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THERAPEUTIC AND PREVENTIVE ROLE OF NUTRACEUTICALS AND PRODUCTION OF VITAMINS & LOW-CALORIE SUGARS FROM FOOD-GRADE MICROORGANISMS AS NUTRACEUTICALS

[1]Anindita Ray Chakravarti, [*2]Prishila Dutta, [3]Sanchita Paul, [4]Souvik Tewari
[1]HOD, Department of Food & Nutrition, Maharani Kasiswari College, University of Calcutta, India
[*2]Department of Food & Nutrition, University of Calcutta, India
[3]Department of Food & Nutrition, University of Calcutta, India
[4]Assistant Professor, Department of Food and Nutrition, Swami Vivekananda University, Barrackpore, West Bengal, India
[*]Corresponding author: duttapriscilla@gmail.com

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Abstract

Nutraceuticals may influence number of disease conditions and many molecular pathways, as well as hundreds of proteins and genes. They frequently influence multiple molecular pathways. The adverse effects of some pharmaceutical therapies and the rise in antibiotic resistance have sparked interest in nutraceutical substances as an alternative therapeutic and preventative approach. They also have the advantage of being more widely available and reasonably priced. Numerous studies have definitely shown how beneficial dietary components are for immune system functions. These include enhancing the mechanism for responding to infections, bolstering immunomodulatory activity, and mitigating the impact of autoimmune disorders and hypersensitivity. Additionally, it has been shown that nutraceuticals have lipid-lowering, anti-inflammatory, anti-cancer, and antioxidant properties. In this review article, we will discuss about the role of microorganisms derived nutraceuticals in human health.

Keywords :- *Nutraceuticals, diet, therapy, treatment, microorganisms*

1. Introduction

The term "nutraceuticals" refers to bioactive compounds that are available in everyday foods or botanical sources which provide beneficial health effects and may be consumed in the form of dietary supplements or functional foods in addition to providing basic nutrients (Joana et al., 2013). Pharmaceuticals and nutrients are combined to form the phrase "nutraceuticals." AAFCO 1996 defines "nutrient" as an edible component in a form and amount that will ensure the continuation of an animals' or individual's life, and "nutraceutical" as any non-hazardous/ non-toxic food component having scientifically demonstrated health benefits, including avoiding and curing of illnesses (Lomartire et al., 2021).

Probiotics, antioxidants, fatty acids, phytochemicals and amino acids are just a few of the bioactive compounds gathered in dietary sources that make up nutritional supplements. Nutraceuticals

are widely recognised for their involvement in illness prevention and cure, anti-aging qualities, and reducing the risk of cancer, with either already documented benefits or prospective effects. The substantial role that probiotics play in the therapy and suppression of gastroenterological illnesses encourages people to consume them. Nutritional components have been shown to have a positive impact on immune system functions in numerous research. These include enhancing the mechanism for responding to infections, bolstering immunomodulatory activity, and mitigating the impact of autoimmune disorders and hypersensitivity. Additionally, it has been shown that nutraceuticals have lipid-lowering, anti- inflammatory, anti-cancer, and anti-diabetic properties (Tambe et al., 2023).

Nutraceuticals can be used **as functional food** as well as **supplements.**

2. Classification of nutraceuticals

On the basis of their **composition and function**, Nutraceuticals can be grouped into **7 categories**. They are as follows :-

2.1 Botanical products and herbs :- Botanical products and herbs are plant-derived nutraceuticals that are consumed for their medicinal characteristics. Ginkgo biloba, ginger, and garlic are a few examples of botanical sources of Nutraceuticals.

2.2 Phytochemicals :- Phytochemicals are chemical substances that are present in plants that have been proved to have positive effects on health. Examples include carotenoids, flavonoids, and antioxidants (Dillard & German, 2000).

2.3 Vitamins and minerals :- The body need certain nutrients in order to perform its functions properly; vitamins and minerals are essential for proper functioning of our body. They can be consumed as supplements or by intake of foods.

2.4 Probiotic and prebiotics :– They both together play an important role in maintaining by gut health by promoting the growth of beneficial bacteria.

2.5 Amino acids and peptides: Amino acids and peptides are the fundamental components of protein and provide a number of health advantages, including lowering of inflammation and enhancement of muscular performance.

2.6 Omega-3-fatty acid: - Omega-3 fatty acids which is a polyunsaturated fatty acid have been found to provide a number of health advantages, including the ability to lower inflammation and enhance heart health (Nwosu et al., 2020).

Nutraceuticals can be **classified on the basis of their source** (Nwosu et al., 2020).

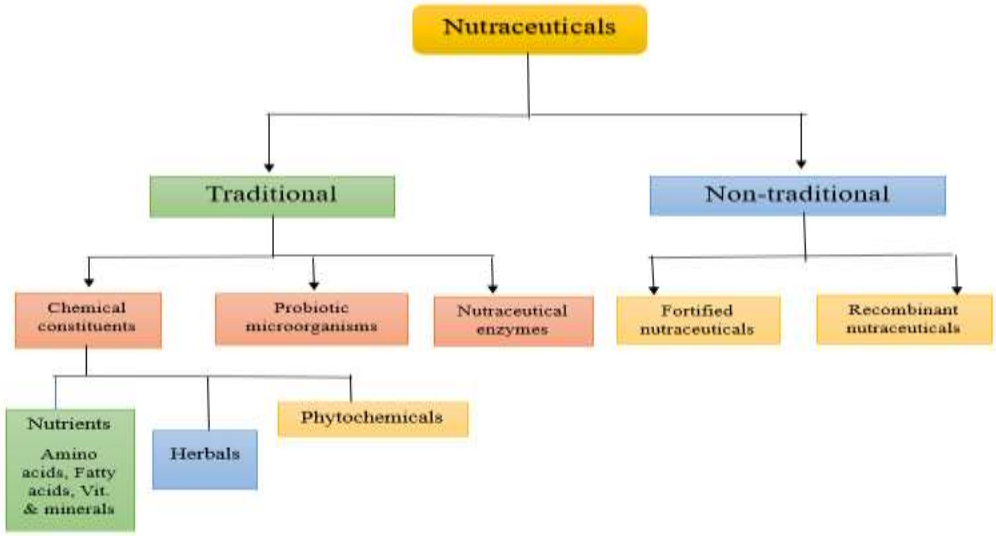

Figure 1: *Classification of Nutraceuticals based on their sources*

3. Role of nutraceuticals in the treatment and prevention of diseases

The spectrum of role of nutraceutical in treatment and prevention of disease is broad. There are various nutraceuticals available and they have a wide range of activity. Some of the relationships between nutraceuticals and diseases are elaborated below :-

3.1 Role in Diabetes

Type 2 diabetes mellitus is the most prevalent kind of diabetes with prevalence of 95% and it is linked with obesity. Recently the use of herbal products rich in nutraceuticals are becoming popular because of their lower or almost no side-effects and because of less economic burden. Nowadays, scientists are working with nutraceuticals at the clinical trial levels. Some of the nutraceuticals that have shown to have positive impact on diabetes are listed below.

a) **Isoflavones** are phytoestrogens that resemble human oestrogen in both structure and activity.

b) **Omega-3-fatty acids** - In those prone to diabetes, omega-3 fatty acids may lower glucose tolerance. Patients with diabetes may benefit from n-3 fatty acid ethyl esters.

c) **Lipoic acid** - In addition to treating diabetic neuropathy, antioxidant lipoic acid appears to be beneficial as a long-term dietary supplement for shielding diabetics against issues. Many plant extracts have been proven to either prevent or treat diabetes, including those from bitter melon, cinnamon, and Toucrium polium (Nasri et al., 2014) (Kumar et al., 2022).

3.2 Role in Cardiovascular disease

Coronary heart disease (heart attack), peripheral vascular disease, cerebrovascular disease (stroke), hypertension, heart failure, and other conditions are all included under the umbrella term of cardiovascular disease (CVD).

For the prevention and treatment of CVD, nutraceuticals in the form of vitamins, minerals, antioxidants, dietary fibres, and omega-3 polyunsaturated fatty acids (n3 PUFAs) are advised, along with physical activity. It is thought that the compounds, like polyphenols, change cellular signalling and metabolism, which lowers disease of arterial system.

Some of the nutraceuticals that play role in cardiovascular system are :-

a) **Flavonoids** - As flavones, flavanones, and flavanols, flavonoids may be found in a variety of fruits and vegetables, including grapefruit, apples, cherries, pomegranate, berries, black grapes, and red wine. They are essential for preventing and treating cardiovascular disease (CVD). Flavonoids inhibit the cyclooxygenase enzymes that break down prostaglandins, block the angiotensin-converting enzyme, and stop platelet aggregation. Consumption of flavonoids is found to have significantly negatively correlation with myocardial infarction incidence and death from coronary heart disease.

b) **Phytosterol** - By preventing the body from absorbing dietary cholesterol and making it easier for the body to expel it from the body, phytosterols compete with it. They therefore have the potential to lower CVD morbidity and death.

c) **Omega-3-fatty acids** - The omega-3 fatty acids (n-3 fatty acids) found in fish are dietary elements that have an impact on the levels of plasma lipids and cardiovascular disease, such as arrhythmias.

d) **Octacosanol** - Octacosanol, a substance found in whole grains, fruits, and the leaves of many plants, has the ability to decrease cholesterol naturally and safely.

e) *Zingiber officinalis rhizome* is a typical seasoning for a variety of dishes and drinks. It has a long history of usage as medicine and is effective against CVD due to its strong anti-inflammatory and antioxidant properties (Nasri et al., 2014).

3.3 Role in eye disorders

For age-related macular degeneration (AMD), a healthy lifestyle and diet that includes foods high in antioxidants, such as n-3 fatty acids, lutein, and zeaxanthin, may be helpful. Nutraceuticals with high polyphenolic flavonoid concentration have been proven to exhibit antioxidant action.

Astaxanthin shields the heart from oxidative damage, guards the neurological system against degenerative illnesses like Alzheimer's disease, and strengthens the body's defences against infection.

Several fruits and vegetables, such as sweet potatoes, carrots, squash, tomatoes, mangoes, maize and leafy greens like kale and collards contain lutein, a carotenoid. Using lutein and zeaxanthin, visual problems are treated.

3.4 Role in immunity

Numerous nutraceuticals have been demonstrated to have important roles in immune function and a person's vulnerability to certain illnesses and disorders. Astragalus promotes the growth and differentiation of lymphatic and bone marrow stem cells into functional immune cells.

The impact of probiotics and botanical remedies on immune responses and intestinal epithelial cell function has given nutraceuticals and probiotic usage in clinical settings fresh support.

The lymphoid tissue may receive maturational signals from probiotic supplements, which can also balance the production of pro- and anti-inflammatory cytokines. The gut microflora is manipulated by probiotics to preserve a healthy balance of pathogenic and non-pathogenic microorganisms. Due to the development of these drugs' usage in the treatment of certain diseases, there is now a very high index of safety, a decrease in the use of antibiotics, and a favourable public opinion of "alternative" or "natural" remedies.

3.5 Role in inflammation

Inflammation is the body's reaction to irritation or damage and is manifested by swelling, discomfort, redness, and heat. Nutraceuticals such as ginger, soybean, unsaponifiable, glucosamine, chondroitin, and S-adenosylmethionine have their effects on osteoarthritis.

The sirtuin-like deacetylase activity of resveratrol, which is found in the fruits of *Vaccinium angustifolium, Vaccinium myrtillus, Vaccinium ashei,* and *Vaccinium corymbosum* is the most potent of any reported phytochemical. They have anti-fungal and anti-inflammatory properties.

The omega-3 and omega-6 series produce powerful modulatory molecules for inflammatory responses, such as prostaglandins, leukotrienes, and interleukins, which have a substantial impact on illnesses. GLA (gamma linolenic acid) is a nutraceutical used to treat autoimmune disorders and inflammation-related issues (Nasri et al., 2014).

3.6 Role in Obesity

Obesity is associated with a number of diseases, such as hypertension, congestive heart failure, angina pectoris, hyperlipidemia, respiratory issues, osteoarthritis, cancer, renal vein thrombosis, and impaired fertility. Large-scale research into the use of nutraceuticals as weight control and obesity therapies is now underway. Nutraceuticals with putative anti-obese qualities include *Momordica charantia*, capsaicin conjugated linoleic acid, and psyllium fibre. Low calorie sugars are nutraceuticals which also help to maintain actual body weight (Nasri et al., 2014).

3.7 Role in Cancer

Meals get their many colours from a class of compounds called carotenoids. They have antioxidant qualities and are effective in preventing cancer. Carotenoids have lately gained attention due to the significance of lycopene for human health, especially in the treatment of cancer. Plants high in genistein, biochanin, daizene, and isoflavones also inhibit the growth of prostate cancer cells. Because lycopene is unsaturated, it is believed to be a potent antioxidant and a singlet oxygen quencher.

Lycopene stores itself in the testes, skin, prostate, and adrenal glands, where it protects against cancer. The importance of fruits and vegetables in the human diet has increased due to the link between carotenoids and the prevention of CAD and cancer.

Some of the compounds that also possess anti-inflammatory and anti-carcinogenic properties are Ginseng, phytoestrogens, flavonoids from citrus fruits and isoflavones from soyabean, Saponins, Tannins, Ellagic acid and Pectin (Nasri et al., 2014).

4. Nutraceuticals derived from micro-organisms

4.1 B-VITAMINS

Vitamins are one of the essential micronutrients required by our body. Various metabolic processes depend on them. They act as antecedents of numbers of intracellular co-enzymes and also act as co-factors in metabolic pathways. They also help to maintain several biochemical reactions of our body, calorie generation & formation of red blood cells. B-vitamins are mainly found to do these kinds of work (LeBlanc et al., 2011). Human body cannot produce most of the vitamins. So, the requirement of these should be met by external sources like daily diet. The main causes are inadequate food intake and unbalanced diet. Vitamin-B complex like Thiamine (B_1), Riboflavin (B_2), Niacin (B_3), Pyridoxine (B_6), Pantothenic acid (B_5), Biotin (B_7), Folic acid (B_{9-11}) & Cyanocobalamin (B_{12}). Although they are present in raw foods but during cooking or food processing some amounts are easily demolished. So, sometimes deficiencies are easily occurred. To overcome such situation fortifications are done by which various vitamins & minerals are incorporated into food particles chemically. But it has side-effects also (Asrar et al., 2005). Now-a-days it is seen that some micro-organisms are also able to produce this natural form of folates which is not the cause of the occurrence of vitamin-B_{12} deficiency. It is more effective and safer than the supplementation or chemical fortification. This process is more economical too and there is less chance of side-effects (Lamers et al., 2006).

Riboflavin (B_2)

Riboflavin helps in several biochemical reactions of metabolic pathways of our body. It plays an important role in formation of the co-enzymes like FMN (Flavin Mononucleotide) & FAD (Flavin Adenine Dinucleotide). These co-enzymes are involved in carrying the hydrogen molecules redox reactions of Nicotinamide Adenine Dinucleotide dehydrogenase enzyme (NADH) (LeBlanc et al. 2011). Milk and milk products contain this vitamin but it is not the good source. If few food processing technologies are applied then the riboflavin content of milk or milk products can be increased like fermentation (Höllriegl et al., 2002). We should culture those strains of *Lactobacilli* which will increase the vitamin-B_2 content in products. *Lactobacillus fermentum* MTCC 8711 is the most effective riboflavin-producing strain which can form about 2.29mgl^{-1} within 24h. *Streptococcus* and *Enterococcus* are the Lactic Acid Bacteria (LAB) which help to increase the riboflavin content of tempeh (LeBlanc et al., 2011).

Lactobacillus lactis, Lactobacillus plantarum, Leuconostoc mesenteroids & Propionibacterium freudenreichii are the natural riboflavin-overproducing variants of micro-organisms. Through genetic engineering techniques we can also obtain such strains which have the ability to increase its production. For example, the genes of *Corynebacterium ammonigenes* which helps in the biosynthesis of riboflavin in foods was manufactured by metabolic engineering procedure with recombinant-DNA techniques. It can produce 17 times more riboflavin the parent strain. Gene technology also modify the *Bacillus subtilis* which is a gram-positive bacterium to produce riboflavin. Through the process of mutagenesis and metabolic engineering of *L. lactis* we can produce folate and riboflavin simultaneously. (LeBlanc et al., 2011).

Folic Acid (B_9)

Folic acid helps in various metabolic reactions of our body by acting as co-factor. The cellular functions are formation of nucleotides, DNA & RNA, vitamins, amino acids, etc. Its deficiency can cause many diseases like coronary heart diseases, Alzheimer's disease, osteoporosis and even it

increases the risk of cancer also. Its deficiency also can cause hearing loss, NTD (Neural Tube Defect), etc. (Hugenholtz, & Smid, 2002) (Hugenholtz et al., 2002).

Milk and milk products contain about 20-50µg/L which is not able to provide one's daily requirement. So, it is tried to increase the folic acid content in milk and dairy products by micro-organisms. *Lactobacillus lactis, Streptococcus thermophilus* are the LAB which ferment milk to form yoghurt. Yoghurt contains more folates (200µg/L). There are various other bacteria which also help to exceed the folate content. They are *L. acidophilus, L. plantarum, Leuconostoc lactis, Bifidobacterium longum, L. reuteri,* etc. *Streptococcus thermophilus and B. animalis* can produce 6 times more folates in the form of 5-MTHF in milk products. Propionibacterium are also able to produce folates but it is seen that in between 6h and 12hour, they produce highest number of folates and then the concentration become decreased (LeBlanc et al., 2011).

Bread can also be used to produce folates. Here, the yeasts help to produce folates. If the folate-producing LAB are used additionally with the product then folate production will be significantly increased. Vegetables are also can be fermented by various micro-organisms by which we can produce more folates in them. Here, LAB starter cultures are usually used to form 5-MTHF. LAB act also upon corn flour to produce folates. Folate content can be increased in it by fermentation for 4 days at 30^{o}C (LeBlanc et al., 2011).

Genetic engineering procedures can increase the tendency of production of folates. By increasing the expression of folKE genes of *L. lactis* we can increase the folate production ten times. Overexpression of combined folKE & folC genes can increase the production and accumulation of folates intracellularly (LeBlanc et al., 2011).

Vitamin-B_{12}

Vitamin-B_{12} is one of the essential vitamins for our human body. There two identified metabolic pathways of lipid metabolism in which this vitamin is used. The two enzymes of those reactions are methionine synthetase & methyl malonyl CoA (Hugenholtz, J., & Smid, E. J., 2002) (Hugenholtz et al., 2002). This vitamin cannot be produced by plants or animals. It is only produced by micro-organisms. We get this vitamin from meat mainly from liver and kidney (LeBlanc et al. 2011).

Micro-organisms are amine producers of this vitamin. So, some bacteria are used to increase the production of vitamin-B_{12}. Mainly *Pseudomonas denitrificans, Propionibacterium* & *Bacillus megaterium* are used for commercial vitamin-B_{12} production (Höllriegl et al., 1982). The amount of nutrients present in it is very significant factor. Various experiments and studies prove that if dimethyl benzimidazole is added then the production of this vitamin will be increased. Even if latter phase of fermentation is involved into aerobic incubation, then also the production will be increased. Propionibacterium also acts upon cheese whey which is very cheap but good growth medium (Roth et al., 1996). *P. freudenreichii* & *Salmonella enterica* also help to produce cobalamin by anaerobic fermentation.

Genetic engineering and mutagenesis procedures are also can be used to increase the cobalamin production. The *hemA* gene containing plasmid of *Rhodobacter sphaeroides* can be transferred into *P. freudenreichii* by genetic engineering process and this gene helps to increase the production of cyanocobalamin 2.2 times more (LeBlanc et al. 2011).

Mechanism: Vitamin-B_{12} acts as coenzyme in metabolic reactions of our body. The coenzyme form of this vitamin is deoxyadenosylcobalamin. Microorganisms produce this by 25 steps. These steps are initiated with the precursor of heme which is uroporphyrinogen-III, F430, cobalamindimethylbenzimidazole and an adenosyl moiety. Amino acids and aminolevulenic acid undergo various steps by which at first porphobilinogen is formed and then uroporphyrinogen-III is produced. Cobalamindimethylbenzimidazole is synthesised from riboflavin in presence of oxygen (LeBlanc et al., 2011).

4.2 Low calorie sugars

Obesity becomes a major health problem in western countries. It acts as a 'silent killer' and can cause other lifestyle diseases like hypertension, diabetes, etc. Controlling body-weight has a major significance now. Low calorie sugars are good for maintaining proper body weight. So, now-a-days scientists are concerned to prepare such food products which will have low calorie sugars which will not induce the excess weight gain. Micro-organisms like Lactic Acid Bacteria (LAB), Propionibacterium, etc. are mainly used to produce such food products. (LeBlanc et al., 2011) (Hugenholtz et al., 2002).

Mannitol & Sorbitol

Mannitol and sorbitol are polyols. They also are low calorie sugars which have equal sweetness and taste like glucose, fructose, lactose and sucrose. We can produce food products without these sugars and also can substitute them with mannitol and sorbitol (Hugenholtz, Sybesma et al., 2002).

Leuconostoc mesenteroides is a LAB which ferment the fructose present in foods and convert it into mannitol. It does not convert the whole portion of fructose; it acts on it partially. When glucose is added with it, the production of mannitol is increased. Breakdown of lactate dehydrogenase (LDH) in *Lactobacillus plantarum* and *Lactococcus lactis* induces the production of new types of metabolites. Mannitol is one of those metabolites (Ferain et al., 1996).

Genetic engineering is a such processes by which the capacity of the mannitol production can be increased in Lactic Acid Bacteria. Few strains of *L. lactis* have low LDH. By metabolic engineering from those strains high production of mannitol-P dehydrogenase (MPDH) is occurred significantly. The mannitol-transporter of *Leuconostoc mesenteroides* can be inserted into *Lactococcus lactis* to induce the over production of polyols (Neves et al., 2000).

Sorbitol is also produced by micro-organisms in this way. *Lactobacillus plantarum* helps to produce this polyol. Sorbitol dehydrogenase breaks the MPDH & LDH to produce sorbitol. Increased dephosphorylation and sorbitol transport enhance the sorbitol production (Ferain et al., 1996).

Mechanism: The Lactic Acid Bacteria (LAB) like *Lactococcus lactis, Leuconostoc mesenteroide*s, *Lactobacillus plantarum* which help to produce mannitol, act upon fructose-6-phosphate and convert it into mannitol-1-phosphate. Then mannitol-1-P is dephosphorylated and mannitol is produced. In this similar way sorbitol is also produced. *Lactobacillus plantarum* acts upon fructose-6-P and produce sorbitol-6-P. After dephosphorylation of sorbitol-6-P sorbitol is produced (Hugenholtz, Sybesma et al., 2002).

Tagatose

Like mannitol & sorbitol, Tagatose is also a low-calorie sugar which acts as a sucrose-replacer. Its caloric value is lower than mannitol and sorbitol. Tagatose cannot be utilized by human body properly. So, it cannot able to exerts its calorie in our body. Usually, arabinose is used to produce tagatose by enzymatic reactions. But microbial fermentation processes get highest preference (Hugenholtz, Sybesma et al., 2002).

Acetic acid bacteria can convert galactitol into tagatose, but it is not an economical procedure. The production of tagatose from lactose by Lactic Acid Bacteria (LAB) is more economical (Manzoni et al., 2001).

Mainly *Lactococcus lactis* is used to produce tagatose in foods because it has *lacABCD* gene which helps to carry out the tagatose producing pathways. Its broad genetic tools, potent gene integration system and simple carbon metabolism make it more potential to synthesize those enzymes which carry out tagatose formation (Van Rooijen et al., 1991).

Mechanism: At first, from lactose lactose-P is formed. Then, *Lactococcus lactis* acts on it. Phospho-β-galactosidase hydrolyses lactose-P. After that, glucose undergoes into glycolysis and galactose-P isomerase acts upon galactose-P-moiety to form tagatose-6-phosphate. Then, tagatose-6-P

becomes tagatose diphosphate by phosphorylation and this reaction is catalysed by tagatose phosphate kinase. At last, dephosphorylation is performed to get the final product Tagatose (Hugenholtz, Sybesma et al., 2002).

Trehalose

Trehalose is one of the low-calorie sugars. It is also known as dietetic sugar because human body can digest it partially (Hugenholtz & Smid, 2002).

There are various micro-organisms like bacteria, yeast & fungi which can produce trehalose. Mainly *Propionibacterium* is used to produce trehalose. When this bacterium is kept in stressful conditions like low temperature, high osmolarity then it can produce this sugar. Different strains of *Propionibacterium* produce different amounts of trehalose and it depends on the growth condition which is provided externally (Cardodo et al., 2002).

Mechanism: From glucose-6-phosphate which is a glycolytic intermediate, trehalose is produced. Trehalose-6-P synthase acts upon glucose-6-P in presence of UDP-glucose and forms trehalose-6-P. then this compound undergoes the dephosphorylation reaction by trehalose-6-P phosphatase to produce the final product Trehalose (Hugenholtz & Smid, 2002).

5. Conclusion

Nutraceuticals are a cutting-edge and exciting research area for the development of novel health products with enormous potential for positive health effects, involving safety, effectiveness, and affordability. Researchers have come to the conclusion that dietary supplements and good nutrition may both prevent and treat chronic illnesses on a global scale. The pharmaceutical and food sectors, as well as academics, are very interested in this study field. Several pharmaceutical companies, notably Ranbaxy and Abbott, have taken the effort to provide a variety of nutraceutical products for customers of all ages. Researchers have discovered that these products have a significant preventative function; hence, further in-depth academic and pharmaceutical industry study is required regarding their safety and efficacy. To enable the revelation of novel approaches in present industrial fields, future investigations must concentrate on elucidating nutraceutical structure, physical and chemical features, and impacts specifically on in vitro and in vivo models. Nevertheless, further research needs to be conducted to enhance the abundance of active metabolites that have previously been identified from microbes.

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