Recent Advances and Use of Tools for Functional Foods and Nutraceuticals

16

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Abstract

Nutraceuticals and functional foods are known to have multiple health benefits from maintaining the proper well-being of the host to prevention and treatment of diseases. The therapeutic areas targeted by nutraceuticals are metabolic diseases, cardiovascular diseases, diabetes, obesity, GIT health, immune system modulation as well as prevention of various chronic diseases such as cancer. The development in the technologies made it possible to consume these bioactive compounds with their maximum bioactivity and functionality. There are several traditional as well as molecular biology techniques that are incorporated in the food and nutritional research to enhance the health benefits obtained from bioactive compounds present in the food. This chapter highlights the introduction and role of nutraceuticals in various diseases and also elaborates the recent research and techniques involved in the nutraceutical research.

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16.1 Introduction

Nutraceuticals and functional foods have gained considerable interest in the recent years due to their nutritional qualities, natural origin and therapeutic effects in many diseases. Modern age lifestyle disorders such as cancer, diabetes, obesity, osteoporosis, hypertension, allergies, etc. are becoming a challenge for the whole world (Chintale Ashwini et al. 2013). Conventional allopathic medicines are available but come with several side effects (Niggemann and Grüber 2003). Also, it has been proved that diet and exercise play a significant role in the maintenance of a good health as well as have the preventive and therapeutic effects against diseased conditions. The term nutraceutical was first coined by Stephen de Felice in 1979 (DeFelice 1992). It can be considered as the merger of two terms, nutrition (which provides health benefits and nutrients) and pharmaceutical (treatment of diseases), to make nutraceuticals and is defined as the 'food or certain compounds present in foods that impart health and medical benefits to the consumer as well as function in the prevention and treatment of targeted diseases' (Chintale Ashwini et al. 2013). The concept of functional foods is not new; people have been using herbs and many medicinal plants like tulsi (*Ocimum tenuiflorum*), neem (*Azadirachta indica*), ashwagandha (*Withania somnifera*), shatavari (*Asparagus racemosus*), pippali (*Piper longum*), etc. for the treatment of many infections and diseases since ancient times. Certain plants and food items like vegetable, fruits, spices and cereals that contain various nutrients, compounds and phytochemicals which provide additional health benefit alongside the basic nutritional needs are termed as functional foods. Functional foods have the provision to include both micronutrients like vitamins and minerals and macronutrients like proteins, fats (omega fatty acids) and carbohydrates. When these nutrients work in the prevention and cure of a particular ailment rather than just fulfilling deficiency conditions, they are termed as nutraceuticals (Sharma et al. 2017). The spectrum of nutraceuticals is very broad including functional foods, herbals, dietary supplements, genetically engineered foods, fermented products, probiotics, etc. All of these are known to have the action against specific targeted diseases. They cover most of the therapeutic areas such as digestion, cold and cough, sleeping disorders, anti-arthritic and prevention of certain cancers, high cholesterol, hypertension, diabetes, etc. Nutraceutical research is now co-supported by the emerging techniques in biological research to develop health-benefitting products which alter the expression and constitution of genes or metabolic pathways in a positive direction (Dahiya 2013). There are many techniques and methods used to enhance the bioavailability and bioactivity of functional foods such as fermentation and probiotic fortification. The use of starter culture for the fermentation of food products to deliver desired result is also one of the techniques. To increase the functionality of nutraceuticals, the delivery systems of the nutraceuticals are also improved by the use of nanotechnology and various carrier vehicles such as emulsions, biopolymers, etc. Lastly, the interrelation of molecular biology with nutritional research has led to the understanding of effect of food on gene expression. The omics technology is involved from the last 20 years and has given a major breakthrough.

16.2 History and Development of Nutraceuticals

The concept of using food, especially herbs for treating many ailments, is a couple centuries old. The idea comes from the statement quoted by Hippocrates, the father of modern medicine, 'let food be thy medicine and medicine be thy food', almost around 2500 years ago. He clearly established the relation of food and its importance in the treatment of various ailments. There are several examples of using traditional herbs as a medicine globally. Ginseng is one traditional drug used for treating cancers and for chemotherapy for over 2000 years in China (Sharma et al. 2017). The medicinal importance of several herbs such as coriander, cumin, turmeric, fennel garlic, curry and dried mint found in the pyramids was identified by Egyptians. Triphala is one of the most preferred tonics in Ayurveda. It is a mixture of three herbs, namely, *Terminalia chebula* (Combretaceae), *Terminalia bellirica* (Combretaceae) and *Emblica officinalis* (Phyllanthaceae). It benefits almost all of the organs in the body particularly the skin, liver and digestive system. Turmeric from South Asia is a well-known anti-bacterial herb and is also a potent inhibitor of HIV (Chanda et al. 2019).

16.3 Concept of Nutraceuticals

As defined earlier, nutraceuticals are food working similar to medicines, although there are more approaches to it. Pharmaceuticals usually undergo clinical trials for the verification of the effects and are patented. However, in nutrition, foods having beneficial properties are not patented as well as there are no verification methods for treating diseases. Nutraceuticals are generally perceived as the preventive measures against any diseased condition. Nowadays, the major side effects of traditional medications have driven people towards more natural and safe treatment. These foods contain a combination of various compounds responsible for their action. These are called phytochemicals, which have a wide range of therapeutic effects against a number of diseases. These phytochemicals can act as (1) substrates for various biochemical reactions, (2) cofactor/inhibitor for enzymatic reactions, (3) scavengers to minimize the effect of toxic compounds, (4) enhancer of the absorption of various essential nutrients and (5) compressor of inflammatory reactions in the body (Dahiya 2013). Hence, the interrelation of food with health is well established now, but the main goal is to apply the benefits of food as therapeutic compounds.

16.4 Classes of Nutraceuticals

There are a wide variety of food items consumed all over the world to slow down symptoms and prevent chronic diseases other than the medications. The broadly range nutraceuticals are classified on different basis. Based on their production, they are classified into traditional and non-traditional nutraceuticals.

16.4.1 Traditional Nutraceuticals

These are the foods or compounds sourced from natural foods and are consumed without making any changes to its form. They are simply natural with new information about their potential health benefits (Chintale et al. 2013). They include all sorts of carbohydrates, proteins, amino acids, vitamins, minerals and phytochemicals present naturally in the food as well all the herbs, probiotic and prebiotics. There are many amino acids and vitamins obtained from the diet, which are involved in various metabolic pathways such as folic acid and vitamin B12. Lycopene is one compound known to have anti-cancer effects by reducing oxidative stress (Atessahin et al. 2005). All the fruits, vegetables, grains, meat and fermented products consumed in the natural form are classified as traditional nutraceuticals (Gupta et al. 2010). They broadly include nutrients/functional foods, herbals, probiotics and prebiotics and nutraceutical enzymes.

16.4.2 Non-traditional Nutraceuticals

As the name suggests, nutraceuticals which are modified artificially to basically enhance the nutritional quality are termed as non-traditional nutraceuticals. They include genetically engineered crops and fortified foods viz. oil fortified with vitamin A, wheat flour fortified with iron and folic acid; and milk fortified with vitamin D. Genetically engineered crops result in producing crops with high nutritional content or with specific properties. One example is golden rice. They are also called recombinant nutraceuticals (Chanda et al. 2019).

Nutraceuticals are also classified into different classes such as functional foods/ nutrients, herbals, dietary supplements and probiotics.

16.4.3 Functional Foods

They are the nutrients which are already present in the food and have well-established functions, such as vitamins, amino acids, fats and proteins. They are called functional foods as they also have the ability to prevent certain diseases to some extent. Omega-3 fatty acids reduce the bad cholesterol in blood and lower the risk of CVD. Oats, bran, psyllium and lignins are beneficial for heart disease and colon cancer (Khan et al. 2014).

16.4.4 Herbals

Many herbs have been used traditionally as therapeutic foods. These may be consumed directly as food or in the form of extracts.

16.4.5 Dietary Supplements

These are the dietary compounds taken orally and contain concentrate of specific nutrients. They are usually meant for treating deficiencies, but some have special functions such as sports nutrition, weight-loss supplements, etc. They are available in the form of tablets, liquid, powders and extracts.

16.4.6 Probiotics

The concept of probiotics is studied most in the recent times as they have the potential to act as therapeutic agents for most of the ailments and thereby helps in improving overall health. These are the live microorganisms, usually lactic acid-producing bacteria, which are ingested orally to maintain the balance of gut microbiota. The main functions are to protect from pathogenic infection and enhancement of the immune system. Apart from these, a wide range of other benefits are being discovered. Probiotics are also being modified to project them for a specific function, acting as a medicine for a disease. This concept is called designer probiotics and is very new in the nutraceutical research.

16.5 Benefits of Nutraceuticals

Several researches over time have shown how beneficial can nutraceuticals be. The pros of nutraceuticals cover all the aspects from health benefits to becoming consumer-friendly. Their popularization in the past decade is a fruit of numerous researches being conducted continuously around the world, trying to untangle their role in the treatment and prevention of risk of several illnesses.

Being a part of our usual diets, nutraceutical does not have any side effects when consumed with the purpose of treating or preventing an ailment. The fact that proper intake of all the nutrients in a balanced diet from childhood can prevent the risk of chronic diseases such as cancer and CVD (cardiovascular diseases) is well known. One of the best examples of nutraceutical is dietary fibre as it prevents the risk of colon cancer, lowers blood cholesterol, improves gut health and prevents the infections in GIT (gastrointestinal tract) such as ulcers and IBD (inflammatory bowel disease). The pros of nutraceuticals also account their ease of availability, and economically, they are much affordable if taken in natural forms. Also, the probiotics are useful for maintaining proper gut health and microbial ecosystem. With time, many nutraceutical compounds present in various foods have been

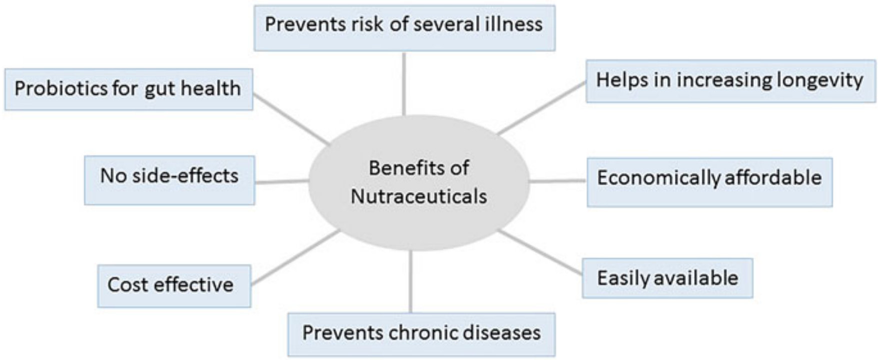

Fig. 16.1 Representation of certain benefits of nutraceuticals

proved to prevent and treat different diseases. The benefits of nutraceuticals have been shown in Fig. 16.1.

16.6 Enhancement of the Bioactivity, Bioavailability, Functionality and Health Benefits of Functional Foods and Nutraceuticals

The growing demand for nutraceuticals and their popularity among individuals have put the burden on nutrition science to find ways for improving the bioactivity, bioavailability and functionality of these functional foods and nutraceuticals. An interdisciplinary approach for this purpose is being carried out to unveil the easier and better strategies for the advancement of techniques and methods that will make this target more approachable. These strategies have been discussed in the upcoming sub-sections.

16.6.1 Enhancement of Bioactivity

Identifying and characterizing the potential of a food to see if the food can be classified as a nutraceutical is easier. The challenges appear when the bioactivity of the nutraceutical compound present in these medicinal foods is low. Demand to search for techniques/strategies to increase or enhance the bioactivity then comes into limelight. The majorly used popular strategies for this purpose are fermentation and probiotic fortification.

16.6.1.1 Fermentation

Fermentation is a metabolic process in which carbohydrates are oxidized to liberate energy. It is one of the oldest techniques, initially adopted for the preservation of foods, but it was also known to provide special aromas, texture and flavours to the food. Today, however, the technique is being used to increase the bioactivity of already present nutraceutical compounds such as phenols, phytochemicals, antioxidants, etc. Fermentation of whole grains and cereals is widely explored as they contain numerous phytochemicals, but low bioavailability is a major issue. Lactic acid fermentation is preferably used because it is comparatively inexpensive and overall nutritional and organoleptic qualities are improved. The activity of LAB (Lactic Acid Bacteria) during cereal fermentation is well documented (Rollan et al. 2019; Petrova and Petrov 2020).

It was also shown that “routine”, which is a flavanol glycoside found in buckwheat and quinoa was metabolized into quercetin by *Enterococcus avium* strain. Quercetin is a flavanol which has many documented health benefits (Shin et al. 2015). Fermentation also initiates the structural breakdown of the cell wall through microbial activity which eventually releases bioactive compounds (Adebo and Medina 2020). This usually occurs in grain fermentation. Enzymes such as proteases, amylases and xylanases synthesized from the microorganisms also play a role in the efficient bioactivity of phenolics in grain fermentation. The phenolics present are esterified to the cell wall matrix in certain cereals like bran; but they are not readily available. Fermentation is an effective strategy to release the bound phenolics and increase the bioavailability (Adebo and Medina 2020). Lactic acid fermentation is the best known method adopted to improve the functionality, nutritional value, taste and safety of food products. In a study including fermentation of whole grain sorghum with *Lactobacillus* strain, the increase in concentration of catechin, gallic acid and quercetin was documented (Adebo and Medina 2020). Another example is the fermented product *koji*, made by the fermentation of millet, and overincrease in the total phenolic compounds (TPC) is observed in the final product due to the mobilization of phenolic compounds to their free state from bound forms by the action of enzymes produced during fermentation (Salar et al. 2016).

16.6.1.2 Probiotic Fortification

The probiotics are a popular functional food consisting of live microorganisms whose ingestion in a certain amount is tagged along with specific health benefits. Several studies have shown the effectiveness of probiotic bacteria for the prevention and treatment of diseases like obesity, type 2 diabetes, non-alcoholic fatty liver disease, insulin resistance syndrome and several types of cancer (Markowiak and Śliżewska 2017). The commonly known probiotic microbes belong to the following genera: *Lactobacillus*, *Bifidobacterium*, *Lactococcus*, *Streptococcus* and *Enterococcus*. Moreover, strains of Gram-positive bacteria of genus *Bacillus* and some yeast strains belonging to the genus *Saccharomyces* are also popular probiotic (Simon 2005). These are the native strains of probiotics and have potential therapeutic effects. This fact gave birth to the need of using probiotic microbes as a functional food. For this reason, the food fortification using probiotic in the name of ‘probiotic fortification’ as a strategy begun. *Lactobacillus reuteri* CRL 1098 has the ability for the production of compounds with vitamin B12 activity. The fortification of food products like soy beverages using this strain has been beneficial in preventing disease caused by the deficiency of water-soluble vitamin B12 (Molina et al.

2012). Another example of probiotic fortification using naturally occurring probiotic microorganism includes the addition of a native strain of *Lactobacillus plantarum* 15HN to yoghurt that has shown to increase the folate concentration in yoghurt manyfolds that makes it a suitable alternative for synthetic folate in cases of folate deficiency without any side effects (Khalili et al. 2019).

The co-inoculum of yeast and *L. fermentum* PBCC11.5 was used in bread production which was measured to have a twofold increase of final vitamin B2 content as compared to the product made with wild-type strain *L. fermentum* PBCC11 (Russo et al. 2014). Another example of using probiotics as a starter culture can be included in soy isoflavones, most of which are bound to carbohydrates in the soy. These glucosides are not broken down in the GIT, so a probiotic supplement rich in β-glucosidase can be used for the fermentation that can initiate the release of isoflavones from their bound form (Laino et al. 2014). LAB, i.e. lactic acid bacteria, and other vitamin-producing microorganisms can be used for food fortification. LAB has strain-specific properties, and some can be designed for specific functions to be used as starter culture in fermented cereals (Rollan et al. 2019). They are the natural alternatives and can have lower production costs. The production of riboflavin and folate was reported by the certain strains of LAB isolated from the amaranth and quinoa sourdough (Carrizo et al. 2017).

Certain challenges using the native strains of probiotics could be achieved; but several functional characteristics were not met by these native strains. This led to the need of developing designer probiotics. Many microorganisms normally involved in food fermentation can be designed for a specific functional characteristic with the help of RDT (Recombinant DNA Technology) and can be added as the starter culture in the food (Steidler et al. 2003). These would ensure the growth of specific microorganisms during the fermentation which when ingested by the host would perform its function. The role of these specially designed probiotic microorganisms can be very broad from targeting a specific disease to production of vitamins to improve the deficiency condition in the body.

16.6.2 Enhancement of Bioavailability

The bioactive impact and health-promoting effects of orally ingested nutraceuticals depend on their bioavailability which involves crossing the epithelial barrier, resistance to the digestive enzymes and stomach acids and stability in the circulation and to reach their target tissue or organ in active form. The bioavailability of these compounds also depends on the diet. The main challenge of using nutraceuticals as health-promoting compounds is their bioavailability after ingestion. To deal with these efficacy issues, novel delivery methods are drawing more attention from researchers.

16.6.2.1 Polymer Coatings

Nutraceuticals need to be protected from the harsh environment of the GIT in order to function properly. For example, 60% probiotic bacteria find it challenging to firstly survive in the GIT, and anthocyanidins' stability depends on the pH of the GIT. Hence, polymers can be designed as the carrier vehicles for them (Lee 2017). They are definitely biodegradable that can be degraded in the body by biological processes. Some natural polymers include proteins (collagen, gelatin, zein) and polysaccharides, and synthetic polymers can be based on ester, anhydride and amide bonds.

16.6.2.2 Microencapsulation

Microencapsulation is the enveloping of the bioactive compounds into a coating, which might be present in the form of solid particles, liquid droplets or gases. There are many requirements that an encapsulation system needs to fulfil. They should protect the bioactive compounds from degradation and keep them activated and stable (De Vos et al. 2010). They also mask the unfavourable taste, if present, and increase the solubility and absorption of the compound. The shelf life and stability under storage are also increased (Manzanares et al. 2019). The size is of typically a few microns in diameter and referred to as microcapsules. The coating used is always biodegradable as mentioned in the previous section, and they can be either protein based, polysaccharide based or lipid based. The final aim of microencapsulation of the bioactive compounds is their proper digestion and absorption from the intestine into the circulation so that they can perform their designated function (Ye et al. 2018). The microencapsulation can efficiently deliver bioactive compounds in foods such as probiotics, minerals, vitamins, phytosterols, lutein, fatty acids, lycopene and antioxidants (Champagne and Fustier 2007).

16.6.2.3 Emulsions

Emulsion is a very useful tool for the delivery of the bioactive compounds. It consists of a dispersed phase (small volume) emulsified into a continuous phase, which generally has a large volume (Lee 2017). The kinetic stability is achieved by controlling many factors such as viscosity, surface charge and droplet size and also adding some thickening agent (Lu et al. 2019). The structure of the emulsion such as the droplet size can affect the kinetics of releasing the nutraceutical compound. So, the basic working of the incorporation of functional foods' ingredients is that they can be incorporated into the dispersed droplet which is again covered by the continuous phase cutting the contact from the external environment (Mao et al. 2015). They are considered to be a great option for delivering bioactive compounds as they provide protection from degradation as well as control the release. One of the advantages is that these emulsions can be modified according to the compound by modifying the structures in water phase, oil phase and interphase. Classification is based on the phase distribution of oil and water. A system consisting of water droplets submerged into oil is called oil-in-water (O/W) emulsion, and the system with water droplets immersed into oil is termed as water-in-oil (W/O) emulsion (McClements 2010). The emulsion can be efficient for the delivery of bioactive lipids like ω-3 fatty acids, carotenoids and phytosterols (McClements et al. 2007). Also, the HIPEs, i.e. high-internal phase emulsions, can be used for enhancing bioavailability and protection of beta-carotene (Tan et al. 2017).

16.6.2.4 Nanotechnology and Nanoemulsions

Nanotechnology is the newest technique used to deliver nutraceuticals to increase their bioavailability. Nanotechnology deals with substances with the capability to measure, image, manipulate, transform and control at the dimensions of 1–100 nm. It has a great potential in improving the efficacy of the bioactive compounds as it increases the absorption and solubility, facilitates controlled release, protects them from degradation and has the most effective function in targeted delivery. Nanotechnology provides tools and techniques to incorporate biological and chemical surface ligands onto the nanoparticles. These ligands recognize the target cells, and with the controlled release mechanism, they increase the efficacy and functionality of the bioactive compound by delivering to the target cell.

Many natural compounds have the nano-sized particles or assembled into nanoparticles after biological changes. For example, milk protein beta-lactoglobulin is about 3.6 nm in length. Nanotubes from the hydrolysed milk protein α-lactalbumin are self-assembled and are potential carrier for nanoencapsulated nutraceutical compounds (Momin et al. 2013). Other than these natural carriers, there are many nanodevices that have been made such as micelles (5–100 nm in diameter), liposome solid lipid nanoparticle, nanoencapsulation with biopolymers, nanoemulsions, etc. (Katata seru et al. 2019).

16.6.2.5 Nanoemulsions

Nanoemulsions is a nano-sized formulation of an emulsion, which means two immiscible liquids mixed together into a single phase, but the size range is from 20 to 200 nm (Sharma et al. 2017). Resveratrol is the antioxidant compound found in grapes and blueberries but has a poor bioavailability, so researchers encapsulated it in a nanoemulsion form by spontaneous emulsification method to overcome the bioavailability issue (Sharma et al. 2017). Fat-soluble vitamins, A, D and E are encapsulated in O/W emulsion. In an experiment, there was more inhibition reported to *E. coli* by essential garlic oil emulsion than just by simply garlic oil on a petri plate (Katata-seru et al. 2019).

16.6.2.6 Liposomes

Liposomes are structurally spherical in nature with a diameter of 20 nm and above. This technique incorporates biological and chemical surface ligands onto the nanoparticles (majorly bilayer of phospholipids) (Singh 2016). The interior core of liposomes is aqueous in nature. Nanoliposomes are nanometric version of a liposome and possess similar properties to a liposome in terms of structure and thermodynamics. Reduced size of nanoliposomes provides increased bioavailability of encapsulated compounds due to more surface area contact (Singh et al. 2012). The bioactive compounds having hydrophobic nature can be packed inside the lipid bilayers of liposomes and can be released gradually, either through diffusion or an instantaneous process of membrane disruption. The stimulation for membrane destruction can be done by changing the temperature or pH (Thomsom et al. 2009). Liposomes can be used as a delivery system for several bioactive compounds including antioxidants, proteins, peptides, vitamins, minerals, fatty acids, etc. (Singh 2016).

16.6.2.7 Microemulsion

Microemulsions are assembly of water, oil and amphiphilic molecules into structurally droplet form. They are thermodynamically very stable. They posses transparency, low-viscosity and show isotropic dispersion. The food-grade surfactants include phospholipids and diacyl glycerides (Flanagan and Singh 2006). Microemulsions can be used with the aim of increasing solubilization and as a delivery system for bioactive compounds. As a co-surfactant, ethanol can be utilized for solubilizing the long-chain triglycerides (Flanagan et al. 2006). For packaging, the lipophilic compounds like lutein and lycopene into aqueous systems O/W microemulsions can be an effective delivery system (Garti et al. 2003). Microemulsions have many applications in several fields of research and application for industries like pharmaceutical sectors, cosmetics, etc. In the food industry, several surfactants are allowed, and several are not suggested making it a less preferable delivery system for microemulsions (Singh 2016). But using the microemulsions for the solubilization of the long-chain triglycerides still remains an important benefit of this technique. Also, the breakdown of microemulsions with increased water concentration adds to its drawbacks restricting its use in food delivery system. Microemulsions can still be useful for oil-soluble bioactive compounds like α-tocopherol when formed using lesser EMG, i.e. ethoxylated mono- and diglycerides, and POE, i.e. polyoxyethylene oleyl ether concentrations (Flanagan et al. 2006).

16.6.2.8 Biopolymeric Nanoparticles

These are biopolymer (proteins and polysaccharides)-based nanoparticles effectively used as a drug delivery system (Sundar et al. 2010). They have a nanoporous structure system which provides the properties for the better development of tissue engineering, diagnosis and targeted drug delivery systems. This technology has a very crucial role in many research studies of medicine and biology and is specially used as a crucial site-specific delivery system with increased efficiency and very lower amount of toxicity (Ramchandran and Shanmughavel 2010). Preparation methods for the protein-based nanoparticles include the following steps: emulsification, desolation, coacervation, nanoprecipitation, liquid-liquid dispersion and electro-hydrodynamic atomization (Jimenez-Cruz et al. 2015). The delivery system can be beneficial for the delivery of polyphenol-based combination (Zhang et al. 2020).

16.6.3 Enhancement of Health-Promoting Effects of Functional Foods

The functional foods show the absence of any side effect when consumed with the aim of attaining health benefits. They not only prevent the occurrence of a disease but also provide relief in the already existing illness. The strategies for enhancing these health-promoting effects of nutraceuticals are dependent on their proper bioaccessibility and bioavailability. Using the identified or potential functional foods as a part of regular diet, creating food supplements, extracting and isolating the bioactive compounds from their sources and producing their drugs or pharmaceutical supplements or using several delivery systems like microencapsulation, nanoemulsions with increased functionality are several strategies that can be used to achieve this target.

16.6.3.1 Oral Delivery Techniques

The intake of nutraceuticals comes with a lot of benefits as well as the challenges. Oral delivery methods are the most effective way to deliver nutraceutical compounds with their proper bioaccessibility and bioavailability. There are many hurdles to overcome such as the solubility and permeability of the compound from a solid oral dosage, especially for fatty acids and phytochemicals. Another challenge is the bioaccessibility, which means that the body should be able to absorb the compound from its delivery matrix. Proper degradation and metabolism of the bioactive compounds is also the main role of an oral delivery system after the solubilization is complete (Gleeson et al. 2016). There are many systems of delivery vehicles mentioned in the above sections, which are used for oral consumption. Some of the examples are lipid- and surfactant-based systems (nanoemulsions, liposomes, solid-lipid nanoparticles), biopolymer-based systems, intestinal permeation enhancers, etc.

16.6.3.2 Probiotic Foods

These are the fermented foods but a little more specific where the fermentation is done by selective bacterial strains which are good for overall health. The probiotics can deliver specific desired results with the incorporation of genetic engineering. They can enhance the concentration of a specific nutrient in the case of nutritional deficiency or can target any specific disease. Other than that, probiotic incorporation in the diet always tends to increase the functional benefits of a particular food; there are plenty of examples available in literature where probiotics act in the prevention of certain diseases such as metabolic disorder, GIT infections, gastroenteritis, immune reactions, etc. Several probiotic foods are available in the market, and some of these are even a part of traditional diet practices. Both dairy and non-dairy probiotic foods have been developed and identified to make the probiotic foods available for the people with lactose intolerance, a metabolic disorder with inability to digest lactose/milk sugar. Curd or yoghurt is a dairy-based traditional food with tons of probiotic microorganisms and accountable health benefits like improvement in the condition of diarrhoea. Usual process for making any probiotic food includes a common step of fermentation. The fermentation is dependent on the addition of probiotic microorganisms like *Lactobacillus* sp. and *Bifidobacterium* as a starter culture. But the use of these probiotic bacterial species is not limited to the dairy products. Non-dairy-based food products produced using these probiotic microbes from fruits, vegetables, cereals and sausages are also available as functional probiotic foods (Karovicova et al. 2002). The non-dairy-based traditional probiotic foods include non-alcoholic beverages produced from the cereals such as Boza (a cold beverage found in Turkey, Romania, Albania) and Mahewu (a sour beverage available in Africa) (Prado et al. 2008). The health benefits provided by these functional foods have also laid the foundation of the production of such probiotic potential carrying new foods. Examples include soy-based probiotic foods as frozen desserts (Heenan et al. 2004) and milk drink (Donkor et al. 2007). This new soy-based products have tremendous health benefits like they have shown to reduce the levels of carbohydrates that are responsible for the production of the gas in the intestine, result in elevated isoflavone levels (Champagne et al. 2009) and have a significant effect on lowering LDL, i.e. low-density lipoprotein (Larkin et al. 2007).

Delivery of probiotics is also a challenge because practically the survival of the probiotic bacteria is conditioned at various steps inside the body sometimes due to digestive tract enzymes or low pH in the small intestine (Lee 2017). In order to protect these bacteria from harsh conditions, the encapsulation of the probiotic bacteria can be done by emulsions, extrusion or spray-drying method. Probiotic therapy, specifically using the designer probiotics, is the alternative approach to target diseases in the most specific way possible. Many genetic alterations and even metabolic disorders can be prevented by probiotic therapy such as type 1 diabetes, cancer, etc. (Sleator 2015).

16.6.3.3 Prebiotic

The probiotic will be needing a food or nutrition source inside the host. Use of prebiotics which is a non-digestible fibrous compound helps in the better absorption and functionality of these prebiotic compounds. They promote the growth of more probiotic bacteria in the gut by aiding as a nutrition source. They are fermented in the colon and make the pH acidic which results in more absorption of the minerals such as calcium and iron. Fibrous foods and foods containing carbohydrates like oat meal, courgettes, broccoli and carrots are rich in prebiotics. The prebiotics include XOS (xylooligosaccharide), FOS (fructooligosaccharide), GOS (galactooligosaccharide), inulin, pectin and several others. These can also be added to foods to increase the health-benefitting potential of that food. Several prebiotic foods are available in the market, viz. the addition of prebiotics to infant formulas like inulin has shown to mimic the bifidogenic effect of human milk (Fan et al. 2016).

16.6.3.4 Synbiotics

Adding two supplements to the diet or maintaining check on the required amount of each with respect to the other seems troublesome. Therefore, new functional food based on ‘synbiotics’ came into existence. The synbiotic is a combination of both probiotic and prebiotic in one supplement. These are often consumed as co-encapsulated forms. *Bifidobacterium* or *Lactobacillus* genus bacteria as probiotic with fructooligosaccharides as a prebiotic seems to be frequently used in synbiotic products (Markowiak and Śliżewska 2017). Like probiotics, the encapsulation can be done for both probiotics and prebiotics in combined form, i.e. co-encapsulation.

This can be achieved by techniques such as electro-hydrodynamic atomization. The co-encapsulation has several benefits like increased survival of probiotic in acidic conditions by encapsulating in a polysaccharide matrix and improved bacterial survival during storage period, viz. co-encapsulation of starch granules along with the *B. lactis* has increased the bacterial survival (Zaeim et al. 2019).

16.7 Technological Trends for Understanding and Improving the Functionality of Nutraceuticals

The improved and better functionality of nutraceuticals remains the major concern of food technologists due to the ever-growing need and demand for these health-promoting food products. Advancements of novel technologies in the field of biotechnology, bioinformatics/computational biology and nutrition sciences have provided an interdisciplinary approach for this purpose. The techniques mentioned below have efficiently improved the functionality of these medicinal foods or nutraceuticals along with the inhibition of associated harmful pathogens.

16.7.1 Omics Technology

While traditional applications of food research were focused on providing and completing nutritional requirements; however, latest research focuses more on using food for improving health as well as for therapeutic effects. To fully understand and accomplish that goal, it is very important to understand the total mechanism and metabolism of bioactive compounds inside the body. The omics study is the new breakthrough involving and connecting genomics (gene analysis), metabolomics (metabolite profiling), transcriptomics (gene expression study) and proteomics (protein expression study) to figure out nutrigenomics in relation to the nutraceutical compounds. Nutrigenomics examine as to how diet influences the gene transcription, protein expression and metabolism (Kussmann et al. 2006). The study of these complex interactions requires the development of advanced analytical approaches combined with bioinformatics. The analytical approach may include new techniques such as NMR, GC-MS, etc. which are constantly being used in the assessment of metabolites in the bodily fluids. These techniques promote the idea of identifying a healthy phenotype which should then be promoted by healthy nutrition (Kussmann et al. 2006). With time, several discoveries and understandings have been established. One such is the understanding of the enteric nervous system, which is a collection of hundreds of neurons functioning independently in CNS and controlling the gut mobility, blood circulation, immune reactions and functions. The genes and their underlying mechanism can lead to defining functional gut disorders on the basis of biological markers rather than symptoms (Mayer and Collins 2002). It is now possible to understand the role of genes in obesity and how diet plays a major role in the activity and functioning of those genes due to the present-day genomics and proteomics technology. Kaput (2004) reported that there are roughly 100 genes known to be involved in obesity and 20 are known to be affected by diet. The examination of dietary fat intake, food restriction and protein intake on gene expression is done by transcriptomics involving microarrays (Iqbal et al. 2002).

16.7.2 Proteomics or Protein Engineering

Proteomics or protein engineering deals with three basic things, protein expression, protein structure and protein function. This basically bridges the gap between gene and phenotypic or metabolic result. One of the best advantages of proteomics in therapy is the early caught of any changes in the protein expression from normal or metabolite changes and eventually detection of early deviations from normal. The assessment of proteins is comparatively easier than the genes (Kussmann and Affolter 2006). A major application of protein engineering regarding nutraceutical is producing the gluten using microorganisms, i.e. expressing the wheat gluten by heterologous expression (Kapoor et al. 2017). The expression system used for this purpose can be *E. coli*, yeasts (*Saccharomyces cerevisiae*, *Pichia pastoris*) or insect cells (cultured). A promoter for gene expression at high level is another need for this purpose along with stability of plasmid and use of codon. Majorly used expression system for gluten production is *E. coli* as it possess certain advantages like high yield and availability of fusion tags (Tamas and Shewry 2006). The wheat gluten so produced is a protein with certain medicinal properties like ability to lower the risk of proximal colon cancer (Um et al. 2020).

16.7.3 Genetic Engineering

Genetic engineering or genetic modification is one of the most researched and practically adopted technologies to increase the efficacy of various bioactive compounds within their source. Genetic modification is applied to crops, microorganism or even multicellular organisms for various specific functions. The main objective of developing GM crops or biofortified crops was to treat the nutritional deficiencies present in populations (Glass and Fanzo 2017). One of the best examples is golden rice in India which was a little yellowish rice having more concentration of beta-carotene than the wild crop.

Nowadays, genetic engineering has vast applications as genetically modified microorganisms are used for various purposes in clinical nutritional research. Many genetic tools are developed; development of cloning vectors is done based on the identification and isolation of plasmids from the particular strain. Using molecular biology techniques, these vectors containing the desired genes are incorporated into the organism. One such example is the use of LAB (*L. lactis*) strain for the treatment of IBD. IBD is the inflammatory disorder of the gut. *L. lactis* is a well-known probiotic strain with already known health benefits, but here the bacterial strain was modified to produce antioxidants and anti-inflammatory cytokines (IL10). These compounds reduce inflammatory reactions and control the immune response in the body (De Moreno de LeBlanc et al. 2015). These are also termed as designer probiotics.

16.7.4 Gene Editing

Improvements and advancements in the field of synthetic biology have successfully manipulated the genome of beneficial microbiota for better functional relationship (Yadav and Shukla 2020). Genome editing is the major technique in this regard as it gave rise to certain microorganisms with nutraceutical value. Application of gene editing to manipulate and regulate a wide range of cells and organisms has created a new era of advancement. Specific tools that can be used for gene editing include CRISPR (clustered regularly interspaced short palindromic repeats)-Cas, i.e. CRISPR-associated systems like Cas9; TALENs, i.e. transcription activator-like effector nucleases (Gaj et al. 2013); and ZFNs, i.e. zinc finger nucleases (Urnov et al. 2010). The discovery of programmable DNA nucleases laid the foundation of the whole concept of gene editing. These mentioned sets of tools help in cleaving or binding the gene or DNA sequences at a targeted locus for desired manipulation. Nowadays, the most reliable and advanced tool for gene editing is CRISPR-Cas9 system due to its certain advantages over other tools. It efficiently recovers the low mutation frequency rate in the oligonucleotides, genome can be modified at several loci using this tool, and this system also has a role in the adaptive evolution of phages. A bulk of genetic studies involving genetic engineering or gene editing are based on CRISPR which is generally an mRNA sequence from the genome of bacteria (including the bacteria used as a food source) (Stout et al. 2017). Gene editing with the application of CRISPR-Cas9 tool can aid to isolate or modulate the strains of a mixed culture and even produce edited bacterial genomes having relevance as bacterial workhorses in the food industry (Stout et al. 2017). This tool utilizes the RNA-guided nuclease in association with Cas9 protein and gRNA. The homology of CRISPR to single-stranded genetic material of bacteriophage facilitates their binding during replication, while Cas protein will act as an endonuclease degrading the genetic material of the bacteriophage. Certain CRISPR families' presence has been identified in microorganisms with probiotic potential like *Lactobacillus* and *Bifidobacterium*. Therefore, endogenous CRISPR-Cas system, i.e. types I and II, can be used for the engineering or gene editing of probiotics. The type II and V systems are only used for heterologous editing in species or strains of microorganisms which do not have CRISPR-Cas9 system relationship (Yadav and Shukla 2020). This tool facilitates the integration of multicopy gene in a single transformation by the introduction of a series of landing pad system from synthetic DNA as used in yeasts (Bourgeois et al. 2018). It can also be used as a novel set of technology to reach the target of reducing the harms caused by detrimental bacteria, thereby reducing the forever concern of the food industry. The application of CRISPR-Cas9 technology can be observed in lactic acid-producing bacteria (LAB), which are widely used as a starter culture and health-providing probiotic bacteria, because LAB have a comparatively frequent or more occurrence of CRISPR-Cas systems (Briner et al. 2015). Traditionally, if we look for natural dodging using this technique, the primary starter culture of yoghurt which consists of *Streptococcus thermophilus* comes into notice as the adaptive immunity to these starter culture bacteria against the bacteriophage also involves the role of CRISPR-Cas tool (Barrangou et al. 2007). The occurrence of CRISPR-Cas in edible/diet-associated microorganisms can be beneficial for identifying and distinguishing closely related strain providing protection against pathogenic phages; and for isolation or modulation of specific strains within a mixed culture. Example of successful gene editing CRISPR-Cas9 tool includes developing the ability to produce enhanced amount of exopolysaccharides in *Streptococcus thermophilus.* The exopolysaccharide is critical for the texture of dairy products and, thus, has a significance in the dairy industry. This enhanced production of exopolysaccharide can be achieved as a result of nucleotide sequence alteration for epsC in *Streptococcus thermophilus*. Another application includes the development of increased ability of bile salt hydrolysis in *Lactobacillus gasseri* by replacing the bshA promoter sequence (Hidalgo-Cantabrana et al. 2017).

16.8 Conclusions

Nutraceuticals and functional foods are the most promising research areas to understand the relationship of food with the body and then, based on this understanding, develop benefitting products and systems for improving health and preventing diseases. Various nutrients present in our foods such as vitamins, minerals, antioxidants and herbals are consumed by human race for centuries. The lifestyle changes in the past 50 years have led us to revisit the beneficial and therapeutic aspects of our foods. There are many functional foods and nutraceuticals established now such as turmeric, cinnamon, fruits and vegetables, omega fatty acids, vitamins, etc. These compounds actually have the ability to prevent the occurrence of various diseases such as cancer, diabetes and obesity and might have a treatment for many diseases. The challenge faced by nutraceutical consumption is its efficient delivery into the body so that it can be properly solubilized and absorbed for its targeted effect. There are various techniques used for improving the delivery systems of nutraceutical compounds such as nanotechnology, microencapsulation, emulsion system and biopolymers. To improve the bioactivity of various nutrients, fermentation and specific starter culture are also used. Other than that, probiotics and prebiotics improve the bioactivity of nutrients if delivered properly, and genetic engineering is used for the development of different nutrient-rich crops to treat nutrient deficiencies and designer probiotics to target a specific function or disease prevention/treatment. Advancements in the field of nutritional biotechnology also improved the functionality of nutraceuticals and functional foods.

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