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# Microbial cell as bio-factory for bioactive compounds: review on microbial nutraceuticals

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## Abstract

Now a days it is a challenging and very serious issue to meet an adequate supply of quality food for growing population which is exploding at a geometric progression. Nutrient deficient diet is one of the major cause of constantly increasing health related problems. To resolve the health issues caused by malnourishments, nutraceutical like polysaccharides, multi-vitamins and enzymes have been produced from plants since many years. However, use of plant-derived nutraceuticals is limited due to low growth rate, seasonal variation, plant diseases or other environmental influences. Instead, microorganisms can be used for rapid, ecofriendly and economically nutraceuticals production in less space and generation time.Scientists are focusing on cultivation of useful microbial strains that have the potential to produce metabolites possessing pharmaceutical as well as nutrition value (nutraceuticals). This modern approach can compensate for food demand (quality diets) and disease curing. Various bacteria, fungi, algae and yeast have been cultivated for the production of the bioactive compounds. Such useful microbial extracted compounds are considered to be food graded healthy nutrition or nutraceuticals. This advance research can bring revolution in the field of medicine and nutrition.

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## Introduction

Proper nutrition is an indispensable requirement for growth, development and normal body functions of human beings. Though, getting sufficient nutrition is of great concern even one is taking enough food. Here and now, lack of proper nutrition is a global issue as one third population suffers from malnutrition (Avula, 2015). In the world, due to malnutrition, significant number of precious life is lost annually with about 3 million young lives every year (UNICEF, 2016). Malnutrition may leads to poor growth and development of children, skin and bone disease, overweight, high level of sugar, fats or cholesterol and salt in blood, minerals and vitamin deficiency, or serious complications in immunocompromised people. Intensification of various diseases due to malnutrition and poor diet are becoming the major risks for health throughout the world. Policies have been established at world level to improve nutrition and to completely finish the malnutrition till 2030 (UNICEF, 2016). To overcome the problems of the malnutrition, different phytochemicals have been used as nutraceuticals. The terms "nutrition and pharmaceuticals" were put together to derive the word 'nutraceuticals' by Dr Stephen de Felice which categorically describe the food or products of the food, used to improve health, prevent and treat various health (Biesalski, 2001). In the course of recent years various new diet ingredients have been introduced to nutrition and pharmaceutical market as nutraceuticals. Bacteria, yeast and micro algae can act as producers or catalysts for the synthesis of food ingredients, compounds like enzymes and nutraceuticals (Hugenholtz and Smid, 2002).

A potential nutraceutical is one that benefits the health as shown in table. 1, and for this purpose various studies have been carried out to analyze the potency of nutraceuticals for biological advantages and provide protection against chronic diseases.

**Table 1.** Beneficial metabolites produced from microorganisms.

| Microorganism | Nutraceuticals produced | Effects on Humans | References |
|---|---|---|---|
| | | Protein | |
| *Lactobacillus acidophilus* | Leptinacidolin, Acidolphilin, Lactocidinand Bacteriocin | Anti-obesity,improvements in the digestive system | Sousa *et al.*,2008; Gupta *et al.*, 2000 |
| *Lactobacillus rhamnosus*GG (LGG) | Specific protein called p75 and p40 | Prevention of inflammatory bowel disorders (IBD) | Gupta *et al.*, 2000; Kassinen *et al.*, 2007 |
| *Escherichia.Coli* | GLP-1 | Triggerscells in the pancreas to make insulin | Bronzwaer, 2008; Cani *et al.*, 2009 |
| *Escherichia intermedia, Ervinia herbicola* | L-DOPA | Brain neurotransmitter | Kumagai *et al.*,1970; Kumagai *et al.*, 1972 |
| | | Carbohydrates | |
| *Agrobacterium radiobacter* | Sulphated derivatives of curdlan | Antitumor and antiviral | Zhan *et al.*, 2012 |
| *Aerobacter levanicum, Zymomonas mobilis, Lactobacillus sanfranciscensis, Bacillus subtilis, Bacillus polymyxa, Acetobacter xylinum, Gluconoacetobacterxylinus,* | Levan | Anti-obesity, hypolipidaemic, antitumor and anti-radiation protective | Kang *et al.*, 2004; Yoo *et al.*, 2004; Bekers *et al.*, 2005; Combie, 2006 |
| *Elsinoe leucospila* | Elsinan | Cholesterol-lowering and Antitumor | Shirasugi and Misaki, 1992; Misaki, 2004 |
| *Agaricus bisporus, Auricularia auricula, Flammulina velutipes, Lentinus edodes* | Edible mushroom glucans | Antioxidant | He *et al.*, 2012 |
| *S. cerevisiae* | Zymosan | Anti-inflammatory | Ohno *et al.*, 2001; Goodridge *et al.*, 2009 |
| *Azotobacter vinelandii, Azotobacter chroococcum* | Bacterial alginate | Anti-inflammatory (Anti-ulcer) | Sabra *et al.*, 2001 |
| | | Fatty acids | |
| *Lactobacillus species* | Conjugated linoleic acid (CLA), Conjugated linolenic acid (CLnA) and 10-Hydroxy-cis-12-octadecenoate (HYA) | Reduces adiposity, Improves insulin sensitivity,Anti-cancer, Reduces atherosclerosis, | Belury, 2000; Bergamo *et al.*, 2014 |

| | | | |
|---|---|---|---|
| | | Anti-inflammatory | |
| *Mortierella alpina* | Arachidonic acid (ARA) | Infant nutrition | Casterton *et al*., 2009 |
| *Isochrysis galbana* | Eicosapentaenoic acid | Treating obesity, metabolic syndrome, nonalcoholicsteatohepatitis and type-2 diabetes | Baker *et al*., 2008; Wen and Chen, 2003 |
| | | Vitamins | |
| *Pseudomonas denitrificans* and *Propionibacteriumshermanii* | Vitamin B12 | Protection against anemia | Kassinen *et al*., 2007 |
| *Lactococcus acidophilus* | Vitamin K | Prevention of inflammatorybowel disorders and colitis | Gupta *et al*., 2000 |
| *Blakeslea trispora* and *Duniella salina* | β-carotene (provitamin A) | Antioxidants | Nelis and de Leenheer, 1991 |

With the evolution and improvement of green technology and production of high yielding cereals varieties, major advancements have been done to food production in last 30 years.

The malnourished proportion of population ranged 46.5% (in the early 1960) to 26.7% (2000) in the under developed countries of the world (Lipton, 2001; Clugston and Smith, 2002).With the present situation of malnutrition and the impact of global increase in population, new polices are indispensable to overcome the food deficiencies and to meet the future demands for world food and nutrients. According to the United Nations (UN) report, there will be a huge change/increase occur in the world's population with growth from 8 billion to 9.4 billion in 2025 and 2050 respectively (93% of the increase in population will occur in the developing countries) (Clugston and Smith, 2002).

Dietary intake of phytochemicals used from decades may promote health benefits, protecting against cancer, cardiovascular, neurodegenerative diseases, oxidative stresses, inflammatory diseases, hypertension, hyperlipidaemia and renal failure (Osawa, 2007; Wojcikowski*et al*., 2006), butthe major risks associated with phytochemicals are the lack of availability of required plant parts due to slow growth, seasonal variation and biotic and abiotic factors.

Therefore, alternate ways have been found for the nutraceutical production from beneficial microbes that can replace the plant based phytochemicals due to cost effectiveness, eco environmentally friendly and short space and generation time (Fig. 1).

Microbial production of substances, for example, amino acids, biocatalysts, proteins, vitamins, anti-microbial and hydrocolloids additionally stays essential to promote health (Dufosse, 2009).

Lactobacillus microbes, specifically *Lactococcus lactis*, have been shown to be perfect cells for the generation of nutraceuticals. Microalgae and cyanobacteria also act like biological machineries for the production of vitamins, ω-3 unsaturated fats, proteins, pigments (Pulz and Gross, 2004).

Various microbial species and aerobic microorganisms like *Corynebacterium glutamicum* is considered one of the best source for the production of antioxidants like Superoxide dismutases (SODs) (El Shafey *et al*., 2008).

Improvement in the genetic abilities of the food graded microorganisms indicates that the production of certain nutraceuticals can be upgraded through over expression of the genes or mutating the microbial metabolic qualities (Hugenholtz andSmid, 2002).

Bacterial cells are genetically engineered to increase the production of human insulin (Humuline), which is then purified and used for diabetes treatment (Barsh *et al*., 2000; Bajzer and Seeley, 2006).

Important nutraceuticals as metabolites isolated and purified from various microorganisms in a variety of mechanisms are detailed in the following headings.

**Table 2.** Bioactive amine molecules produced via various microbial enzymes.

| Amino acids/Peptides/Derivatives | Enzymes | References |
|---|---|---|
| Glutamylpeptides | Glutamylcysteine synthetase | Nakayama *et al.*, 1981 |
| Glutamylmethyl amide and theanine | Glutamine synthetase | Yamamoto *et al.*, 2005 |
| Aspartic acid | Aspartase | Sato and Tosa, 1993 |
| Alanine | L-aspartic acid β-decarboxylase | Chibata *et al.*, 1965 |
| DOPA | Tyrosine Phenol-Lyase | Kumagai *et al.*,1970; |
| Hydroxyphenylglycine | Hydantoinase | Yamada *et al.*, 1978 |
| Hydroxy-L-proline | Proline 4-hydroxylase | Shibasaki *et al.*, 2000 |
| Aspartame | Thermolysin | O'Donnell, 2006 |
| Glutamyl-L-tryptophan | Glutamyltranspeptidase | Suzuki *et al.*, 2004 |

*Microbial biosynthesis*

*Amino acids and derivatives*

Amino acids are the monomer or precursor for the proteins. There are twenty amino acids and several of their derivatives have been identified for their role in maintenance of health. Body will face a number of disorders upon missing any of the amino acids.

Amino acids are considered to be the building block of life that have long been performed significant role in the nutrition and health maintenance of both animal and human (Bercoviciand Fuller, 1995).

Nitrogen-bearing molecules, for example, oligopeptides, amino acids and its derivatives have gotten unusual consideration by influencing human physiology in different ways as shown in Table 1.

Microorganisms possess wide range of useful properties and such microbial strains can be used for the human wellbeing. In 1957, Shukuo Kinoshita and his partners obtained amino acids from direct fermentation technique using *Corynebacterium glutamicum* also known as *Micrococcus glutamicus* (Kinoshita *et al.*, 1957a).

According to an estimation more than 2.3 million tons of amino acids were produced in 2000 by using microorganisms or bacterial enzymes (evaluated by the Essential Amino Acid Association, Japan).

As some amino acids can't be prepared in enough amount by just simple fermentation, enzymatic strategies utilizing microbial catalysts were discovered.

**Table 3.** Food graded polysaccharides produced and isolated from microorganisms.

| Microorganisms | Products | References |
|---|---|---|
| *Xanthmonas campestris* | Xanthan | Kennedy and Bradshaw, 1984 |
| *Acetobacter xylinum* | Acetan or xylinan | Van Kranenburg *et al.*, 1999 |
| *Leuconostoc mesenteroides*, *Lactobacillus curvatus* | Commercial dextran | Leathers, 2002; Ruhmkorf *et al.*, 2012 |
| *Sphingomonas paucimobilis* | Gellan | Giavasis *et al.*, 2006 |
| *Agrobacterium* and *Rhizobium* species | Curdlan | Sutherland, 1998 |
| *Alcaligenes faecalis* and *Pseudomonas* species | Succinoglycan | Freitas *et al.*, 2011; Moosavi-Nasab *et al.*, 2012 |
| *Lactobacillus hilgardii* | Kefiran | Ghasemlou *et al.*, 2011 |
| *Pullularia pullulans* or*Aureobasidium* | Pullulan | Leathers, 2003 |
| *Sclerotium glucanicum* and *Sclerotium rolfsii* | Scleroglucan | Giavasis *et al.*, 2002 |
| *Schizophyllum commune* and *Lentinus edodes* | Schizophyllan and lentinan | Giavasis *et al.*, 2002; Giavasis and Biliaderis, 2006 |
| *S. cerevisiae* | Glycan | Xu *et al.*, 2009 |

Table No. 2 enlists various mode of action of Microorganisms that they perform to produce various peptides, amino acids and their derivatives via the enzymatic action. Usage of an auxotroph for amino acids production requires the expansion of an insignificant quantity of substrates to help the development of the bacterium as Kinoshita and his partners reported that some arginine or citrulline auxotrophs utilized L-ornithine in a medium supplemented with limited amount of L-arginine for growth and multiplication (Kinoshita *et al.*, 1957b). As some amino acids can't be delivered productively by fermentation, enzymatic strategies utilizing microbial catalysts were created. Applying immobilized aspartase enzyme produced from *E. coli*, Sato and Tosa (1993) built up a continuous enzymatic production technique to make L-aspartic acid from fumaric acid.

**Table 4.** Microbial transformation pathway to produce fatty acids.

| Metabolites | Pathways/ Mechanisms | References |
|---|---|---|
| Acetate | Acetyl Coenzyme A (acetyl-CoA) | Thauer *et al.*, 1989 |
| Propionate | Succinate pathway | Reichardt *et al.*, 2014 |
| Butyrate | Butyryl-CoA: Acetate CoA transferase | Duncan *et al.*, 2002 |
| Trimethylamine and Trimethylamine N-oxide | Cleavage of choline toTMA (Trimethylamine) and acetaldehyde | Craciun *et al.*, 2014 |
| Indole | Tryptophanase catabolize tryptophan | Kim and Park, 2013 |
| Para-cresol | Fermentation of tyrosine or its metabolite hydroxyphenylacetate | Dawson *et al.*, 2011 |
| 4-Ethylphenol | Tyrosine metabolitepara-coumaric acid via cinnamate decarboxylase and vinyl phenol reductase | Yasuda *et al.*, 2001 |
| Conjugated linoleic acid (CLA), conjugated linolenic acid (CLnA) and 10-hydroxy-cis-12- octadecenoate (HYA) | Transformation of linoleic acid (LA) to CLA, linolenic acid to CLnA and intermediate from linoleic acid pathway | Yang *et al.*, 2014 |

The biosynthesis of the amino acid derivatives such as selenocysteines and selenomethionines have been produced from both *Lactobacilli*(Lamberti *et al.*, 2011) and yeasts (Porto *et al.*, 2015). Lysin and ornithine can be metabolized by *E. coli* to produce cadaverine and putrescine respectively (Applebaum *et al.*, 1975). Similarly another bacteria such as *proteus* can harvest putrescine from ornithine as a communication signal (Visick and Fuqua, 2005).

Single cell proteins (SCP) have been produced from the cultures of different microbes, moulds, yeast and algae. SCP produced from microorganisms have over 80% protein despite the fact that they are poor in S-amino acids and have high nucleic acids constituents (Kurbanoğlu, 2001).

*Polysaccharides and derivatives*

Polysaccharides are the carbohydrates, formed by polymerization of saccharide monomers. Polysaccharides were the first known long term ago for its bioactivities and due to vital role in medicines. Microbial polysaccharides are thought to be ideal candidate for use in functional foods or nutraceuticalsbecause of having significantimmuno modulating properties like anti-tumor, anti-inflammatory, antimicrobialor hypo-cholesterolemic and hypo-glycemic properties (Giavasis and Biliaderis, 2006). The global market for this kind of health promoting nutrients is right now extending and scientific interest for this field is developing, as user understand the significances of such food graded medicine to solve health issues(Hardy, 2000). Table 3 contains data of various microbial polysaccharides which have some application in food industries, isolated from fungi, yeasts or bacteria.

Few Fungal strains of the phylum basidiomycetes, some Gram negative (*Xanthomonas, Pseudomonas,Alcaligenes*, etc) and gram positive

Lactic acid bacteria (LAB) bacteria are the common producers of microbial polysaccharides. Polysaccharides in significant amount are also synthesized by the members of the genus *Saccharomyces*, mainly by yeasts (Giavasis and Biliaderis, 2006). Some of extracellular polysaccharides (EPS) have been harvested in fermented dairy items from a large number of LAB, especially from Lactobacillus, Streptococcus, *Lactococcus, Pediococcus*, as well as *Bifidobacterium sp*. and *Weissella* strains (Notararigo *et al*., 2012).

**Table 5.** Shows vitamins production via various microorganisms.

| Water solublevitamins | Fat soluble vitamins | Microorganisms | References |
|---|---|---|---|
| _ | Vitamin A and pro-vitamin A | Microalga *Dunaliella* and *Blakeslea trispora* | Borowitzka, 1989 |
| _ | Vitamin D | *S. cerevisiae* | He *et al*., 2007 |
| _ | Vitamin E | *Dunaliella* and *Spirulina* | Valentin and Qi, 2005 |
| _ | Vitamin K | *Bacillus subtilis* and *Propionibacteriumfreudenreichii* | Furuichi *et al*., 2006; Sato *et al*., 2001 |
| Vitamin B1 | _ | *Bacillus subtilis* | Goese *et al*., 2006 |
| Vitamin B2 | _ | *Ashbya gossypii* and *Candida famata* | Kato and Park, 2012; Dmytruk et la., 2011 |
| Vitamin B3 | _ | *Rhodococcus rhodochrous* | Nagasawa and Yamada, 1989 |
| Vitamin B5 | _ | *E. coli* and *Corynebacterium glutamicum* | Moriya *et al*., 1997; Sahm and Eggeling, 1999 |
| Vitamin B6 | _ | *Flavobacterium* sp and *Rhizobium meliloti* | Tani, 1989 |
| Vitamin B7 | _ | *E. coli*, *B. sphaericus* and *B. subtilis* | Sanyal *et al*., 1996; Ohshiro *et al*., 1996; Bower *et al*., 1996 |
| Vitamin B9 | _ | *B. subtilis* and *Ketogulonigenium vulgare* | Zhu *et al*., 2005; Cai *et al*., 2012 |
| Vitamin B12 | _ | *Pseudomonas*and *Propionibacterium* | Eggersdorfer *et al*., 1996 |
| Vitamin C | _ | *Chlorella pyrenoidosa* | Running *et al*., 1994 |

The most well-known bacterial polysaccharide, to be the first industrially produced is the dextran, used in many food ingredients as well as in pharmaceuticals as important substrates (Leathers, 2002). Polysaccharides are produced as extracellular substances by the most LAB (*Lactobacillales* or lactic acid bacteria) using glycansucrases or intracellularly by the enzymes glycosyltransferases from sucrose and sugar nucleotide precursors respectively (Ruas-Madiedo *et al*., 2002). A mushroom *Agaricus blazei,* discovered in Brazil, having edible and medicinal value such as polysaccharides in its fruit body possess an anti-tumour activity (Mizuno *et al*., 1990).

Mizuno (2002) reported the synthesis of polysaccharides with somewhat different medicinal properties in submerged cultures of *A. blazei* as compared to those polysaccharides contained in fruit body of mushroom.

*Fatty acid and structural lipids*

Lipids contain the most important biological molecules, called fatty acids, found every in living world i.e. in organism's body structures, foods and play important role in cell membrane composition by providing integrity. According to the report of Nagy and Tiuca (2017), lipid bodies are the rich energy sources and are very crucial for the structures and functions of all living organisms (signaling, biosynthesis, nutrition and health)as well as, having important applications in the field of nanotechnology, food industries and cosmetics (Mashaghi *et al*., 2013). Table 4 indicates a significant number of the metabolites (lipid bodies) characterized by these report, resulting from the metabolism of particular dietary supplements by selected types of organisms

that express the important enzymes to ferment the ingredients in the provided supplements and enhancing the production pathways. In this way, the variation of microorganisms using these diet-dependent metabolic pathways might be critical to understanding the variable host reaction to particular dietary components (Zeevi *et al*., 2015). Den Besten *et al.* (2013) investigated the biochemical pathways prompting the formation of the short chain unsaturated fats (SCUF) by microorganisms, having the potential to hydrolyze sugar molecules. Poly unsaturated fatty acids (PUFA) playing an important role in the development of human body. Because, cell membranes of all living organisms are composed such fatty acids as a major components of the phospholipids due to which membrane fluidity is regulated as well as interaction of other protein/enzymes to the membrane promoting signals transduction and other important metabolic pathways (Li *et al*., 2003; Gogus and Smith, 2010). Fatty acids produced by various microorganismspossess some potential medicinal properties as mentioned in Table 1, which reflects its use as quality diet. Oil produced by the microorganisms are commercially available for human use and have been given the name of single cell oils (SCO). *Mucor circinelloides*, *Thraustochytrium* speciesand microalgae *Isochrysis galbana* have been studied for the commercially available SCO like Gamma-linolenic acid, Docosahexaenoic acid and Eicosapentaenoic acid production respectively (Wen and Chen, 2003; Ratledge, 2005; Burja *et al*., 2006).

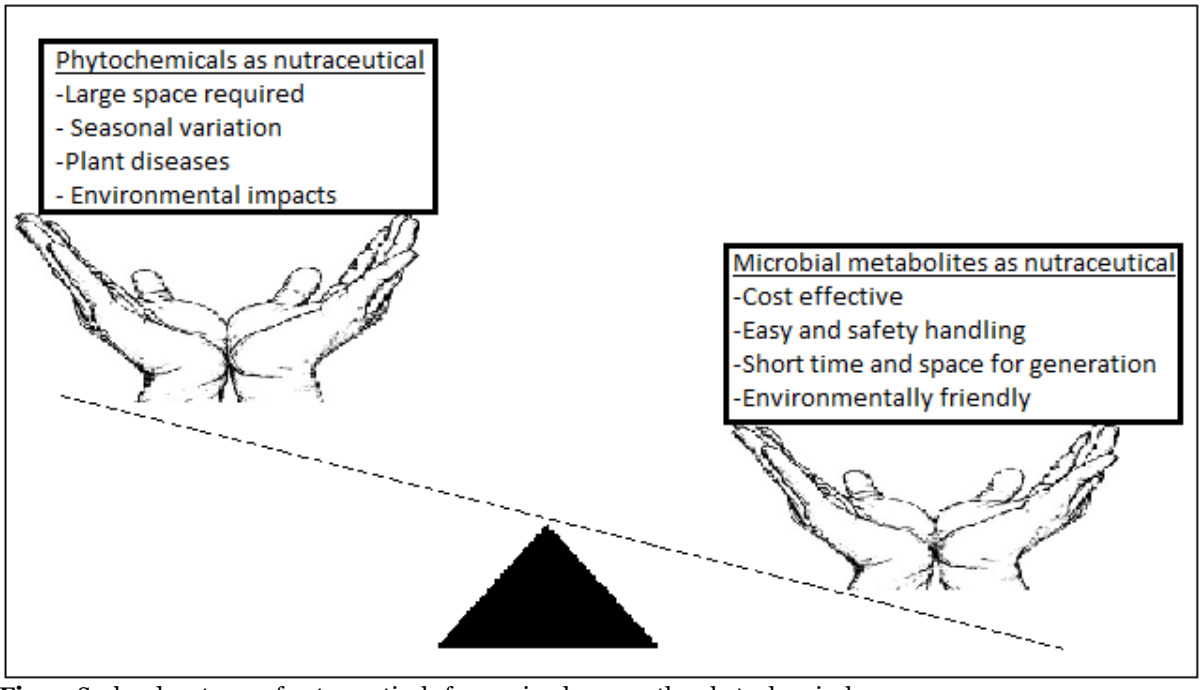


**Fig. 1.** Scale advantages of nutraceuticals from microbes over the phytochemicals.

*Vitamins*

Vitamins are characterized as natural compounds that are fundamental for normal development and nutrition and are required in little amounts in the diet since they can't be produced by the body. Thus, biological synthesis of vitamins has been investigated, by identifying the microbial flora, finding the optimized culture conditions, scaling up production methods and upgrading downstream procedures to remove the other by-products. Vitamin A produced from *Arthrospira* concluded that it has high quality and a valuable impact on human health as compared to artificially produced vitamin A (Annapurna *et al*., 1991). *Arthrospira* is also known to be a source of vitamin B12. Market available *Arthrospira* contains up to 244 µg vitamin B12 per g dry weight (Watanabe, 2007). Recently, a few metabolic engineering techniques have been discovered keeping in mind the

end goal to produce carotenoids (vitamin A precursor) in various biological pathways (Ye and Bhatia, 2012).

The growth pattern of various fungi like, *Trichoderma*, *Cephalosporium* and *Fusarium* have been researched with respect to their ability to yield ergosterol (vitamin D precursor)(Shimizu, 2008). The two fungal strains, *Eremothecium ashbyii* and *Ashbya gossypii,* belongs phylum ascomycete and commonly used for vitamins production on industrial scale(Stahmann *et al.*, 2000). Table 5describes biological industrial production of eachvitamin within a group, depending on its chemical nature: water-soluble or fat-soluble. Nicotinamide and nicotinic acid have been produced by chemical means as well as through the techniques of the biotechnology (fermentation) (Eggersdorfer *et al.*, 1996). Some other researchers have reported successful production of vitamin B9 by mixed type of microbial fermentation (Miyata and Yonehara, 1999).

**Conclusion**

Microbial nutraceuticals have the advantages due to well controlled production procedures, in an extensive upscale production inside a relatively constrained space and less generation time, stable harvested bioactive compounds and unhindered accessibility in the market, rather than plant sources whose accessibility, annual production and substance qualities frequently change. These nutraceuticals exhibits medicinal properties like anti-carcinogenic, immuno modulating properties, antidiabetic, anti-obesity, anti-inflammatory, anti-allergic and cholesterol lowering properties, as well as these nutraceuticals also act as prebiotics,promoting the growth of the producer strain or other LAB (Lactic acid bacteria) which could be highly significant in synthesis of novel foods with bioactivity and health promoting properties. However, sometimes during production of microbial nutraceutical, high production costs, low nutraceuticals yields, and tiresome downstream procedures required for isolation and purification are still the matters of consideration for microbial culturing procedures, therefore, applicable approaches for the optimization of bioprocess can be implemented to improve the nutraceutical production process.

*Conflict of interest*

Author 1 and author 2 whose names are listed declare that they have no conflict of interest or any kind of financial or organizational involvement.

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