Biotechnology as a Method of Nutraceuticals Production

Since their market introduction in the mid-nineties, biotechnology crops have enjoyed steady growth and fast adoption rates at farm level. Improved agronomic traits, such as pest resistance and herbicide tolerance, have been valued by farmers for their cost reducing and/or yield increasing effects. However, such technologies have had few recognizable consumer benefits, which was identified as a primary reason for weak public acceptance in certain parts of the world, especially in the European Union. Similarly, it has been argued that second-generation bioengineered foods, which provide direct consumer benefits, will be more easily accepted and will create lucrative markets. Nutraceuticals/functional foods that demonstrate physiological benefits and reduce risk of disease fall within that category. These foods are easily incorporated into an everyday diet because they are similar in appearance to conventional foods. Nutraceuticals can be produced through chemical synthesis, fermentation and genetic engineering. They can be then incorporated into our diet in a form of fortified foods, supplements or through a direct consumption of genetically enriched foods.

The market potential for functional foods/nutraceuticals is steadily growing. Nutraceutical sales (including vitamins, dietary supplements and herbs) in the USA were valued at $86 billion in 1996. By 2020, the international market is supposed to reach $500 billion mark (“Food or Medicine”).

In terms of the industries involved, several trends will impact the growth of nutraceuticals. Large food companies in efforts to diversify their product line set up functional foods/nutraceutical divisions. Pharmaceutical companies join the producers of dietary supplements, “the move into less expensive and time-consuming nutraceutical research process is a logical progression” for companies that have already invested in research necessary for drug discovery (Schutt). Acquisitions are also an indicator of an increased interest among the companies, as small and large manufacturers’ strategies “vary from vertical integration to market dominance in a particular segment of region to gaining complementary technologies or products”(Schutt).

Another trend, according to Ellen Schutt, is the effort to standardize in terms of “fingerprinting” and consistency. Well-founded clinical and scientific data about the effectiveness of nutraceuticals is important for their promotion and marketing, because consumer acceptance depends on it. Current regulations regarding labeling and advertising claims require that companies conduct clinical trials, which in turn calls for sufficient financing. Patentability of products would be a major step forward in terms of protection of clinical research and will ensure profitability of research and manufacturing. High cost of research sometimes requires cooperation of small and medium size companies with public research institutions. Strategic alliances in food industry provide access to the funding for research and development and “to the marketing, technical and regulatory expertise needed to develop functional foods/nutraceuticals successfully. Potential partners in such alliances include other food manufacturers, pharmaceutical companies, universities, government research centers and professional and industry associations” (“The Nutraceuticals”).

One of the challenges of this developing industry is convincing the public that nutraceuticals are effective in preventing disease and improving general health of people. However, according to International Food Information Council (IFIC), "virtually all consumers (95%) agree that certain foods have health benefits that go beyond basic nutrition and may reduce the risk of disease or other health concerns" (Sloan).

According to Applied Biometrics survey, "one out of three shoppers report that they are more likely to self-treat themselves than they were a year ago. In 1997, 40% of Americans used alternative therapies. Perhaps more importantly, total visits to alternative medical practitioners (629 million) exceeded the visits to all U.S. primary physicians, increasing by 50 % since 1990… 42% of all alternative therapy use is attributed to the treatment of existing illness and 58% to prevention of illness and/or health maintenance" (Sloan). Nutraceuticals are a part of alternative therapy that doesn't require consumption of drugs, they are relatively inexpensive and simple to incorporate into the everyday life.

Over the next three years it is expected that the market for natural products will increase at a rate of 10-13% a year, for dietary supplements it is 8-10%, for herbs and botanicals the number is 12-18%. Top 10 up and coming nutraceutical industry targets are (in no particular order): joint health, gut remedies, blood and body fat, skeletal strength, hormones, optimal vision, mental and emotional health, breast and prostate cancer, and gender specific. Starting in 1993, 95% biotech companies, 55% of food industry and 35% of pharmaceutical industry reported funding research and development projects in these key markets. Two thirds invested in coronary heart disease, 56% in cancer, 56% in cholesterol, 37% in osteoporosis, 37% in diabetes, and 30% in hypertension research. A recent survey by Monsanto showed that 31% of people would "definitely" and 72% would "probably" buy foods that would reduce their risk of getting cancer (Sloan).

The United States is the largest consumer of healthcare products and home to the world's largest and most aggressive pharmaceutical companies. Research for most drugs must go through three extensive phases of testing before and if FDA approves it. (Featherstone) Nutraceuticals, in turn, have a better change at succeeding in the market because some of them make use of elements already proven to have therapeutic value, such as antioxidants and fiber, which cuts down on expenses on clinical trials.

One of the examples of nutraceuticals effect is that of vitamin E. Studies show that an intake of 150 International Units (IU) (in comparison with 15 IU Recommended Daily Allowance (RDA)) daily lowers risk of cardiovascular disease, and an intake of 400 IU reduces the risk of some cancers, improves immunity and slows the progression of some degenerative diseases, such as Alzheimer's (Good). Vitamin E is a powerful antioxidant, it is important for preventing peroxidation of polyunsaturated membrane fatty acids. Natural-source vitamin E is extracted from vegetable oils, primarily soybean; synthetic version is a petroleum by-product. Natural-source vitamin E has a 36% greater potency than its synthetic version.

According to another study, if large numbers of Americans consumed at least 100 IU of vitamin E daily, "hospital charges related to coronary heart disease could be reduced by as much as $5.6 billion annually for men and women over 50"("Natural…"). Their conclusion is that vitamin E therapy is cost-effective. Biotechnology could provide an inexpensive natural way of vitamin E supplementation. "It is estimated that 40% of all untimely deaths could be prevented by diet modification," says DellaPenna, the world's leading researcher in vitamin E production.

Yet, there is another promising antioxidant, considered more potent that vitamin E. Resveratrol, which belongs to a group of phytoalexins, is produced in plants to protect against oxidation and fungal infections during times of environmental stresses, such as weather, ultra-violet radiation, insect, animal or pathogenic attack. 70 species of plants have been identified as containing resveratrol. They include mulberries and peanut, but a particularly good source of it is grape skin. University of Illinois scientists discovered that resveratrol was highly effective in all three stages of the cancer process: initiation, promotion and progression. Besides antioxidant activities, resveratrol also exhibited antimutagenic activity and "also increased levels of the phase II drug – metabolizing enzyme quinone reductase, an enzyme capable of metabolically detoxifying carcinogens, thereby ridding them from the body" ("Resveratrol…").

Besides a great potential for reducing the risk of diseases in developed countries, nutraceuticals may prove to be of great assistance in other part of the world, such as developing countries, where malnutrition takes toll on human lives. According to plant physiologist Ross Welch, "The Green Revolution increased overall production of high-yielding rice, wheat and maize. Unfortunately, the huge boost in production was followed by a global increase in micronutrient malnutrition"(Becker). The shortage of iron, zinc, iodine, essential trace elements and vitamins affects billions of people. The international effort is centered on breeding plants able to take up trace metals from the soil and store them in edible parts of the plant; to synthesize more phytochemicals, such as beta-carotene, and to increase bioavailability of the nutrients (Becker).

Iron deficiency is a serious nutritional problem and it affects about 30% of the world population (2 billion), especially where vegetables are a major food source. One of the symptoms of iron deficiency is anemia, which is characterized by low hemoglobin; but there are also other serious problems such as impaired learning ability in children, reduced immunity and work capacity. Iron deficiency is not a problem in many industrialized countries, because of diverse diets that include meat, food fortification and access to information. In many developing countries, supplementation is difficult "because of the associated costs and the small number of primary health programs"(Goto).

According to World Health Organization (WHO), between 140-and 350 million pre-school children are deficient in vitamin A worldwide. This deficiency triggers xerophthalmia, the leading cause of blindness in developing countries; it also results in increased susceptibility to diseases, such as measles, respiratory infections and diarrhoea. According to European Commission, supplying children with required dosages of vitamin A would decrease mortality by 23%, measles mortality by 50% and diarrhoeal disease mortality by 33%. Another report suggests that increasing vitamin A intake would prevent 1.25-3.5 million of the nearly 8 million late infancy and pre-school-age child deaths each year (Hogan).

There are several ways of combating nutrient deficiencies in developed, as well as developing countries. They are food fortification, supplementation and consumption of food that is naturally rich in micronutrients.

Supplements are not incorporated into a food supply and are taken separately in various forms, such as pills, powders, liquids, etc.

Food fortification is achieved through addition of supplements to food in the best form for a particular type of food, so the food consistency, taste, appearance, etc. are not altered.

The following are the types of intervention used to combat vitamin A deficiency in developing countries.

1. Dietary modification.

Modification in patterns of food production, consumption and distribution that can be accomplished through "the application of agricultural or horticultural, educational, and poverty alleviation strategies." (Arroyave) It requires a long-term commitment and is not always compatible with the magnitude of vitamin A deficiency.

2. Periodic distribution of high-dose vitamin A supplements.

Administering a high dose of vitamin A every 4 to 6 months is assumed effective in all individuals in need receive the dose. It requires direct and active participation by the target population. Continuos and adequate supply of capsules needs to be established and the effective distribution system needs to be maintained. Uninterrupted control over distribution of capsules is required to avoid overdose.

3. Food fortification

When widespread coverage is required, this method is the most effective. It doesn't require any changes in people's eating habits, provides uninterrupted yet low dosage supply of vitamin A, so that intakes remain within a safe range. Also, food fortification is most cost-effective methods out of the three.

Food fortification program requires a technically developed food industry and a control system that would allow monitoring the fortification process itself and the vitamin A status of the population. A major obstacle in developing countries is the large number of small-scale millers.

Cost per metric ton CMT $9.51
Cost per person $0.36 per year
Cost per person covered $0.40 per year (90% of the population)
Cost per possible beneficiary (percent of people consuming 70% RDA or less, 60%) $0.67 per year

Cost effectiveness
Cost per protected beneficiary (protected beneficiaries are people whose vitamin A intake is the result of sugar fortification, 80% of possible beneficiaries) $0.84 per year

Cost per recovered beneficiary (who moved from inadequate category to adequate, or who remained in the latter due to fortification $10.53 per recovered child, per year. (Arroyave)

Fortification is cost effective when compared to other methods: fortification costs $0.98 per person, capsule distribution $1.81 per person, and vegetable gardens $2.71 to $4.16 per person. (Phillips)

Active collaboration of all sectors, such as government, donor agencies, food industry, local academic institutions, food legislators and consumers is required for a successful fortification program. Constant and adequate monitoring of critical control points in the production and distribution of food fortification, and monitoring of micronutrient status of target population are also important. ("Food")

Foods successfully fortified with vitamin A are margarine, fats and oils, milk, sugar, cereals, and instant noodles. Moisture in excess of 7% and repetitive heating are known to negatively affect the content of vitamin A. Vitamin E is added to fats and oils. Vitamin C fortification technologies are available for fruit juices, drinks, other beverages, dairy products and cereals.("Food") Moisture content in excess of 7% adversely affects vitamin C stability. It is the most unstable vitamin in foods. The main loss occurs during processing and storage, and is a result of oxidation, which is increased by the presence of light, oxygen, heat, increased pH, copper or ferrous salts. ("Vitamin")

Cereals are most likely to be fortified with iron, but dairy, sugar, soy sauce and cookies have been fortified. Selection of iron fortificant depends on the food vehicle. The presence of polyphenols, phytates and calcium negatively affect the bioavailability of non-heme iron.

Flour fortification with iron is one of the cheapest and most effective methods of combating anemia. A miller spends about $1.31 for premix of iron and zinc per ton of flour. It amounts to 0.67% of the total production cost. While it doesn't seem like a big amount, the Indonesian government must spend $4 million a year to cover the premix cost because of the large volume of processed flour. Also, the millers cannot pass this cost on to consumers, distributors or bakers. (Sarmiento) The fortification process is done by adding micronutrients through a volumetric feeder at the end of the milling process. The cost of a feeder varies from $2000 to $5000. The cost of wheat flour fortification with mandatory micronutrients in the U.S. (B1, B2, niacin and iron) is less than a dollar per metric ton of flour, which is about 0.1% of the total cost. With the average consumption of 205 g/person/day, the total cost of fortification is $0.07 per person per year. ("Fortification Basics:Wheat…")

In developing countries, for a fortification program to be efficient, it has to be done in a few centralized locations rather than in hundreds small mills. Otherwise, it is difficult to implement effective control over the quality of fortified materials. The cost of maize flour fortification includes the cost of premixed micronutrients, equipment, maintenance, quality control and personnel. In Venezuela, cost of fortification with a premix of 5 vitamins and minerals (A, B1, B2, niacin and iron), ranges from $2.4 to $3 per metric ton of maize flour at a rate of 0.2 kg of premix (priced at $12-15 per kilogram) per metric ton. It amounts to 0.3% of the retail price of the flour. In Zimbabwe, fortification with vitamins A, B, B2, B6, niacin, folate and iron, costs between $2.5 and $3 per metric ton of maize meal. ("Fortification Basics: Maize…")

The following are several examples of conventional production methods of supplements used in premixes.

Isoflavones

ADM sells its branded isoflavone product at a wholesale price of $500 per kilogram. The mixture of wet soybean meal, from which protein is removed, is passed through a resin designed to bond with isoflavones. The resin is then separated out by using a solvent, such as ethanol. Raw soybeans contain 0.2% isoflavones. Monthly output of a single isoflavone plant operated by just 6-7 workers is about 30,000 pounds. The plant's annual production could be worth more than $80 million. (Fuhrig)

Vitamin C

Ascorbic acid is a product of a complex synthesis. It is manufactured from d-glucose, which is converted through microbiological oxidation to a keto acid, and which is then reduced to 1-idonic acid. Microbiological oxidation converts it to 2-oxo-1-gulonic acid. This acid is converted to its methyl ester, which is then isomerized and cyclized to 1-ascorbic acid. A new method was developed by Genencor and Eastman for ascorbic acid production from glucose, a refined product of corn. The process employs chemistry and biotechnology, eliminates several chemical steps from the conventional method and is totally aqeous. It achieves significant cost cuts through lower capital costs and higher yield and productivity. ("Genencor")

Vitamin B

A new fermentation process was discovered by Hoffman-La Roche. It will replace the conventional method, which employs chemical synthesis involving ribose sugars. The new process doesn't use any solvents, and utilizes only natural and renewable resources, which will have a favorable affect on environment. "The new process uses a natural microorganism, Bacillus suptilis, which has been genetically engineered to improve yield. Because of the increased productivity, together with reduced labor costs and cheaper raw material, production costs are expected to be cut in half."(Ondrey)

To see how biotechnology affects the sourcing decisions of a food manufacturing company, we can compare methods of production for conjugated linoleic acid (CLA). CLA is a fatty acid, isomeric mixture of molecules that have varying double bonds. It can be manufactured through organic synthesis, fermentation and biotechnology. (Mirasol)

Chemical synthesis is capital intensive, and depending on the scale of the manufacturing facility, it ranges from $2 to $3.5 a pound. It is also hard to predict and control the consistency of an isomeric mix, which could cause problems with regulatory issues. On the other hand, this method is widely used and techniques are already established, suppliers are well known, and the regulatory approval process for organic synthesis would not bring any surprises.

Fermentation method is also capital intensive, although not as much as chemical synthesis, at a cost of only $1.10 to $2.90 per pound of CLA. Advantages to using this particular method are the simplicity of testing and control over the isomeric mixture**.** The disadvantage, according to

Mirasol, is that "the acquisition of a discovery step, which can result in a potential two-year time lag to market." Also, few companies have the technology and, therefore, could become third-party partners.

Production of genetically engineered plants is the least capital intensive, and through biotechnology, levels of CLA in a plant could be increased to make up a predominant fraction in plant's oil. The costs amount to $0.35 to $1.50 per pound. The manufacturers can control the isomeric mixture precisely, and that should ease the regulatory approval.

The last two methods involve certain risks because they are dealing with biological matter and they require discovery steps that could lengthen the time needed to bring the product to market. Manufacturing is also limited to the seasons in which the plants are grown. And although the products of genetic engineering might have some trouble being accepted, biotechnology is a highly reliable and productive production method for nutraceuticals. (Mirasol)

Companies investing in agricultural biotechnology hope to make profits from producing plants with increased nutritional content, improved bioavailability of nutrients or processability of plants. The reason is hope that producers would pay extra for crops that save them the cost of additives, cut processing costs by eliminating some of the steps, or add novel features to their product, so that it differentiates them from others in the market. Also, stacking the genetically engineered traits increases sales without adding costs because, according to IFIC, 55 percent of consumers said they would pay extra for the products enhanced through biotechnology, and these extra costs would be incurred by the manufacturers, and come from the necessity to separate the value-added crops during storage and processing. (Dahm)

There could be some problems that might arise with nutraceutical patents. Some of the R&D work could never be patented because of the minimal "changes in formulations or existing ingredients." Patented products don't always enjoy market success, especially if they await FDA approval for a prolonged period of time. Companies have to conduct costly and time-consuming clinical studies to support a health claim. Patent approval also takes up to two years. (Neff) On the other hand, biotechnology has been pronounced one of the most promising ways for innovation in this area, granted its "ability to provide patent protection, market exclusivity, research incentives and consistently adequate levels of an active ingredient." (Culhane) However, it is hard to measure "the practical and profitable contribution of genetic engineering to the nutraceutical revolution." (Culhane) According to Culhane, consumer research showed that consumers considered nutraceuticals to be "an uncomplicated, mild and safe solution to their healthcare needs." Some consumers do not regard biotechnology as having the same attributes. So, genetic engineering could be "counterproductive to the aims of nutraceutical revolution," although a survey shows that most of the consumers would accept biotechnology if it were to bring nutraceutical benefits. (Culhane)

The following are the latest achievements in biotechnology that show that genetic engineering could be used not only to produce nutraceutical supplements but for a direct consumption by consumers in order to combat micronutrient deficiencies, reduce risk of diseases and prolong lives.

"Yellow Rice"

According to European Commission, the "Carotene Plus" project was completed by successfully modifying a rice plant to make it produce beta-carotene in its endosperm. Rice feeds nearly half of the world's population, but milled rice does not contain any beta-carotene, which creates a big health problem in developing countries. New modified rice contains enough vitamin A to satisfy the vitamin requirements in Asian diet. A research team from the Federal Institute of Technology in Zurich in collaboration with the University of Freiburg in Germany used microprojectile bombardment to create rice with genes providing necessary enzymes to produce beta-carotene. (14) Four plant genes coding for the enzymes isolated, but with help of a bacterial phytoene desaturase, only three genes are needed to achieve carotene production. Two of these genes are from daffodil. The presence of beta-carotene in rice endosperm is responsible for its yellow color of the milled grains. Traditional techniques will be used to transfer this trait into local rice varieties and free access to the seed will be given to subsistence farmers in developing countries. (Hogan)

The same type of research was done with tomatoes, scientists from University of London in Egham have developed tomato lines that have increased levels of lycopene, a vitamin A precursor, twice the normal level, and beta-carotene, up to four times the normal level. "The gene for beta-carotene synthesis was placed under the control of fruit-specific promoters so that the provitamin A would be produced only in a ripening fruit." These tomatoes don't taste different, only look redder. (Prakash, "And now…")

A group of scientists from Japanese Central Research Institute of Electric Power Industry utilized the gene for ferritin, an iron-rich soy storage protein, under the control of an endosperm-specific promoter to create rice grain that contained three times more iron than normal rice. Scientists from Institute of Plant Sciences in Zurich, created transgenic rice using the ferritin gene from beans. Besides creating plants with elevated iron levels, scientists are trying to influence bioavailability of iron in a plant. Bioavailability of iron is affected by phytate, sugar alcohol molecule that seeds store for germination. It strongly chelates iron, zinc, and calcium, making it difficult to absorb them. This problem has been alleviated by adding a gene from fungus, which encodes an enzyme that breaks down phytate, to a rice plant. (13)

A high-tech golden rice has also been developed through genetic engineering, that has increased levels of both iron and vitamin A precursor. It "will offer improved nutrition for the billions of people in developing nations who depend on rice as a staple food." (Whelan)

Genetic manipulation of the aryl migration enzyme and the O-methyltransferase of isoflavanoid biosynthesis can increase production of isoflavones and other phytoalexins in alfalfa. (Dixon)

Stilbene synthase increases the production of resveratrol using metabolic intermediates found in plant cells. Two genes encoding for stilbene synthase have been transferred from grapevine to a tomato plant, and made it rapidly accumulate resveratrol.(22)

The range of new GM products increases every day, the tools are improving and the scientists are acquiring new knowledge and better understanding of gene transfer processes. Biotechnology has had a tremendous impact on agriculture and now it is making its way into our everyday life. Our intentions to improve health and prolong life are being supported by innovations in genetic engineering. The possibilities for advancement seem limitless as novel genes are being discovered and applied. As a result of genetic engineering, new compounds previously not available from plants are generated in plant tissues. Production of certain elements is increased several fold which cuts the costs of mining them from the plants. The nutrients are produced in parts of plants that do not usually produce them and their bioavailability is improved with help of biotechnology. Plants can be used as environmentally friendly, renewable and inexpensive resources of nutrients and chemicals.

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