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RESEARCH ARTICLE

BIOCHEMICAL PRODUCTS OF THE GUT MICROBIOME: INSIGHT INTO DISEASES AND PROBIOTIC NUTRITION

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Abstract

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Probiotics are compounds that are finding increased relevance and markets in the health in- dustry.Bacteria, archaea, viruses, and eukaryotic organisms live in and on our bodies, making up the human microbiome. These bacteria have enormous potential to influence human physiology in both good and bad health. They support metabolic functions, protect against infections, train the immune system, and influence most of our physiologic functions directly or indirectly through these basic roles. Continued research into the roles of the microbiome and the mechanisms under- pinning host-microbe interactions will help researchers better comprehend the microbiome’s role in health and disease. This paper focusses upon the variant nature of the human gut microbiota, its expressions and roles in different diseases. It also devels into the applications, upliftment and effects caused by probiotics on the same. Finally we explore the relevance of these biota to the probiotics markets.

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Introduction:-

In the past century or so in the field of medical sciences, the importance of the gut microbes and the role that they play has become a major field of study. Various medical as well as generic ”probiotic” products being available commercially has led to increased general awareness about the gut bacteria. However, this has resulted in majority of the focus falling on the bacterial symbionts in the gut.

The human gut is one of the most densely populated areas of the human body, having and area of about 200 m.sq, is estimated to to contain between 300-400 trillion micro-organisms and in most envi- ronments, the viruses and phages are found to at least equal the number of bacteria if not outnumber them by a large factor. However, recent studies show that fungi consist of about 0.1 percent of the total gut microbe population. This paper goes on to explore the Gut virome and mycobiome and later dwells onto the different causative diseases influenced by the gut microbiome and their implications.

Gut Mycobiome and Virome

Fungi in the Gut

Despite the large amount of data produced in the gut, and yet these fungal communities are poorly understood. There is no standaradised way of defining a healthy gut mycobiome due to the realtively low diversity and

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abundance of fungi in the gut.In terms of phyla, thus far, most studies have suggested that Ascomycota is the most predominant phylum found in the gut, followed by Zygomycota and Ba- sidiomycota phyla[1]. In the context of genus, a recent review by Hallen-Adams and coworkers had identified potential fungal species that inhabit the intestinal niche, belonging to the genera Candida, Cryptococcus, Malassezia, Aspergillus, Saccharomyces, Galactomyces, Trichosporon, and Cladospo- rium.Recently, through the Human Microbiome Project (HMP), Nash and coworkers (2017) sequenced 317 stool samples in a healthy cohort via Internal Transcribed Spacer 2 (ITS2) region and 18S rRNA gene[2]. The authors reported that gut mycobiota is mainly dominated by Malassezia, Candida, and Saccharomyces, with S. cerevisiae, M. restricta and C. albicans identified in 96.8 percent, 88.3 percent, and 80.8 percent of the samples, respectively. A study by LaTuga et al. identified several fungal species in extremely low birth weight infants in their first postnatal month. These fungal species include S. cerevisiae followed by Candida spp., Cladosporium spp., and Cryptococcus spp.[3]

Fungal Interactions

Interaction with Bacteria

It is well known that antibiotics specific to anaerobic bacteria or broad-spectrum antibiotics can have differential impacts on the susciptibility of fungi, in particular C. albicans[4]. The equilibrium of the mycobiome is known to have an imapct on the stability of the overall microbiome. On the other hand, a study by Jiang et al. demonstrated that commensal fungi such as C. albicans or S. cerevisiae can functionally replace intestinal bacteria in the event of bacterial dysbiosis after antibiotic exposition[5]. Fungi and bacterial cells are also believed to interact with each other within a biofilm habitat, a so called “mixed species biofilm.” Such a habitat can help them to persistently colonize and survive in specific microenvironments such as gut, skin, and oral cavity. Fungi are also known to increase their virulence in these biofilms by increasing the the production of aspartic proteinases and invading the host through hyphal induction. Hence, there is a strong connection between fungal and bacteria cells[6].

Interaction with the Gut-Brain Axis

Growing evidences from both clinical and experimental studies suggest that fungi are involved in the bidirectional communication between brain and gut through neuro-immuno-endocrine mediators, which is comparable to microbiome-gut-brain axis. In a study by Botschuijver et al., the authors inves- tigated the association of intestinal fungal components in patients with inflammatory bowel syndrome (IBS) and in a rat model of visceral hypersensitivity.the authors observed a mycobiome dysbiosis inthe rat model of visceral hypersensitivity, where administration of fungicide, cecal mycobiomes, and soluble -glucans improved hypersensitized rats[7].

Interaction With Immune System

Dectin-1 appears as one of the most crucial pattern recognition receptors (PRRs) in shaping fungal immunity.Dectin-1 interacts with -1,3 glucan motif found on the fungal cell walls and elicits host immune response against them.clinical study has pointed out that polymorphisms in Dectin-1 gene are likely to contribute towards disease exacerbation in patients with ulcerative colitis (UC).Caspase recruitment domain-containing protein 9 (CARD9), a crucial downstream molecule for antifungal re- ceptors including C-lectin receptors, is also implicated in defense against fungi[8]. IL-17, an effector cytokine for Th-17 helper cells, is involved in the mucosal immune response against fungi. The roles of IL-17 during mucosal fungal infections have been documented in both clinical and animal experimental studies.Conti et al. also suggested the pertinent role of IL-17 against opportunistic C. albicans. Fungal species such as S. cerevisiae and C. albicans are known to impact immune responses in major ways[9]. Chitin from S. cerevisiae is able to induce “trained immunity” in monocytes in a strain dependent manner by increasing cytokine productions such as TNF- and IL-6 and through direct antimicrobial activity upon stimulation with bacterial, fungal, and TLR ligands[10].

Viruses in the Gut
In the human gut, phages are believed to exist at levels comparable to their bacterial hosts. Basedon microscopy counts, bacteria appear typically at 1 billion/g feces and VLPs at approximately thesame range[11]. Similar to their bacterial hosts, phages have been found to accumulate on gut mucosal surfaces and within mucous, but here are found at much higher levels with phage, bacteria ratios of approximately 20:1 within the mouse intestinal mucosa[12].The genetic symbiosis established by temperate phage, persisting as prophage within host cells, is important for genetic exchange between bacterial hosts, alteration of host phenotypes via lysogenic conversion. The human gut virome is also seemingly characterized by a high degree of inter-personal variation. Greater similarity between vi- romes is found when individuals eat the same diet[13]. Many of these assumptions have, however, been made based on the analysis of a relatively limited number of individuals.

Viral Interactions
The contribution of phages to the human gut microbial ecosystem is well-established. The functional landscape of the human gut virome is, however, beginning to be mapped, revealing a surprisinglyrich functional repertoire. Metagenomic surveys show that gut associated phages have genes that are beneficial for intestinal bacteria, and help host bacteria adapt to their environment, relate to bacterial virulence, and functions that help maintain host microbiome stability and community resilience[15]. Phages may also constitute a repository of functionally beneficial genes in the gut microbiota, pro- tecting essential activities and genetic information during adverse events that lead to disruption of the community, and its re-establishment[16]. The phage-encoded antibiotic resistance gene pool within thehuman gut has been shown to be significant and diverse. These observations show that phages may play a more significant role in the emergence and spread of antibiotic resistance genes than previously thought.

Phages in Human Health
IN recent times, a lot of work has been done on the characterization of bacterial dysbiosis, with al- terations in the structure and functioning of the human gut microbiome being associated with many conditions from inflammatory bowel disease (IBD) and colorectal cancer, to diseases of the central ner- vous system[17]. Quantitative and qualitative differences in phages isolated from fecal samples derived from healthy individuals and those with leukemic and internal disorders, with generally higher levelsof coliphages in patient samples as compared to healthy subjects has been noted in several studies. Deep sequencing of blood samples (plasma DNA) has also provided some evidence of altered phage taxonomic and abundance profiles associated with host bacterial species, within patients suffering car- diovascular disease. Barr et. al., recently suggested that phages residing in metazoan mucosal surfaces provide a non-host derived anti-microbial defense. the human host genetic background and/or lifestyle factors may lead to an altered representation of anti-microbial mucosal phage, e.g., increased abun- dance of phages leading to selected reduction in bacterial species, potentially propelling the microbial community into dysbiosis, leading to deregulation of protective microbial-epithelial cell interactions[18].

Gut Microbiota and GI Immunity
The GI tract's plethora of microbial cells, which outnumber our body cells by a factor of at least ten, contains a huge species variety and includes both farmed and uncultured species. According to a recent estimate, 442 bacterial, three archaeal, and 17 eukaryotic species make up the cultivable fraction of the GI tract microbiota[19].

Dysbiosis and GI disorders
In the facade of the large number of disorders, this section explores some of the widespread diseasesand the reaction, changes and dependancies on the gut microbiome for the same.

Hirschsprung disease and Hirschsprung-associated enterocolitis
Affecting one in 5000 live births, Hirschsprung disease refers to the absence of neural sections in the intestine. This intestinal disorder has a unique four to one sex ratio of infection biasing towards males. The disease description involves the absence of enteric neural ganglia (aganglionosis) over a fair length of the distal colon[20]. This is said to have been caused by the failure of neural crest-derived ENS progenitors to reach this region during prenatal development.

Upon the studies read it has been noticed that the microbiota composition of patients with HD, showing decreased overall microbial richness . Seventy-seven percent had experienced HAEC. Patients also had a significantly increased abundance of Proteobacteria[21]. This as expected results in a reduced carbohydrate breakdown potential.

Type 1 diabetes

Type I diabetes is a disorder where the human being or patient is unable to produce insulin, due to the T cell-mediated destruction of pancreatic cells. Diabetes is usually associated with a decline in biodiversity within the gut microbiome[22]. Children and young adults with type I diabetes have decreased Clostridium and Prevotella species coupled with an increase in Bacteroides. Certain Bacteroides species have the ability to produce an integrase enzyme which generates peptides that on certain grounds are similar to an antigen present on pancreatic cells[23].One of the main differences between children who developed type I diabetes and controls was the abundance oh the SCFA synthe- sising enzymes. SCFAs have the ability to induce pancreatic cell production of cathelicidin-related antimicrobial peptides (CRAMP)[24].

Celiac disease

Dysbiosis of the gut microbiota is hypothesised to play a role in the onset or progression of celiac disease. Celiac disease is essentially an autoimmune state that is triggered by the intake of gluten and related compounds. Ideally in the human gut this gluten is digested by bacteria into peptides, this is inclusive of the gliadin peptide[25]. Gliadin is later transported into the lamina propria where it is subjected to deamination by the transglutaminase enzymes. This increases immunogenicity. Gliadin or even the gliadin-transglutaminase complexes are presented to T cells and an immune response is initiated[26]. This autoimmunity leads to villous atrophy and crypt hyperplasia, causing diarrhoea and malabsorption of nutrients .

Genetic and environmental factors that have been said to be associated with an increase in Celiac risk have also been linked to shifts in the gut microbiota composition in infants. Certain epigenetic mechanisms also seem to be able to modify the gut microbiota composition and function and, hence, have been hypothesised to influence Celiac disease risk[27].

Colorectal Cancer

Several hypotheses state that there is a possibility that the microbiome contributes to the development of CRC. There are certain lifestyle factors that not only affect the risk of CRC but also directly impact the gut microbiome as well , like low fibre diets and red meat rich diets[28].

Dysbiosis of the gut microbiome in CRC patients shows a decreased abundance of Bacteroidetes and increased Proteobacteria. Certain Proteobacteria species have the ability to secrete carcinogenic substances that initiate CRC development.

E. coli strains can release the toxin colibactin, that induces single strand DNA breaks ultimately promoting mutagenesis . On similar grounds E. faecalis has a superoxide secretion which when converted to hydrogen peroxide can have DNA damaging effects[29].

Age-dependent changes in GI physiology and microbiota

For ageing in general, several minor age-related decreases in GI tract physiology have been observed, with frailty and poor health status appearing to play a role in the deterioration. However, investiga- tions on GI physiology and function in patients with age-related health decline or disease resistance as they age, such as centenarians, as well as studies directly relating host function and outcome in the elderly to microbiota composition and activity, are still lacking[30].

Probiotic Studies

FIRST AUTHOR AND YEAR	PROBIOTICS	STUDY	RESULTS
Viramontes-Hörner D et al	Synbiotic: Lactobacillus acidophilus and Bifidobacterium lactis+prebiotic	Multicenter, double-blinded, placebo-controlled, randomised, clini-	It is safe, Improves gastrointestinal symptoms, Trend to decrease plasma C-reactive protein level.

	(inulin)	cal n = 42; HD Dietary advice (30–35kcal/kg/day and protein 1.1–1.2 g/kg/day) Vitamins and omega-3 fatty acids supplementation2 months	
Natarajan et al	Streptococcus thermophilus KB 19, Lactobacillus acidophilus KB 27, and Bifidobacterium longum KB 31	Single-center, double-blind, placebo-controlled, randomized cross-over trial n = 22;HD 8 weeks	Improves quality of life, Trend in a reduction of serum indoxyl glucuronide and C-reactive protein.
Cruz-Mora J et al	Synbiotic: Lactobacillus acidophilus and Bifi- dobacterium lactis+prebiotic (inulin)	Single-center, double-blind, placebo- controlled n = 18, HD	Increases Bifidobacterial counts in fecal samples, Reduction of Lactobacilli counts in fecal samples, Improves gastrointestinal symptoms
Wang et al	Bifobacterium bifidum A218, Bifidobacterium catenulatum A302, Bifidobacterium longum A101, and Lactobacillus plantarum A87	Single-center, double-blind, placebo-con- trolled, randomized n = 39, peritoneal dialysis patients 6months	Decreases serum, TNF-, IL-5, IL-6, and LPS Helpsin preservation of residual renalfunction
Ranganathan et al	Lactobacillus acidophilus KB31, Streptococcus thermophilus KB27, and Bifidobacterium longum KB35	Single-center, prospective, randomized, double-blind, cross-over, placebo-controlled trial n = 16; CKD stage 3–4 6 months	Decreases blood urea nitrogen, decreases uric acid concentration, Improves quality of life

Probiotics in the treatment of Chronic Kidney Disease

Chronic kidney disease (CKD) is defined as a syndrome caused by the progressive reduction of renal function which is characterised by progressive deterioration of organic biochemical and physiologi-cal function secondary to the accumulation of catabolites, disturbed fluid-electrolyte and acid-base balance, hyperkalemia, hyperphosphatemia, anemia, hormonal disorders, hyperparathyroidism, infertility,metabolic acidosis, hypovolemia and growth failure[31].

Patients with CKD and ESRD i.e end-stage renal disease present quantitative and qualitative alterations in the gut microbiota which includes increased concentration of urea and ammonia in the bowel, compromised integrity of the intestinal barrier, and increased levels of inflammation[32]. Considering the bacteria living in the lower gastrointestinal (GI) tract, an estimated 100 trillion microorganisms live in the human bowel[33].

Probiotics include a vast array of products with living microorganisms whose purpose is to improve intestinal microbial balance and produce beneficial effects on one’s health.

Studies related to CKD and Probiotics:

Most of the microorganisms used in the studies belonged to the Lactobacillus (100 percent = 8 studies) and Bifidobacterium genera (87.5 percent = 7 studies)
One of the many complications patients with CKD experience, according to the researchers,is constipation . Constipation — caused by low fiber intake, low fluid consumption, lack of activity and other comorbidities — can lead to alterations in the gut microbiota and bacterial overgrowth in the stool. The bacteria produce uremic toxins and are associated with the progression of CKD.One study reviewed assigned 24 patients with CKD to the experimental group (low-protein diet with prebiotic and probiotic supplements) or the control group (low-protein diet and no supplements). Results showed the declining eGFR improved in participants who consumed a low-protein diet supplemented by prebiotics and probiotics[34].

The researchers also considered a study in which patients with CKD were given prebiotics and probi- otics or a placebo. Here, it was determined that patients who consumed Lactobacillus, Bifidobacteria and Streptococcus with prebiotics had positive changes to the stool microbiome, as well as a decrease of p-cresol and indoxyl sulfate in their gastrointestinal tract.

Probiotic Products and their Market

The global probiotics market size was valued at USD 58.17 billion in 2021 and is expected to expandat a compound annual growth rate (CAGR) of 7.5 percent from 2021 to 2030.

The growth of the market is being driven by a number of factors like:
1. Increasing Health and Wellness Awareness: People are becoming aware of the health benefits of probiotics, such as improved digestive health, boosted immune system, and reduced risk of allergies.
2. Growing demand for functional foods and beverages: Functional foods and beverages are those that contain ingredients that have health benefits beyond basic nutrition.
3. Increasing research on the health benefits of probiotics: There is a growing body of researchthat is being conducted on the health benefits of probiotics. This research is helping to to raise awareness of the potential benefits of probiotics and to drive demand for probiotic products.

Market segmentation

The global probiotics market is segmented by product type, application, end-user, and region.
- **By product type:** The market is segmented into dietary supplements, functional foods and beverages, animal feed, and cosmetics.
- **By application:** The market is segmented into improved digestive health, boosted immune system, reduced risk of allergies, vaginal health, and others.
- **By end-user:** The market is segmented into adults, children, and infants.
- **By region:** The market is segmented into North America, Europe, Asia-Pacific, Latin America, and Middle East and Africa.

Regional analysis

The countries covered in the probiotics market report are U.S., Canada, and Mexico in North America, Germany, France, U.K., Netherlands, Switzerland, Belgium, Russia, Italy, Spain, Turkey, Restof Europe in Europe, China, Japan, India, South Korea, Singapore, Malaysia, Australia, Thailand, Indonesia, Philippines, Rest of Asia-Pacific (APAC) in the Asia-Pacific (APAC), Saudi Arabia, U.A.E, South Africa, Egypt, Israel, Rest of Middle East and Africa (MEA) as a part of Middle East and Africa (MEA), Brazil, Argentina and Rest of South America as part of South America.

North America is the largest market for probiotics, followed by Europe and Asia-Pacific. The growthof the market in North America is being driven by the increasing awareness of the health benefits of probiotics and the growing demand for functional foods and beverages. The growth of the market in Europe is being driven by the increasing research on the health benefits of probiotics and the growing demand for animal feed. The growth of the market in Asia-Pacific is being driven by the increasing awareness of the health benefits of probiotics and the growing demand for functional foods and bever-ages.

Leading companies

Some of the leading companies in the global probiotics market include:

1. Yakult Honsha Co., Ltd (Japan)
2. Nestlé (Switzerland)
3. DuPont (U.S.)
4. MORINAGA and CO., LTD (Japan)
5. Protexin (U.K.)
6. Danone (France)
7. Deerland Probiotics and Enzymes, Inc. (U.S.)
8. Goerlich Pharma GmbH (Germany)
9. SANZYME BIOLOGICS PVT. LTD (India)
10. DSM (Netherlands)
11. NutraScience Labs (U.S.)
12. Kerry Group plc (Ireland)
13. Lallemand Inc. (Canada)
14. Lonza (Switzerland)
15. Winclove Probiotics (Netherlands)

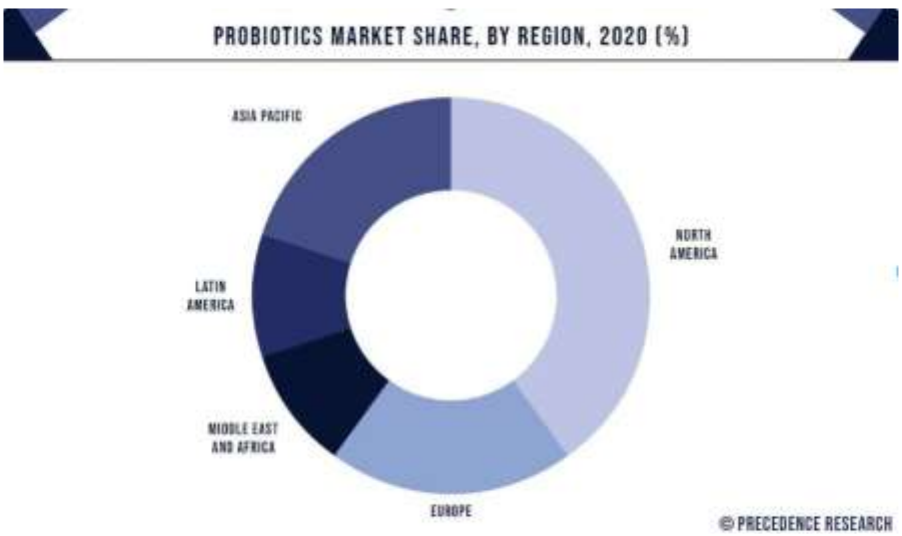

Figure 1:- Probiotics Market.

Growth opportunities

The global probiotics market is expected to continue to grow in the coming years. Some of the growth opportunities for the market include:

1. Increasing demand for functional foods and beverages: The demand for functional foods and beverages is expected to grow in the coming years, as more people become aware of the health benefits of these products.
2. Increasing research on the health benefits of probiotics: The research on the health benefits of probiotics is expected to continue to grow in the coming years, which will help to raise awareness of the potential benefits of probiotics and drive demand for probiotic products.
3. Expanding into new markets: The probiotic market is still relatively small in some parts of the world, such as Africa and Latin America. There are opportunities for companies to expand into these markets and capture growth.

Challenges

The global probiotics market faces some challenges, including:

- **Regulatory challenges:** The regulatory environment for probiotics varies from country to country. This can make it difficult for companies to market and sell probiotic products in some countries.
- **Intellectual property challenges:** There are a number of intellectual property disputes in the probiotic market. This can make it difficult for companies to develop and market new probiotic products.
- **Safety concerns:** There have been some safety concerns raised about probiotics. These concerns need

to be addressed in order to ensure the safety of probiotic products.

Analysis of Probiotic Products in the Market

Overview:

Probiotic products have gained significant popularity in the health and wellness market. These products contain live beneficial bacteria that are believed to promote gut health and boost the immune system. As consumers become more health-conscious, the demand for probiotic products has surged, leading to a wide range of options available in the market.

Market Growth:

The market for probiotic products has experienced robust growth over the past few years. The increasing awareness of the importance of gut health and its impact on overall well-being has been a key driver for this growth. As a result, both established and new companies have introduced various probiotic supplements and food items to cater to the rising demand.

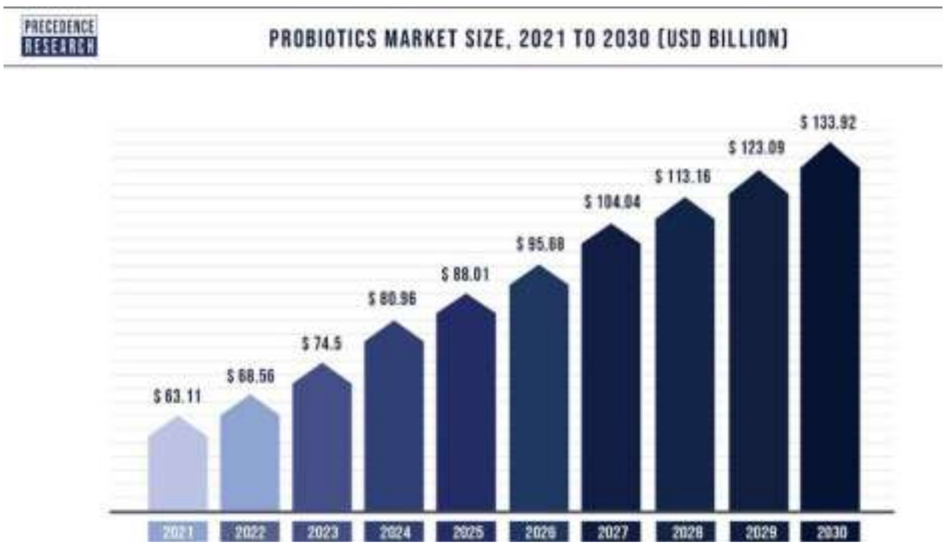

Figure 2:- Market Size.

Product Varieties:

Probiotic products come in various forms, including:

Probiotic Supplements: These are available in pill, capsule, and powder forms, offering consumers a convenient way to incorporate probiotics into their daily routine.

Probiotic Foods:

A wide array of probiotic-rich foods such as yogurt, kefir, sauerkraut, kimchi, and kombucha are available in the market. These products cater to health-conscious consumers who prefernatural sources of probiotics.

Probiotic Drinks:

Apart from traditional dairy-based probiotic beverages, non-dairy options like probiotic-infused juices, water, and plant-based milk have emerged to cater to lactose-intolerant indi- viduals and vegans.

Probiotic Skincare:

Some companies have introduced probiotic skincare products, such as creams and serums, claiming benefits for skin health and rejuvenation.

Competition:

The probiotic market is highly competitive, with both large pharmaceutical and food companies, as well as smaller specialized firms, vying for market share. Established brands have an advantage due to their strong distribution networks and brand recognition. However, smaller players have been successful in targeting niche markets and offering innovative probiotic formulations.

Regulations and Challenges:

The regulatory environment for probiotic products varies by country, and manufacturers must comply with specific labeling and health claim regulations. Probiotic efficacy and the ability to survive through the digestive system remain key challenges for manufacturers, as maintaining bacterial viability until consumption is crucial for product effectiveness.

Consumer Awareness and Education:
While awareness of probiotics has grown, there is still a need for educating consumers about the differences between various strains, proper dosage, and the potential benefits of probiotic products. Consumer education can lead to better-informed choices and increased brand loyalty.

Discussions and interpretation:-

In many host bodies and diseases, probiotic bacteria species establish a reproducible gut microbiota community. Obesity, diabetes, cancer, cardiovascular disease, malignancy, and liver illness are just a few of the neurological disorders that have been linked to probiotics. An imbalance in the composition of the gut microbiota can contribute to a variety of disorders.

Diets and different nutrients have been shown to affect gut microbial communities in a productive and noticeable way; nevertheless, further research is needed to understand the metagenomics link between gut microbiota composition and probiotic species under different diets or nutrients. Furthermore, fu- ture research to boost host health would benefit from the identification of new probiotics and their separation from the microbiome and a mixture of probiotic species.

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