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Patents in the Field of Probiotics, Prebiotics, Synbiotics: A Review

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Abstract

The review is aimed at presenting the advances in the field of probiotics based on information gleaned from the patents filed internationally in last 15 years. The review explains the concept of probiotics and discusses the established microbes like *lactobacilli* and *bifidobacteria* and some emerging new candidates. The global market trend for probiotics is presented with related aspect of business, how patents can be leveraged as business tool to create monopoly and secure future business. Patents related to GIT are discussed at length. The scope has expanded considerably now and patents related to important findings as judged from claims from such patents are explained in depth. Further, more patents that are studied pertain to novel applications related to fat metabolism, obesity, weight management, oral health, anticancer treatments, cardiovascular disorders, diabetes, etc. Few other patents foraying in to the area of immunomodulation, allergies and antioxidant activity are taken into consideration. Other patents are also included that address the challenges related to dreadful viral diseases including AIDS and rare but serious inborn errors of metabolism. The review also enlists salient features of patents dealing with therapeutic effects with existing gut probiotics but with increased viability, use of unconventional bacterial probiotic strains capable of surviving in hostile gut conditions, innovative compositions to increase acceptability and novel methods to deliver the same. New research pertaining to probiotics having role in cosmetics & skin care and veterinary applications is also taken into account. The review is concluded by throwing some light on the trend in the ongoing research as well as some speculation on the future trend. It can be envisaged that the rapid advances in the field certainly hold a huge promise to mankind as it has tremendous scope to deliver a plethora of health advantages.

Keywords: Probiotics; Patents; Gastrointestinal tract; Obesity; Cardiovascular diseases; Anticancer; Oral health; Inborn errors of metabolism; Cosmetics; Personal care

Introduction

Probiotics, prebiotics, synbiotics, postbiotics

The joint Food and Agriculture Organization (FAO), World Health Organization (WHO), the International Life Science Institute (ILSI) and the European Food and Feed Cultures Association (EFFCA) all have included in their definition of probiotics, that these are viable microorganisms and when administered in sufficient numbers, confer health benefits to the host [1]. The increasing popularity of probiotics (as well as associated prebiotics and synbiotics) is accredited to the abundance of likely advantageous effects in diverse aspects of health and personal care. These include predominantly reported prevention or treatment of gastrointestinal diseases, enhancement of mineral bioavailability, antioxidant potential and immunomodulation. Some upcoming health benefits also reported are maintenance of oral health, regulation of lipid metabolism, treatment of cardiovascular diseases, anti-allergic and anti-infectious effects, anticancer activity, application in cosmetic and personal care [2-5]. The candidate to be recognized as probiotic needs to fulfill the criteria like ability to resist gastric acidity, bile acid, and digestive enzymes, antimicrobial activity against potentially pathogenic bacteria, proven safety and health benefits in the target host along with identification up to strain level [1]. A large number of microbes are found to be suitable as probiotic strains and Table 1 gives a summary of commonly used probiotic bacteria and patents describing their uses.

The term prebiotics was coined by Gibson and Roberfroid [6]. Prebiotics are non-digestible selectively fermentable ingredients that allow specific changes in the composition and/or activity of the resident microflora by selectively augmenting the proliferation of probiotic bacteria responsible for exerting beneficial effects upon host well-being and health [7]. Prebiotics impart many health benefits like improvement in bowel movements, stimulation of mineral absorption, reducing post-prandial glucose levels, reducing risk of obesity [8-10]. A food item to qualify as a prebiotic has to have desirable attributes like resistance to acid or enzymatic attacks in the GIT environment, improved absorption in upper GI tract, selective fermentability by microbes to selectively stimulate indigenous gut microflora [11]. The main types of prebiotics are inulin, variety of oligosaccharides, pyrodextrins, lactulose, lactosucrose, polydextrose and lactitol [11,12]. Prebiotics are obtained directly, or by enzymatic hydrolysis or transgalactosylation of mono or di-saccharides from plant sources [13]. Few others are derived from yeast cell wall, seaweed, and microalgae [14]. The various plant sources of prebiotics can be many vegetable, root and tuber crops like onion, garlic as well as some fruit crops like dragon fruit and the prebiotic-rich grain crops like barley, chickpea, lentil, lupin and wheat [15].

Any composition that combines probiotic and prebiotic is termed as a synbiotic [16]. Synbiotics are expected to provide improved benefits in consumer health and wellbeing. Few examples include *Bifidobacteria* combined with FOS and/or GOS, *Lactobacilli* with lactilol, *Saccharomyces* combined with GOS [17,18]. Some of the

health claims for synbiotics include reduced stress, boosting immunity, and chemoprevention of colon cancer, better feed conversion efficiency, enhanced convenience of formulation, handling and storage and flexibility of foodstuffs or feed delivery [19-21].

Probiotic bacterial genera	Species involved	Some Patents
Lactobacillus	*L. plantarum, L. paracasei, L. acidophilus , L. casei, L. rhamnosus, L. crispatus, L. gasseri , L. reuteri, L. bulgaricus*	US20160151434A1, US8460917 B2, US6797266 B2, EP2477637 A1, EP1824500 A1, WO/2015/090349, EP 2519108 A1
Bifidobacterium	*B. longum, B. catenulatum , B. breve, B. animalis, B. bifidum*	EP2318513A1, US20100183559, US20040202749, EP1224867A1, WO/2008/117267A2, EP2990045A1,US8058051
Streptococcus	*S. sanguis, S. oralis, S. mitis, S. thermophilus, S. salivarius,*	WO/1999/053932A1,WO/1995/006736A1, US20140023620, WO1998000035A1
Bacillus	*B. coagulans, B. subtilis, B. laterosporus*	EP0975227A1, US8697055B2, WO1998047374A1, US9144588, US20130302299A1, US5455028A
Lactococcus	*L. lactis*	EP0573768A2, US20080305089, EP 2467031 A1, WO 2005034970 A1, EP 1243181 A1
Enterococcus	*E. faecium*	US 20070098744 A1, EP 1510135 A1, WO 2001090311 A1
Pediococcus	*P. acidilactici*	US20150246082, WO 2011092261 A1, US9011877, EP1656150
Propionibacterium	*P. jensenii, P. freudenreichii*	US 7427397 B2, CA 2689862 A1, US 9011838 B2
Peptostreptococcus	*P. productus*	US 20140234260 A1
Saccharomyces	*S. boulardii*	EP 2519108 A1, US 6010695 A, US20140205581A1

Table 1: Commonly used probiotic bacteria and corresponding patents.

Postbiotics refer to the by-products of microbial origin like enzymes, peptides, teichoic acid, peptidoglycan derived muropeptides, exopolysaccharides, cell surface and secreted proteins, pili type structures, bacteriocins and organic aids accumulated by probiotic microorganisms [22,23]. They are metabolites which aim to mimic the beneficial therapeutic effects of probiotics while evading the probable risk of administering the live microorganism [24]. After a probiotic organism eventually dies off, they exude these postbiotics amassed as nutrients during its lifespan that continues to support health. There are apprehensions with respect to side effects of probiotics like dissemination of antibiotic resistance gene, strain specific virulence factors, risk of sepsis in premature babies, etc. [23,25]. Postbiotics have inherent benefit owing to their obvious chemical structure, safety dose parameters, longer shelf life and avoiding the side effects of live or dead cells which can alter unfavorably the physiological functions of an individual [26].

Global market for probiotics, prebiotics and synbiotics

Today's consumers are becoming increasingly conscious of their health and diet due to growing awareness of the relation between diet and health. The trends with respect to food choice are changing [27]. Foods containing probiotic microorganisms or prebiotic components are included in the category of functional foods, i.e., foods, which have additional positive effect on some physical conditions [28,29]. Since its entry, such functional foods have grabbed attention because of the array of attributes to maintain sustained health. This is a relatively new concept for the food industry and it is trying to develop functional foods as products that have been targeted to modulate the balance of the microbiota [30]. Lab scale as well as industrial scale research is on the rise to screen for different probiotics, prebiotics, as well as effective synbiotic preparations and methods to deliver them to the host. Hence, this field has witnessed an increased commercial interest in exploring and also exploiting their proposed benefits as a result of which probiotic based functional foods have contributed appreciably to the swift growth and development of this sector [31-33].

The health benefits of Lactic acid bacteria family, predominantly forming the probiotic group, have resulted in their increased incorporation in dairy as well as non-dairy foods, creating a new niche of health foods. Food companies are delighted to produce and promote such products because the supplementary ingredients give an impetus to the value of food nutrition and thus to their sale. This has boosted the sale of probiotic foods especially in US, Europe, Japan and Australia which forms the largest segment of the functional foods [31,34,35]. The global market for functional foods was estimated to represent approximately 3% of the total food market with the US, EU and Japan as front runners [36]. More than 100 probiotic products are available globally such as yoghurt, buttermilk, powdered milk, juices, chocolates and frozen desserts [37]. They can be categorized into functional food and beverages having the major share followed by dietary supplements and animal feed in close contention as depicted in (Figure 1).

The Consumer acceptance towards probiotics differs significantly across Europe-where in Northern European countries, having a long tradition of consumption of fermented dairy products, have shown maximum growth of this sector [38]. Germany dominates the probiotic products market followed by U.K. and France, respectively [39]. Despite this fact, North America is one of the largest probiotic hubs in the world showing a huge promise owing to their inherent practice of consuming dietary supplements [40]. Probiotics available in

the United States lie in the category of medical or functional foods, dietary or nutritional supplements etc. [41].

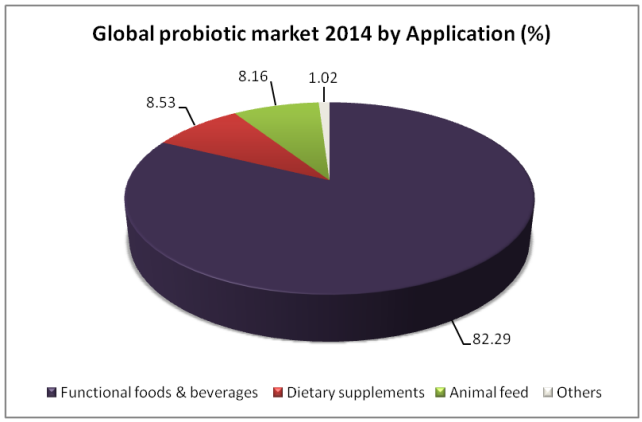

Figure 1: Categories of probiotic products and their share in the global market. Source: Jesse, 2015 (Available at: http://www.technavio.com/blog/technavio%E2%80%99s-top-14-probiotics-companies)

Apart from the health benefits of probiotic, prebiotic and synbiotic formulations in food sector, the cosmetic and personal care industry is also exploiting its beneficial properties. Probiotics with such cosmeceutical applications could make the North American market outgrow Europe and even Asia in probiotic consumption [42]. America and Canada alone has more than 100 companies in this sector wherein the combined revenues of Chr. Hansen, Danisco and Lallemand make up 70 percent of the total probiotic cultures market [40].

Many functional food products have been available commercially, though currently Asia-pacific countries are more likely markets as compared to Europe and USA [43]. In 2014, the market was dominated by Asia-Pacific, followed by Europe and North America (Figure 2).

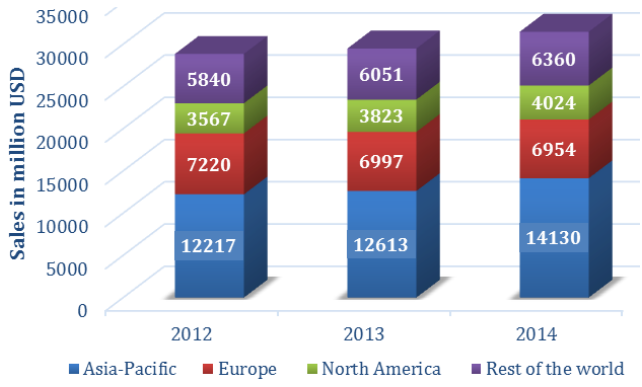

Figure 2: Retail sales value of probiotic functional foods worldwide from 2012 to 2014, by region (in million U.S. dollars) Source: Statista, 2016. Available at: http://www.statista.com/statistics/252941/probiotic-products-sales-worldwide-by-region/

The Asia-Pacific market is projected to grow at the highest CAGR (Compounded Annual Growth Rate), with rapid growth in the food & beverage industry in countries such as Japan and India [44]. Japan is the torchbearer as far as the probiotic sector is concerned in the Asian continent. In Japan, the functional foods market was over $15 billion and has been growing consistently for the last decade [41,45]. According to a report, the Japanese spend close to $100 per person annually with regards to functional foods which is way above other areas like US ($67.9), Europe ($51.2) and Asia ($3.20). Five to six percent of Japanese food expenditure is utilized for this aspect, which is also higher than any other country [42]. Even though globally probiotics have captured the market more in the West and Japan, representing the Asian market, the Indian probiotic market occupies <1% of the total global market and is now likely to grow due to efforts by some leading companies like Amul, Yakult, Nestle India and Mother Dairy gradually entering the scenario [46-48]. The probiotic market in India is projected to register a CAGR of 19.8% during 2014-19. Probiotic products mainly in the area of gastrointestinal health form the core of Indian functional food market. More than 25 companies have established themselves in India. Major pharmaceutical players who have invested in manufacturing probiotics or prebiotics in India include companies like Sun pharma, Dr. Reddy's Laboratories, USV, Zydus Cadila and Unichem [49].

The world probiotic market has experienced a substantial growth and momentum due to the entry of giants like Nestle (Switzerland) in this area [42]. Probiotic and prebiotic based products have in fact helped Nestle to add value to the food and beverage brands in more than 30 countries which has had a significant impact on consumer acceptance and sales growth, especially in the area of infant and dairy products [50]. The other prominent players operating in the global probiotic market and their respective countries are shown in (Figure 3). The list continues to grow due to the rising popularity of such products [51].

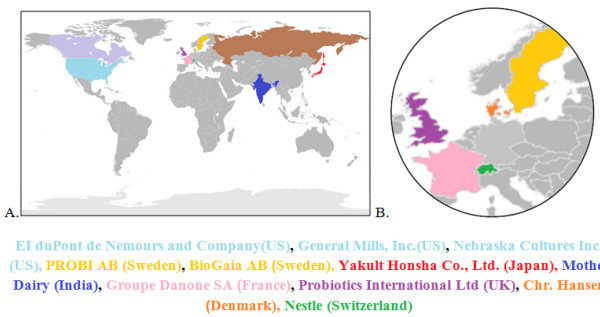

Figure 3: A. Region-wise distribution of leading companies in global probiotic market, B-zoomed image of Europe region from figure 3A. Source: Markets and Markets, 2015. Available at: http://www.prnewswire.com/news-releases/probiotic-ingredients-market-worth-4655-billion-usd-by-2020-520269311.html

Global probiotics market was valued at USD 32.06 Billion in 2013. The probiotic ingredients market was estimated to be valued at USD 33.19 Billion in 2015 and growing at a (CAGR) of 7.0% it is projected to reach USD 46.55 Billion by 2020 and USD 63 Billion by 2022 [52]. Some other reports have also claimed that the global functional food market is flourishing with estimates indicating up to USD 50 Billion by 2020 as it is consistently growing at a pace of 5 to 20% depending on

the area and product [53,54]. Thus looking at the present and predicted scenario of global probiotic market, the leading manufacturers will be competing to outdo one another with more innovative product sand hence will be compelled to protect the same using patents as an Intellectual Property Right.

Patent as a Business Tool

To convert any new idea into a marketable product, companies have to spend extraordinary amount of time, energy, resources and money. As there are rapid advancements in the field of technology and innovations, intellectual property rights (IPR) has become fundamental to future growth and corporate success. Intellectual property is not mere an idea or a concept but when company's core business assets are protected by IP it increases company's long term viability. It can boost a company commercial prospects and in turn, increase its brand value [55].

Patents being one of the most important form of IP, are considered as valuable assets (though intangible) which can be bought, licensed or sold as intellectual commodities [56,57]. Patent right is considered as a negative right as it definitely gives the owner legal right to exclude other manufacturers of similar products from making, using, selling, offering for sale, or importing his claimed invention. Filing of patents is considered as smart investment for the company's future [58]. Patents can not only protect a company's innovations by creating a defensive weave around its creation but can also allow a company to consume its competitor's business aggressively.

Companies try to build a strong and comprehensive portfolio of patents to make it difficult for others as the rivals always run a risk of (knowingly or unknowingly) trespassing or infringing of claims [59-61]. Thus, patents have become growing resource of both steady revenue and strong defense for many companies. Studies have revealed a significant connection between number of patents and type of patents in the portfolio of a company and the market value and image of a company [62]. Hence, patents as one of the forms of IPR have become crucial strategic business tools of competitive intelligence in today's commercial scenario [60,61].

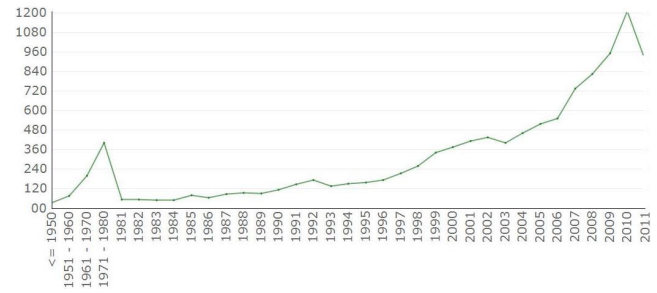

Figure 4: Probiotic patent publication trend (Technology Insight Report, Probiotics by Patent Insight Pro, 2011 Available at (http://www.patentinsightpro.com/techreports/1011/Technology%20Insight%20Report%20-%20Probiotics.pdf)

Patents in the field of probiotics did not show any noticeable and consistent rise before year 2000. However, the market has experienced transformation in favor of functional foods with rapid increase in the number of probiotic patents filed across the globe between year 2000 and 2010 (Figure 4).

This may indicate the interest of manufacturers in investing their resources for the products with good market potential. This trend has shown some decline between year 2011 and 2012 after which it is gaining steady pace in the past 5 years but not as compared to the previous decade (Figure 5).

Possible reasons for the decline could be the abundance of prior art, stricter scrutiny of patent applications, increased stringency in regulatory requirements, ongoing validity of earlier filed patents and slower development of technology and inventions as compared to some sectors like information technology,

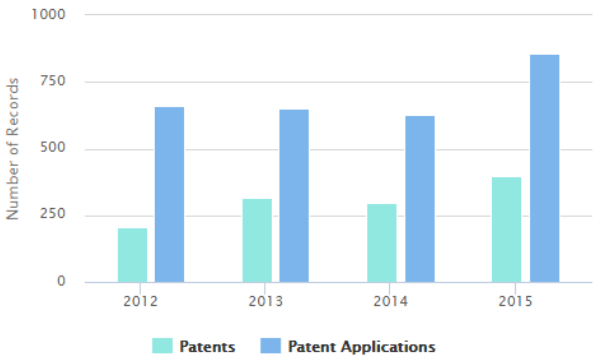

Figure 5: Probiotic patents issued and applied. (Source: www.patexia.com)

Electronics, etc. Additionally, conversion of active research in this field into IP could be in the stage of dormancy. But this trendofpast 5 years, is expected to shift positively as this specialized upcoming area has enormous scope for research and innovation and increase in consumer demand is luring more companies to further invest in this sector.

Earlier reviews in this field of probiotics have been focused on compositions, health benefits, uses, pharmacology, safety of probiotics, prebiotics, and synbiotics. Keeping in mind, the heightened interest of manufacturing companies, the increased interest in generation of intellectual property by industry as well as academia coupled with increased awareness of consumers regarding sustaining their health, it was thought timely, interesting as well as appropriate to review the patents in this field of probiotics, prebiotics, synbiotics and highlight some of the novel inventions in addition to claimed commonly encountered gastrointestinal health benefits.

Patents in the Field of Medicine

Fat metabolism and obesity

The growing modernization in all over the world has led to changes in the food habits showing replacement of unique regional traditional foods by high fat, high energy-dense fast foods & soft drinks [63]. High-fat diet has been associated as a major factor causing obesity where as some foods like whole grains, vegetables, fruits and nuts are categorized as weight–control foods [64,65]. Few probable ways by which diet affects body weight are control of satiety and metabolic efficiency, or modulation of insulin secretion and action [66]. In addition to the changes in diet, mechanization has changed the lifestyle from physically vigorous to sedentary one [63]. Both these factors have

contributed to increase in obese or overweight population. Overweight individuals are likely to face a wide range of health problems like diabetes, high blood pressure, cardiovascular diseases, indigestion, arthritis, depression, etc. [67]. Consequently, the current trend in general health of mankind is inclined towards weight loss and improved metabolism. Diet plays a very pivotal role in this aspect and probiotics can be made a regular part of it [68-70]. Abnormal metabolic profile particularly lipid profile has been associated with various gastrointestinal disorders and diseases like mucosal inflammation, gut permeability disorders, inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), oxidative stress, abdominal pain, etc [71,72].

The invention of Kajander and Korpela relates to the use of probiotics in the manufacture of a composition for enhancing a desirable metabolic profile in an individual. Herein, the probiotics are claimed to be particularly effective in down-regulating levels of lysophosphatiydylcholines (LysoPCs) and ceramides [73]. Ohlson et al. have claimed the use of probiotic bacteria like *Lactobacillus* and *Bifidobacterium* to manufacture a food or feed product, dietary or nutritional supplement, natural or pharmaceutical active formulation to be used for controlling weight gain, preventing and treating obesity, increasing and prolonging satiation, reducing food intake, reducing fat deposition, improving energy metabolism, enhancing insulin sensitivity [74].

Research has revolved predominantly around treating obesity at an older age rather than preventing its occurrence. Prevention of obesity is rather more logical and preferred route in combating weight gain related disorders. Isolauri and Salminen have corroborated this hypothesis with their invention on the use of probiotic bacteria promoting the development of an early bifidogenic intestinal microbiota for reducing the risk of development of overweight or obesity of an infant later in life [75]. The inventors have investigated the likelihood of connection between gaining weight by infants in later ages and their intestinal microbiota. They have reportedly found a strong association between an establishment of an early, strongly bifidogenic microbiota and protection against later development of obesity. Accordingly, any aberration in the intestinal microbiota particularly Bifidobacteria colonization may be followed by obesity.

Similarly, a probiotic composition developed by Lemieux et al. comprises of an effective amount of *Lactobacillus kefiranofaciens* along with an appropriate carrier [76]. The applications of this composition like protection against hypertension, allergies and systemic infections, weight disorder, diabetes, hyperlipidemia, cardiovascular diseases, colon cancer are noteworthy. Research work reported by Oberreuther et al. has shown promising cholesterol reducing effects of a synbiotic composition of rice bran fermented with *Lactobacillus acidophilus* in hyper cholesterolemic male rats [77]. Similar activity is evident from a study with a synbiotic formulation of *Lactobacillus acidophilus* ATCC 4962, FOS, mannitol, and inulin fed to 24 hypercholesterolemic male pigs for 8 weeks period [78].

Immunity and allergies

Harthoorn disclosed an invention of a nutritional composition comprising a synbiotic to be used in the treatment or prevention of infections in allergic patients [79]. A combination of probiotic lactic acid bacterium (*Bifidobacterium breve*) and an indigestible short chain or long chain fructooligosaccharide fibre and a protein source consisting of free amino acids reduced microbial infection rate and consequently antibiotic use in allergic patients. Treatment of the infection before inflammation has a beneficial consequence of no need of using analgesics or other anti-inflammatory agents. Similar synbiotic combination disclosed by Thomas and Buck consisted of *Lactobacillus rhamnosus* HN001 and a carbohydrate based prebiotic which was administered prior or subsequent to onset of an allergic disease to prevent the occurrence or reduce the allergic response [80]. Increased opportunistic infections or suboptimal responses to vaccination are one of the major immunity problems [81]. Dietary supplementation of micronutrients has potential to improve immunity in such cases. Composition comprising micronutrients in combination with probiotics, prebiotics or synbiotics reported by Zlotkin Stanley and dietary supplements comprising probiotics and ingredients like vitamins C,E and beta carotene reported by Czarnecki-Maulden et al. claim to enhance the immune system to augment the beneficial effects of the probiotics [81,82].

Gastrointestinal health

The development of probiotics originally commenced keeping in view their application in improving health of gastrointestinal tract [83]. The various recognized diseases and syndromes affecting the gastrointestinal tract are known to be diarrhea, pouchitis, irritable bowel syndrome, liver disease, Crohn's disease, ulcerative colitis [4,84,85]. Consequently, this area has been flooded with research inventions focusing on different aspects of probiotics like bacteria employed, production process, compositions, dosage forms, combination with prebiotics as well as novel delivery processes, etc. Table 2 summarizes some of the patents encompassing commonly used probiotics, prebiotics, synbiotics for specific use in gastrointestinal tract health. The table lists various bacteria used in probiotic or synbiotic patented compositions along with few common prebiotic dietary fibers comprised in patents. Their claimed health benefits and possible dosage forms are also included.

Patents for gut probiotics with increased viability

Stomach pH is lethal to many probiotics and may wipe out almost 90% of the bacterial dose during their passage through it [86,87]. It is advantageous to have a probiotic resistant to gastric destruction. Therefore, till date, majority of efforts have been focused on use of enteric coated capsules and microencapsulation to shield the probiotics from stomach acid [87]. Attempts are being made to develop formulations to increase the shelf life and/or to enhance their survival efficiency on administration.

Bengtsson-Riveros et al. have reported a novel means of using probiotics from fermented liquid medium by directly applying them to any consumable product [88]. Additionally they have also considered the application of metabolite comprised in a fermented medium separated from the probiotics cultivated therein. Such direct application of freshly recovered probiotic biomass is claimed to have excellent storage stability and its appearance and organoleptic properties are similar to the consumable product not containing probiotics.

Another means to achieve the enhancement of shelf life as well as better survival is to prepare delivery systems which prolong the viability of microorganisms. The delivery system in the form of pellets comprising of viable microorganisms and a coating, has been developed by Ubbink Johan Bernard et al. and it can be easily supplemented in food products [89].

Sr. No	Microorganisms utilized	Prebiotic ingredient	Dosage forms suggested	Health claims& Patent number	
1	*Lactobacillus sporogenes*	Arabinogalactan	Nutraceutical formulation	Increasing colonization of intestinal microflora	EP1607096B1
2	*Lactobacillus casei* or *rhamnosus*	Tagatose	Fermented milk	Promoting the active intestinal growth of *Lactobacillus sp.*	EP2837292 A1
3	*Lactobacillus* strain NCIMB 41114.	Galacto-oligosaccharide fructo-oligosaccharide xylo-oligosaccharide soybean-oligosaccharide isomalto-oligosaccharide gentio-oligosaccharide, fructan, lactulose, glucco-oligosaccharide, lactosucrose	Nutritional , pharmaceutical composition	Promoting gut health Stimulating the immune system Combating candidiasis Aiding digestion in general Alleviating the symptoms of irritable bowel syndrome	US 20060165670 A1
4	*Enterococcus faecium*	-	Fermented milk product, spread, dressing, beverage, edible capsule	Treatment of irritable bowel syndrome	EP0508701A2
5	*Bifidobacterium, Streptococcus, terococcus, Lactococcus, taphylococcus, Peptostreptococcus, Lactobacillus, Saccharomyces, Propionibacterium*	High amylose carbohydrate , high amylose resistant starch product , fructooligosaccharide, potato protein	Food product, nutritional product, pharmaceutical product	Promoting gastrointestinal health	US 2011/0052538 A1
6	*Bacillus circulans* ATCC PTA-5614, 5615, 5616	Solid or liquid carrier and animal feed	Inoculant paste	Treating of Salmonellosis in food production animals	US 7361497 B2
7	*Lactobacillus acidophilus, Bifidobacteriumbifidum, Lactobacillus salivarius, Bifidobacteriuminfantis, and Bifidobacteriumlongum*	Fructooligosaccharides, L-glutamine, and N-acetyl glucosamine.	Food supplement	Reestablishing beneficial bacteria to the body's intestinal tract	US 6468525 B1
8	*Bifidobacterium* genera, *Lactobacillus* genera, and combinations thereof.	-	Milk, Infant formula	Improving the consumer's intestinal health.	US20030017192 A1
9	*Bifidobacteriumlactis* , *Lactobacillus johnsonii* , *Lactobacillus paracasei* , *Streptococcus thermophilus*	-	Breakfast cereal, infant cereal powder,	Improving the consumer's health and well being	WO 2002065840 A2
10	*Saccharomyces, Bifidobacterium, Eubacterium, Clostridium, Lactobacillus, Streptococcus, Enteroccus, Lactococcus* and *Staphylococcus, Peptostreptococcus* (invention not limited to these)	High amylose starch	Food additive	Improving the consumer's health	WO 1996008261 A1
11	-	Polydextrose, Galactooligosaccharide, Lactulose	Infant formula	Increasing production of acetate decreasing production of butyrate, increasing population of live bacteria	US8557320 B2
12	-	GOS compositions lacking FOS	-	Preferentially stimulate growth of specific bifidobacterium sp. and sub sp., treatment of IBS, constipation, diarrhoea, colitis, Crohns disease, colon cancer	US8245930 B2

Table 2: Examples of patents related to gastrointestinal health

A probiotic tablet with probiotics and nutritionally active ingredients is disclosed by Kristian et al. [90]. It is claimed to maintain the viability of microorganisms despite the relatively high overall moisture content of the tablet. The tablet is divided in 2 zones, one containing the probiotic and selenium whereas the other completely separated zone comprises other ingredients such as vitamins, minerals, iron, etc.

Although the exact mechanism of storage increasing attribute of selenium is not clear, the possibility of its beneficial influence arising as growth medium, a compression distributor, stabilizer, dessicant or antioxidant cannot be ruled out.

Another attempt has been made by Monte of the development of a unique delivery tube such as an enteral feeding tube that deposits probiotic, prebiotic or combination directly to a position downstream of the stomach, most preferably to the jejunum where it is to benefit maximally [91].

Borek et al. have a technology of a controlled release formulation for oral delivery of probiotics to an intestinal system and was patented by Nutraceutix, Inc. which has now been acquired by Swedish probiotic giants Probi [92,93]. This formulation comprise of a hydrophilic agent, a modifying agent, an electrolytic agent, and a probiotic. It stands out for its novelty of delivering beneficial bacteria to GI tract from a monolithic tablet without an enteric coating to achieve gastric bypass which is a prerequisite for prior art compositions of similar kind. It provides mechanisms to isolate live bacteria from enzymatic degradation and available water, increasing stability of the dosage form.

Henriksson has disclosed a novel way of increasing survival rate of probiotic strains *Lactobacillus acidophilus* or *Bifidobacterium* animalis ssp. lactis by *Lactobacillus* strains included in the food or feed product [94]. Few similar attempts have been made where *Propionibacterium freudenreichii*, *Streptococcus thermophilus*, a combination of *Lactococcus lactis* and *Streptococcus thermophilus* is used to improve survival of lactic acid bacterium in food products [95-97].

Innovative compositions for gut probiotics

A variety of food compositions containing probiotics, prebiotics or synbiotics have been enlisted by Wang et al. [98]. Such food products namely an infant cereal product, a dry cereal mix, a preparation for porridge, a breakfast cereal product, a powdered diet product, a cereal bar, a powdered beverage, a milk based product or a pet food may also comprise added nutrients selected from minerals, vitamins, amino-acids, unsaturated fatty acids, polyphenols, plant sterols, and mixtures thereof.

Availability of probiotics in forms that are generally well liked will benefit a broad range of consumers. Probiotics in desserts can be strikingly apposite for particularly children and teenagers. Mercenier et al. disclose an anti-inflammatory, immunity boosting rice pudding preparation containing non-replicating probiotics i.e. heat treated probiotic bacteria that are inactivated, dead, non-viable and/or present as fragments such as DNA, metabolites, cytoplasmic compounds, and/or cell wall materials [99]. Further nonexistence of live bacteria has no influence on the texture of fiber present in the product, so that the mouth feel of the rice pudding remains unchanged with time allowing the incorporation of prebiotics in the composition. The above particular patent demonstrates that non-replicating probiotics may be able to deliver the same or even improved health benefits as their living counterparts. If such approaches succeed then the difficulties associated with keeping probiotics viable in a product and their survival in the presence of gastric juices could be overcome.

To further increase acceptability of probiotics amongst different age groups, another delivery system with chocolate has been invented by Judy Davis making the formulation pleasant tasting and palatable [100]. Chocolate has been one of the most popular flavors with consumers around the globe, primarily due to its appealing taste but it may also additionally contribute to proven health effects. The patent discusses a chewable composition comprising chocolate and a compound (at least one probiotic/prebiotic or symbiotic), wherein the compound is blended with the chocolate during conching of the chocolate. Different enrichments given to chocolate have been claimed in this composition such as chocolate liquor, cocoa butter, natural cane sugar.

Also Giffard and Kendall have disclosed a foodstuff in the form of a dried or semi-moist ready-to-eat kibble or powder mix, which contained a combination of a probiotic, prebiotic and a coating of colostrum targeted for infant gastrointestinal health [101].

The invention by Skop and Chokshi provides a soft, chewable confection achieved without using high heat or dehydration wherein it contains at least one probiotic organism selected from the group consisting of *Lactobacillus*, *Bifidobacteria*, *Lactococcus*, *Streptococcus*, and combinations thereof [102]. The invention states that the confection essentially comprises of least one probiotic organism, at least one prebiotic derived from inulin, chicory or honey, a nutrient contained in a glycoprotein matrix which may be coenzyme Q10, L-carnitine, or alpha lipoic acid, or a combination thereof, or an enzyme (lactase or papain), or both and contains no dairy. This particular invention not only offers increased viability, extended shelf life and improved compliance among users, when delivered in a soft, chewable confection form but also could be extremely useful for providing probiotic organisms to a lactose intolerant host.

Oral health

As compared to general health improvement, probiotics have been less explored in the field of oral health as is evident from a very small number of patents in this area. This could be due to the late surge of research post 2010 on the oral health aspect. Though many devices and chemicals such as tooth brushes, dental floss, tongue cleaners, toothpastes, mouthwashes, mouth fresheners, etc. have been marketed for control of halitosis and treatment of oral disorders, many are ineffective, expensive, or complicated to use. Use of probiotic formulation seems to be a promising new approach to address the issue of oral health.

The probiotic or synbiotic compositions patented for oral health include bacteria predominantly from genus *Streptococcus* and *Lactobacillus* formulated alone or in combination with each other or an appropriate prebiotic ingredient. Kenneth Fine disclosed a composition and method for the treatment and prevention of halitosis, gingivitis, periodontitis, containing probiotics from the groups *Lactobacillus*, *Bacillus*, *Escherichia*, *Enterococcus*, *Streptococcus*, *Bifidobacterium* and /or *Saccharomyces* [103]. The composition can be used in a variety of dosage forms including toothpaste, mouthwash, oral spray, cream or gel, chewing gum, candy, lozenges, dissolvable pill, strip or powder.

Where most of these bacteria have been the normal flora of human oral cavity or intestine, Hillman has exploited a notorious dental caries

causing bacterium-Streptococcus mutans by using its Lactate dehydrogenase (LDH) deficient strain [104]. The general type of dosage forms protected under oral probiotic patents is not just restricted to the common lozenges, chewing gums (center filled and coated), oral rinses, pills, tablets, capsules, topical agents etc. but also few uncommon & interesting ones like lollipops, dissolvable films, sachets [105]. An Unconventional composition by Knusten et al. attracts our attention where probiotic chewing gum has an inactive form of bacteria which gets activated upon contact with water [106].

Castellana Jordi provides a composition of *L. plantarum* and *L. brevis* which exhibit properties like antagonistic activity against oral pathogens, ability to colonize oral cavity, low acidification profile making them suitable as medicament for improved oral health [107]. The USA being the most developed market most of these patents have been filed in USPTO.

Novel Applications of Probiotics

Anticancer activity

In-vitro studies on anticancer potential of probiotics and prebiotics has shown promising results as reported by Macfarlane etal. where reduction in activity of an enzyme nitroreductase involved in producing genotoxic metabolites was observed upon GOS consumption in humans [12]. *L. acidophilus* and *L. bulgaricus* were demonstrated to prevent tumor proliferation up to 41% and induce antitumor activity in case of sarcoma-180 and solid Ehrlich ascites tumors [108,109]. This kind of fundamental research has further lead to the development of probiotic composition patents assigned to various organizations like London Health Science Centre and California Institute of Technology, etc [110,111].

Hani El-Nezamy et al. have published a patent pertaining to probiotic compositions and methods of treating hepatocellular carcinoma [112]. The probiotic composition includes 3 bacteria namely heat inactivated *L. acidophilus*, viable *Escherichia coli* and heat inactivated bacteria belonging to genera *bifidobacterium*, *lactobacillus*, *streptococcus* and combination thereof and is meant to be administered orally. Efficacy of such a composition in cancer development is suggested by scientific evidence related to increasing immune cell activation, increase of antitumor surveillance immune activity, promotion of anti-inflammation and suppression of bacteria converting procarcinogens. Thus probiotics offer a secondary reliable treatment in preventing onset of cancerous tumors.

Mazmanian and Lee have reported methods for preventing/delaying the onset of or reducing the development of colorectal tumorigenesis in a subject by adjusting the composition of gut microbiota by administering the subject via fecal transplantation or oral administration, a probiotic composition of Bacteroides (*B. fragilis*, *B. thetaiotaomicron*, *B. vulgatus*, or a mixture thereof) [110]. Further the patent also provides methods for relieving gastrointestinal distress to the subject suffering from the disorder. The inventors have disclosed that the anti-tumour activity could be related to suppressing the expression of pro inflammatory cytokines, chemokines and inducible nitric oxide synthase (iNOS). Reid et al. have patented methods of using bacterial profiles of breast samples(detected test sample with control) for the diagnosis and prognosis of breast cancer [111].The invention also reveals methods of using probiotic bacterial compositions of *Lactobacillus rhamnosus*, *Eubacterium hallii* and *Bifidobacterium longum*, or a combination thereof in the prevention, risk reduction and treatment of breast cancer. Such work in future could be reliable in early detection and management of the disease.

Cardiovascular disorders

Pang et al. (2004) have revealed a method of preventive or therapeutic treatment of a cardiovascular disorder that involves administering probiotic compositions comprising Lactobacillus, *Bifidobacterium* and *Mycobacterium* species to a subject [113]. An effective amount of one or more of these agents upregulates a cytokine profile characteristic of a Th1 T-cell response relative to a cytosine profile of a Th2 T-cell response associated with inflammation of blood vessels in a cardiovascular disorder. Thus this noteworthy invention is concerned with methods for diagnosing or detecting significant Th2-mediated atheroma e.g. coronary artery disease. This is based on the assessment of various markers and indicators of a Th2 response in blood. The above said compositions act as therapeutic or prophylactic agents by promoting a Th1 response and/or and suppressing the Th2 response bias. Peter Rothschild et al. have disclosed the novel use of Lactobacillus reuteri oral compositions selected for its capability to increase the BSH-activity and consequently lower serum LDL-cholesterol and simultaneously decrease the pro-inflammatory cytokine TNF-α levels, for prophylaxis and/or treatment of atherosclerosis and other cardiovascular diseases [114]. A method of selecting such strains and products containing inflammation-reducing component from cell free supernatants has been disclosed.

Anti-diabetic activity

The remarkable invention by Rémy Burcelin et al. relates to food or feed products, dietary supplements and pharmaceutical formulations containing particularly *Bifidobacterium animalis* ssp. lactis which are applicable for the treatment of Type 2 diabetes, insulin resistance, impaired glucose metabolism and consequences thereof [115]. The formulations are also claimed to have beneficial effects on obesity and related conditions, metabolic syndrome, tissue inflammation, hepatitis, myositis and cardiovascular conditions. The probiotic bacteria are said to show anti-diabetic effects by normalizing plasma glucose concentrations, improving insulin sensitivity, and reducing the risk of its development in pregnant women and preventing gestational diabetes. Such dietary supplements also function by controlling weight gain, preventing obesity, increasing satiety, prolonging satiation, reducing food intake, reducing fat deposition, improving energy metabolism as obesity increases the risk of developing diabetes and metabolic syndromes. Similar notable and interesting work has been carried out by Park et al. which is based on the use oral pharmaceutical composition containing probiotic microorganisms belonging to any from the group *Acetobacter*, *Leuconostoc*, *Bacillus*, *Lactobacillus*, *Streptococcus*, *Bifidobacterium*, *Lactococcus* and *Pediococcus* for the prevention and treatment of corpulence or diabetes mellitus [116]. The work claims to reduce the amount of monosaccharide or disaccharide which may be absorbed into human body by converting them into non-digestible polymeric materials like isomaltotriose, dextran and pullulan which cannot be absorbed by the intestine and thus inhibit the increase of blood glucose level originating from glucose.

Antiviral activity

Park et al. have patented a prophylactic and therapeutic composition comprising acid and bile tolerant L. reuteri from animal source which has the ability to inhibit rotavirus infection as well as other enteric pathogens [117]. Rotavirus infections are difficult to treat

when accompanied by secondary bacterial infections enhancing the severity. The usual approach in such cases is based on supportive treatment addressing starvation and dehydration. Antibiotic treatment in such cases is effective only against the secondary bacterial infections. Hence the above mentioned invention is of prime importance to reduce the severity of rotavirus attacks.

James Allen Lemke has disclosed a method for preventing as well as treating HIV infection in a subject [118]. The method makes use of a genetically modified probiotic *L. reuteri* RC14 which colonizes the gastrointestinal tract of the subject wherein it secrets 2 or more fusion inhibitors preventing HIV production by blocking or reducing HIV entry. It is suggested by the authors that it interferes with the binding, fusion or entry of HIV virion into CD4+T cell.

Rare diseases related to inborn errors of metabolism

A patent has been filed by Naz Al-Hafid et al. which claims to have produced genetically-modified probiotic *Lactobacillus* or *Lactococcus* bacteria to treat poly phenyl ketonuria (PKU) [119]. The bacterium is capable of expressing phenylalanine ammonia lyase (PAL) and thus metabolizes phenylalanine to metabolically insignificant amounts of ammonia and trans-cinnamic acid, even when the PAL was expressed intracellularly. The claims were supported with animal studies in mice models for PKU following administration of the amino acid. The probiotic was able to survive exposure to conditions mimicking various compartments of the human GIT.

Individuals with kidney disease, as well as a number of other diseases such as inborn errors in urea cycle enzyme deficit result in waste nitrogen accumulation in the body thereby manifesting toxic symptoms. Microencapsulated and/or enteric coated compositions of probiotics, prebiotics and ammoniaphilic bacteria with high urease activity with specific adsorption affinities for uremic toxins such as creatinine, uric acid, phenol, indoles, inorganic phosphate and water absorbents have been patented by Ranganathan et al. [120]. Also provided are methods of alleviating symptoms of uremia in patients which comprises of administering orally the above mentioned composition comprising of *Bifidobacterium* or *Lactobacillus* probiotics and prebiotics like fructan oligosaccharide or araban oligosaccharide to a patient suffering from it. These synbiotic compositions are beneficial in treating renal and hepatic diseases and bacterial overgrowth in the gastrointestinal tract.

Antioxidant activity

Antioxidants have gained enormous attention due in part to their health claims of antiaging & anticancer potential, prevention or treatment of cardiovascular diseases, Alzheimer's, etc. [121-123]. Matar and Martin claim to have identified a bacterial strain of Serratia vaccinii to be used to increase the antioxidant potential of food products including probiotics [124]. This strain capable of fermenting fruit extracts increases the phenolic acids (gallic acid, chlorgenic acid) content leading to increase in radical scavenging activity and thus its antioxidant potential. Mogna et al. have proposed in their invention a probiotic composition of *Bifidobacterium lactis*, *Lactobacillus acidophilus* and *Lactobacillus brevis*, having antioxidant activity [125]. The bacterial strains can be alive or dead or cellular components thereof, cell extracts and/or inactivated, lysed etc. The composition may include a prebiotic such as those belonging to oligosaccharide group, inulin, resistant starch, pectin, arabinogalactans, galactomannans, xylans, lactosucrose, lactulose, lactitol and various other types of gums, acacia in general, fibers containing a soluble and an insoluble portion, etc. The medicated preparation meant for treating oxidative stress preferably induced by drug intake, can be a food composition, synbiotic composition, a dietary supplement or a pharmaceutical composition. Anti-oxidative potential of *B. coagulans* probiotic culture has also been demonstrated in vitro by Pandey et al. [126].

Probiotic application in iron rich gut environment

Probiotics have been predominantly from lactic acid bacteria group and these typically fail to thrive in unfavorable conditions of excess iron in the environment as other bacteria growing in response to presence of iron outgrow them. In this regard, an unconventional probiotic formulation comprising *Streptococcus thermophilus* strain capable of proliferating in iron-rich environment is patented by Cogan and Bailey and is exceptional and truly remarkable invention [127]. This attribute of the invention offers additional advantage over usual LAB-based probiotics used to treat intestinal diseases associated with intestinal bleeding leading to higher levels of iron in the environment.

Cosmetic and personal care

Probiotic patents have forayed into the alluring field of cosmetics and personal care very recently. Castiel and Gueniche have claimed the cosmetic use of a probiotic microorganism or its fraction or metabolite thereof to prevent and/or treat oily skin associated disorders [128]. The composition made up of at least one of *Lactobacillus* and *Bifidobacterium* sp. can be used to treat dull, muddy skin, redness or rough skin, patchy or dry skin, acne, white heads, etc. The route of administration of this composition is not restricted to topical application but can also be given orally so as to see the effectiveness.

Role of probiotic bacteria to treat vaginal or skin infections has been well established by Koenig et al., and Huang, respectively with their topical probiotic compositions in the forms of lotion, cream, jelly, powder, liniment, etc. [129,130]. The genera involved in probiosis are from group comprising *Lactobacillus*, *Saccharomyces*, *Bifidobacterium*, *Pediococcus*, *Leuconostoc*, *Micrococcus*, *Escherichia*, *Staphylococcus*, *Streptococcus*, *Candida*, and *Bacillus*, and combinations thereof. Catherine & Andrew have employed lysates of probiotic bacteria additionally for regeneration or repair of skin barrier thus extending the use of bacteria to their non-viable state [131]. Apart from the probiotic compositions, an outstanding work of Lanzalaco et al. reports a method that provides a time efficient and cost effective screening to predict in vivo prebiotic activity of a test agent on skin commensal microorganisms [132]. This method will allow the use of normal flora in skincare without any need to introduce bacteria externally. The advantage of such an application will be much greater to the conventional probiotic cosmetic product.

Veterinary Applications

An anti-anemic formulation containing genetically modified probiotic bacteria (*Pseudogluconobacter saccharoketogenes*) was developed in 1995 by Toshihiro Ishiguro et al. [133]. The probiotic was complexed with dextran carboxylic acid. This iron containing formulation was useful for preventing or treating anemia of piglets. Probiotic preparations containing dog-specific probiotic strains (belonging to genus *Lactobacillus*) were developed for preventing and treating canine gastrointestinal disorders by Boileau et al. [134]. Knorr et al. have patented compositions and methods for modulating

immunity and vaccine efficacy in feline animals [135]. Dietary supplements with probiotic organisms such as *Enterococcus faecium* NCIMB 10415 (SF68) in kittens increased the number of CD4+ lymphocytes.

The invention by Patil relates to a herbal cattle feed supplement composition for enhancing the productivity and quality of milk by improved bioavailability/bio enhancing of nutrients [136]. The composition comprises an extract and/or at least one bioactive fraction or powder from herbs along with probiotic additive, minerals, amino acids etc. Low bioavailability of the essential nutrients is due to inadequate absorption of nutrients in the intestine due to lack of necessary enzymes systems in the digestive system of the cattle. Including probiotics like yeast preferably *Saccharomyces cerevisiae* as in this case helps to effectively utilize fibrous feeds and provide increased milk which is nontoxic, free from any side effects and has increased shelf life. Stanton et al. have provided a probiotic composition consisting of *Lactobacillus* and *Pediococcus* to alleviate *Salmonella* infection in farm animals like pigs [137]. The composition formulated also as an animal feedstuff offers the potential alternative to antibiotics, by controlling pathogen carriage, improving growth rate, weight gain and feed conversion. The probiotic invention could be very beneficial for use in the pig industry as a means of improving performance and health, particularly because pig rearing has become more intensive over the years.

Novel Compositions and Applications of Synbiotics

Usually synbiotics developed constitute one or more probiotic bacteria along with a prebiotic component but research has been on the rise to expand the utility of synbiotics by incorporation of unique prebiotic ingredients which may provide additional effects like antioxidant activity.

Carlo Angelotti has creatively used aloe (a topical anti-inflammatory agent) and carageenan in combination with prebiotic ingredients and suitable probiotic bacteria to improve intestinal health [138]. According to the claim aloe and carageenan in suitable quantities minimize mortality of probiotic bacteria during the gastric transit by forming a protective thickening after passing the gastric barrier. On similar line, Cheruvanky et al. have claimed a synbiotic, comprising phytonutrient prebiotics such as tocol, phytosterol, γ-oryzanol, inositol hexaphosphate from soluble and insoluble rice bran derivatives and combinations thereof [139].

Traditionally raw beans are fermented to improve their digestibility, flavours, detoxification followed by cooking before consumption. The step of cooking after fermentation makes the final food product lose its content of vital microorganisms. In the context of this problem, Alexander and Evan disclose the process for manufacture of improved symbiotic that involves fermentation of cooked beans to obtain symbiotic composition with wide range of antimicrobial substances and exceptionally long shelf life [140].

A process patented by Ehlich and Kramer reveals steps to produce a prebiotic animal feed product [141]. It comprises the by-products like beta glucans and/or mannan-oligo-saccharides obtained after enzymatic degradation of fermentation mash post separation of primary product resulting in improved prebiotic activity.

Summary

Extensive efforts are being undertaken in the upcoming area of probiotic and prebiotic based functional foods. Research has led to creation of intellectual property by various food and pharmaceutical industries identifying beneficial health prospects of such products. In the current review patents in the last 15 years have been screened and most of these have been filed in USPTO. An attempt has been made to discuss innovative patents related to gut health as well as several novel applications including obesity, diabetes, cardiovascular diseases, cancer, viral diseases and inborn errors of metabolism. Widened scopes of application like cosmetics, skin ailments, veterinary applications, etc. are also taken into account. The attempt by industry to obtain products with extended utility of probiotic, prebiotic and synbiotic compositions, increased stability and shelf life and methods to administer are also included in the review. Some specialized and path breaking ideas like synbiotics with antioxidant potential or combinations with phytonutrients are also touched upon. With the development of molecular biology techniques and advanced instrumentation the field of probiotic is likely to be expanding at a rapid pace.

Discussion and Future Research Direction

The notable health benefits and myriad of possible new applications of probiotic organisms as well as synbiotics as witnessed in past several decades have resulted in sky rocketed interest in research both, in academic as well as commercial establishments. The enthusiasm in turn, has led to a plethora of new research initiatives; advent of a new field called metagenomics, the ongoing Human Microbiome Project by the NIH to identify and characterize the microbial communities that inhabit both healthy and unhealthy people coupled with increased efforts by the National Center for Complementary and Alternative Medicine to investigate mechanism of action as well as the clinical effects of probiotics, has generated intense interest and further research. The scope is rapidly widening and includes studies to elucidate the efficacy of the various health benefits, analyses of the diet-microbe interaction for modulating the gut microbiota composition.

Due to the recent developments in analytical techniques and its application for analysis of the composition of complex microbial ecosystems, our understanding of the intestinal microbiotais increasing rapidly and is expected to assist in evaluating microbiota itself as a therapeutic target to improve health. Further, hyphenated techniques like GC-MS, NIR spectroscopy, GC-NMR, may help in identifying short chain fatty acids (SCFA) and other metabolites produced by various members of probiotics that may have impact on the human health. The ongoing research may soon reveal what role the SCFA has on how it inhibits pathogens, and act as signaling molecules on specific receptors. In the future, more detailed information on the exact role of each individual SCFA and on the proportion of the SCFA produced from different prebiotic substrates will be essential to further exploit the benefits.

Continued research on *Bifidobacterium*-host interactions is expected to bring knowledge on the mechanisms involved in these health effects. Industrial-scale production of *bifidobacteria* has remained a challenge and industry is expected to carry on research on developing robust production technologies. Non-Lactic acid bacteria like *Bacillus* sp. (Spore Formers) are also attracting attention of lot of researchers as they are also increasingly finding applications for improvement of animal health and for aquaculture for enhancing the

growth and disease-resistance of cultured fish and shrimps. *Propionibacteria* were earlier known only for industrial application as dairy starters and now they have also displayed probiotic potential and hold other promising properties like the production of nutraceuticals and vitamins B & K, conjugated linoleic acid (CLA), exopolysaccharides (EPS), trehalose, bifidogenic factors, bacteriocins, etc. Dairy Industry is more likely to invest in research on potential of *propionibacteria* to be used as probiotic supplements for human and animal nutrition. The urge to find new microbes which will offer distinct advantage over established probiotics is expected to gather momentum as academic as well as industrial endeavor, as new intellectual property can be created.

The probiotic microbes are quite a diverse group and new microbes are getting added as potential candidate at regular intervals. Obviously they are not identical and hence likely to show different response in different individuals Moreover, dose-dependency has rarely been studied and will have to be addressed soon. From microbiology point of view, more research will be required to optimize culture conditions, to do media optimization, find out and streamline the scale-up issues and to establish how such optimizations may affect their efficacy as probiotics.

Though there are several well-studied probiotic strains that have already found their way in the market, the understanding about the mechanism of their action is hardly clear. Also, there are several new applications and diseases and disorders for which dietary supplements were previously unthinkable. The ongoing research is now likely to focus more on substantiating the efficacy of such products.

Similarly, research on prebiotics for established and new applications is progressing very rapidly. New biomolecules beyond the well-characterized galacto and fructo-oligosaccharides are also advancing and in near future carbohydrate-based foods that provide accessible glycoside substrates to the gut microbiome, polyphenols and glucosinolates are likely to open up new opportunities for the industry. Finally, pharmaceutical aspects of Probiotics and Prebiotics are too getting addressed by companies engaged in their production. The emphasis is on enhancing their viability during transport and storage, even at ambient temperatures and further assists in their successful delivery to and establishment at, the site of action in a viable form.

As is evident from our review and abundance of patents by large number of companies across the globe, research on possible role of probiotics in controlling life style diseases like cancer, immunological disorders, cardiovascular ailments, obesity, diabetes is rapidly progressing and the scope is widening further to include more aspects like weight management, oral health, cosmetics, personal care products, improved animal/pet health etc. Few very novel ideas revealed in some patents are related to treatment of allergies, antioxidant potential, dreadful viral infections and rarely encountered but serious inborn errors of metabolism. The authors are of the opinion that the field of probiotics holds a tremendous scope to deliver a plethora of health advantages and research in this area is at a very exciting stage.

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