Review

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An overview of regulation for nutraceuticals and concept of personalized nutraceuticals

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Abstract

Nutraceuticals are essentially nutritional components that have a vital role in developing and maintaining the body's regular functions, which keeps people healthy. The nutraceutical sector is also primarily driven by the existing global population and trends. Examples of foods considered as nutraceuticals include prebiotics, fibre, polyunsaturated fatty acids, probiotics, antioxidants, and other natural or herbal foods. Some of the most serious health problems of the 20th century, like COVID-19 and diabetes mellitus, are managed with the help of the preceding nutraceuticals. As we move into a time of health and medicine, the food industry as a whole has become more focused on research.

Keywords

Nutraceuticals, regulation, innovation, regulatory guidelines, COVID-19, diabetes, personalized nutraceuticals

Introduction

In latest generations, nutrition scientific knowledge has already been based on the detection and knowledge of inadequacies. To increased understanding of vitamin presence and activity, recommendations have been developed with the aim of avoiding traditional nutritional deficiencies like beriberi, xerophthalmia, and others. The scientific data that diet relates to a threat of certain ailments was a next phase. The primary insight had been a link between a high fat diet and various cancers and heart disease. As a result, specialized low-cholesterol and low-fat foods were developed. Moreover, growing understanding of micronutrients on a cellular scale, such as nutrients, minerals, and other substances (flavonoids, carotenoids, anthocyanins, and so on), combined with findings from observational studies, begins a fresh and exciting ground of human nutrition, nutraceuticals (NC), as a connection among medicine and nutrition. Stephen DeFelice invented the phrase "nutraceutical" in year 1979.[1] These can include everything from isolated nutrient content, food supplements, and dietary to genetically modified "developed" food products, herbal supplements, and highly processed like cereal grains, beverages, and soups. Customers' strong demand in nutraceuticals represents etiological research suggesting that a particular nutrition or element of a meal is linked to a reduced risk for a particular disease. Until lately, micronutrients and vitamins and were only advised to prevent classic deficiency. Advanced biology methods, on the other hand, have provided us with greater insight into cellular and molecular requirements of a human. It has resulted in a much more precise description of micronutrient health advantages and demands. Medical deficits seem to be the result of a long-term pattern of inadequate micronutrient consumption. Before these symptoms appear, insufficient micronutrient distribution to targeted tissue involves changes that could be the backbone of infectious conditions. Antioxidants are the substances which have received most attention. Numerous advantages of antioxidants with in popular dietary consumption or dietary supplements have been identified. Antioxidants in could use for the prevention of carcinoma or vascular disease. Vitamin C supplementation could help asthma clients, and an increased nutritional level of vitamin E could help to prevent Parkinson's.[2] Increased plasma homocysteine, for instance, has given rise to a new independent predictor for coronary heart disease. Numerous

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researchers have discovered that a mild to moderate increase in plasma homocysteine is highly involved in the development of atherosclerosis.[3] Genetic and nutritional factors are important determining factors of plasma homocysteine concentration levels. A prevalent base - pair transfer at nucleotide 677 of cytosine to thymidine of a methylene tetrahydrofolate reductase (MTHFR) gene results in thermolabile MTHFR with lowered enzymatic activity, leading to increased plasma homocysteine amounts.[4] The above mutation has already been related to the growth of heart disease.[5] In times of extreme homocysteine in group with mutation or reduced folate consumption, an ingestion just above regular reference might serve to shield against CHD. Selenium concentration in the body is low in people who are predisposed to pancreatic cancer. As a result, it is assumed that selenium intake could aid in the prevention of this situation.[6]

Due to its capability to thicken up and produce viscosity, the molecules that can be absorbed from soluble fiber slow down the body's stomach emptying.[7] It causes a sense of fullness and alters the pace of digestion and nutritional absorption. It's been demonstrated that soluble fibre improves glucose resistance and reduces blood LDL cholesterol in a targeted manner.[8] Additionally, they boost insulin receptor binding and glycemic response. Due to greater fluid retention, longer transit times, or a rise in faecal bacterial mass brought by soluble fibre fermentation, dietary fibre causes faecal bulking in the colon. Additionally, the fibre helps Bifidobacteria flourish in the intestines. Similarly, increasing the consumption of higher fibre-based foods increases serum lipoprotein levels, decreases blood pressure, enhances blood sugar control for diabetics, helps in losing weight, and encourages consistency.[9]

Classification of nutraceuticals

Nutraceuticals could be classified according to their ease of knowledge and implementation, such as teaching methods, clinical study design, nutritional and functional advancement, or nutrient intake. Among the main techniques of categorizing nutraceuticals include sources of food, mode of action, chemical nature, and so on. Nutraceutical sources of food are all organic and it can be classified as:

Dietary fibre

Food, and more specifically plant matter, is degraded by microorganisms in the intestine rather than by proteolytic enzymes generated by intestinal tract. It consists of resistant starches, dextrin's, and non-starch polysaccharides (NSP) like hemicelluloses, celluloses, pectin, and gums lignin. Oats, fruits, beans, and barley are among the foods high in dietary fibre. In terms of chemistry, it refers to carbohydrate polymer with a polymerization degree of at least three that are neither processed nor absorbed from the gastrointestinal. These can be classified into two categories depending on how easily they dissolve in water.

i. The colon only partially ferments insoluble dietary fibre (IDF),that comprises celluloses, some lignins, and hemicelluloses.
ii. The term "soluble dietary fibre" (SDF) refers to hemicelluloses which are processed inside the colon, such as pectins, -glucans, mucilages, and gums.

Polyunsaturated fatty acids

They are recognized as "essential fatty acids" since they are needed by the organism and thus are obtained from the food. Omega-3 (n-3) and Omega-6 (n-6) fatty acids are 2 of their subcategories. Eicosapentanoic acid (EPA), and Docosahexanoic acid (DHA), linolenic acid are also the three main omega-3 fatty acids (ALA). ALA comes before DHA and EPA. Fish oils and fatty fishes like salmon, mackerel, trout, herring, and blue fin tuna are the principal sources of DHA and EPA. Arachidonic acid,. γ-Linolenic acid (GLA), and linoleic acid (LA), make up majority of omega-6 Polyunsaturated fatty acids (PUFAs). Most vegetable oils, including safflower, corn, sunflower, and soyabean, contain LA. Animal items like chicken, pork, and eggs contain ARA. According to research, omega-3 fatty acids had major effects on treating and preventing arrhythmias that are anomalies within heart's force or beat.[10] Antithrombotic and hypolipidemic (helping to lower serum lipid levels).[11,12]

Probiotics

It could be described as a live microorganism's feed additive that, when given to the host organism in sufficient proportions, improves the balance of bacteria in its intestines are offered in various types, like gel, powder, liquid, granules, paste, capsules, etc..[13] To treat intestinal problems like lactose intolerance, severe diarrhea, and GI adverse effects linked to antibiotics, particular probiotics are typically employed. Probiotics are non-toxic, non-pathogenic, resistant to gastric acid,

and cling to intestinal epithelial cells, where they produce antibacterial compounds. There has been research that suggests probiotics lowers the chance of developing systemic diseases like cancer, asthma, allergies, and a number of ear and urinary tract ailments.[14]

Prebiotics

These were all food components that specifically change the intestinal microbiota's structure or physiology to have a positive effect on the host.[15] Particularly fructose-based oligosaccharides which occur naturally in some foods and are introduced to it are examples of shorter-chain polysaccharides with distinctive structural features that cannot be absorbed by mammals. Consuming prebiotics often encourages the growth of *Bifidobacteria* and *Lactobacillus* in the intestines, which aids in metabolism. Fruit and vegetable sources of fructo-oligosaccharides include bananas, chicory roots, alliums, and tomatoes. Stachyose and raffinose, which are present in peas and beans, are some other types of these oligosaccharides.

Antioxidant vitamins

These vitamins refer to vitamins like vitamin E and C, also carotenoids. These vitamins work individually and in concert to stop the oxidative processes that cause cataracts, cancer, and other neurodegenerative disorders as well as cardiac diseases. Those vitamins, which are numerous in several fruits and vegetables, work through free-radical scavenging systems to protect us from harm. Tocotrienol and Tocopherols which make up vitamin E, transfer hydrogen ions and scavenge single oxygen and other reaction products, preventing LDL and PUFA peroxidation in biological membranes.

Polyphenols

Vit C, often known as ascorbic acid, quenches single oxygen free radicals, eliminates o2, and gives hydrogen to phospholipid radicals. A known antioxidant method involved ascorbic acid and tocopherol supplementation working together to scavenge water radicals.[16] A most effective single oxygen quenchers in living organisms without producing any oxidising byproducts are recognized to be carotenoids like lutein, zeaxanthin, lycopene, and beta-carotene. At low levels of oxygen, βcarotene traps peroxy free radicals in tissues. As a result, β-carotene enhances vitamin E's antioxidant abilities. A fascinating feature of polyphenols has also been the subject of research. Flavonoids have previously been shown to attenuate the articulation of glutamylcysteine synthetase, a critical rate-limiting enzyme involved in glutathione output. The attenuation of glutathione by polyphenols has a significant impact on physical effects like detoxifying xenobiotic and protein glutathionylation. Glutathione is essential for the scavenging free radicals of transcriptional regulators and signaling enzymes.[17]

Spices

For centuries, people have employed spices as esoteric food additives to improve the sensory appeal of food. Spice use is widespread in tropical nations, both in terms of number and diversity. They give food its distinctive flavour, colour, or piquancy, which arouses our appetites and alters the consistency of the food. Terpenes as well as other essential oil constituents make up most of the ingredients in spices. They have already been discovered to be useful in various ways. For example, 5–6 raw garlic clove and 50 g of raw onion are sufficient to decrease cholesterol inside the body. New studies on mildly hypercholesterolemic individuals' lipid profile and blood pressure revealed that old garlic extract supplements had superior health benefits than fresh herbs.[18] By decreasing the levels of LDL cholesterol, total cholesterol, and triglycerides simultaneously, co-administration of fish oil and garlic had a more favourable impact on blood lipid and lipoprotein levels.

Regulations of nutraceuticals

The term "foods for particular dietary needs" refers to nutraceuticals throughout India. "Foods for specialized dietary applications or functional food ingredients or nutraceuticals or health products," according to the Food Safety and Standards Authority (FSSA), are defined.[19] The Food Safety and Standards Act of 2006 in India created the Food Safety and Standards Authority of India (FSSAI), that combines several statutes and rules and were in place to address food-related problems in several Ministries/Departments. In place to ensure that there is a supply of healthy, safe food for humans, the FSSAI was established to establish scientific food standards commodities and to control their production, preservation, delivery, sales, and purchase. Therefore, it also pertains to goods like nutritional supplements and food supplements. Several central laws, including the Prevention of Food Adulteration Act of 1954, the Fruit Products Order of 1955, the Vegetable Oil Products (Control) Order of 1947, the Meat Food Products Order of 1973, the Edible Oils Packaging (Regulation) Order of 1988, the Milk and Milk Products Order of 1992, the Solvent Extracted Oil, De-Oiled Meal, and Edible Flour (Control) Order

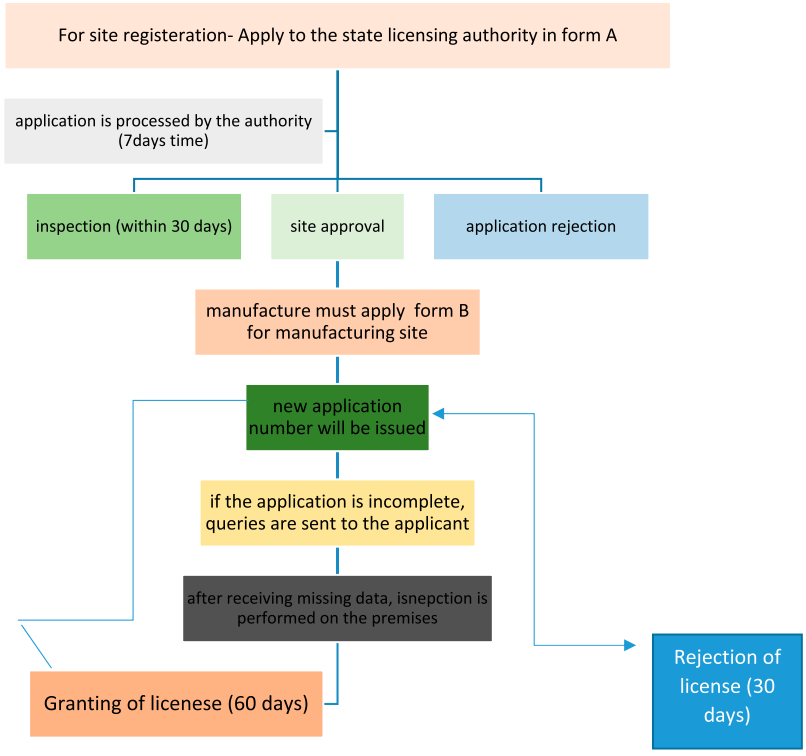

Figure 1. Regulatory process of nutraceuticals in India.

of 1967, and others have been repealed since the FSS Act of 2006 took effect.[20] (Figure 1)

Indian regulatory requirements

1. Product assessment: evaluation of every compound and active component. There are several steps in the product evaluation, including:
   - Creating document contents
   - Sample gathering
   - Sending out samples to relevant authorities (various procedures for large and single packages)
   - Evaluation of food
   - If assessment is not finished in the allotted time, the assigned officer will take additional action.
   - judiciary procedures (holding an investigation, an appeal, a hearing, etc.)
2. Licenses: About 4–5 licences, including the following, may be necessary to register a product.
   - Import permits
   - License for manufacturing
   - Licencing for marketing
   - Before releasing those items in India, additional regulatory permissions and licences at the state and federal levels must be obtained.
3. Health claims on food labels: A "health claim" is any statement, suggestion, or implication that there is a connection in between food or one of its ingredients and health. It comprises:
   - Regulations for labelling requirements peculiar to India
   - Consignment package, content, and marketing strategy all must be consistent.
   - Test piece and a statement are required for certification.
   - Content and claim on labels
   - Claim of structure and function

Regulatory process in US

The United States Food and Drug Administration (FDA) authorizes the regulation of nutritional supplements in the United States into its different food industry facilities. Eventually, the Food and Drug Cosmetic Act regulated or modified the DSHEA, or Dietary Supplement Health Education Act of 1994. And the DSHEA establishes plenty of requirements for dietary supplements. The USFDA has met the needs of nutritional supplements, but authorization by the agency is not considered necessary. (Figure 2)

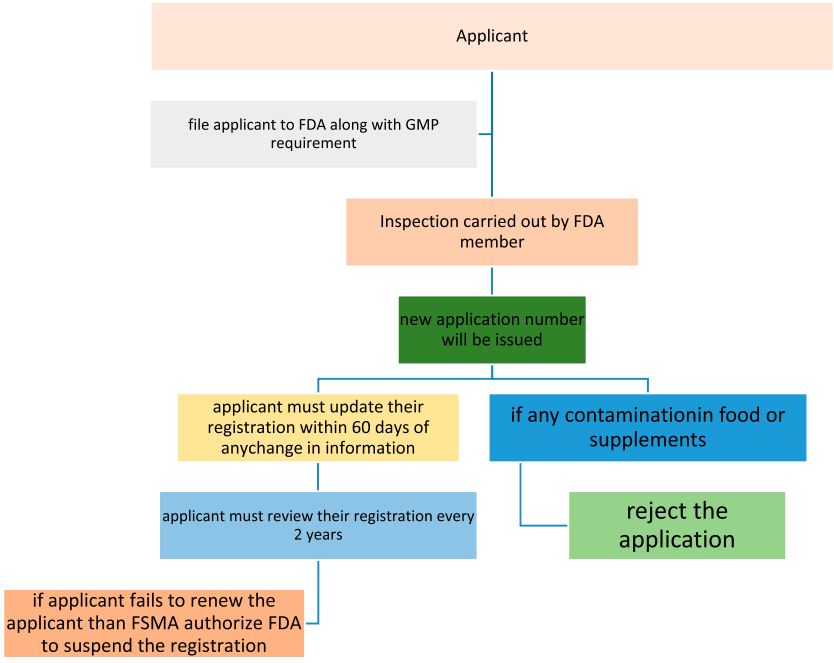

Figure 2. Regulatory process of nutraceuticals in US.

Nutraceuticals used in Covid-19

Unexpectedly, information from the Oxford University Lab's COVID-19 Trials Tracker show that conventional medications are most enrolled invasion for clinical trials against COVID-19, to Vit. C, probiotics, and Vit. D are among several pharmacological therapies under research.[21,22] Of all the other nutrients of significance, vitamin D has attracted the attentions of researchers and several people on the internet.[23] It was due in part to the fact that deficiency of vitamin D was reported widely between COVID-19 patient populations but was linked to COVID-19 incidence. People benefit from vitamin D's immunomodulatory properties.[24] As a result, the connection among vitamin D and COVID-19 has become the focus of much research and multiple clinical studies. The incredible growth data can be found for nutraceuticals and multivitamins industry are inclined to grow, and industry demand is forecasted to normalise to pre-pandemic levels within coming days. Given that worldwide intake of dietary supplements is increasing, and given the direct observation during disease outbreak, this is not unusual that regulatory bodies are closely examining the sector. Even so, officials in the U.K. are contemplating new legislation to address oversight shortfalls within nutraceutical sector. Various immunomodulators, vitamins, minerals, dietary supplements are used for COVID-19 infection are discussed below.

Vitamin D

Patients with COVID-19 had shown to have reduced vitamin D concentrations, with mean plasma levels ½ those of standard control,[25] even though the study's population was uncertain and unadjusted comparative to essential confounding variables, releasing one's findings uncertain. As a result, vitamin D supplementation is recommended to enhance body's immune system against COVID-19 and lower human death rates; though, the theory necessities testing in human clinical trials. It has been proposed that adequate nutrient amounts may aid in protecting the respiratory epithelium from bacterial invasion, lowering the infection risk. A pre-print study population in Israel discovered that vitamin D was linked to disorder occurrence also after controlling for comorbidity and sociodemographic factors.[26] Furthermore, nations with high incidence of deficiency of vitamin D have a heavier threshold of COVID-19 incidence and death.[27] Vitamin D has already been related to higher anti-inflammatory and lowered pro-inflammatory cytokines in elderly persons. The beneficial effect of vitamin D upon innate immunity is beneficial during cytokine storms, which is appropriate to COVID-19 patient populations of ARDS.[28] Vitamin D have been shown to minimize the occurrence of viral infections, so there's an inverse correlation among serum 25-hydroxyvitamin D concentration and upper respiratory tract infection.

Vitamin C

Vitamin C had shown to decrease pro-inflammatory cytokines such as TNF-α and enhance anti-inflammatory cytokines (IL-10). Clinical evidence that intake of vitamin C rises IL-10 release by mononuclear cells. IL-10 acts as a negative reaction loop with IL-6 to regulate inflammation, which is important in COVID-19. Because of decreased immune cellular functions and immunosenescence, elderly people are at increased risk to infection.[29] A patient study exposed to increased vitamin C level upon developing ARDS has been able to be brought off airflow within a week of 5 days, which has been considered uncommonly early, but should be mentioned that person received antiviral medications.[30]

Zinc

Zinc can be a helpful therapy in COVID-19 people owing its antiviral and immunomodulatory properties. It was proposed that supplementation with zinc could improve the effectiveness of all other therapies that are currently being studied, such as hydroxychloroquine.[31] A case report of 4 COVID-19 patient populations exposed to high level of zinc demonstrated clinical and symptomatic advancements.[32] Zinc intake was associated in methods to determine COVID-19-related signs like respiratory illness. Such impacts, which may be pertinent to COVID-19, have already been attributed to inhibitory activity of viral binding, and uncoating, replication. An Australian clinical study will evaluate the use of intravenous administration of zinc in COVID-19 people.[33]

Vitamin B12 (cyanocobalamin/cobalamin)

It regulates cytokine/chemokine production and mediates interactions with lymphocytes involved in pathogenetic routes. As a result, it is suggested it can preserve against a variety of microbial infections. Moreover, because it is involved in colonic immune tolerance and adds to barrier function, it may play a key role in immune function and security against coronavirus, since there is evidence that probiotics like lactobacilli and bifdobacterial could attenuate the immune reaction and safeguard against infectious diseases, such as respiratory infections.[34]

Vitamin B9 (folic acid, folate)

It's a type of vitamin that is required for protein and DNA synthesis as well as for the protective immune system. It impedes the furin enzyme, which is liable for infectious pathogens infections, and inhibits the adhesion of the SARS-CoV-2 spike protein, according to a new analysis. It may thus be helpful in the development of COVID-19-associated respiratory illness.[35] According to a recent survey, folic acid as well as its derivative products, tetrahydrofolic acid and 5-methyl tetrahydrofolic acid, have a high affinity for SARSCoV-2.[36]

Vitamin B2 (ribofavin)

It's a neuroactive substance with immunomodulatory effects, and its deficiency results in proinfammatory expression of genes. In animal studies, it was discovered that ribofavin offers a protecting effect against liver failure caused by CCL4, upheld by TNF, implying it could be used as a hepatoprotective agent as discussed in *Yoshii* et al. *2019*.[37] Ribofavin combined with Ultraviolet rays creates irreparable harm to nucleotides, inhibiting bacterium replication. As a result, it could be used to decrease pathogenic organisms in COVID-19 patients' plasma, lowering the risk of COVID-19 transmission.

Copper (Cu)

Copper is implicated in the proper functioning of B - cell, Helper T cells, macrophages, and natural killer (NK) cells, which are also engaged in cell-mediated immune function, confront virulent organisms, and create antibodies against microorganism has been explained in *Raha et. al. 2020*.[38] According to research, Cu's exposed to coronavirus 229E damages the viral vector and has an irreversible effect on viral morphological features has been discussed in *Warnes* et al. *2015*.[39] Moreover, Cu processing seems to have the possibility to neutralise contagious viruses like bronchitis, poliovirus, and HIV-1, as well as boost immunity. Since these research shows that viral infections are sensitive to Cu, copper supplementation could be a potential treatment for COVID-19 patient populations.

Nutraceuticals used for diabetes

Diabetes is ranked 5th most deadly illnesses in the civilized countries. Even though a comprehensive pool has been evolved to battle this old ailment, the emphasis has shifted to recognize vitamins, minerals, and nutraceuticals which could be used in conjunction with advanced medications to help this ailment cohesively.

Acacia Arabica (Babul)

It is a member of the Acacia genus and the Fabaceae family. *A. arabica*, also recognized as *A. nilotica*, had

also traditionally been shown to cure high diabetes, cancer, cholesterol, stomatitis (mouth sores), and gingivitis, pharyngitis. Powder form of *A. arabica* seeds and roots of *Caralluma edulis* assessed in dose levels of 2–4 g/kg bodyweight to ordinary rabbits stimulated hypoglycemic activity by instituting secretion of insulin from pancreatic islets.[31,40]

Allium Cepa (Onion)

They are high in flavonoids like sulphur and quercetin compounds. Onions' medical benefits have already been connected to anything from colds to diabetes and bone loss. In a comparative evaluation, 100 g of *Allium cepa* (red onion) contributed to an 89 mg/dl decrease in fasting blood glucose level (after 4 h), while administration of insulin resulted in a 145 mg/dl decrease levels (after 4 h).[41,42]

Allium Sativum (Garlic)

As per preliminary research, members of Allium family have mild hypoglycemic effect. The active components are thought to be sulphur containing volatile compounds (over 20 were separated from garlic), such as allyl propyl disulfide, alliin (diallyl disulfide oxide), allyl mercaptocysteine, and allyl cysteine. Garlic's sulphur molecules are thought to slow the rate about which insulin is deteriorated, increasing insulin concentration.[43]

Alpha lipoic acid

Until now over 15 trials have been conducted with ALA. The authors conclude that a 3-weeks therapy with 600 mg/day of active component lowered the primary signs of diabetic neuropathy, a severe form of diabetes that impacts the nerves, as well as conferred sustained betterment in sensory and motor nerve function in the lower extremities.[44] It was shown to enhance sensitivity to insulin by attracting glucose transporter4 to cytoplasmic membrane, resulting in glucose absorption. Latest research also suggests that ALA helps to stimulate glucose discharge in patients with T2dm. ALA significantly reduced diabetic ailments such as cataract formation, vascular injury, and neuropathies in clinical and experimental studies.[45]

Carnitine

It is produced by the body in attempt for excess weight to be used properly in the energy production. It naturally occurs and is derived from soluble amino acids. Diabetic patients who attempt carnitine tend to react well, and increased blood fat levels (triglyceride and cholesterol) could quickly fall. It aids in the collapse of fatty acids in the blood and joins to acyl byproducts. It could be effective at preventing diabetic ketoacidosis for such purposes.[46,47]

Coenzyme Q10

This is a naturally occurring compound inside the body which may aid in metabolism of carbohydrate. It's been established that diabetic animal are lacking in coenzyme Q10. Clinical studies with this supplement recommended that it could drastically reduce blood glucose levels. Also, it oxygenates the blood, which could assist in some instances of retinopathy caused due to diabetes.[48]

Conclusion

Nutraceuticals, that provide medical benefits and would be a substitute to conventional medicines, have gained significant popularity. These have great possibilities since they are advantageous for today's style of living. Customer exploring the relationship among health and diet has expanded the market for nutraceutical data. Even though these show great potential in the field of promoting infection prevention and control, clinical investigations are necessary to determining the required the nutraceuticals in a variety of ailments. Nutraceuticals are on their way to becoming our favored prescription of the future. It is critical to consume enough minerals and vitamins via diet in order for the immune system to work properly. Fruits, meat, vegetables, poultry, and fish, as well as dairy products, are good sources of such minerals and vitamins. Higher daily intake of vitamins C, E, and D, as well as zinc, may be helpful in supporting immune system function during COVID-19 disease. High concentrations of such supplements have already shown successful effects during COVID-19 disease, and due to their lower risk level, are a reasonable inclusion for treating patients.

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