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REVIEW ARTICLE OPEN ACCESS

Lactobacillus Species as Probiotics: Isolation Sources and Health Benefits

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Abstract

Recently, the attention to exploring and applying probiotics has been increased. Probiotics are living microscopic organisms that have valuable impacts on health when consumed in adequate amounts. One of the most popular widespread utilized probiotics for many years until now is the *Lactobacillus* species which exemplifies the hugest heterogeneous group among the lactic acid bacteria (LAB) that normally occupy many environments that contain high nutrient levels such as soil, humans, waters, plants, animals and even air without causing any illness. The purpose of this work is to review and demonstrate the wide diversity of lactobacilli isolation sources and related health benefits applications of the strains discovered in order to break the familiar sources of *lactobacillus* spp., thereby encouraging more research into unconventional sources and opening up opportunities for clinical applications of *Lactobacillus* spp. As a result, the isolation sources of *lactobacillus* spp. in this review have been split into two groups based on the environmental condition, including fermented and non-fermented habitats described as lactobacilli probiotic sources. The unique Lactobacilli isolated from various sources are regarded as potential therapies for a variety of illnesses and physiological abnormalities, including immunomodulation, suppression of carcinogenesis, and cholesterol reduction, in addition to their capacity to guard against infections. This will be highly significant for revealing updated information about *Lactobacillus* spp. that has attracted considerable attention due to its potential application in clinical practices.

Keywords: *Lactobacillus* spp., LAB, Probiotics, Health Benefits, Isolation Sources

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INTRODUCTION

Probiotics

The probiotic term refers to nonpathogenic living microorganisms that are intended to have beneficial health to humans and animals when consumed in adequate volumes.[1,2] The term was created from the Greek words Pro (favor) and bios (life).[3]

Probiotics have earned enormous attention due to their valuable impacts on health. Furthermore, probiotics can be considered a healthy alternative therapeutic method to minimize drug resistance due to the excessive use of antibiotics to fight infections in people and animals. They can be helpful for the host by enhancing the intestinal microbial balance in the gastrointestinal tract, strengthening the epithelial barrier, and improving mucosal immunity.[4,5] In addition, boost-up the immune system and its own antagonistic activity against many pathogens by producing antimicrobial compounds such as bacteriocins.[6,7] Probiotics can prevent and heal many health issues and diseases including decreasing liver lipids concentrations,[8] common cold, Fever blisters, Lyme disease, improving the general digestion problems,[9] constipation,[10] cancers, cardiovascular diseases, diabetes,[11] allergic diseases,[12] *Helicobacter pylori* infection,[13] and even relief of anxiety and depression.[14] According to the statement of a conducted study related to antibiotics, probiotics particularly the ones that belong to the genus *lactobacillus* found powerful enough to kill the HIV-1 virus when given at a high dosage. Moreover, *Ligilactobacillus salivarius* had the ability to inhibit the formation of carcinogenic biofilms of *Streptococcus mutans* and *Candida albicans* reducing its pathogenicity.[15]

Probiotics contain several genera and species of bacteria, yeast, and molds such as *Lactobacillus, Bifidobacterium, Candida pintolopesii, Streptococcus, Aspergillus niger, Leuconostoc, Aspergillus oryzae, Propionibacterium, Bacillus, Pediococcus, Saccharomyces cerevisiae,* and *Enterococcus*.[16] Among the above-mentioned, the widely used genera belong to bacteria and particularly to the lactic acid bacteria (LAB) mainly represented by *Bifidobacterium* and *Lactobacillus*.[17] The LAB that belongs to the genus of *Lactobacillus* has been one of the most popular and widely used probiotics for many years until now which exemplifies the hugest heterogeneous group among LAB.[18]

Lactobacilli are members of LAB, a diversified group of catalase-negative, Gram-positive, non-spore-forming and anaerobic or aero tolerant, coccobacilli, or rod-shaped that is mainly characterized by the lactic acid production as the main end product of their carbohydrate fermentation.[19]

Lactobacilli occupy many nutrient-rich habitats and environments such as spoiled and fermented food and are found in animal feed, soil, and body of invertebrate and vertebrate animals.[20] They live naturally in our body by inhabiting the digestive tract, oral cavity, genital and urinary system.[21] Members of the *Lactobacilli* group have been generally renowned as safe (GRAS) by Food and Drug Administration (FDA) due to their frequent abundance in our food like cheese and yogurt without causing illnesses.[22]

Lactobacillus genus characterized by a massive genome possesses a high grade of genetic diversity and physiology which make them a targeted candidate in many important applications, such as the production of fermented food, food bio preservation strategies to prolong the shelf life while guaranteeing their safety, and in health improvement applications.[23,24]

The reason behind the focus on *Lactobacillus* is due to their vast impact on the host immune system, considered safe in use, show a competitive exclusion, and own a high adhering ability.[25] This work is aimed to review the wide variety of *lactobacilli* isolation sources and associated health benefits applications of the strains discovered to break the acquainted sources of *lactobacillus* spp., thus also inspiring more research to isolate new strains from unconventional sources and providing possibilities for more clinical applications.

Taxonomy of *Lactobacilli*

Lactobacilli were one of the earliest classified bacteria due to their ubiquitous existence in many fermented products. Numerous classifications have been improved since the first description of the *Lactobacillus* genus by Beijerink in 1901.[26]

The base of the initial taxonomy of *lactobacilli* was depend on the observable and measurable traits including cell morphology, gram stain, colony appearance, optimum growth temperature, pH tolerance, oxygen requirements, and pathways for carbohydrate fermentation which classified *lactobacilli* according to the type of fermented sugars and fermentation products into three general groups; obligate homofermentative, facultative heterofermentative and obligate heterofermentative.[27,28]

In the 1980s, with the entrance of bacterial taxonomy the genetic age, genotypic and chemotaxonomic characteristics were used in classification. The availability of 16S rRNA sequencing allowed the first phylogenetic analysis of the *Lactobacillus* which uncovered an extensive diversity by the generation of a true phylogenetic tree that contributed to the development of the taxonomy of *lactobacilli*.[27,28] After the evolution of molecular techniques, most species have been named again and some reclassified to other genera.

Based on NCBI taxonomy, the current taxonomic hierarchy for *Lactobacillus* is Domain: Bacteria, Phylum: Firmicutes, Class: Bacilli, Order Lactobacillales, Family Lactobacillaceae, Genus: *Lactobacillus*.

The *Lactobacillus* genus implicates more than 200 species distinguished by phylogenetic and metabolic diversity. About 540 species and 54 subspecies of this genus have been identified according to the online database of List of Prokaryotic names with standing in Nomenclature (LPSN) (http://www.bacterio.net/*lactobacillus*.html) which is classified by the taxonomy requirements of the International Code of Nomenclature of Prokaryotes such as *L. achengensis*.[19,20,29]

Isolation Sources of *Lactobacillus* spp.

Biological Sources

Fermented Biological Sources

Lactobacillus spp. are food spoilage organisms that control the vast majority of the microbiota of fermented foods.[30,31] Fermented vegetables, silage, also various grains rely on the basic material type as an inoculum source. Other fermented sources such as the majority of dairy fermentations, fermented meats, and sourdough, are produced by the manufactured environments of diverse lactic acid bacteria isolated from natural sources.[32,33] Microorganisms in fermented products are subjected to centuries of growing continuously, becoming accustomed to the fermented product. [34, 35] As a consequence of *lactobacillus*' capacity to adapt to multiple conditions in different environments, *lactobacilli* isolation may be inoculated into many different types of goods or natural environments in order to produce novel strains and, as a result, prospective therapeutic uses.

Traditional fermented foods have recently been investigated as potential natural probiotic bacteria sources, according to recent studies. The *Lactobacillus* genus is home to the bulk of microorganisms isolated from fermented environments.[36] The Genus of *Weissella* was obtained from traditional food under fermentation conditions in Nigeria followed by an evaluation of potential probiotics abilities in a recent investigation.[37]

Lactobacillus delbrueckii subsp. *bulgaricus* appears to be adapting to conditions in fermented products, as evidenced by a rapid and continuing decrease in the size of the genome.[37] As a result, despite the fact that the vast majority of the strain types were obtained from fermented foods, they are improbable to serve as *Lactobacillus*' main habitat. *Lactobacillus* species can be isolated directly from a variety of natural and man-made fermented environments and products:

Dairy Products

Probiotics are used in a variety of dairy products, including sour/fermented milk, cheese, yogurt, butter/cream, new-born formula, and ice cream, according to the dairy industry. Probiotics are also utilized as starting cultures in conventional starters, either alone or in combination, or integrated into dairy products after fermentation, where their presence adds many functional characteristics to the fermented product (for example, improved taste, aroma, and textural characteristics), as well as conferring many health-promoting effects.[38]

The fermented milk includes multiplex species of LAB and hence serve as an excellent probiotic supply. It should come as no surprise that *Streptococcus thermophilus* and *L. delbrueckii*

subsp bulgaricus are the most prevalent microbiological communities were found recently in the fermented yak milk (Kurut).[39] Furthermore, probiotic *lactobacillus* strains and yeasts were identified from kefir grains, Koumissm, a fermented milk drink; and Masai milk; these bacteria have the capacity to favorably alter immunological responses.[40,41]

Some products, such as yogurt, cheese, and butter, can benefit from the addition of starting cultures made from milk or milk alone. In comparison to the traditional Luria-Bertani medium, milk whey, a dairy by-product from the cheese manufacturing industry, is utilized to develop LAB to create more lactic acid. As a result, it might be one of several sources from which advantageous LAB strains can be obtained[42] (Figure 1).

Meats

LAB strains used to be detected in a variety of traditional fermented foods, such as beef,[43] fish,[44] pork,[45] and seafood.[46] *Enterococcus* is the most common LAB strain recovered from fermented crustaceans and fishes, whereas *Lactobacillus* is the most common LAB obtained from fermented meats and plants.[47,48] Due to the complex components of meats, LAB extracted from such environments is likely to be more diversified functionally and physiologically and it is likely to provide further therapeutic applications than LAB isolated from other sources (Figure 1).

Grains, Fruits & Vegetables

Lactobacilli strains from Plant-derived LAB are the most halophilic and flourished at NaCl concentrations greater than 22%. Significance species of *lactobacillus* were collected from fermentation condition of the plant parts are *L. plantarum* and *L. fermentum*. In addition, the various basic substance of dry wheats, garlic, olives, as well as parsley used in fermented food are high in LAB and may be tested for probiotic strains.[45]

Lactobacilli isolated from the natural brine of Algren, green olive fermented, was discovered in recent research.[48] Several health benefits can be obtained from *L. buchneri* P2 as a potential probiotic collected from pickle juice was proved to have properties of antimicrobial activity, cholesterol reduction, and tolerance to acid and bile juice.[49]

Lactobacillus spp. or *Leuconostoc* spp. Were represented the majority of LAB isolated in a study from sauerkraut fermentations and investigated to discover their probiotic properties and determined genotypic and phenotypic characterization of the isolates were found in four different sauerkraut fermentations[50] (Figure 1).

LAB isolated from manufactured fermented products that basically contain plant parts are generated due to the contamination conditions during production processes or from endophytes bacteria. Endophytes *lactobacillus* spp. recovered from plant parts have the capacity to survive in a wide variety of PH gradients, allowing LAB to be separated from mild PH conditions of plant tissues or surfaces. *lactobacilli* did, however, exhibit a definite preference for improved development in a low pH environment.

Traditional Food & Beverages

Many of the isolated species of Traditional fermented foods and drinks flourished in NaCl concentrations of less than 6%.[51] Traditional Thai salted crab also contains NaCl-like LAB (Poo-Khem). The fish dressing is identified as meal prepared under fermentation condition created from various basic ingredients including fish and shellfish. Probiotic isolates of *L. plantarum* was isolated from fermented soybean, popular traditional food in India, in addition, other genera of LAB including *Lactobacillus*, *Vagococcus, Weissella*, and *Enterococcus* were discovered.[52] After conducting several tests to determine LAB genera isolated from natural fermented dry sausage, *L. plantarum* and, *L. brevis* have been identified as the crucial *lactobacillus* spp.[53] The majority of *L. plantarum* isolates from LAB came from traditional fermented Turkish beverages (Boza). To overcome Bacteria that cause disease including *B. subtilis, B. cereus, E. coli, P. aeruginosa, L. monocytogenes,* and *K. pneumoniae,* the antagonistic activity of isolates was exanimated by produced substances (primarily hydrogen peroxide and organic acids).[54] In addition, various studies reported that probiotic LAB was collected from ungerminated cereal crops mixed with millet cereals known as (Kunu-zaki) as a traditional fermented beverage in Nigeria[55] (Figure 1).

Lactobacilli utilized in traditional meals are either mesophilic or thermophilic, depending on the kind of ingredients and preparation circumstances, and may live at low temperatures as Psychrophilic bacteria. *Lactobacillus* spp. thrive in a wide range of temperatures, putting them at the forefront of bacterial species found in traditional meals.

Waste & Sewage

L. delbrueckii is one of the other species of *lactobacillus* that can be obtained from Fermented veggies that were discarded and inhibited the development of various harmful bacteria such as *E. coli, P. aeruginosa* and *P. vulgaris*.[56]

Lactobacilli can be discovered in sewage due to fecal contamination.[57] potential probiotics had been located in diffusion of areas of the human body, consisting of human feces remoted from each healthful adult and youngsters[58] and breast-fed newborns[59] (Figure 1).

Lactobacilli found in waste or sewage come from a variety of original environments, including humans, animals, and plants. Because of the abundance of complex components and the availability of growth nutrients, waste circumstances enable optimal development for *Lactobacillus* spp.

From Non-fermented Biological Sources

Traditional Food & Beverages

In numerous traditional non-fermented drinks have an excessive number of probiotics. Non-fermented drinks are created from a range of ingredients, including grains, millets, fruits, legumes, and vegetables.[60]

These meals and beverages are mostly composed of fresh items infected with *lactobacillus* spp., such as "waldorf" salad[61] (Figure 1).

Grains, Fruits & Vegetables

Microorganisms containing Probiotic properties may be isolated from raw materials of plant origin including fruits and their liquids,[62] honeycomb,[63] cereals,[64] and dirt.[65,66] *L. plantarum* specifically and many other LAB strains were isolated in a study from different kind of fruit juices, whereases *L. mesenteroides* is seldom isolated from fruits, however, it has been found in tomato.[62] Another growing medium may be utilized to produce LAB and isolate *lactobacilli* from origin including pineapple waste and tomato juice.[67,68] *Lactobacillus kunkeei* is one of the most common strains from the majority of *Lactobacillus* spp. among LAB. These species have been shown to have antibacterial properties against yeast development as well as spoilage-related effects

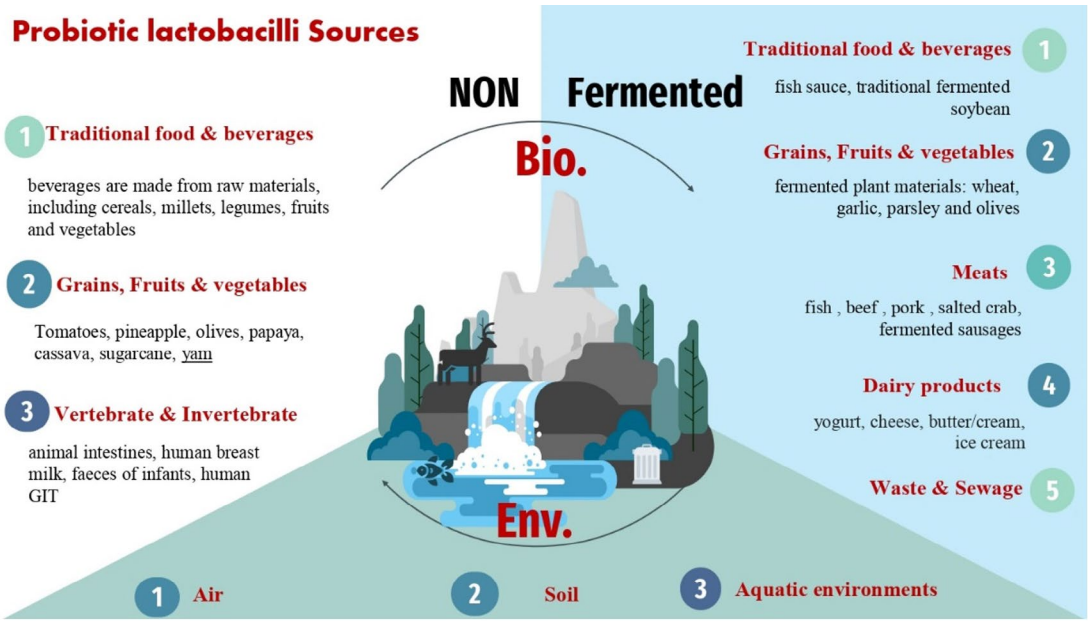

Figure 1. Diagram of various sources of *lactobacillus* spp. identified as probiotics

in honey by yeast.[69] Several studies have indicated that fruit juice, vegetables, and long grass may be used to isolate LAB. Green olives were used to isolate *L. plantarum*, *L. pentosus,* and *L. paracasei,* whereas *L. mesenteroides* and *L. pentosus* were isolated from dark olives.[70,71]

Several characteristics were examined to identify the probiotic potential of specific strains after isolation in a propitiate nutrient media of LAB. Plants Sources like papaya, yam, cassava, sugarcane, and taro leaves were confirmed to contain isolates of *lactobacillus* spp. by reading the sequence of 16S rDNA of the samples, species were recognized as *L. paraplantarum* and *L. plantarum* isolated from crops leaves.[72]

According to one study, these LAB isolated from plant sources may not be present in the regular microflora of plants grown recently, *Lactobacillus* spp. can be isolated from dead plants or raw materials such as olives, cabbage, carrots, beets, and fruits (for example pears and grapes).[73] However, identification of *lactobacillus* spp. from surfaces of flowers or in the tissues of the other plant parts is restricted.[74,75]

The leaves of *P. aquilinum* and, Aloe Barbadensis, also seeds of *L. usitatissimum,* roots of *D. carota,* and flowers of *P. cerasifera* were investigated, and 14 distinct LAB were identified as Lactococcus and *Lactobacillus*, as well as 8 various enterococci. species were initially identified by API kit, and then again analyzed given information by PCR technology, which corroborated the biochemical outcomes. The strains of LAB were isolated from plants' parts comprised of *Lactobacillus delbrueckii* subsp. *Bulgaricus, Lactobacillus brevis, Lactococcus lactis, Lactobacillus acidophilus,* and some species of *Leuconostoc*[76] (Figure 1).

The epiphyte *Lactobacillus* spp. outnumbered the endophyte bacteria, the reason may back to the species coming from surrounding sources such as animals, humans, waste, and soil. Climate, geographical factors, plant type, resident microbial communities, and Physical factors of the environment can impact *lactobacilli* dispersion in plants.

Vertebrate & Invertebrate

Animal intestines, according to Siddiqee et al., are the most likely source of LAB.[77] Several probiotic strains have been identified from human sources, including human breast milk, from various regions of the human body.[78]

the non-sterile breast milk, even if amassed aseptically, still makes the chance of containing isolates of *lactobacillus* spp. in high odds.[79] Breast milk bacteria were long thought to be the result of cutaneous or fecal infections. Although genotypes of *lactobacillus* spp. in breast milk differ from the genes of the isolates *lactobacilli* collected from the skin,[80] also the strains of LAB detected in breast milk also were discovered inside newborns' excrement.[78] *Lactobacillus* spp. can be found in numerous amounts in breast milk as a natural source of probiotics to be for incorporation into food products.[74]

Lactobacillus species are among the most common bacteria isolated from breast milk,[81] also its consumption promotes the predominance of one more source of probiotics in the human intestinal tract. over 500 various species of bacteria can be obtained from the stomach of adult humans Indeed, many of today's probiotic strains, including *L. gasseri* and *L. reuteri*, were isolated from this source.[82] It's a common misconception that the digestive tract should be the sole residence for the probiotics strains to be more beneficial.[83]

Probiotics are present in the stomachs of many animals, including rats, pigs, and even chickens.[84] Lately, strains of *Lactobacillus johnsonii*, collected from *Apis mellifera* stomach, were proven to boost honeybee colonies.[85] Probiotics' isolates were also identified from the digestive tract of freshwater and marine fish, including *Carassius auratus gibelio,*[86] rainbow trout,[87] and shrimp.[88]

In vitro research has shown that some strains of bacteria obtained from meats (*lactobacillus sakei, Staphylococcus carnosus,* and *lactobacillus curvatus*) and fruits (*L. plantarum* and *L. paracasei*) exhibit functional and metabolic features comparable to bacteria of adult's intestine.[89]

Lactobacilli may be isolated consistently from a broad variety of insects, including bees and flies, as well as vertebrates such as rodents, birds, people, and agricultural animals. Because scientific research has mostly concentrated on domesticated animals and people, the host range is likely to be substantially greater.[90-92] *Lactobacilli*

tend to favor food storage organs in animal hosts, such as the crop and forestomach. Insects including bees, flies, bumblebees, and vertebrates' organs were used to isolate *lactobacillus* species. digestive tract, mouth cavity, vagina, and saliva and feces of healthy adults can be considered as non-fermented sources of *lactobacillus* isolates.[93] Tajabadi et al. extracted LAB from honey collected from massive honeybees.[94]

Lactic Acid Bacteria (LAB) from ten healthy wild giant freshwater prawns' stomachs and hepatopancreas, *Macrobrachium rosenbergii*, were identified in a recent study to investigate native probiotic strains for additional uses. According to the findings, two LAB isolates, *L. plantarum* and *E. faecalis*, have been recommended as prospective Probiotics derived from huge freshwater prawns to enhance the aquaculture sector[95] (Figure 1).

The presence of *Lactobacillus* spp. species in many terrestrial and marine organisms gives a clear indication of the concept of one health approach. Therefore, the balance of these species in other organisms and environments can provide solutions for environmental balance, food security, and public health alike.

Environmental Sources

Environments around food products, for example, have also been isolated as unconventional sources of high potential probiotics.

Air

The air in the surrounding environs, as well as the air in a bakery's storage and working rooms, can be a source of *lactobacilli* during the sourdough preparation process. *L. plantarum* was discovered in the samples, which is comparable to the one collected from the dough. in addition, *Lactobacilli* were isolated from the air around palm plants[56,96] (Figure 1).

Soils

Probiotic bacteria isolated from soil in Japan and Taiwan have been discovered and categorized. In order to isolate LAB in Japan and Taiwan, 68 soil samples were collected from various animal areas including the area surrounding the horse farm and floors of the henhouses. Several tests were conducted Physiologically and genetically to determine strains of LAB. 54 out of 68 isolates identified as LAB. This clearly indicates the existence of LAB in significant numbers. According to the findings, dirt may be a frequent source of lactic acid bacteria isolation.

The initial habitat of many isolates came from soil sources. These *lactobacillus* isolates can be transferred to any product or habitat derived from the rhizosphere or phyllosphere of plants[57,74,97] (Figure 1).

Aquatic Environments

In aquatic environments, scientists are interested in isolates from the gastrointestinal tract of marine organisms. *Lactobacillus* spp. Were collected from the GIT of several fish and shrimp. However, the environment surrounding and hydro planktons that form as nutrients for the marine organisms are rich in probiotic strains (Figure 1).

The Significant Roles of *lactobacillus* Species in Our Life

Human has very tight contact with an enormous number of microorganisms that exist in the mouth, skin, or in gut. Some of them possess remarkable health functions such as inducing the immune system, owning an agnostic activity against invading pathogens, enhancing the digestion process, and amending many diseases.[98]

There are many identified *Lactobacillus* species that have been reported as probiotics and have beneficial effects on health (Figure 2).

Protection against Pathogens

Inhibiting the growth of pathogens is one of the ways probiotics benefit human health. These probiotics compete for resources that pathogens would use for growth and proliferation. As a result, they provide protection against pathogens colonization by causing direct death and competing for resources.[99]

In the Gastrointestinal Tract

Probiotics are one of the most effective ways to influence human health and disease by balancing the gut flora.[100]

Several studies demonstrated the role of *Lactobacillus* as a probiotic against many pathogens such as *Lactobacillus acidophilus* is safe for human epithelial colorectal cells and efficacious enough to be utilized as a supplementary

treatment for reducing toxin generation in *Vibrio cholerae* and *Shigella dysenteriae* caused acute infectious diarrhea.[101]

Furthermore, it was reported that taking *Lactobacillus rhamnosus* HN001 on a regular basis lowered the risk of *Staphylococcus aureus* carriage in the human gastrointestinal tract (GI). Competitive inhibition is the key possible mechanism of *L. rhamnosus* HN001, in which pathogen colonization is limited by beneficial commensal microbes out-competing them for vital resources in the GI tract.[102]

In another study, Jun Meng and others found that the surface layer protein (SLP) of *Lactobacillus casei* fb05 might reduce *Escherichia coli* and *Salmonella's* harmful effects on the digestive tract in two ways: by lowering pathogen adherence and avoiding apoptosis caused by pathogens.[103]

The leading cause of disruption of the normally protective gastrointestinal microbiota is *Clostridium difficile* infection (CDI) and antibiotic usage is a common cause of this condition. However, the supplementation of a certain probiotic combining *Lactobacillus casei*, *L. rhamnosus*, and *L. acidophilus* strains has been shown to be effective in inhibiting a number of undesirable consequences., including CDI and antibiotic-associated diarrhoea.[104] The information about the gut microbiome is constantly accumulating which has heightened the interest in gut microbiome-based healthcare (Figure 3).

Because of the strong connections between gut microbiota, health, and disease, there is a lot of interest in utilizing probiotics to alter the gut microbiota in order to treat or prevent certain diseases. However, more research is required to ascertain which probiotic species and strains, dosage, and duration of treatment are efficient. It is also necessary to look into any potential probiotic-diet interactions and interindividual variability that may result in disparate responses to probiotics.

In the Vaginal Tract

There are a variety of normal mycobiota and microbiota that colonize the human vagina, but *Lactobacillus* is the most prevalent bacteria

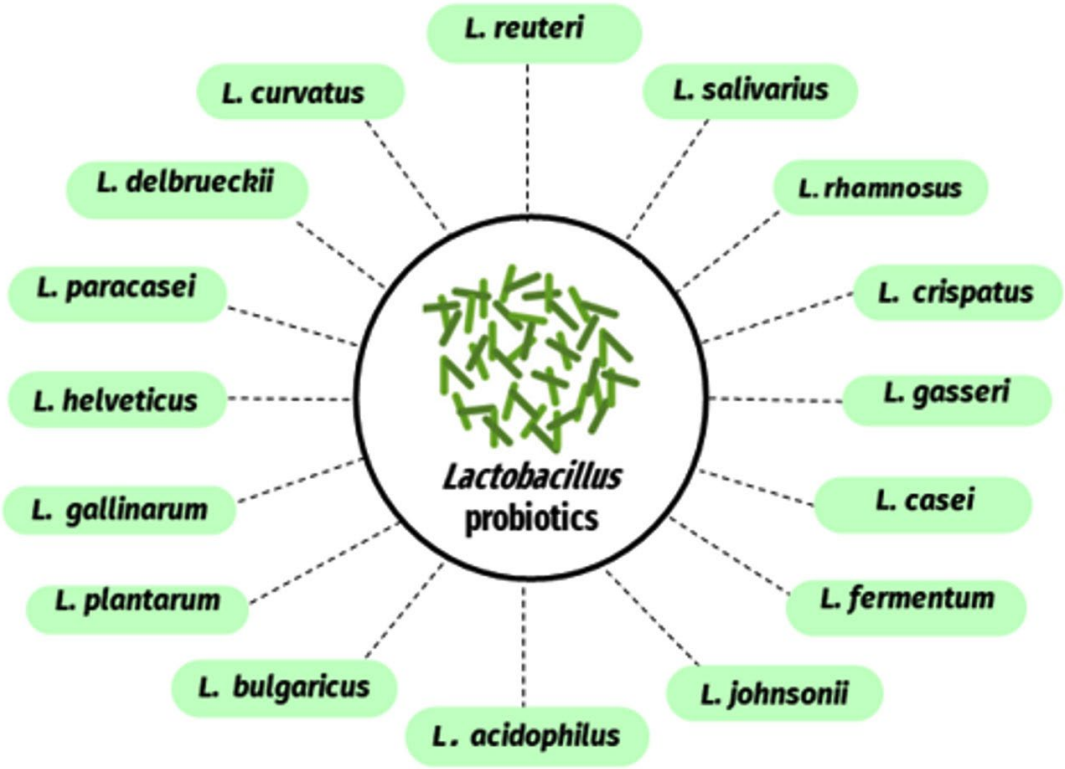

Figure 2. Reported *Lactobacillus* species as probiotics

found in the normal vaginal tract. These vaginal *lactobacilli* have been claimed as having the ability to prevent disease invasion by controlling their population.[105]

Lactobacillus has been shown to have fundamental probiotic effects against infections in the vaginal tract in several investigations. Fermentation of *Lactobacillus* acidophilus KS400 has been shown to generate bacteriocin that prevents urogenital pathogens growth like *G. vaginalis, S. agalactiae,* and *P. aeruginosa*.[106]

In addition, *Lactobacillus acidophilus* GLA-14 and *Lactobacillus rhamnosus* HN001exhibit antibacterial activities against several pathogens that were responsible for aerobic vaginosis (*Staphylococcus aureus* and *Escherichia coli*) and bacterial vaginosis (*Atopobium vaginae* and *Gardnerella vaginalis*) by means of a co-culturing assay.[107]

The *L. Plantarum* new isolates called ZX1, ZX2, ZX27, and ZX69 were found to limit *Gardnerella vaginalis* growth, the Bacterial vaginosis causative agent.[108]

In another study, they demonstrated that the major *Lactobacillus* species linked to a healthy vagina is *L. crispatus* may effectively block the growth of C. Albicans and the formation of hyphae. In an NRG1-dependent way, *L. crispatus* may also suppress the hyphae-specific gene expression (ALS3, HWP1, and ECE1). Furthermore, *L. crispatus* B145 is an excellent candidate for probiotic research.[109]

Also, a *Lactobacilli* dominated vaginal ecology has the ability to protect the host from human immunodeficiency virus (HIV) and sexually transmitted infections (STIs).[110,111]

L. crispatus BC3 and *L. gasseri* BC12 protect isolated cells and ex vivo tissues from infection with the Human Immunodeficiency Virus 1 (HIV-1) by releasing their extracellular vehicles (EVs) this finding could lead to new HIV-1 prevention measures for male-to-female sexual transmission[112] (Figure 3).

Moreover, *Lactobacillus* shows to be a promising influence to use in the prevention of vaginal infections such as vulvovaginal candidiasis (VVC) and bacterial vaginosis (BV).[105]

To reduce the need for antimicrobial medications, a complementary method involving *Lactobacillus* to correct the imbalance of vaginal microbiota is urgently needed. To treat the heterogeneity of probiotic effectiveness, there should be more scientific investigations on the effectiveness of probiotic *lactobacilli* against vaginal infection.

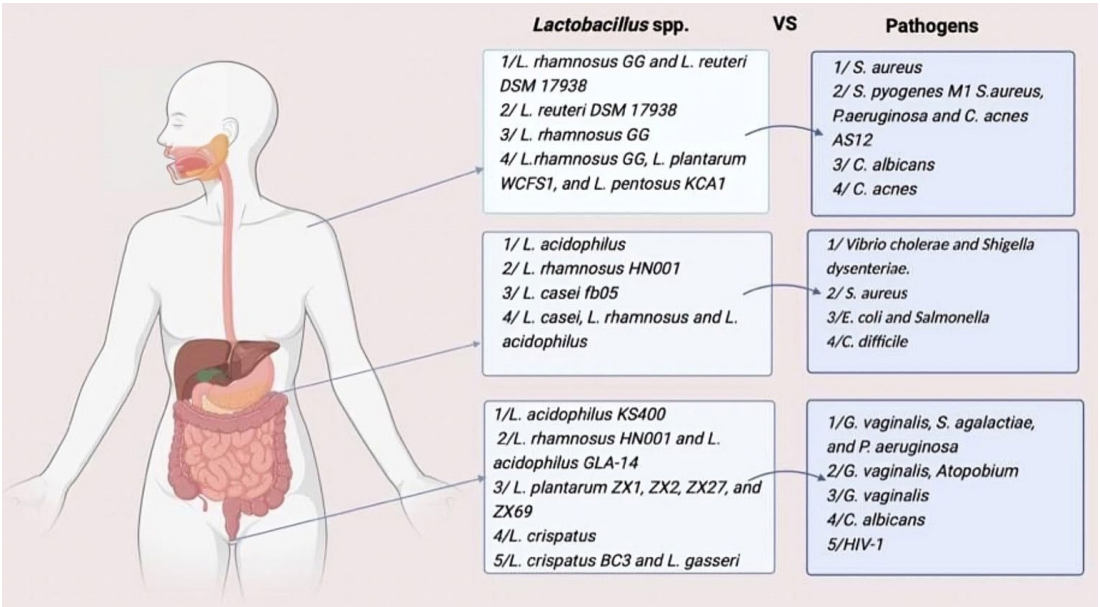

Figure 3. Different *Lactobacillus* species identified as human body protectors against various pathogens in the gastrointestinal tract, the vaginal tract, and the skin

In Skin Health

The skin is one of the largest organs in the human body, and it serves as a vital barrier and protective barrier against pathogen invasion.[113]

For many years, various studies on *Lactobacillus* and skin health have been published, including prevention of skin illness and improvement of skin diseases.

Several studies have shown that exogenously applied *lactobacilli*, for example *Lactobacillus rhamnosus GG* and *Lactobacillus reuteri* DSM 17938 have been found to have anti-pathogenic properties both directly and indirectly. *Lactobacilli* or their lysates, through direct binding interactions, can prevent infections from adhering to keratinocytes or actively displace adherent pathogens, as proven *in vitro* against *S. aureus.* For *L. rhamnosus* GG at least in part, these effects appear to be caused by SpaCBA pili, it has a high level of adhesion to human keratinocytes.[114-116]

Furthermore, live *L. reuteri* DSM 17938 demonstrated antibacterial activity against pathogens on the skin including (*Streptococcus pyogenes M1 Staphylococcus aureus*, *Pseudomonas aeruginosa,* and *Cutibacterium acnes* AS12).[116]

Exopolysaccharides and the primary peptidoglycan hydrolase Msp1 were identified as important components of *L. rhamnosus* GG that reduced *C. albicans* hyphae production and attachment to host epithelial cells.[117]

Under the influence of *Lactobacillus* pentosus KCA1, *L. rhamnosus* GG, and *L. plantarum* WCFS1 has greatly reduced the lipase activity of *Cutibacterium acnes* that helps in the conversion of sebum into free fatty acids, contributing to acne (Figure 3).

These mechanistic insights have already been converted into positive therapeutic outcomes in a few clinical trials, demonstrating that topically applied *lactobacilli* can colonize the skin for a short period of time and improve skin health, However, in order to generate *in vivo* mechanistic insights and in-depth skin microbiome analyses, more and larger clinical studies are required.[118,119]

Numerous novel probiotic products are being developed for the treatment of various skin problems as a result of these studies on the gut and skin microbiomes, which have produced some extremely insightful findings. Additionally, Eczema, atopic dermatitis, acne, and allergic inflammation are just a few of the skin conditions that probiotic bacteriotherapy may help prevent and treat. It may also help reduce skin hypersensitivity and help protect against UV-induced skin damage and wounds. It can also be applied topically.

Combating Physiological Disorders

Lactobacillus probiotics have demonstrated effectiveness in a variety of clinical disorders and conditions ranging from diarrhea, female urogenital infection, *Helicobacter pylori* infections and inflammatory bowel disease to cancer[98,119] (Table).

The impact of gut microbiota on host physiological regulation has recently gotten a lot of attention, especially in crucial areas including the immune system and metabolism.[153]

Immunomodulation

The immunomodulatory activities of probiotics can act both directly and indirectly. Directly such as by increasing the activity of natural killer cells or macrophages modulating the secretion of cytokines or immunoglobulins. Indirectly by competitive exclusion of other (pathogenic) bacteria, enhancing the gut epithelial barrier and altering the mucus secretion.[154]

Anti-commensal antibodies, innate cytokines, and Th17 responses were all reduced after oral gavage with *L. reuteri*, reducing immunological hyper-reactivity (Table). Also, autochthonous *Lactobacillus* may also aid in the restoration of immunological homeostasis and the resolution of infectious illness.[155]

Lactobacillus-free (LF) mice were used to establish the physiological relevance of *L. reuteri*'s immunological effects *in vivo*.[156,157] Proinflammatory cytokines and chemokines generated by intestinal epithelial cells in the ileum and jejunum were activated as a result of the administration of *L. reuteri* in this animal.[158]

Furthermore, probiotics have been shown in multiple studies to strengthen the integrity of the intestinal barrier by increasing gene expression in tight junction signaling. By tight junctional protein phosphorylation, enhancing (actinin, occludin) cytoskeletal or preserving (actin, ZO-1). *L. acidophilus* inhibited enter invasive *E. coli*

Table. Uses of Lactobacillus spp. as probiotic against various human diseases. the clinical outcomes had been conducted on humans as a subject

Probiotic	Effective against	Clinical outcomes	Ref.
L. reuteri	Bowel diseases	Improved inflammation along with increased cytokine expression levels	120
		restoration of gut flora and the prevention of diarrhea.	121
	Coxsackieviruses	Reduce the antiviral activity	28
	Periodontitis	reduced abundance of the pathogenic bacterium	122
	Gingivitis	Decreased bleeding during chewing gums containing probiotics	123
	Type 2 diabetes mellitus	Beneficial effects on patients	124
	Diarrhea	Minimize the frequency and period of diarrhea	125
	Respiratory tract infection	Decrease the rate of the infection	125
	H. pylori infection	Lower the pathogen load in the stomach.	126
	Cholesterol	Reduce cholesterol levels.	127
L. salivarius	Halitosis	enhanced physiologic halitosis and appeared beneficial impacts on bleeding from the periodontal pocket	128
	Atopic dermatitis	Enhance scoring atopic dermatitis and itch values from baseline	129
L. gasseri	Obesity	Reduce the risk of obesity by Lowering NEFA levels	130
	Chronic Stress	Enhance sleep quality and mental state	131
L. casei	Influenza virus (H3N2)	Increasing survival rate and preventing weight loss.	132
	respiratory tract infection	Decreased prevalence of symptoms	133
		lowering the infection occurrence and duration of the upper respiratory tract.	134
L. fermentum	respiratory tract infection	Decreased prevalence of symptoms	133
	Conjunctivitis	Lowered the incidence of conjunctivitis in infants.	135
L. johnsonii	Type 1 diabetes	provide prevention against T1D	136
L. acidophilus	Autism disorder	Improved concentration and carrying out orders	137
	Perennial allergic rhinitis	Reduced the symptoms	138
L. plantarum	Irritable bowel syndrome	Relief the abdominal pain and reduce the bloating	139
	Autism Disorder	improve some autism symptoms	140
L. helveticus	Neurological and psychiatric diseases	Beneficial psychological effects in healthy humans	141
	Cognitive fatigue	Enhancement of cognitive function.	142
L. paracasei	respiratory tract infection	Decreased prevalence of symptoms	133
	Allergic rhinitis	Reduction of nasal symptoms	143
L. delbrueckii	influenza virus	Help by preventing the infection	144
L. crispatus	Urinary tract infections	Decreased recurrence	145
	Vaginal wounds	expedite vaginal epithelial cell wound healing	146
L. rhamnosus	severe watery diarrhea	Reduce the duration and frequency of diarrhea	147
	Dental caries	lowered Streptococcus mutans counts	148
	Bacterial vaginosis	Decreased pH and the rate of recurrence	149
	allergic disease	Protect and reduce the eczema symptoms.	150
		Particularly to prevent or treat food allergies Cow's milk intolerance	151
	Respiratory and gastrointestinal tract infections	Decreased the danger of infection, and the duration of symptoms	152

invasion and adhesion in the human colon cancer cell line (HT29) and Caco-2 cells.[159]

Inhibition of Carcinogenesis

It is well proven that *Lactobacillus* can modulate-ameliorate specific mechanisms against cancers via stimulating anti-cancer effects like enhancing apoptosis of cancer cells and protecting them from oxidative stress.

Probiotic bacteria, particularly *Lactobacillus* microorganisms, have been reported to cause anti-cancer action through increasing apoptosis of cancer cells and the protection against oxidative stress.[160,161]

In similar research involving colon cancer, it was demonstrated that the administration of *L. fermentum* NCIMB 5221 and *L. acidophilus* ATCC 314 in a murine colon cancer model had been discovered to stop or slow the growth of the tumor by triggering an anti-cancer immune response.[162]

Moreover, in mice models of colorectal cancer and melanoma, it has been shown that the administration of live *L. rhamnosus* GG orally enhanced the antitumor effectiveness of anti-programmed cell death 1 (PD-1) immunotherapy by boosting tumor-infiltrating dendritic cells (DCs) and T cells.[163]

In addition, *L. paracasei, L. casei, L. fermentum,* and *L. rhamnosus* were the most frequently isolated species from head and neck cancer patients. moreover, *L. paracasei* had the highest proportion of antimicrobial activity and the best acid-producing capacity against *S. mutans*.[164]

Probiotics might alter the micro-environment of the intestine, causing pro-inflammatory cytokines to decrease. As in the study of Zaharuddin and his group they have shown that pro-inflammatory cytokines were reduced in colorectal cancer patients by using probiotics consisting of six live *Lactobacillus* and *Bifidobacteria* strains.[165]

In addition, in breast cancer metastases in a mouse model, it has been shown that the fermentation of Milk by *Lactobacillus casei* CRL431 (probiotic fermented milk (PFM) help in breast cancer metastases by altering the immune response.[166]

Furthermore, probiotic *L. rhamnosus* MD 1 produced metabiotics that exhibited both cytotoxic and antigenotoxic potential against colon cancer.[167]

Another study has shown that *lactobacillus* E6-1 can inhibit the proliferation of Cal-27 and effectively induce apoptosis of tumor cells *in vitro.*[168]

The exopolysaccharide (EPS) generated by *L. plantarum*-12 was found to suppress the colon cancer cell line's proliferation HT-29 in humans via the mitochondrial route.[169]

The findings of a study about colorectal cancer (CRC) suggested that consuming *Lactobacillus acidophilus* in persons with polyps and people that have a family history of CRC may be a means to prevent, treat, or lower the severity of CRC.[170]

Because of their activity against cervix cancer cells, other research suggests that *Lactobacillus casei* SR1, *L. casei* SR2 and *L. paracasei* SR4 strains derived from the breast milk of humans can be employed as topical therapy with a potential therapeutic index.[171]

The results of recent investigations support the hypothesis that probiotics may be used in cutting-edge cancer treatments. Therefore, to validate these findings and develop treatment plans, additional research on the subject is required. This could theoretically result in a breakthrough in many areas of medicine, including the support of immunotherapy in the treatment of cancer and the development and production of novel vaccines, as well as the improvement of drug delivery in the treatment of other bowel diseases while simultaneously preventing and reducing inflammation.

Reduction of Cholesterol Level

Numerous studies have demonstrated *Lactobacillus*' potential to lower cholesterol levels. Such as In C57BL/6 mice fed a hypercholesterolemia diet, *L. plantarum* H6 lowered serum cholesterol levels. It improved the microbial community of intestinal structure in mice by preventing the pathway of farnesoid X receptor to increase the synthesis of bile acids *in vivo* via promoting the expression of the CYP7A1 gene.[172] (Table).

It was shown that *L. plantarum* YS5 can reduce the level of cholesterol by 84% due to its ability to remove cholesterol *in vitro*. furthermore,

in male Wistar rats, probiotic supplementation was observed to lower serum total cholesterol, low-density lipoprotein cholesterol, and triglyceride levels.[173]

There is evidence that consuming probiotic-rich dairy products lowers blood cholesterol, which could help prevent diabetes, obesity, cerebral stroke, and cardiovascular disease.[174]

Lactobacillus, such as *L. fermentum*, *L. plantarum*, and *L. acidophilus* decrease cholesterol and ameliorate the advancement of nonalcoholic steatosis. Thus, *Lactobacillus* can be used as a beneficial strategy for non-alcoholic fatty liver disease (NAFLD) treatment.[175]

Furthermore, the administration of *L. rhamnosus* BFE5264 resulted in a major reduction in serum cholesterol in a mouse model fed a high-cholesterol diet and changes in the gut flora and the production of short-chain fatty acids were also observed (SCFA). Also, this strain has a positive impact on the metabolism of cholesterol in the liver in a manner like that resulting from statin treatment, which is a drug that can inhibit the biosynthesis of cholesterol in the liver.[176]

L. kefiri DH5 has anti-obesity benefits via lowering the lumen cholesterol and upregulating the PPAR gene in adipose tissues.[177]

Along the AMP-activated protein kinase (AMPK) pathway, *lactobacilli* could exert cholesterol-lowering properties by AMPK phosphorylation that lowered 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) expression.[178]

L. plantarum (LP06CC2) was tested for its effect on cholesterol metabolism in mice fed a cholesterol-rich diet. The consumption of LP06CC2 inhibited the hepatic damage indices as well as the increase of liver cholesterol. The deconjugation of bile acids was clearly boosted by LP06CC2, indicating that bile acid absorption was reduced. LP06CC2 appears to be a promising *Lactobacillus* for lowering cholesterol levels by modulating deconjugation of bile acid.[179]

Probiotics' effects on total cholesterol levels have been thoroughly studied. Researchers have made an effort to elucidate the mechanisms of probiotics on the hypocholesterolemic effect through *in vitro* and *in vivo* experiments in order to explain the variable cholesterol-lowering effect displayed by distinct probiotic strains. Numerous theoretical explanations and experimental data focusing on cholesterol-lowering effects are still debatable. Therefore, better-designed *in vivo* studies may reveal more information that can help resolve disagreements, better understand underlying mechanisms, and determine whether a substance is safe to consume before it is used.

Probiotics as "One Health" Perspective

According to the World Health Organization, One Health is an integrated, unified strategy aimed at continuously balancing and optimizing the health of humans, animals, and ecosystems; in order to intimately connect the interdependence of all these domains.

Increasing the risks of antibiotic resistance and pathogen transmissibility between humans and animals, changing climatic conditions, people's migrations, and increasing the rate of communication are all factors that have contributed to disease spread and will require the application of the concept of "one health." Some of the most often used antimicrobial medications in animals, for example, are likewise reserved for the most difficult cases in humans.

Beneficial domestic multi-dominant agents such as probiotics, which are used to dwell in ecosystems and organisms, can apply the "one health" principle. Ecosystems contain and maintain the most biodiversity on the planet, which may be transmitted to humans via animal and plant products. Probiotics found in soil and plants are primarily favorable to humans and animals. Probiotics, which demonstrate dynamic relationships with different bacteria across the animal and plant kingdoms, developed alongside plants, invertebrates, and vertebrates, forming mutualism, symbiosis, commensalism, or even parasitic behavior with their hosts. *Lactobacillus* spp., with their ability to colonize the phyllosphere, endosphere, and rhizosphere, as well as the fruits and flowers of many plants, make these probiotics species suitable for achieving the "one health" notion.

The diverse *lactobacilli* isolation sources, as well as the species' capacity to transmit and reside in multiple locations and habitats, enhance the implementation of the "one health" concept. Many studies have shown that *Lactobacillus* spp.

can restore environmental balance and enhance human and animal health. For example, in human health, the remarkable flexibility and adhesion of *lactobacilli* in the host's gastrointestinal system may help enhancement of the host's gut health. Furthermore, *lactobacilli* species may be useful as plant growth promoters. Probiotics with the ability to ferment a wide range of carbohydrates, probiotic benefits on human and animal health, and are found in vegetables, dairy products, pickles, sauerkraut, cheeses, fish products, and sausages are likely the greatest candidates for "One Health."

Improving the quality of animal products, increasing production and food security, and lowering the risk of pathogenic agents can all be accomplished by using probiotics as nutritional supplements in scientifically studied ways, in addition to providing an alternative solution to the use of antibiotics. Despite its critical and helpful properties, a high concentration of *lactobacillus* spp. in food can induce food spoilage.

CONCLUSION AND FUTURE PERSPECTIVES

Almost a century after *Lactobacillus* species were initially characterized, researchers are constantly working to identify new *Lactobacillus* species from previously unknown sources. Probiotics may be found in a number of locations; however, as development techniques have been employed, scientists have begun to seek probiotics in unorthodox sources that can aid in the discovery of novel probiotic strains such as non-dairy fermented goods and inanimate surroundings. Lactose-intolerant persons are given probiotics obtained from plant sources, which also demonstrate potential new antibiotics activities of isolates that can be utilized as a replacement or supplement to current chemical antibiotics. *Lactobacillus* species may be separated from fermented and non-fermented biological sources, as well as from environmental sources. The *lactobacilli*'s unique habitat features and wide range of environments indicate the possibility of searching for and isolating new *lactobacillus* probiotics strains from unexpected sources.

It's far viable that they may grow to be greater effective strategies inside the remedy of diverse issues which includes immune gadget stimulation, high cholesterol level, oral infections, urinary tract infections, vagina inflammation, diarrhea symptoms, and so forth as an alternative or supplement to other well-known treatments in the future. It is a natural remedy for newborn animals and humans, as well as for nutrition and sickness treatment. Aside from therapy, they are now widely used in newborn diets and milk. In terms of liver disease, lowering liver enzymes and bilirubin levels can be achieved by *Lactobacilli* isolated from sugar cane following the fermentation process.

Probiotics are vital for restoring normal gut flora, increasing the development of good bacteria, and decreasing the chance of acquiring chronic conditions including cardiovascular disease. As a result, there is widespread interest in these molecules as components for the development of innovative meals with functional qualities. seeking to the roles of native microbiota affecting health and balance restoration, the most current scientists in this regard are still in the early stages of discovering connections and relationships between native probiotics and intestinal microbiota, which might enable for successful customization of probiotic treatment, the commitment of supplementation time, and description of optimal doses for patients in order to improve cardiovascular efficiency or treat certain disorders.

Gut microbiome research is a young and difficult topic with methodologies that are a way to be uniform and coordinated. Massive datasets created from the microbiome, metabolomics, genomics, and transcriptomics are analyzed as consolidated investigation data could be a challenge to interpret, and a variety of complicated bioinformatics approaches have been conducted. the requirement for improving this field of inquiry is crucial through empirical and disarranged controlled studies. To increase existing understanding, well-designed clinical studies including all components of life routine, intestinal microbiome, metabolite, and genetics data are better to be improved.

Although additional clinical evidence is needed to further assess probiotics' therapeutic value, procaryotes such as *Lactobacilli* strains are now among the most extensively utilized agents in GIT diseases. According to *in vivo* investigations,

Lactobacillus survives well in the human GI tract. *Lactobacilli* are one of the most common LAB species that have played important therapeutic functions since their discovery. The increasing amount of research shows that it may be beneficial for diarrhea prevention and alleviation, as well as the treatment of recurring *Clostridium difficile* colitis.

By upgrading methodologies, tools, and techniques for isolation and identification, new pathways for probiotics will open, resulting in additional discoveries of local probiotic strains. New approaches, such as those that enable real-time human study and monitoring of a microbe's integration into an established microbiome, are being developed, along with technologies capable of assessing hit points, which can move this area ahead. after moving on to physical tests henceforth, information on the presence of bacteria, their interaction with the host, and the effect of environmental stimuli (including medications, and nutrition) going to be routine. revolutionary pattern technology will disclose how a probiotic interacts with the host in several stages such as immune machine, all microbiome components, and metabolism. The integrated approach will aid in the establishment of dose-response connections for diagnosis, as well as in coordinating what gets into our systems, which probiotic bacteria have the most predicted impact, and how they will be absorbed.

Probiotic strains isolated from marine organisms have several applications and can be used for Aquaculture species and to prevent microbial pathogens that could threaten marine life. Studies that aim to isolate novel strains of probiotics from aquatic organisms present alternative treatments for the human and marine organisms' pathogens and shed the light on the significant importance to intensify research for probiotics isolated from marine organisms in the future.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS' CONTRIBUTION

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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DATA AVAILABILITY

All datasets generated or analyzed during this study are included in the manuscript.

ETHICS STATEMENT

This article does not contain any studies with human participants or animals performed by any of the authors.

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