PL2

NEW TECHNOLOGIES FOR HEALTH FOODS AND NUTRACEUTICALS

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The Nutrition Products Market

Current world consumption of natural health products, nutraceuticals and functional foods is estimated to be anywhere between $70 and $250 billion annually, depending on which product categories are included in the statistics. The U.S. market for "healthy foods" encompassing low fat, low cholesterol, sodium reduced and vitamin/mineral enriched products, is pegged at about $50 billion.[1] U.S. sales of nutrition products consisting of natural health products (including dietary supplements and herbs), natural and organic foods, functional foods and natural personal care products, generated $44.5 billion in consumer sales in 1999.[2,3] Medical foods are defined as foods consumed or administered under medical supervision for the specific dietary management of a disease. This product category had U.S. sales of 150-200 million in 2000.

Total US sales of dietary supplements (including vitamins, herbs, botanicals, sports nutrition, meal supplements and specialty categories) reached $15.7 billion in 2000 (Table 1). However, sales of the specialty ingredient segment have seen considerable growth. Sales of this category have grown 98% from $690 million in 1994 to $1.24 billion in 1999 (or $2.12 billion, according to another source) and

Table 1. US Nutrition Industry Retail Sales ($ Millions)*

Product Category	1996	1997	1998	1999	2000	Change (%) 1996-2000
Vitamins	4,780	5,190	5,460	5,770	6,070	27
Herbs & Botanicals	2,990	3,530	3,920	4,290	4,650	56
Sports Nutrition	1,070	1,270	1,410	1,540	1,660	55
Minerals	900	1,070	1,130	1,200	1,270	41
Meal Supplements	620	660	670	690	710	15
Specialty Ingredients & Others	920	960	1,110	1,240	1,380	50
Total Supplements	**11,280**	**12,680**	**13,700**	**14,730**	**15,740**	**40**
Natural/Organic Food	7,010	7,990	8,730	8,440	10,120	44
Natural/Organic Personal Care	3,660	2,940	3,230	3,520	3,790	4
Total Nutrition Industry	**20,950**	**23,610**	**25,660**	**27,690**	**29,650**	**42**

*Nutrition Business Journal, San Diego

$1.38 billion 2000. Sales of functional foods accounted for about $16.1 million in 1999. This functional foods definition broadly includes any product with added ingredients or fortification specifically for health or performance purposes. Hence, this category includes "designer foods" ranging from cholesterol-lowering spreads, such as Benecol® and Take Control®, to ready-to-drink teas with herbs, "performance" foods, e.g., sports drinks and bars, hypoallergenic baby foods and soymilk and "enriched" foods, e.g., cereal, milk and yogurt.

Following years of double-digit growth, consumer sales of supplements grew approximately eight percent in 1998 and 1999, and seven percent in 2000, or about twice the rate of the U.S. economy (Table 2).[3] In comparison, the $466 billion conventional food business grew at an annual rate of only 2-3%.[4] In 1999, projections for dietary supplements, functional foods and nutraceuticals had anticipated a 10% annual growth rate for the next few years. However, the market for dietary supplements entered into an adjustment period. US sales of herbal and botanical supplements have been negative or flat lately. Similar trends are witnessed in Europe, where growth was limited to five percent during this period. The slower growth rates are partly attributable to consumer concerns about product quality and efficacy, and new US Food and Drug Administration (FDA) regulations on structure/function claims for dietary supplements.

Table 2. US Specialty Supplement Sales ($ Millions)*

Specialty Supplement	1996 Sales		1997 Sales		1998 Sales		1999 Sales	
	Bulk	Retail	Bulk	Retail	Bulk	Retail	Bulk	Retail
Melatonin	20	105	17	90	16	80	16	80
Probiotics	16	80	17	90	19	95	19	100
Docosahexanoic acid	10	50	10	55	10	50	10	50
Fish Oils/Shark Cartilage	15	75	17	90	21	110	23	120
Glucosamine	17	90	24	130	47	240	62	320
Bee Products	9	45	9	50	11	55	12	60
Coenzyme Q10	6	30	8	40	16	80	19	100
5-Hydroxytryptophan	4	22	6	30	7	35	8	40
Amino Acids	8	40	9	50	11	55	12	60
Homeopathics	43	220	49	260	58	300	66	340
Others (Enzymes, Hormones, Oils, etc.)	32	163	14	75	16	80	18	90
Total	**178**	**920**	**180**	**960**	**230**	**1,180**	**265**	**1,360**

*Nutrition Business Journal

Specialty Supplement Categories

Glucosamine sales were at an estimated $10 million in 1994 and reached $871.8 million in 1999, making it the top selling supplement (Table 3). The raw material cost of glucosamine is about $20/kg and a 10-20 day supply typically costs the consumer $14-15. Whereas the average retail gross margins for specialty supplements are about 80%, those for glucosamine are over 320% (Table 4).

Glucosamine has established itself as effective remedy for arthritis and other joint problems over

Table 3. US Sales of Top Ten Specialty Supplements 1999*

Specialty Supplement	Sales ($ illions)
Glucosamine	871.8
Chondroitin Sulfate	394.1
Coenzyme Q10	288.1
Methylsulfonyl methane	102.6
Soy isoflavones	84.5
Fish Oils	82.5
Lactobacillus acidophilus	68.6
Amino Acids	63.7
Flax oil	57.9
Docosahexanoic acid	44.4
Total	**2,058.2**

*Hartman Group

Table 4. Average Retail Gross Margins For Selected Specialty Supplements*

Specialty Supplement	Gross Margin (Percent)
Melatonin	80
Probiotics	100
Docosahexanoic acid	50
Fish Oils & Shark Cartilage	120
Glucosamine	320
Bee Products	65
Coenzyme Q10	100
5-Hydroxytryptophan	40
Amino Acids	60
Homeopathics	340
Others (Enzymes, Hormones, Oils, etc.)	100

*Nutrition Business Journal, 2000

recent years. This carbohydrate is a natural component of cartilage and is involved in the production of joint lubricating synovial fluid. It is commercially derived from chitin from shellfish sources. Some 13 clinical studies involving over 2000 people globally have substantiated its efficacy and safety claims. One of these large-scale studies was conducted by the National Institutes of Health (NIH) Center for Complementary and Alternative Medicine and the National Institute of Arthritis and Muscoskletal and Skin Disease in 2000. This is NIH's first clinical study of a non-pharmaceutical product.

The second leading selling supplement, Chondroitin sulfate is derived from bovine trachea or shark cartilage. It is a complementary supplement for arthritis and other joint problems. The raw material cost of Chondroitin sulfate is about $110-130/kg, and a 15-25 day supply retails for $19-22. 1999 sales reached $394.1 million. Some 100 glucosamine and chondroitin products are available in US health food stores, pharmacies, supermarkets and the Internet.

The third largest sales supplement is Ubiquinone or Coenzyme Q10. Coenzyme Q10 is a lipophilic antioxidant involved in energy production. Coenzyme Q10 suppliers include Kyowa and Nisshin Flour Milling. The supplement is also used in personal care products. The fourth ranking supplement is Methylsulfonyl methane (MSM). MSM provides a natural dietary sulfur source and has functionality in muscle formation, hair, skin and nails. MSM offers benefits for reducing allergies, arthritic pain and inflammation, tendonitis, constipation and gastrointestinal problems. Other potential applications include treatment of lupus, breast cancer and diabetes.

Numerous medical benefits have been identified for marine and vegetable oils based on clinical trials. These include improved visual acuity, brain function, cholesterol reduction and pre- and postnatal development. The essential polyunsaturated fatty acids (PUFAs) are also implicated in boosting the immune system. The omega-3 fatty acids, eicosapentaenic acid (EPA), docosahexanoic acid (DHA; see Tables 2-4), and the omega-6 acids arachidonic and linoleic acid are the most prominent algal or fish derived representatives. Conjugated linoleic acid is another physiologically active lipid whose potential benefits include body weight management, cardiovascular health and immune modulation. Other important sources include canola, coconut, flax and palm oils. Flaxseed oil (see Table 3) contains α-linolenic acid, which can act as fish oil substitute, since it is metabolized into EPA and DHA.

Borage and evening primrose oils contain high levels of the omega-6 fatty acid, γ-linolenic acid (GLA). Among GLA's indications are the reduction of cholesterol, rheumatoid arthritis, inflammation and joint pain and the relief of skin conditions, e.g., allergic dermatitis and eczema. The essential fatty acids (EFAs) represent omega-3 and omega-6 acids that are implicated in cell growth, nerve function and respiration. EFA deficiencies can manifest themselves in circulatory problems, dry skin, fatigue,

gastrointestinal and heart disorders and growth retardation. The market for DHA alone could climb as high as $2 billion in retail sales, if clinical trials currently in progress verify additional benefits for diseases such as cancer, cardiovascular disorders and depression.

Flaxseed contains high levels of lignans that bacteria can convert into estrogen-like compounds. These reduce menopausal symptoms and the risk of hormone-dependent cancers, e.g., breast, endometrial and prostate cancer. Canola oil is a rich source of phytosterols such as brassicasterol, campesterol and β-sitosterol. Brassicasterol, unique to canola oil, reduces water loss on skin surface and enhances moisture penetration. β-Sitosterol is well known for its hypocholesterolemic activity[5] and has found commercial outlets in Benecol® (McNeil Consumer Healthcare) and Take Control® (Unilever).

The prebiotics and probiotic product category, ranked as the 7th top selling (see Tables 3 and 4), is receiving increasing attention and consumer awareness. Among new prebiotic products are Nestle's *Lactobacillus johnsonii*. This proprietary bacterium adheres to the intestinal walls, displacing "bad" bacteria stimulates the growth of bifidobacteria and other immune-modulating components, activates phagocyte activity in blood and enhances immunoglobulin production. Considerable attention is also being focused on arabinogalactans of late. Arabinogalactans are found in carrots, radishes, pears, wheat, coconuts, tomatoes and other vegetables. Other sources include larch, Echinacea, *Angelica acutofolia* and *Curcumina longa*. Several clinical studies have demonstrated arabinogalactan's bifidobacteria and bacteroides stimulating activity. It is fermented in the large bowel to short chain fatty acids (SCFAs), a special feature being the high proportion of butyrate among the SCFAs. Butyrate levels from arabinogalactan are higher than those from pectin or xylan. Butyrate provides an important energy source for the colon epithelium and regulates cell growth and differentiation. Its metabolic absence can be linked to ulcerative colitis. Larch arabinogalactan has immune modulating and cell proliferating properties.

5-Hydroxytryptophan (5-HTP; see Tables 2 and 4), is a serotonin precursor and as such implicated in several vital biological processes, including sleep, emotional stability, pain sensitivity and addictive cravings. Inadequate serotonin levels can cause a vast array of symptoms, ranging from anxiety and insomnia to obsessive/compulsive behavior and suicidal depression. 5-HTP reduces appetite and has also been proposed as a non-drug alternative in the treatment of depression. In several trials, 5-HTP has proved to be as effective as its prescription drug counterparts, without causing side effects. It reportedly reduces the severity of Parkinson's disease symptoms and the severity of migraine headaches. 5-HTP relieves PMS pain by countering the hormone-induced decrease in serotonin levels that occur naturally during menstruation.

The FDA's 1999 approval of coronary heart health claims for soy-based foods has boosted sales of this product category by 28% from $2 billion in 1999 to $2.56 billion in 2000 (see Table 3).[6] The health claim is permitted for products containing a minimum of 6.25 grams of soy protein per serving. Soy products offer broad health benefits and are being increasingly incorporated into various functional foods. Among the new entries are TolyTerber's (Netherlands) SoyLife, Oil Co.'s (Japan) Soy Embryo tea, Schouten's (USA) SoyLife series products, and Archer Daniels Midland's (USA) Novas Isoflavones condensate as food additive and nutrition supplement. Whilst the growth of soy-based food products is projected at about 8% annually through 2005, the specialty market segment comprising nutritional beverages, food bars, sports supplements and diet/medical products, is expected to increase by 16% in the same period. Sales of soy-based food products, such as meat analogs (veggie-burgers), soymilk, soy yogurt, cheeses, ice cream, butter and similar products are expanding almost exponentially (by 40-45 percent annually). Tofu sales are rising 15 percent annually, with Asian Americans being the main consumers.

Soy products are derived from soybeans or rice and contain a range of nutrients, including isoflavones, saponins, vitamin E, omega-3 and omega-6, folic acid, lecithin, phytosterols, proteins and fiber. The isoflavones are considered to be responsible for many of soy's biological activities. Soy isoflavones and their three main constituents, Genistein, Daidzein and Glycitein, are powerful antioxidants. Recent studies confirm that soy isoflavones may reduce the risk for certain cancers, such as colon cancer, breast cancer and ovary cancer by preventing free radical damage. Soy Isoflavones can also reduce cholesterol, ease menopausal symptoms, prevent heart disease and osteoporosis. Soy products may also exhibit prebiotic features. Consumption of soy isoflavones can be as effective as hormone replacement therapy (HRT), without potentially increasing the risk of breast cancer as in HRT. They may additionally offer benefits for the prevention of prostate cancer. The number of men at risk for prostate cancer is expected to grow 32 percent in this decade, and the number of women entering menopause will rise 22% from 52 million in 2000 to 63 million by 2010.

Tocotrienols represent four structurally related dietary supplements in the vitamin E (tocopherol) family, whose medical significance has emerged in recent years. It is increasingly being recognized that the whole vitamin E family should be used, as the individual tocotrienols and tocopherols each have important and distinct health benefits. Thus, γ-tocopherol has stronger anti-inflammatory and anti-oxidant properties than α-tocopherol. γ-Tocopherol is also a more potent inhibitor of nitrogen radicals that are considered the causative agents in arthritis, multiple sclerosis, and mental diseases, such as Alzheimer's. The common commercial sources of natural vitamin E (canola, corn, cottonseed, soy, and sunflower oil) contain little or no tocotrienols. Synthetic vitamin E is pure α-tocopherol without the other tocopherols and tocotrienols.

Tocotrienols are present in the oil of rice bran, palm fruit, barley, and wheat germ and are commercially extracted from the distillate of palm and rice bran oil. Suppliers include CarboMer, Carotech, Eastman Chemical, Fuji Chemical Industries, and Pharmachem Laboratories. Manufacturing sources for Vitamin E, natural sources of tocotrienols, such as rice bran and palm oil, contain a mixture of tocotrienols and tocopherols. The naturally most prevalent tocotrienol, γ-tocotrienol appears to offer the strongest potential for dietary health benefits. Tocotrienols are powerful antioxidants and activate antiproliferative and apoptic signal pathway in mammary epithelial cells.[7] They induce apoptosis of human breast cancer cells and display cholesterol-lowering activity.[8,9] γ-Tocotrienol in particular modulates 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA), the enzyme involved in cholesterol production in the liver. The tocotrienol distillates from palm and rice bran oil contain in varying proportions a series of other important phytonutrients, such as squalene, phytosterols (β-sitosterols), coenzyme Q10, terpenes, sterol fatty acid esters, glycerides, and mixed carotenoids.

Canadian companies have pioneered eggs with increased levels of omega-3 fatty acids, whole grains including wheat, oat and barley products with enhanced amounts of dietary fiber (soluble and insoluble), lactose free and fermented dairy products, modified fatty acid vegetable oils, legumes and fruit products. There are the occasional setbacks, however. Just as new health spreads were settling in on grocery-store shelves, the Canadian government recently cautioned that some may not be so healthy for everyone after all. Health Canada declared Unilever's Becel Pro-activ spread potentially unsafe, issuing an advisory warning that Becel may pose health risks to pregnant women, children, and people on cholesterol-lowering medications. The new variety of Becel margarine, approved for sale in Europe and Australia, contains added soy phytosterols that help reduce plasma cholesterol. Pro-activ has ten fold higher plant sterols levels than similar fat spreads.

Fungal glucans have been of considerable interest as immune stimulants.[10,11] The diverse physiological activities of zymosan, a crude cell wall preparation from *Saccharomyces cerevisiae,* are known for several decades.[12] Zymosan's active components are β-1,3-glucans. Many natural product glucans share a common linear β-1,3-glucan backbone that may bear varying degrees of branching, usually β-1,6-linked, single glucose residues. In addition, there are β-1,6-glucans with varying degrees of β-1,3-branching. β-Glucans may be derived from *Saccharomyces* (Bakers yeast), *Alcaligenes* (curdlan), *Aspergillus, Fusarium, Laminaria digitata* (laminarin), Lentinan edodes (Shitake mushroom), Maitake mushroom, *Poria cocus* (pachyman), *Schizophyllum commune* (schizophyllan), *Sclerotinia* (scleroglucan) and several other sources.[13] The immune-modulating β-1-3; β-1-6-glucan from wild Yunzhi (umbrella mushroom) has reported potential in immunotherapy of chronic hepatitis, diseases of the digestive and respiratory systems, and anti-tumor activity for breast, cervical, liver and

uterine cancers. PSK or Krestin, from *Coriolus versicolor* is a polypeptide-linked β-1,4-, β-1,6-glucan with 1,3- and 1,6-linkages. It is an immune stimulant with antineoplastic activity and is widely used as an adjunctive treatment for cancer and hepatitis B and C, AIDS, herpes genitalis, general immune suppression, and post-surgical recovery.[14] Glucans stimulate hematopoesis, anti-tumor response, wound healing and resistance to microbial challenge.[15] Several β-glucans are currently in clinical trials.

The FDA's recent approval of cholesterol-lowering claims for oat has significantly boosted sales of β-glucan containing products from oat and barley.[16] One of the newer β-glucan entries is from the *Agaricus blazei Murill* mushroom. It significantly stimulates the production of interferon and interleukin, activating the immune system.[17] The β-glucan is effective against Ehrlich*s ascites carcinoma, sigmoid colonic cancer, ovarian cancer, breast cancer, lung cancer, and liver cancer as well as against solid cancer. The Agaricus β-glucan also exhibits anti-viral properties. A wide range of β-glucans is available from CarboMer. Other suppliers include Quaker Oats and Deutsche Hefewerke.

New Nutraceutical Trends

Continued strong sales growth is expected for sports nutrition drinks and herbal products. The top 20 selling herbal products generated $2.5 billion in 1999. Among the top selling US botanicals are ginkgo biloba ($396 million), garlic ($281 million), St. John's wort ($209 million), saw palmetto ($193 million), Echinacea ($193 million), ginseng ($159 million), and grape seed extract ($122 million) (see also Table 1).[18] Some of the more recent health foods and nutraceutical developments are highlighted below.

Functional Foods For Children

Growing evidence shows that the seeds of many adult disorders are planted in childhood, and it is therefore important that pediatric care providers recognize risk factors for adult disease in children and institute effective interventions. Many adult medical disorders are significantly related to nutritional factors.[19]

It is well known that about half of all US adults are obese and at risk for coronary disease. However, less widely recognized is the fact that childhood obesity rose by 14 percent in the 1990s, and about one quarter of the American youth (16 million) between the ages of 4 and 18 are clinically overweight, i.e., exceed their ideal weight by ten percent or more. The frequency of Type II diabetes among diabetic adolescents has alarmingly risen from one percent 20 years ago to 50 percent today. Since fat cells produce estrogen, obesity may trigger puberty at younger ages. This presents elevated

risks for diseases such as breast cancer. Whilst teenage milk consumption was twice as much as that of soda ten years ago, it has dropped to the same level today. Soft drink consumption rose 37% among 9 year olds over the last two decades, and 21% among 2-5 year olds. Snack foods now constitute 25% of children's caloric intake. Snacking, sugar-rich juices and "on the go" meals have contributed to behavior changes, which are compounded by increased meal and beverage serving sizes and lack of physical activity.

As alarming as these trends are, no slow down is evident in the record levels of childhood obesity and related diseases. Obesity is the most critical problems for youth, bringing with it an increased risk of diabetes, elevated blood pressure, coronary artery disease and certain cancers. These developments comprise not only a long-term problem of catastrophic proportion for the nation's health system. The childhood disorders manifest themselves at ever-lower ages. A recent New York survey found obese preschoolers as young as three with elevated blood pressure and cholesterol levels. An Ohio clinic found significant arteriosclerosis for 16% of teenage heart donors.

A new product category, functional foods for children, is targeting this population segment. Most health foods have to date not taken into consideration the specific dietary requirements of children. These can differ drastically from those of adults. Energy bars for kids have been introduced based on Recommended Dietary Allowances for children.[20]

Diabetes Prevention

Diabetes is on the rise globally. Diabetes has a significant impact on the world's healthcare costs with an estimated 130 million diabetics requiring treatment. The total diabetes care market is projected to exceed $11 billion this year. Controlling the morbidity and mortality of this debilitating disease is on the agenda of all health care providers – both public and private. Diabetes is a devastating disease of immense proportions. The number of people afflicted continues to grow at an alarming rate. The World Health Organization expects the number of diabetics to increase globally from 130 million to 350 million over the next 25 years. In all its forms, the chronic disease now affects about 16 million Americans (6% of the population). It is the fourth leading cause of death, accounting for the loss of 160,000 lives a year. Despite extensive therapeutic development and disease management programs, the cost of diabetes in the U.S. alone is exceeding $120 billion, or more than 10 percent of the nation's total annual healthcare costs, taking into account the secondary illnesses associated with diabetes—including circulatory, retinal, and renal complications leading to blindness, kidney disease, limb amputations, and heart disease.

By 2005, India will have the largest number of 30-35 million diabetics and every fifth diabetic in the world will be an Indian. India is not at all prepared to deal with this impending epidemic. In the

early 1970s, the Indian Council of Medical Research reported a diabetes prevalence of 2.3% in urban areas and 1.5% in rural areas. Recent studies have shown that the prevalence of type II diabetes in urban southern India increased by 40% to 11.6% between 1989 and 1995, while the population's age structure largely remained unaltered. Furthermore, the disease onset appears at a much younger age and most cases come with complications at the time of diagnosis itself. Almost 50% of the cases have some tissue damage.

Some 7 million diabetics are estimated for Japan. The highest incidence levels are seen for the 50-60 year old group. This is of particular concern, since Japan has the world's most rapidly aging population. Some eight percent of Japan's population, or ten million people are estimated to be at risk for developing diabetes.

The high cost of diabetes in terms of health care expense and quality of life has prompted a search for alternative therapies. Non-drug interventions against diabetes can clearly play a key role in stemming this epidemic tide. Some of the available approaches are described below.

Weight Management Products

Among the possible approaches to diabetes prevention are weight management products. Chitosan has found widespread use for fat absorption and weight management. Konjak glucomannan and guar are traditional food ingredients in Asia, where they are increasingly used in low-calorie and health foods.[21,22] Several clinical studies have demonstrated that modest Konjak consumption can significantly lower plasma glucose and cholesterol levels.[23,24,25] *Garcinia cambogia* fruit powder concentrate from India and Thailand has reputed weight loss features. Many Chinese teas have been clinically tested for their ability to reduce weight. The Indian Gymnema sylvestre Ayurvedic (gurmar) herb blocks sweet taste and could therefore act as a natural appetite suppressant. The pseudotetrasaccharide Acarbose is a natural β-glucosidase inhibitor and highly effective antidiabetic.

Hypoglycemic Management Products

The lipid lowering properties of β-glucans have been demonstrated in many human trials.[26] β-Glucans reduce the risk of arteriosclerosis, hypertension and obesity. Their value has also been established for the treatment of diabetes.[27] In addition, they are also considered to lower the risk of colon cancer.

Fenugreek (*Trigonella foenuim-grecum*) is a common spice that the FDA recognizes as GRAS (Generally Recognized As Safe). Among its traditional uses are as remedy for diabetes, gastrointestinal disorders, gout, hyperlipidemia, inflammation and wound healing. Fenugreek's active

components include alkaloids (carpanine, gentianine, trigonelline), amino acids (such as the insulin secretogogues arginine and 4-hydroxyisoleucine), coumarins, galactomannan, nicotinic acid, saponins (diosegenin, fenugreekine), and other vitamins and minerals. The hypoglycemic activity is likely attributable to the galactomannan's inhibitory effect on glucose absorption. Fenugreek's activity has been verified by clinical studies with both type I and type II diabetes patients.[28]

The Japanese ministry under its Foods for Specific Health Use (FOSHU) regulations has approved several products that assist in moderating sugar absorption. Among these are guava leaf polyphenols (Yakult Honsha), indigestible dextrin (Matsutani Kagaku) and wheat albumin (Nisshin Flour Milling). Other products may be beneficial in this respect, including Chinese fenugreek gum, Taiwanese golden vein lotus, Indian *Salacia oblongata* tea, green tea polysaccharides, black soybean extract and Japanese akamoku seaweed. Some other traditional ingredients that may lower plasma glucose levels are psyllium seed husk, konnyaku flour, Mitake mushroom extract, mulberry leaf extract, and evening primrose seed extract. Another prominent example is resistant starch, a recently developed product.[29,30]

Aloe barbadenesis (aloe) has many traditional medical benefits, including wound healing and anti-diabetic activities. Its main components include glucomannan, saponins, sitosterol, salicylic acid and amino acids. Oral use of aloe gel resulted in reductions in fasting plasma glucose (40%) and hemoglobuin Alc levels in one study.[31]

Among other botanicals with hypoglycemic activity is *Momordica chantia* (bitter melon). The fruit and juice are prevalently used in diabetes control in Asia, Africa and South America. Its active ingredients include plant insulin or polypeptide "p", an insulin-mimetic peptide, and the steroid glycoside, charantin.[32] Several clinical studies suggest potential benefits, although limited data exist at this time.[33,34]

In addition to its sensory inhibitory properties, *Gymnema sylvestre* or gurmar reportedly increases glucose uptake and utilization, and improves the function of pancreatic β-cells. Gurmar's active ingredients are amino acids (betaine, choline, trimethylamine), the acid-insoluble gymnemic acids (triterpenoid saponins), and steroids (quescitol, stigmasterol). Clinical studies found reductions in fasting blood glucose levels (19-35%), postprandial blood glucose (21%) and hemoglobuin Alc. (29-35%).[35]

Panax quinquefolius (ginseng) was reported to have similar activities in patients with type II diabetes.[36] Nopal and prickly pear cactus (*Opuntia streptacantha Lemaire*) has also been studied in type II diabetes where postprandial blood glucose decreased (10-20%) within 2-4 hours after nopal intake or up to 30% after a 10 day nopal regimen.[37]

With the increasing concern about macular degeneration and consumer awareness of the importance of nutrition for eye health, sales of lutein and other carotenoids have continued their strong performance recently. Among the top ten US multivitamins sold in 2000, only the three lutein containing brands experienced positive sales growth of 20%, compared to a 11% overall decline of the other brands. Lutein, prevalent in many fruits and vegetables, was recently granted GRAS status and is expected to enter into cereal and juice products. Lutein may also have cardiovascular benefits that could boost its sales even further.[38] Lutein and zeaxanthin act as antioxidants and blue light filters in the macula. A related caroteinoid, Astaxanthin inhibits lipid peroxidation and is considered to be a more potent antioxidant than vitamin E or other carotenoids.[39] Fuji Chemical Industries extracts Astaxanthin with supercritical carbon dioxide from *Haematococcus pluvialis* algae.

Recent Innovations

Many commercial efforts are focused on facilitating the enhanced delivery, bioavailability and stability of nutraceutical ingredients. Extraction of plant constituents with supercritical fluids (SCFs) can be employed as a mild alternative to conventional processes for the manufacture of concentrated active or solvent-free extracts. Astaxanthin, mentioned above, and other carotenoids represent examples of very labile molecules that benefit from SCF extraction processes and stabilization on inert carriers. Microencapsulation and enteric coating of probiotics and coating of lactic acid bacteria are being introduced to permit consumers to take probiotics without food. Such innovative processes and formulations allow manufacturers to potentially attain proprietary positions for well established natural ingredients and distinguish their products from those of competitors.

One of the exciting new approaches to disease control may be on the horizon in the probiotic arena. Chromosome sequencing of probiotic bacteria may open the way for targeting certain diseases. The engineered bacteria may be designed to release chemicals aimed at warding off undesired species.

Perhaps one of the greatest nutraceutical opportunities is just emerging, as increasing evidence is being established between nutrition and aging and mental disorders, such as Alzheimer's disease (AD). AD is the most prevalent cause of dementia in the United States. Some 50-60% of individuals age 65 and over (about 4 million Americans) have AD and another 20% have Parkinson's or Lou Gehrig's Disease. The proportion of the US population (and similarly of most other industrialized nations) that will be 65 years or older is expected to increase exponentially. The AD patient population alone is expected to reach 14 million by 2050. Current therapeutics for AD, the most prevalent cause of dementia, offer only modest curtailments in the progression of cognitive impairment. New, effective and safe therapeutics would constitute a major milestone in dementia treatment.

Apoptosis (programmed cell death) is an integral part of the aging and development of the central nervous system and is linked to the pathogenesis of neurodegenerative diseases.[40,41] The free radical nitric oxide acts as neurotransmitter and is implicated in apoptosis. Ample evidence indicates that various natural products, including dietary ingredients and herbal products, may have beneficial antioxidant and other neuroprotective functions. Because increased oxidation is an important feature of AD and low concentrations of antioxidant vitamins C and E have been observed in the cerebrospinal fluid of AD patients, supplementation with these antioxidants may delay the development of AD.[42,43] Diets with high levels of vitamins B6, B12 and folate appear beneficial, as are certain minerals, while red wine in moderate quantities appears protective.[44] These materials also offer the benefit of established safety profiles. One hypothesis is that some of these natural materials will inhibit radical-mediated apoptosis and could serve as anti-aging and neuroprotective agents.

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