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Fermented Foods: Patented Approaches and Formulations for Nutritional Supplementation and Health Promotion

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Abstract

Fermentation has had a long history in human food production and consumption. Fermented foods and beverages can comprise anywhere between 5-40% of the human diet in some populations. Not only is this process beneficial for extending shelf-life for foods and beverages, but also fermentation can enhance nutritional properties in a safe and effective manner. In many developed countries, traditional methods are now replaced with specific technologies for production of fermented foods, and an emerging industrial practice allows for higher quality standardization of food products in the market place. Due to changes in fermentation processes and the increased consumption of these products, a detailed review of recent patents involving fermented foods and beverages and their impact on health is warranted. Fermented food products that can enhance nutrition, improve health, and prevent disease on a global level will require consistent fermentation methods, evaluation of nutritional compositions, and food safety testing. This review is intended to guide the development of fermented foods for enhanced human health benefits and suggests the need for multidisciplinary collaborations and structural analysis across the fields of food science, microbiology, human nutrition, and biomedical sciences.

Keywords

Diet; fermentation; health; lactic acid bacteria; nutrition; patents; traditional foods

1. INTRODUCTION

Food fermentation involves the addition of edible microbes and has been a common practice all over the world. It is considered an essential food production technique for preservation and has been referenced in the scientific literature for almost thirty years [1-5]. Fermented

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foods enrich nutrition in the human diet while providing satisfying flavors, aromas, and textures. It is estimated that fermented foods and beverages incorporate about one-third of the human diet [6]. Examples of commonly fermented foods include alcoholic beverages, vinegars, pickled vegetables, sausages, cheeses, yogurts, vegetable protein amino acid/ peptide sauces and pastes, and leavened and sour-dough breads [2]. The beneficial mechanisms associated with microbial fermentation include the chemical conversion of sugars into simple acids, alcohols, and carbon dioxide for carbon metabolism, biotransformation reactions such as the removal of glycol-side-residues that create health-beneficial activities, removal of anti-nutrients from food substrates, and the delivery of probiotics [7]. Furthermore, the biological activity of microorganisms produces an array of metabolites that create a preservative effect by limiting the growth and survival of pathogenic microflora in food products.

Given cultural and socioeconomic differences, traditional methods for fermentation vary and may be at increased risk of contamination by food borne pathogens. Food safety issues are mainly due to improper fermentation conditions or procedures rather than the fermented foods [1]. Therefore, emerging attention has been given to standardize the protocols and microorganisms used in fermentation for improved food safety and enhanced health benefits. This review will summarize fermented food patents using novel mechanisms and microorganisms that may enhance nutritional composition and safety of fermented food products. Patented approaches may improve the quality of fermented foods and resulting food products, and represent a promising strategy for the prevention, control, and treatment of both infectious and chronic diseases.

2. METHODS OF FERMENTATIONS

It is possible that original fermented foods and beverages were serendipitous discoveries that eventually developed into artisanal practices, and not only acted to preserve foods but also offered improved sensory qualities. Although chemical preservatives, refrigeration, and other means have reduced the need to ferment foods for preservation and storage, many of these traditionally fermented foods have become incorporated into the modern diet due to beneficial health properties. The popularity of fermented products such as yogurt, cheeses, and cured meats, as well as the renewed trend in consuming probiotics for improved health, has resulted in increased investigation of fermentation processes. Figure **1** illustrates the substantial increase in the number of articles relevant to the topic of "fermentation and health" that are cited in PubMed Central over the last 50 years. Modern fermentation practices have moved beyond their artisanal roots towards techniques driven by empirical science, and now utilize industrialized and life-science driven technologies [7]. Recent developments include the production of starter cultures, multi-step fermentation processes, and production of fermented functional foods to be used for improving health outcomes.

Starter Cultures

Knowledge of domestication of wild strains of microbes has become a priority area in food science research because of their importance in food quality, safety, and shelf-life [8]. In an era of industrial food production, it has become necessary to identify and optimize these

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naturally occurring microorganisms to produce starter cultures that contain defined types and amounts of particular organisms to ensure the consistency, safety and quality of the final product. Analyzing microorganisms in different environments allows quantification of metabolic fluxes that can be used to predict and optimize starter culture performance. Evaluating the diversity of strains within a species with similar metabolic functions is also used to speed up the process of target strain improvement [9] or produce foods with unique sensory qualities. *Lactococcus lactis*, which is widely used in cheese production, provides a beautiful illustration of this concept. Metabolic differences at the subspecies level of the widely used laboratory strains *L. lactis* subsp. *cremoris* strains LM0230 and MG1363 result in production of hard cheeses, while *L. lactis* supsp. *lactis* strain IL1403 produces a soft cheese. In addition to preservation and sensory improvements, fermentation also alters the chemical composition and nutritional status of a food. Therefore, a number of food fermentation starter cultures are chosen or developed because they impart particular benefits to the host, such as delivering health impacting molecules or desirably altering the intestinal microflora [7]. Many fermented products are consumed as a means of delivering probiotic organisms such as *Lactobacillus* and *Bifidobacterium* spp.

There is substantial diversity in the microorganisms used in traditional food fermentation; however, the majority of the patented organisms used for commercial food fermentation are lactic acid bacteria (LAB). These are Gram-positive, acid-tolerant organisms that produce lactic acid as the primary product of carbohydrate fermentation. The lactic acid contributes to the organoleptic properties of the food but is also thought to create an intestinal environment that reduces establishment of pathogenic bacteria. Among the more important probiotic bacteria used in the food industry are the genera *Lactobacillus*, *Bifidobacterium*, and *Streptococcus*. Two common bacteria in commercial yogurt production are *Lactobacillus delbrueckii* subsp. *bulgaricus* and *Streptococcus salivarius* subsp. *thermophiles* [10], and there are countless protected strains that have been developed for industrial use [11, 12]. In addition to these starter cultures, some products employ additional species or strains to impart particular health benefits. Recently, a controversy regarding the association of health claims with particular probiotic cultures has arisen surrounding *L. casei* strain DN-114001, which was patented by the company Danone and is present in the probiotic beverage marketed as DanActive in the United States [13]. Discontent over the company's claims that their patented bacteria, branded *L. casei defensis* or *immunitas*, prevented bacterial or viral infections has resulted in implementation of new regulations regarding health claim labels on foods by the European Commission as well as a change in the designation of the isolate to *L. casei* Danone. Other LAB's that are commonly used as starter cultures in industrial food fermentation include *L. brevis*, which is commonly employed in fermentation of vegetables to produce sauerkraut, pickles, and kirn chee, *L. helviticus* used to produce American Swiss and Emmenthal cheeses, and *L. acidophilus* and *L. casei* that are employed in dairy production.

Fungal cultures, particularly the yeast *Saccharomyces cervisae*, are also important microorganisms in the food industry, enjoying widespread use in brewing and baking. Unlike the LAB that utilize carbohydrates, such as hexoses, pentoses, and disaccharides to produce lactic acid, the result of carbohydrate metabolism of yeast is alcohol and carbon dioxide [14]. Although Baker's yeast is one of the oldest microbial food fermenting

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organisms, patented improvements include strains that are faster replicating, produce more carbon dioxide in dough, survive better in commercial starter culture preparations, produce better aroma, impart anti-molding properties, or improve nutritive properties of baked goods [15]. Saccharomyces yeasts, such as the top-fermenting *S. cervisae* or the bottom-fermenting *S. carlsbergensis*, are also utilized in the beverage industry for production of beer and wine. Yeast strains used in brewing, methods to identify and differentiate yeasts, and the actual brewing processes are often proprietary [16]. The nutritional benefits attributed to *S. cervisae* include an excellent source of protein, along with high fiber content, B vitamins, and folic acid. It is a great supplement alternative for people who are wheat-intolerant since it is gluten-free.

Other fungi are also employed in food production, but most of these are not used commercially to produce foods in the United States. *Aspergillus spp.*, referred to as koji, are widely used in producing fermented Asian foods such as miso, tamari, and tempeh. *Actinomucor* spp., *Mucor* spp., and *Rhizopus* spp. are also employed in a number of fermented soy products.

Multi-step Fermentations Utilizing Yeast and LAB

Wild yeasts and acid-producing bacteria naturally co-exist in many foods and plant sources, but there are a few examples of intentionally controlled, multi-step fermentations utilizing these organisms in tandem. The best known examples come from the beverage industry where the production of wine, "sour" beers, and kombucha fermented tea all involve both yeast and bacterial fermenters. Kombucha, a fermented beverage of Russian origin is made by adding a symbiotic colony of bacteria and yeast (scoby) to ferment an infusion made with tea leaves and herbs and sweetened with sugar. The scoby usually contains various yeasts and acetic acid-producing bacteria, such as *Gluconacetobacter xylenus* (Acetobacteraceae), which converts the alcohols produced by the yeasts into acetic acid [17]. In wines, the development of aroma and a de-acidification of the wine occur by conducting a secondary fermentation with LAB in the final stages of alcohol fermentation with yeasts [18]. This secondary malolactic fermentation is carried out by wine LAB and results in the conversion of dicarboxylic l-malic acid to monocarboxylic l-lactic acid and aroma modifications [19]. Although these fermentations may occur as a result of naturally present yeast and bacteria in beers and wines, concentrated freeze-dried preparations of yeast and bacteria have been used to induce these processes for better quality control. The presence of LAB in beer are primarily responsible for spoilage and the addition of hops (*Humulus lupulus*), which is high in anti-microbial compounds, is both an agent to add a flavor dimension to beers and too prevent the growth of LAB. However, sour beers have become a popular artisanal beer where the LAB are allowed or encouraged to grow in the final stages of alcohol fermentation. The malolactic fermentation results in a beer with a sour, acidic flavor as opposed to the bitter hops-laced beers.

3. NUTRITIONAL COMPOSITION OF FERMENTED FOODS

The ability to obtain proper nutrition through the adequate supply of macro- and micronutrients is critical to overall health. Fermenting foods and beverages through starter

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cultures or multi-step processes can enhance human nutrition by enriching protein, amino acids, essential fatty acids and vitamins contents [3]. These fermented foods may prevent and treat numerous deficiencies, and the methods involved in the fermentation process are sustainable and safe [1, 20]. The following paragraphs review recent fermented food patents (2000-2012) that pertain to impacts on health outcomes. Table **1** provides an overview of health utility and production details for selected fermented food-relevant patents.

Fermented Milk Products

Understanding the health benefits of fermented milk products is a growing field of research in nutrition and biomedical science. Favorable properties of fermented milk products may include improved lactose tolerance, shorter duration of diarrheal bouts, improved immunity, reduced cholesterol, protection against cancer, and improved mineral absorption [21, 22]. Gurr reports that the increased concentration of lactic acid, galactose, free amino acids, fatty acids, and vitamins such as B complex in fermented milk products are a result of fermentation. While the nutritive value of fermented milk products can be similar to raw milk, there are marked differences in the absorption of these nutrients [23]. Yogurt is a well-recognized fermented milk product that has health attributes related to modulation of gut microflora and enhanced gut associated immune response [22].

Izvekova *et al.* invented cultures of LAB from the *Lactobacillus acidophilus* species that allows multiple embodiments of the fermented milk product (liquid for infant formula, solid for yogurt or ice-cream composition, and powder for pharmaceutical inclusion). The authors claim this invention results in nutritive, prophylactic, and therapeutic properties [24, 25]. Cardiovascular disease (CVD) has become a major chronic disease and contributor to mortality worldwide. Given that lowering heart rate is one physiological solution that aids in reducing the risk of arrhythmias and ischemia, Flambard developed a fermented food composition that includes milk proteins and at least one LAB strain with registration number DSM 14998. This fermented food product (DSM 14998) includes bioactive components able to affect adrenergic receptors and/or serotonin receptors for reduced and/or stabilized heart rate. Although there are numerous beta blocker medications available, this invention offers an alternative solution for the prevention of increased heart rates during early stages of disease development [26]. A similar invention has been further developed using vegetable proteins [27].

Fermented Tea

Fermented tea is another popular beverage with purported health benefits for cardiovascular disease, cancer, diabetes, and gastrointestinal infection [28-30]. The antimicrobial activity of tea may be affected by the degree of fermentation and manufacturing. A review shows the effects of *Camellia sinensis* (tea) fermentation by different strains of bacteria against Salmonella and Staphylococcus [31]. Fermentation of tea appears to change the content of organic acids and tea polyphenols [32]. Nutritional and medicinal improvement of black tea by yeast or fungal fermentation shows accumulation of vitamins, reduction of caffeine, and excess tannins and increased therapeutic value of bronchodilator [33].

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Patents involving fermented tea generally focus on the methods involved in the fermentation process that help provide a consistent product for mass distribution. Toba *et al.* created two patents [34, 35] that describe an antioxidation food product that is produced with *Lactobacillus plantarum* strains and manganese-containing natural material. Even though the end product is a dried extract that can be added to milk or yogurt, the method to develop this product involves the addition of fermented tea for promotion of its natural nutritional and medicinal applications. Incorporating microorganisms isolated from traditional fermented foods also provides a promising opportunity in the preparation of fermented tea. Kwack *et al.* invented a method for preparing fermented tea that are treated with stabilized *Bacillus* sp. strains derived from Korean traditional fermented foods [36]. The authors claim that this process results in a fermented tea with improved flavor and safety, alongside nutritious benefits.

Fermented Staple Crop Foods: Soy and Rice

Fermented staple plant foods offer an alternative from dairy products, especially for individuals with lactose intolerance or who prefer vegetarian or vegan options. Soy and rice are two examples of widely grown and consumed staple foods that address these needs. Fermented soy products include, but are not limited to, miso, soy paste, soy sauce, and tempeh. The health benefits related to soy may include possible reduction of age-related and hormone-related diseases and the phytochemicals known as isoflavones have received the most attention for these actions in this food crop. When soy is fermented, there is a chemical conversion of the isoflavone glycoside precursors genistin and daidzin to active isoflavones – genistein and daidzein, respectively [37].

Nair provides an overview on processing two common fermented products: HAELAN 951®, and SoyLac™. The current invention involves various formations of mushrooms grown in fermented soy which result in numerous embodiments that can be used to treat or relieve a variety of disease-related symptoms. These health utilities range from malnutrition and mood related disorders, to metabolic syndrome and chronic diseases [38]. Another potential healthful product is a fermented soy extract that includes a *Lactobacillus* strain and *Saccharomyces* species. A dose-response study with this fermented soy extract is warranted for understanding its utility in the prevention and/or treatment of inflammatory diseases or health disorders such as cancer, infection, autoimmunity, and asthma [39].

Fermented rice and rice bran are other plant-based products that have been shown to prevent and/or treat disease. Red yeast rice (RYR) is produced after fermenting rice with *Monascus purpureus* and its nutritional profile includes unsaturated fatty acids, sterols, B-complex vitamins, and monacolins with antioxidant properties. Research has shown health benefits involving treatment of cholesterol, type II diabetes, cardiovascular disease, and for cancer prevention [40]. Zhang *et al.* developed methods and compositions of RYR to be used as a dietary supplement to improve blood lipid panels [41]. Further research is needed on RYR bioavailability and clinical outcomes to provide concrete conclusions for improving human health. Red mold rice is another *Monascus*-fermented rice product that was used in China for many centuries for flavor enhancement and medicinal treatments. Modern health claims include prevention of cardiovascular disease, cancer, and Alzheimer's disease [42]. A recent

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patent provides a method for the treatment and prevention of Alzheimer's disease that is comprised of a *Monascus*-fermented product derived from red mold rice. The invention claims no evident side effects, which are major concerns for current medications used to treat aging-related diseases [43].

BioBran® is a rice bran functional food product [44] that was developed using a water-soluble rice bran dietary fiber component. It is involved in immunomodulation and purported to enhance overall health and improve quality of life. Finally, novel metabolite profiles with bioactivity have been shown in rice bran fermented with the yeast, *Saccharomyces bouldardii*. This is new evidence for the role of rice bran phytochemical diversity in the presence and absence of fermentation that may confer disease fighting activities [45].

4. SAFETY OF FERMENTED FOODS

Fermentation can enhance food safety through the inhibition of pathogenic bacterial growth, toxin degradation, and the improvement of the shelf-life and digestibility of raw food materials [46-48]. The preservative nature of LAB species involves the ability to block the growth of pathogenic microorganisms by nutrient competition and bacterial inhibitor production. Some of the inhibitors include organic acids, hydrogen peroxide, and bacteriocin [49]. Lactic and acetic acids are particularly effective at inhibiting the growth of Gram-negative bacteria [47], whereby hydrogen peroxide has a strong oxidizing effect on most pathogenic bacteria [50]. In addition, a number of LAB strains produce the antimicrobial compound, bacteriocin. The presence of bacteriocin in fermented foods results in the interference of cell wall biosynthesis and the formation of pores in the cell walls of pathogenic microorganisms, most notably endospore-forming Gram-positive bacteria [51]. LAB and other microorganisms with fermentive abilities have also been proposed to enhance food safety through the reduction of toxic environmental substances such as cyanide found on the surface of foods that result from pesticide application [52, 53]. Similarly, fermentation has been shown to aid in the degradation of mycotoxins, such as aflatoxin, that can sometimes be a problem on legume/peanut and cereal staple food crops [47]. Therefore, the fermentation of raw food materials is important in the establishment of protection against food borne pathogens and emphasizes the importance for continued study for food safety applications.

Fermented foods have had a promising safety record even in countries where household fermentation practices are common [52, 54]. The organisms utilized in the patents highlighted in Table **1** of this review have been found to be safe and relatively non-toxic [55-57]. However, although LAB strains have a long history of safe use in fermentation reactions, new emergent strains still need to be confirmed as safe with proper studies. A study by Jia *et al.* investigated the use of *Lactobacillus paracasei* in a 90-day oral toxicity study in rats and found no observed adverse effects when examined in a macro/microscopic manner [56]. A similar toxicity study was performed using the fermentative fungi, *Monascus*, and the authors were able to show a complete lack of nephrotoxicity and hepatotoxicity following 90 days of dietary intake at relevant doses [57].

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5. DIET TRANSITIONS AND THE IMPACT ON HEALTH

Over the past couple decades, diet has transitioned into a dietary composition of convenience. Processed foods, fast food restaurants, and sugar-sweetened beverages have become mainstream commodities in both the developed and developing world. This change in food consumption has resulted in various health issues, including obesity, cardiovascular disease, diabetes, and cancer. It has become more essential to promote foods that not only provide adequate nutrition but also that may have properties for health promotion and disease prevention.

As biotechnologies involved in the fermentation processes advance, understanding the health benefits of both traditional and novel fermented foods will be critical throughout the world. “Westernized” food products have become available and affordable globally and this has led to a decline in traditional food systems and a decrease in the practice of fermented food traditions in many communities [58]. However, traditional fermented foods have much to offer in human health, particularly for their integrated role with gut microbiota. With a diet shift from complex carbohydrates to high fat, high proteins, and low fiber (i.e. “western diet”) occurring on a global level, further research is needed to understand how traditional diets can provide health benefits. A recent study compared an African rural diet to a Western diet in children from these distinct geographical regions and found the African diet resulted in major differences in gut mircobiota that included an overrepresentation of plant polysaccharide-degrading genera, and that correlated to higher fecal, anti-inflammatory short chain fatty acid content [59]. The role of diet and how it affects health has become an emerging field of study across diverse disciplines, however more work is needed to understand what traditional fermented foods are still prevalent in rural parts of the world and how they can impact health benefits [58]. Further knowledge of traditional fermented foods and their relationships to new fermentation techniques can be helpful to promote culturally-appropriate food choices and provide insight on mechanisms and microorganisms to include in fermentation.

6. CURRENT AND FUTURE DEVELOPMENTS

There are an increasing number of patents that exist for fermented foods for health benefits. Because consumers are becoming more aware of the active role of food on health promotion and well-being, there is substantial opportunity to advance fermented food research with a multidisciplinary team of food scientists, nutritionists, microbiologists, and biomedical scientists. An integrated, systems biology approach will advance our understanding of how certain foods are functional for diverse populations and disease conditions. This article highlighted patents involved in fermented foods and beverages that provide evidence of human health improvement. Further discussions between researchers and food companies are needed to determine an evidence-based, scientific process from patent to health product, and eventually human health outcome.

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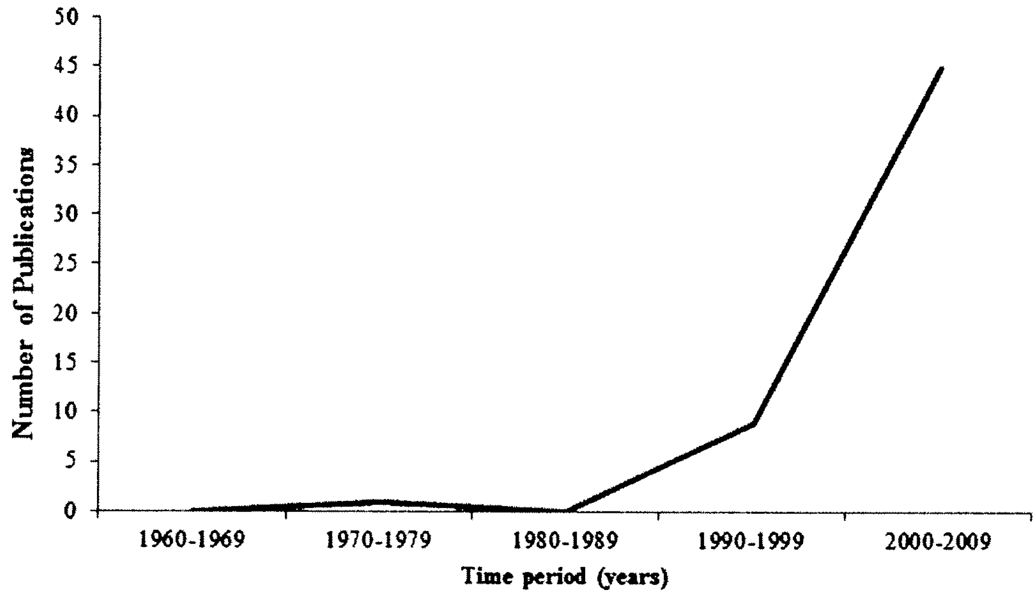

Fig. (1).

Increased number of publications on "fermentation and health" cited in PubMed Central (n=55).

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Table 1

Fermented Food and Beverage Patents for Enhanced Human Health

Patent Title	Health Utility	Mechanism/Novelty	Patent ID (Year)
Fermented Milk Products			
Fermented milk nutraceuticals	Treat diseases or conditions resulting from opportunistic and pathogenic microorganisms	Novel cultures of *Lactobacillus acidophilus* – combination of group Er-2 strain and *L. acidophilus* N.V. Er 317/402	US 6,156,320 (2000) and 6,357,521 B1 (2002)
Fermented milk proteins comprising receptor ligand and uses thereof	Reduce and/or stabilize heart rate in CVD. Treat or relieve benign prostate hypertrophy	Comprised of LAB strain DSM 14998 and a receptor ligand	EP1796480B1 (2011)
Fermented milk or vegetable protein comprising receptor ligand and uses thereof	Reduce and/or stabilize heart rate in CVD. Treat or relieve benign prostate hypertrophy	Comprised of LAB strain DSM 14998 and a receptor ligand	US20110195891A1 (2011)
Fermented tea			
Method of producing fermented milk containing manganese and tea	Prevent diseases caused by active oxygen	Bacteria with catalase activity (*Lactobacillus plantarum*) with manganese-containing natural material	US6228358B1 (2001)
Antioxidation food product, antioxidation preparation, and antioxidation method	Prevent disease caused by active oxygen	Antioxidation to express superoxide dismutase-like activity and catalase activity *Preferred that tea or other natural material is added to the food product in the form of powder*	US6884415B2 (2005)
Method for preparing fermented to using *Bacillus* sp. strains	Improve flavor and safety	Fermenting tea leaves by treating with stabilized *Bacillus* sp. strains from Korean traditional fermented foods	US20110250315A1 (2011)
Fermented soy			
Fermented soy nutritional supplements including mushroom components	Wide ranging – malnutrition to mood related disorders to metabolic support	Comprised of a mushroom grown in fermented soy growth medium and curcuminoids	US20110206721A1 (2011)
Methods for inhibiting cancer growth, infection and promoting general health with a fermented soy extract	Promote general health, prevent and/or treat cancer, prevent infections, reduce incidence of infections, treat infections, asthma, inflammation. Modulate the immune system and treat immune disorders	Fermented soy extract	US6855350B2 (2005)
Fermented rice			
Methods and compositions employing red rice fermentation products	Treat/prevent hyperlipidemia and associated disorders and symptoms (CVD, cerebrovascular diseases, diabetes, hypertension, obesity, etc.)	Fermentation of at least one *Monascus* strain with red rice products to be used as a dietary supplement	US6046022 (2000)
Method for prevention and treatment of Alzheimer's disease	Treat and prevent Alzheimer's disease	Administration of effective amount of *Monascus*-fermented product extracted from red mold rice (powder or beverage)	US8097259B2 (2012)