

A Review On: Nutraceuticals Challenges in Formulation and Its Regulatory Aspects

Radheshyam

Assistant Professor, Department of Pharmacology, Shakti college of Pharmacy, Balrampur, U P, India

***Corresponding author**

Radheshyam, Assistant Professor, Department of Pharmacology, Shakti college of Pharmacy, Balrampur, U P, India

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Abstract

Nutraceuticals have sparked great attention because of their perceived safety, The current article focuses on the need for appropriate diets, health issues associated with failure to adhere to the known healthy eating models, development of new nutraceuticals/functional foods/food supplements with novel health benefits, elucidation mechanisms of action of these products, and to define and understand the analytical, challenges during the formulation of different dosage form, current scenario in India, future and regulatory aspects of nutraceuticals. the Indian industry and regulatory scenario are relatively nascent and have great potential to develop and compete with other international agencies. This is a rapidly growing industry in India and several initiatives have been taken in this direction to make India one of the key future players in the area of nutraceuticals. This article can help you stay up to date on the latest advancements in nutraceutical research.

Keywords: Nutraceuticals, Food Safety, Probiotics

Introduction

The word “nutrition” and “pharmaceutical”, was coined in 1989 by Stephen L. Defelice, founder and chairman of the Foundation of Innovation Medicine. Nutraceuticals are products derived from food sources that are purported to provide extra health benefits, in addition to the basic nutritional value found in foods. Depending on the jurisdiction, products may claim to prevent chronic diseases, improve health, delay the aging process, increase life expectancy, or support the structure or function of the body [1].

The Following are the Causes Behind the Move Toward Nutraceuticals:

1. A growing percentage of customers are concerned about rising healthcare prices.
2. People who are dissatisfied with pharmaceutical agents for health promotion are turning to nutraceuticals to improve their health and avoid chronic disease.
3. Health care providers know that our overly processed food supply, which is derived from crops cultivated with chemical fertilizers, pesticides, herbicides, and frequently genetically engineered seeds, lacks the nutrients required for optimal health.
4. People who believe in prevention rather than treatment.
5. People suffering from chronic ailments who have found no relief from allopathic therapy.

6. Economically challenged patients [2-6].

With few exceptions, the U. S. Food and Drug Administration (FDA) has not approved nutraceuticals for health benefits or disease prevention; nonetheless, the manufacturers of nutraceuticals have been touting them as health-promoting agents.

Categories Based on Natural Source

- Carbohydrates & Fiber
- Fat & Essential fatty acids
- Protein
- Minerals like Macro minerals & Trace minerals
- Vitamins
- Water

Other nutrients like Antioxidants, Phytochemicals & Intestinal bacterial flora Recombinant nutraceuticals. Are simply natural with no changes to the food. Food contains several natural components that deliver benefits beyond basic nutrition, such as lycopene in tomatoes, omega-3 fatty acids in salmon or saponins in soy [7, 8].

Dietary Supplements

Dietary supplement is a product that provides concentrated nutrients taken from food sources in liquid or pill form. The term was

defined in the United States by the Dietary Supplement Health and Education Act (DSHEA) of 1994: “A dietary augment is a product taken by mouth that contains a “dietary element” designed to supplement the diet.” Vitamins, minerals, herbs or other botanicals, amino acids, and components such as enzymes, organ tissues, glandular, and metabolites are examples of “dietary ingredients” in these goods. Dietary supplements can also be extractors concentrates, and may be found in many forms such as tablets, capsules, soft gels, gel caps, liquids, or powders.

Dietary supplements do not need to be authorized by the US Food and Drug Administration (FDA) before being marketed, but firms must register their production facilities with the FDA.

Dietary supplements, with a few well-defined exclusions, may only be marketed to maintain the structure or function of the body and may not claim to cure a disease or condition, and must include a label that states: “These statements have not been evaluated by the Food and Drug Administration.” This product is not meant to be used to diagnose, treat, cure, or prevent illness.” It accomplishes this by utilizing the efficiency of such nutraceuticals in detoxifying the body, avoiding vitamin and mineral shortages, and restoring good digestion and dietary habits [9, 10].

They are Grouped on the Basis Of Chemical Constituents

- A) Nutrients
- B) Herbals
- C) Phytochemicals

Phytochemicals are plant nutrients that have specific biological functions in maintaining human health. They work in the following ways.

1. Biochemical reaction substrate.
2. Enzymatic reaction cofactors
3. Enzymatic reaction inhibitors
4. Absorbents that attach to and remove unwanted constituents in the gut.
5. Improve critical nutrient absorption and/or stability.
6. Beneficial bacteria’s growth factor of choice.
7. Beneficial bacterium fermenting substrate
8. Inhibitors of harmful gut bacteria that are selective.
9. Chemical scavengers that are reactive or poisonous.
10. Agonizing or antagonistic ligands for cell surface or intracellular receptors [11].

Microorganisms that are Probiotic

They push away pathogens like yeasts, other bacteria, and viruses that may otherwise cause sickness and form a mutually beneficial relationship with the human gastrointestinal system. They have an antimicrobial effect by altering the microflora, preventing pathogen adhesion to the intestinal epithelium, competing for nutrients required for pathogen survival, producing an antitoxin effect, and reversing some of the effects of infection on the intestinal epithelium, such as secretory changes and neutrophil migration.

- Probiotics should be derived from humans.
- Commonly found gram-positive organism.
- Has the ability to survive after passing through acid and bile.

- Has the ability to attach to human intestinal cells and proliferate in the gut.
- Can function as an antagonist against pathogenic or carcinogenic microorganisms.
- Clinically verified and confirmed health benefits [9].

Nutraceutical Enzymes

Enzymes are an essential part of life, without which our bodies would cease to function. Those people who are suffering from medical conditions such as hypoglycemia, blood sugar disorders, digestive problems and obesity, eliminate the symptoms by enzyme supplements to their diet. These enzymes are derived from microbial, plant and animal sources [12, 13].

Prebiotics

Prebiotics are a relatively recent addition to our lexicon and are chemicals that we do not digest when we ingest them. Instead, they serve as a source of nutrients for the beneficial probiotic bacteria. This promotes the growth of probiotic bacteria in a favorable environment, lowering the likelihood that dangerous germs may begin to proliferate in our digestive system. Inulin is a prebiotic that is commonly found in processed meals. It is, in essence, a form of fiber derived from the roots of plants such as chicory, Jerusalem artichoke, and even dandelions [14].

Non-Traditional Nutraceuticals

Are artificial foods prepared with the help of biotechnology. Food samples contain bioactive components which are engineered to produce products for human- wellness. They are arranged into.

- Fortified nutraceuticals.
- Recombinant nutraceuticals.

Fortified Nutraceuticals

They are enhanced by vitamins and minerals, normally up to 100 percent of the nutritional dietary reference intake. It consists of fortified foods derived through agricultural breeding, as well as additional nutrients and/or additives containing folic acid. Some examples include cholecalciferol-fortified milk, which is used to treat vitamin D insufficiency [15].

Recombinant Nutraceuticals

Biotechnology is used to make energy-saving foods such as bread, wine, fermented starch, yogurt, cheese, vinegar, and others. Biotechnology enables the manufacture of probiotics and extraction by enzyme/fermentation technologies of bioactive constituents as well as genetic engineering.

Commercial Nutraceuticals

It’s more expensive and dangerous than ever before to find the new chemical. Many pharmaceutical firms are currently striving to produce nutraceuticals because of the enormous and increasing market, without a doubt. Most of the treatment fields, for example anti-arthritis, cold and cough, sleep problems, digestion and prevention of certain malignancies, osteoporosis, blood pressure, cholesterol management, pain-mongering, depression and diabetes, include nutraceuticals. Recognition of the health advantages of omega 3 rich marine food intake is one of the most promising advances in research into the prevention of human nutrition and

illness in the past 3 decades [16].

- Dietary supplements,
- Functional food,
- Medicinal food,
- Pharmaceuticals.

Medicinal Food

A food formulated to be consumed or administered internally by a physician for a specific dietary treatment of a disease or condition, for which distinguished nutritional requirements are established by medical assessment, even with no components that promote disease or contents. Physicians have been recommended for different health problems leading to impairment of conventional intake, digestion, absorption or metabolism of foods like phenyl ketonuria, coeliac disease and lactose intolerance [17].

Functional Foods

Functional foods are “all foodstuffs or food ingredients, which can offer health benefits other than those included within, according to their commonly recognized definition. Functional food is intended to enable customers, rather than by ingesting foods produced in the form of fluid or pill, to eat enhanced food near to their natural condition. Functional foods, called nutrition, have been either supplemented or strengthened. This method restores the nutritional content of a meal to similar levels prior to processing. Additional nutrients such as vitamin D in milk are sometimes supplemented [18].

Functional foods are defined by Health Canada as “ordinary foods that have components or substances added to provide a specific medicinal or physiological advantage other than a merely nutritional impact.” In Japan, three standards must all functional foods meet: food.

1. Present in its natural form instead of a capsule, pill or powder.
2. Eaten as frequently as day in the diet; and.
3. In order to prevent or manage diseases, it must regulate a biological process [19].

Dietary Fibers are of Two Types

1. Water insoluble fibers.
2. Water soluble fibers.

Daily recommended intake is 30-40 gms.

Sources

Whole grain cereals, wheat products, Oats, dried beans, legumes.

Antioxidants are of 3 Categories

1. True antioxidants.
2. Reducing agents.
3. Antioxidant synergists

Deficiency causes diseases like Cancers, rheumatoid arthritis, alzheimers disease, cardiovascular diseases.

Lipids

- Fats are highly concentrated sources of energy for body.
- Saturated fatty acids
- Monosaturated (MFA)

- Polyunsaturated (PUFA)
- Eicosapentaenoic acid -EPA (20:5n-3)
- Docosahexaenoic acid - DHA (22:6n-3)
- Saturated fats- animal based products
- MFA&PUF – plant origin
- Trans fatty acids are products of partial hydrogenation of PU fats and are typically solids at room temperature.

MFA & PUFA do not promote formation of the fatty deposits that can clog the arteries.

Saturated Fatty Acids Palmitic, lauric, myristic acids are major cholesterol-elevating fatty acids in our diets.

Eskimos –diet is rich in cholesterol and fat therefore they are free from heart diseases Fish rich linolenic acid, found in fish + soy-bean oils

Linoleic acid –corn, soy bean oils.

Linolenic acid- Omega 3fatty acids

Linolenic acid (18:3n-3) 18C, 3 double bonds, the 1st being at C-3 from the methyl end.



Precursor of

- Eicosapentaenoic acid -epa (20:5n-3)
- Docosahexaenoic acid - dha (22:6n-3) [20].

Challenges in Formulation of Nutraceutical Dosage Form

Analytical Challenges

1. the nutraceuticals are a cluster of a chemical entity, and it is comparatively difficult to identify and quantify all the ingredients in the products.
2. defining and identifying the impurities and ensuring that these impurities are not harmful to the consumer.
3. Having Structural Analysis of each entity in formulation is difficult.

Formulation Challenges

• Tablet Dosage form.

- Botanicals are complex with multiple chemical components, can contain up to 50 active. ingredients; 70- 90% of the formula can be actives.
- There are no of active ingredients and excipients
- Nature of nutraceutical Ingredients bring challenges related to particle size, flow, compressibility, moisture sensitivity, ingredient interaction, content uniformity and quality control (QC) testing as Botanicals and extracts can vary based on region the crop was grown, season grown in and other factors.
- Quantity of each ingredient to enable sufficient delivery of the beneficial ingredients, dose size of the active constituent is large hence very less space for excipients in final formulation.
- Nutraceutical formulations normally have more actives present in higher weights than pharmaceutical formulas. The limits of dose size typically result in restricted room for excipients. A typical nutraceutical formulation has 70–90% actives with the balance as excipients, whereas traditional pharmaceutical formulations have 70–90% excipients and 10–30% actives.

The fewer excipients and variety of actives in the same formulation make it difficult to achieve certain desired outcomes, such as disintegration time, hardness and friability.

- Careful design of the tablet shape and form needs to be considered when choosing suitable tooling- Adding to the challenge, many nutraceutical tablets tend to be produced using neutral colours such as browns and greys with mottled, textured or granular appearances, which can make any embossing difficult to read.
- The addition of natural ingredients in nutraceuticals, which have a tendency to be unrefined, abrasive, corrosive and hard, results in the components used to process them being subjected to damage [21].

Liquid Dosage Form

Most of nutraceuticals are phytoconstituents, fatty acids, flavonoids volatile oils etc, Problems faced by these ingredients are.

1. Solubility of these ingredients. example: carotenoids.
2. Stability of these ingredients. example: Coenzyme Q10, Omega 3 fatty acids. The oral delivery of probiotics is hampered by the low instability of the bacteria in the GIT and consequent loss of viability under the effect of high acidity and bile salt concentrations [22].
3. Bioavailability and permeability of these ingredients. Example: Curcumin. Even the bioavailability of the lipophilic antioxidant coenzyme Q10 was challenged by its.
 - low aqueous solubility and slow dissolution rate in GI fluids furnished by its highly lipophilic character (log P=21).
 - permeability is limited by its large molecular weight (863),
 - P-glycoprotein efflux and active transport by a number of transporters (including peptide transporters (PEPT1), cation/camitine transporters (OCT1, OCTN1, OCTN2 and OCT3) and organic anion transporters (AE2 and MCT1) [23].
4. Interactions: Active constituent and excipient interaction. Active constituent and Active constituent interaction.

Processing Challenges

Large variation in heat, light and moisture sensitivity of ingredients within one formula. Example in Probiotic encapsulation technology Conditions that maintain cell viability like,

– biomaterial selection-natural and synthetic polymers are used; factors to be addressed are:

- (i) physicochemical properties (chemical composition, morphology, mechanical strength, stability in GI fluids)
- (ii) toxicity assay;
- (iii) manufacturing and sterilization processes.

– solvent type and

– toxicity and

– choice of proper technology are of paramount concern.

– A subsequent challenge is to ascertain that the gastro-protected encapsulated probiotics are released in simulated intestinal fluid (SIF) in vitro, a step that must be preceded by development of a standard protocol that simulates conditions prevailing in the GIT.

Psychological challenges: nutraceuticals manufacturers must first separate the products and treat nutraceuticals differently from functional foods.

- Tailoring products to domestic tastes and preferences. These might include vegetarianism, Halal or Hindu dietary practices, traditional remedies, flavor and formulation preferences reflecting social and cultural diversity, or reluctance to see functional benefits in staple foods.
- Choice of Study Population is difficult. (Based on age, disease condition etc) [24].

Regulatory Challenges

1. Need to furnish adequate information with scientific evidence to prove that the product is safe, reproducible, and therapeutically efficient and whether it offers such effects for a definite period of time, say two or three years.
2. The need is to create a mechanism to prove that the product quality is reproducible, and this mechanism needs to be in place with solid, scientific support experimentally that can be proved using a reliable technique [25].
3. Certification requirements often apply to excipients as well as active ingredients.
 - GMO Free
 - Halal
 - Kosher
 - WADA Compliance (World Anti-Doping Agency) country and product specific
4. Registration category/classification
 - According to claims and ingredients, the formula may fit into different categories by country.
 - Registration complexity varies by category and country; dossier requirements vary greatly.
 - Testing requirements for finished products, as well as ingredients and excipients, are not uniform.

Concepts of Nutraceuticals

In the pharmaceutical development process, it is a requirement to have clinical test results from animal tests and studies, for verification of the effects. On the other hand, in the case of nutrition, there was no verification method for foods in preventing diseases in the past. In recent years however, as food composition has been scientifically proven to cause lifestyle-related diseases, and has become a social issue.

Regulatory Aspects of Nutraceuticals

The regulatory framework of nutraceuticals in India needs attention from the relevant authorities. Globally, the regulatory authorities are aware of changing needs of consumers and proactively protect consumers by amending existing laws to accommodate changes but in India old laws such as Prevention of Food Adulteration Act, 1954, which regulates packaged foods, still exist for manufacturers. In addition, they need to abide by many other cumbersome laws such as:

- Standards of Weights and Measures Act, 1976, and the Standards of Weights and Measures
- (Packaged Commodities) Rules, 1977 (SWMA)
- Infant Milk Substitutes, Feeding bottles and infant foods (regulation of production, Supply and Distribution) Act, 1992 with Rules, 1993 (IMS)
- Edible Oils Packaging (Regulations) Order, 1998
- Fruit Products Order 1955 (FPO)

- Meat product Order 1973
- Milk and Milk Products Order 1992
- Vegetable Oils Products (Regulation) Order 1998 (VOP)
- Atomic Energy Act, 1962 and Atomic Energy (Control or irradiation of Food) Rules 1996
- Consumer Protection Act 1986 and the Consumer Protection (Amendment) Act, 2002 and Rules 1987
- Environment Protection Act, 1986 and Rules 1986
- Agricultural Produce (Grading and Marking) Act, 1937 (as amended up to 1986) and 49
- General Grading and Marking Rules 1986 and 1988 (AG Mark)
- Bureau of Indian Standards (BIS) Act 1986

Further, there is lack of clarity in classifying functional foods and Nutraceuticals. This causes confusion amongst the regulators. At times, the drug regulators are tempted to classify these products as drugs. This has resulted in trouble for genuine manufacturers. The revolutionary step to introduce Food Safety and Standards Act will replace the old PFA. The new act will take India on the path of new regulatory framework to make it capable of global competition [26].

This legislation was the result of a reform effort that spanned nearly two decades. It brings about a balance in FDA regulations

between approving therapeutic products so that they can benefit patients and protecting public health by assuring that those products are safe and effective [27]. In 1993, the Ministry of Health and Welfare in Japan established a policy of “Foods for Specified Health Uses” (FOSHU) by which health claims of some selected functional foods are legally permitted. In 2001, a new regulatory system, foods with health claims (FHC) with a ‘foods with nutrient function claims’ (FNFC) system and newly established FOSHU was introduced. In addition, the Govt. changed the existing FOSHU, FNFC and other systems in 2005. Such changes include the new Subsystems of FOSHU such as

- Standardized FOSHU
- Qualified FOSHU
- Disease risk reduction claims for FOSHU

Categories of Nutraceuticals

Nutraceuticals are non-specific biological therapies used to promote wellness, prevent malignant processes and control symptoms. They are categorized as follows:

Based on chemical constituents

Nutrients

Substances with established nutritional functions, such as vitamins, minerals, amino acids and fatty acids. Common nutrients and their associated health benefits shown in Table 1 [28].

Table 1: List of Nutrients and their Relevance

S.NO.	Nutrients	Health benefit
1.	Vitamin A	Antioxidant, essential, for growth and development and in the treatment of certain skin disorders.
2.	Vitamin E	Antioxidant, helps form blood cells, muscles, lung and nerve tissue, boosts the immune system.
3.	Vitamin K	Essential for blood clotting.
4.	Vitamin C	Antioxidant, for healthy bones, gums, teeth and skin, in wound healing, prevent common cold and attenuate its symptoms.
5.	Vitamin B1	Helps to convert food in to energy, essential in neurologic functions.
6.	Vitamin B2	Helps in energy production and other chemical processes in the body, helps maintain healthy eyes, skin and nerve function.
7.	Vitamin B3	Helps to convert food in to energy and maintain proper brain function.
8.	Vitamin B6	Produce the genetic material of cells, formation of RBCs, maintenance of central nervous system and synthesize amino acids and metabolism of fats, protein and carbohydrates.
9.	Folic acid	Produce the genetic materials of cells, in pregnancy for preventing birth defects, RBCs formation, protects against heart disease.
10.	Calcium	Bones and teeth and maintaining bone strength important in nerve, muscle and glandular functions.
11.	Iron	Energy production, carry and transfer oxygen to tissues.
12.	Magnesium	Healthy nerve and muscle function and bone formation, may help prevent premenstrual syndrome (PMS).
13.	Phosphorous	Strong bones and teeth, helps in formation of genetic material, energy production and storage.
14.	Chromium	With insulin helps to convert carbohydrates and fats into energy.
15.	Cobalt	Essential component of vitamin B12, but ingested cobalt is metabolized in vivo to form the B12 coenzymes.
16.	Copper	Essential for hemoglobin and collagen production, healthy functioning of the heart, energy production, absorption of iron from digestive tract.
17.	Iodine	Essential for proper functioning of the thyroid.

Research in Nutrigenomic

Genome research and technology are being integrated to discover a new notion of food with a new function to prevent diseases, which is now known as Nutraceuticals; also, a genome approach known as Nutrigenomics (nourishment genome science) was developed. Nutrigenomics incorporates the three omics disciplines of gene, protein, and metabolite profiling (transcriptomics, proteomics, and metabolomics) as they apply to nutrition and health. Nutrigenomics is the scientific foundation for designing nutrition that is tailored to the needs of consumer groups, whether they are healthy, at risk, or ill. RO Brennan coined the word “nutrigenetics” in his 1975 book *Nutrigenetics. New Hypoglycemic Treatment Ideas*. Nutrigenomics is a new methodology that combines various genomic techniques and molecular biology technology. Nutrigenomics is a technology used in a variety of academic sectors, as illustrated below, to conduct scientific analyses of the relationship between food and food ingredients and health care and disease prevention. A yeast study found that raising the activity of a single gene, SIR2, could increase their life span. SIRT1, a gene similar to SIRT2, was discovered in humans. In a laboratory study, polyphenols such as Quercetin (found in apples and tea) and Resveratrol (found in grapes and red wine) were found to boost SIRT1 activity. Interestingly, Resveratrol was found to increase SIRT1 activity 13-fold. In terms of chronic diseases, particularly relevant are the effects of dietary cholesterol and fatty acids on gene expression. Dietary cholesterol exerts a profound inhibitory effect on the transcription of the gene for β -hydroxy- β -methyl-glutaryl (HMG)-CoA reductase [29].

Nutraceutical Scenario in India

The Indian nutraceutical business has a bright future. A vast selection of items have been accessible throughout the last decade, providing insight into the phenomenal expansion. On the one hand, a thriving economy has resulted in an overall increase in population disposable income. In addition, improper eating habits combined with a sedentary lifestyle have resulted in an increase in the occurrence of diet and its linked health disorders. On the other side, there is a rising understanding of the significance of nutrition and food for long-term health [30]. These factors have contributed to the Nutraceutical industry’s positive market conditions in India. India offers numerous advantages, including qualified human resources and world-class infrastructure. R & D facilities and varied raw material-aspects that give our country a leading edge. The Indian nutritional market is projected to be worth one billion dollars [31]. While the global market is increasing at a CAGR of 7%, the Indian market has been rising at a CAGR of 18% over the last three years, led by functional food and beverages. The latent market in India, on the other hand, is two to four times the current market size and is worth between USD 2 and USD 4 billion, with around 148 million potential buyers. In a USD 1 billion market, functional food has a 54 percent market share, followed by dietary supplements with a 32 percent market share and functional beverages with a 14 percent market share. The Indian nutraceutical business is predominantly controlled by pharmaceutical and FMCG companies, with very few pure play in nutraceutical companies. Some major companies Marketing Nutraceuticals in India are Glaxo Smith Kline consumer healthcare, Dabur India, Cadila Health care, EID Parry’s, Zandu Pharmaceuticals, Himalaya herbal Healthcare, Am-

way, Sami labs, Elder pharmaceuticals and Ranbaxy [32].

The Future of Nutraceuticals

Increased fitness and health awareness, fueled by media attention, is motivating the majority of people to live healthier lifestyles, exercise more, and eat healthier. The growing nutraceutical sector implies that end customers are looking for minimally processed foods with additional nutritional and organoleptic value. This development, in turn, is propelling growth in the global nutraceutical markets. The growing nutraceuticals business appears to be set to dominate the landscape in the next millennium. Its tremendous growth has implications for the food, pharmaceutical, healthcare, and agricultural industries [33].

Enzymes, according to many scientists, constitute a new and intriguing area in nutraceuticals.

“Enzymes have been underutilized... they are going to be a hot sector in the future.” Technology that uses bacteria to manufacture novel food products also has promise. Global tendencies toward healthier products are irreversible. Companies that take the lead by strategically investing in science, product development, marketing, and customer education will be rewarded [34].

Conclusion

Many nutraceuticals, functional foods, and naturally occurring substances that have been examined and reported in various studies have showed that these products are incredibly active, have a dramatic effect on cell metabolism, and have little to no harmful effect. It is natural that people’s attention is turning to a positive approach to disease prevention in order to stay healthy. Nutraceuticals is scientific area generated all over the world. In many circumstances, nutraceuticals outperform synthetic medications under development by the pharmaceutical sector. It is novel pharmacological action that has piqued the curiosity of researchers because of its potential clinical application in illness prevention and treatment. Most pharmaceutical corporations are typically unmotivated to pursue these problems in securing a patent. It is hoped that government agencies and academic institutions will provide funding for additional nutraceutical research.

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