurally resemble synthetic molecules effective against certain clinical targets. Synthetic compounds that interact with certain protein targets can be analyzed to define the ideal pharmacophores [53]

that can then be referenced against known structures of phytochemicals. Plants containing the natural analogs of synthetic bioactives identified through RSB are grown, elicited, if necessary, putative bioactives extracted and their activity validated in in-vitro and cellular screens. This approach forgoes the need for chemical synthesis of putative leads and relies instead on the tens of thousands of compound-strong libraries stored inside green plants- some of the best chemists living on earth. The identification of gaultherin as a potential alternative to aspirin with reduced potential for gastrointestinal irritation and ulceration [54] is a good example of the application of the RSB approach to the discovery of botanical therapeutics.

Changes in gene expression are important in many biological processes, such as the onset and progression of human diseases. Until recently these changes were difficult to study particularly when multiple genes were affected simultaneously. The progress of molecular biology now allows effective simultaneous monitoring of the effects of therapeutic agent on transcription of multiple disease associated genes, using Real Time reverse transcription polymerase chain reaction (RT-PCR) technology pioneered in 1993 [55] and microarray strategies [56, 57]. While the latter is still too expensive and cumbersome to be generally useful as a discovery method, the former provides an effective discovery tool for the more biorational, lower throughput discovery approaches.

Microarray ethnology may also allow identification and cloning of genes encoding the biosynthesis of bioactive phytochemicals in wild plants for subsequent transfer to the cultivated species. Application of the above high-throughput genomic tools to nutritional research and medicinal food development is called nutrigenomics, a term commonly used but poorly defined.

Real Time RT-PCR is particularly useful for studying the effects of multi component botanical therapeutics in intact cells. Real time RT-PCR based assays are uniquely compatible with biological extracts, since they measure the effects of compounds in living cells rather than *in vitro* binding or enzymatic systems that usually utilize isolated target proteins. Extracts often produce artifacts in such *in vitro* systems. Cell based systems, while cumbersome to use in a high throughput format, are much less prone to the artifacts associated with multi-component mixtures. Real time RT-PCR technology also permits studying the effects of various agents on the expression of selected genes in animal organs and tissues [58].

Just as real time RT-PCR, whole cell high content screening approaches go beyond the affinity binding information obtained through high throughput screening. High content screening uses complex cellular assays that monitor the effects of molecules on many morphological and functional parameters documented with imaging/pattern recognition technology and analyzed with informatics software. This emerging discovery technology dovetails nicely with the needs of identifying the pharmacological effect of complex mixtures of phytochemicals.

### **8. Development of botanical therapeutics**

Multi-component botanical therapeutics also presents unique challenges in identifying their active ingredients and in validating their clinical effects. Activity-guided fractionation and reconstitution experiments currently used to characterize compound interferences within a mixture are cumbersome and time consuming. Clinical confirmation of the efficacy of multi-component botanical therapeutics proved to be an elusive and complex goal. For example, despite at least 83 clinical trials, our understanding of the potential health effects of

phytoestrogen-containing foods and supplements is far from complete. Factors that contribute to this lack of understanding include the functional and structural diversity of phytoestrogens in tested preparations, variability in their content from different batches of plant materials, inconsistent use of extraction methods and formulations, and interference from other compounds present in various phytoestrogen sources. Similar factors interfere with the final clinical confirmation of the effects of Echinacea, *Ginkgo biloba* and St. John's Wort. Undoubtedly, many of these factors would not exist for clinical trials involving a single NCE.

### **9. Manufacturing of botanical therapeutics**

Public distrust of dietary supplements and some functional foods is justly fueled by reports of the presence of adulterants, variations in the amount of active ingredients, safety concerns and unproven health benefits. Sales of ephedra, one of the most popular dietary supplements, were recently banned by FDA which has never before ordered a dietary supplement to be pulled from the market for safety reasons. Ambiguous clinical data continue to plague these products. For example, contrary to the earlier studies, a recent large clinical trial of Echinacea showed that, not only was it ineffective in reducing upper respiratory tract infections in children, but actually increased the incidence of skin rash. Similarly a recent well-designed human study of *Ginkgo biloba* extract has shown no effect on age associated memory impairment [59] while others showed much more promising results. Such discrepancies can be explained by the inherent difficulty in achieving functional and biochemical consistency between batches of botanical therapeutics prepared and administered at different times. While chromatographic analysis is often employed to produce biochemical fingerprints used for product



comparison [60], the apparent similarity in the biochemical fingerprints between batches does not approve pharmacological equivalence. Actually, in the absence of information about the identity of active ingredients, such analysis is hardly reliable, since chromatography provides an incomplete picture of the qualitative and quantitative composition of a complex extract.

The inclusion of functional assays in quality control protocols performed by the manufacturer, in addition to chromatographic analysis, will provide a partial solution to assuring batch to batch consistency. It is also important to strictly monitor the condition at which the source plants are grown, harvested and extracted in order to avoid environmentally imposed variations in their chemical composition. In some cases elicitation may be used to increase the content of

pharmacologically active ingredients in botanical therapeutics. While difficult to administer in the field, environmentally benign elicitors can further reduce variability and rapidly multiply individual plants enriched in medicinal phytochemicals. Novel reliable and enforceable quality control approaches to manufacturing and cultivation of botanical therapeutics have to be established, since issues associated with their production differ from the issues associated with the manufacturing of single active ingredient drugs.

## 10. Future

People ingest a vastly greater diversity of pharmacologically active chemicals in the form of foods than as drugs, often not realizing that many drugs were derived from the compounds originally discovered in foods. The 20th century introduced a clear separation between drugs and foods where drugs became primarily synthetically manufactured components of pills

Table 1. Multi component botanical healthcare products

Category	Description	Example
Botanical drugs	Clinically validated and standardized phytochemical mixtures approved by the FDA	None in U.S., several in clinical trials
Dietary supplements/nutraceuticals	A plant component with health benefits developed under DSHEA and carrying only structure-functional claims	Garlic, St. John's Wort or Echinacea extract
Rational/medicinal foods	A plant-derived food engineered or supplemented to provide health benefits	Modified canola oil, high fiber cereals, golden rice

Table 2. Single-component botanical drugs

Category	Description	Example
Drugs(NCE)	Single active ingredient, NCE based pharmaceuticals originating from plants approved by the FDA	Vinblastine, Taxol

and capsules while foods retained their character as naturally produced mixtures of compounds presented on the plate. Consumers learned that they could eat unhealthy foods and then at least partially correct their indiscretions by swallowing a synthetic pill. Extracts, powders and potions used by herbalists and shamans were officially reincarnated in the form of botanical nutraceuticals. What will come next?

It is likely that plants' contribution to future medicine will move beyond the realm of NCE discovery into the next generation of multi component botanical therapeutics delivered as functional foods, both standard and individually tailored, scientifically designed, optimized, standardized and validated dietary supplements and botanical drugs. Major technological improvements in the ways we discover, develop and manufacture botanical therapeutics, assisted by a favorable regulatory environment will be required to achieve this transition. It is yet unclear whether pharmaceutical companies, food companies or chemical life science companies will market these innovations or whether the area will develop as an independent industry from fledgling biotechnology companies. Yet, it seems that the pleiotropic clinical effects that may be achieved by the interacting components of botanical therapeutics are slowly gaining serious attention by the scientific and regulatory community. Foods, beverages and extracts with medical claims are moving onto the shelves of grocery stores in greater numbers each year. Plant scientists are now breeding crops for the greater amounts of antioxidants, carotenoids, vitamins, flavonoids and other therapeutically active compounds. Creating plant varieties with enhanced nutritional and medicinal qualities will become a much larger component of private and public breeding programs. Metabolic engineering, while still on the fringes of public

acceptance and in search of methods for cloning and transformation of complex biochemical pathways, will soon be able to augment our crops with a much greater variety and quantity for pharmacologically active compounds than can be achieved through conventional breeding or elicitation [61].

Multi component botanical therapeutics may provide an effective delivery vehicle for the prevention of genetic and life style associated diseases. Individualized functional diets and supplements prepared from specially cultivated plants and recommended by a physician may reduce the incidence of disease, providing that the future consumer can mentally and physically reconnect plant derived foods and health. On the other hand, FDA approved and physician prescribed or recommended botanical drugs, may help to eventually replace botanical nutraceuticals and assure much greater levels of consistency, safety and regulatory compliance. Their presumed ability to deliver concentrated and optimized mixtures of interacting compounds may effectively supplement existing single component drugs, providing that care is taken to understand and manage potential interactions between these groups of pharmaceuticals.

While, the first generation botanical therapeutics go back to ancient times, their modern successors are just emerging from the proof of concept stage, having somewhat shaky reputation with many scientists, pharmaceutical companies and regulatory agencies. Clearly many technologies required for the successful discovery, development and production of botanical therapeutics are not yet in place, and efforts required for their emergence may be substantial. Yet if successful, these efforts may result in the partial merger of grocery stores and drug stores as well as healthier and a greener planet.

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