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Review

Nutritional and Health Potential of Probiotics: A Review

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Abstract: Several products consist of probiotics that are available in markets, and their potential uses are growing day by day, mainly because some strains of probiotics promote the health of gut microbiota, especially *Furmicutes* and *Bacteroidetes*, and may prevent certain gastrointestinal tract (GIT) problems. Some common diseases are inversely linked with the consumption of probiotics, i.e., obesity, type 2 diabetes, autism, osteoporosis, and some immunological disorders, for which the disease progression gets delayed. In addition to disease mitigating properties, these microbes also improve oral, nutritional, and intestinal health, followed by a robust defensive mechanism against particular gut pathogens, specifically by antimicrobial substances and peptides producing probiotics (AMPs). All these positive attributes of probiotics depend upon the type of microbial strains dispensed. Lactic acid bacteria (LAB) and *Bifidobacteria* are the most common microbes used, but many other microbes are available, and their use depends upon origin and health-promoting properties. This review article focuses on the most common probiotics, their health benefits, and the alleviating mechanisms against chronic kidney diseases (CKD), type 1 diabetes (T1D), type 2 diabetes (T2D), gestational diabetes mellitus (GDM), and obesity.

Keywords: probiotics; health benefits; alleviating mechanism; CKD; T1D; T2D; obesity

1. Introduction

Good health is a fundamental need of human beings [1]. Humans' priority was to rely on natural resources for good health outcomes [2–5]. In the 20th century, it was observed that healthy children fed mothers' milk had *Bifidobacteria* in their gut microbiota [6]. It established a positive association between health and gut microbiota, and numerous studies have been conducted to investigate the proper mechanism of this association, and some found that some bacteria have a positive correlation with health [7]. The term probiotics were first used in 1965 by Stillwell and Lilley to describe these beneficial bacteria [8]. At the beginning of the 20th century, a Nobel laureate in Paris named Élie Metchnikoff, a professor by profession noticed the health-enhancing properties of fermented dairy products. He then reported that the presence of lactic acid bacteria in fermented dairy products helps keep the defensive system activated, resulting in higher longevity of its consumers [9].

Some crucial characteristics of probiotics were introduced in the 1980s, and these include: (a) strains to have a beneficial impact, (b) non-toxic, non-allergic, and non-pathogenic, (c) available in large quantity as viable cells, (d) suitable for the environment of the gut, and (e) storable as well as stable [10]. Although the most commonly used probiotics are bacteria, especially lactic acid, molds and yeasts can also be probiotics [11]. In 2001, the Food and Agriculture Organization and the World Health Organization council defined probiotics, which was later refined in 2014 by Hill et al. as "live micro-organisms that, when administered in adequate amounts, confer a health benefit on the host," which can be understood to mean that probiotic strains must be (i) sufficiently characterized; (ii) safe for the intended use; (iii) supported by at least one positive human clinical trial conducted according to generally accepted scientific standards or as per recommendations and provisions of local/national authorities when applicable, and (iv) alive in the product at an efficacious dose throughout shelf life [12]. Examples include living bacteria containing *Lactobacillus*, *Bifidobacterium*, and some others [13].

From the start, probiotics have been considered beneficial to the health of gut microbiota, studies have also confirmed their positive associations with many other chronic diseases [14]. Although *lactobacillus* is the most commonly used probiotic, many other beneficial microbes are present, and their usage depends upon their origin and health-friendly properties [15]. All bacterial strains have specific properties; some are useful in treating obesity, some treat diabetes mellitus (DM), some help with CKD, and some deal with osteoporosis. In addition to these highly prevalent diseases, several studies have confirmed the beneficial role of probiotics in the case of autism, irritable bowel syndrome (IBS), and wound healing [16,17].

Probiotics have also been investigated to promote oral health and strengthen the immunological system [18–20]. Additionally, they are an essential contributor in the field of agriculture as well as in food processing [21].

In this article, we review and discuss some essential probiotics that can be useful for human health, how they affect an individual's nutritional status, and how probiotics perform their action to prevent disorders. In addition, the health-promoting role of probiotics and action mechanisms in the case of several of the most prevalent diseases are reviewed.

1.1. Nutritional Impacts of Probiotics

Lactic acid bacteria (LAB) most commonly ferment fruit, vegetables, and cereals. It impacts taste, and, when fermenting rice bran, sprouts of bean sprouts, and buckwheat, it also produces bioactive components that benefit inflammatory, compromised immunity, glycemic imbalance, and fatigue conditions [22].

1.2. Nutritional Impacts of Probiotics in Inflammation

Currently, people are highly concerned about their health. There is an increasing focus on disease prevention compared to cures. The consideration of probiotics and their health benefits began about a century ago. It was discovered that the people of Bulgaria and Russia lived longer than other populations because they use sour milk that contains beneficial bacteria [23]. Probiotics play an important role in preventing and improving diseases like allergies, liver disorders, intestinal ailments, and metabolic syndromes leading to diabetes, cardiovascular diseases, and obesity [24]. *Escherichia coli* and LAB are extensively used to treat inflammatory bowel disease, colon cancer, and constipation because lactic acid bacteria directly deliver cytokines to the target sites within the host [21,25,26]. Investigators indicated a significant inhibiting role of non-pathogen apoptosis induction within carcinoma cells, which helps protect against colon cancer (HGC-27) and human colonic cancer cells (Caco-2, DLD-1, HT-29), especially with the action of *Escherichia coli* K-12 strains, *Lactobacillus rhamnosus*, and *Bifidobacterium latis* [27].

1.3. Nutritional Impacts of Probiotics in Dental Carries

LAB probiotics in cheese seem to reduce the number of mutant streptococci in saliva and therefore have a beneficial impact on dental carries; the LAB in cheese also prevents the demineralization of enamel and dental plaque [28]. However, the decrease in streptococci number is independent of the strain used, and the effect is not the same in all studies. Therefore, no exclusive report has been made on dental carries [29].

The health of an individual depends upon the status of a healthy microbiota. Pathogenic bacteria cause inflammation during acute infection, whereas symbiotic bacteria regulate the immune responses to such inflammations and protect the host from different diseases [30].

1.4. Nutritional Impacts of Probiotics in Obesity, Diabetes and Associated Issues

Gut bacteria play a vital role in the pathogenesis of bile duct diseases. Probiotics are also used for the treatment of liver diseases [31,32]. The result of a study on a boy suffering from primary sclerosing cholangitis treated with the combination of drugs and probiotics showed improvement in symptoms and laboratory tests [33]. According to the result of a study on a group suffering from type 2 diabetes mellitus, eating yogurt that contains probiotics (*Lactobacillus acidophilus* La5 and *Bifidobacterium lactis* Bb12) improved fasting glucose level and antioxidant ability, and it was therefore concluded that probiotic yogurt has a positive impact on patients with type 2 diabetes [34]. *Bifidobacteria* play a role in the development of obesity. Mothers who are overweight give birth to neonates with low levels of *Bifidobacterium*. A low number of *Bifidobacterium* at birth is associated with overweight issues later in childhood. The *Bifidobacterium* level in obese adults is lower as compared to that in lean people [35]. The gut microbiota provides opportunities for the fermentation of non-digestible compounds like fibers that support the microbes that produce short-chain fatty acids and gases [36]. The short-chain fructo-oligosaccharides increase intestinal magnesium absorption in postmenopausal women in whom magnesium deficiency leads to osteoporosis [37].

Probiotics also prevent and treat gastrointestinal inflammatory conditions like inflammatory bowel diseases, irritable bowel syndrome [38], allergies, and respiratory disorders [39]. When probiotics were administered in pregnant women, no increase or decrease in the risk of preterm birth and other pregnancy-related adverse effects was seen [40]. *E. coli*, *Staphylococcus aureus*, *Bifidobacterium*, and *Firmicutes* have been reported by researchers to have an impact on obesity, thus can be used as obesity inhibitors [41]. Type 2 diabetes (T2D) is one of the most prevalent diseases globally that can be cured by using probiotics as an adjuvant. It was proved that probiotics exhibit anti-diabetic and anti-inflammatory properties and therefore play a vital role in diabetes prevention and treatment. Probiotics have also been proven beneficial in autistic children, especially for GIT disturbance caused by this disorder. Bone mineral density has also been proven to be affected by these gut microbes, as these microbes lead to enhanced absorption of various nutrients and minerals. These microbes improve human health and improve the health of plants and crops, increasing the overall yield of the land [42].

Traditional probiotics have marginal ameliorative effects on diseases, so the next generation probiotics (NGP) now serve as new preventive and therapeutic tools. These NGP include *Prevotella copri* for controlling insulin resistance, *Akkermansia muciniphila*, and *Bacteroides thetaiotaomicron* that are used to reverse obesity and insulin resistance, and *Bacteroides fragilis* is used to reduce inflammation and facilitates anticancer effects [43].

2. Probiotics and Their Benefits

The use of probiotics in the form of live bacteria for health promotion in animals and human beings is emerging daily. Today, a vast array of fermented food items and beverages is available, accounting for approximately one-third of worldwide human diets [44]. The level of probiotics in foods range from 2 to 20 g/day depending on the component and desired effect and can be added to different food products, including cereals, biscuits, bread, sauces, yogurts, and drinks [45]. Curd is considered the most preferred source of probiotics, as it is globally consumed [46]. Interest and development of functional foods consisting of both probiotics and prebiotics have increased due to increased awareness of their health-promoting properties. They positively affect gut health and decrease the risk of diseases, which is why they are used as therapy [47].

All probiotic products have different nutritional and therapeutic characteristics, due to various conditions, such as the genetic make-up of the strain, amount of the probiotics used in the product, the purpose it is used for, and its shelf life. The selection of probiotic strain depends on its production, impact, and health benefits in the host [48]. A probiotic food must have 10^6 CFU/g of probiotic micro-organism to achieve a health benefit. The dosage recommended for human consumption is 10^7–10^9 CFU/mg/day. It is known that the effect of probiotic food consumption depends on the specific strain used in that product [49]. To get the beneficial strains of probiotics, the following genera are of great importance: *Lactobacillus*, *Escherichia coli*, *Bifidobacterium*, *Enterococcus*, *Saccharomyces*, *Pediococcus*, *Streptococcus*, and *Leuconostoc*. The most common micro-organisms used as probiotics are lactic acid bacteria (LAB) and *Bifidobacteria* [50].

Strains of lactobacillus species that are commonly found in saliva samples include *L. paracasei*, *L. plantarum*, and *L. rhamnosus*. The *bifidobacterial* species are the anaerobes that are also found in the oral cavity, and both species are found in breast milk and are generally regarded as safe [51]. Several elements, such as nutrition, age, environmental difficulties, incompatibilities, illnesses, and treatment routes, strongly impact gut microbiota growth, maintenance, and functionality [52]. When selecting the strain it must be kept in mind that it should be originated from target and natural microflora as it is vital for its survival in an acidic environment during its travel to the intestine [53,54].

Probiotics have a positive effect on the immune system of the host and it was proven that they influence the healthy bacteria present in the gut or intestine [55]. Probiotics improve the immunity system by modifying the humoral and cellular immune response [56]. Figure 1 summarizes the benefits of different probiotics on health.

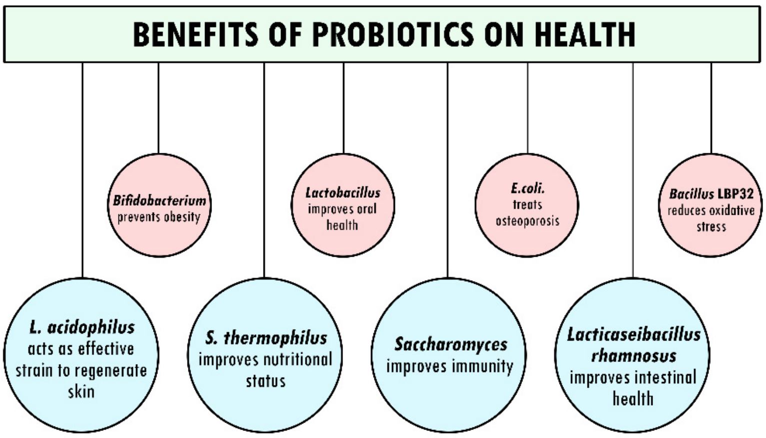

Figure 1. Benefits of probiotics on health [57].

The strains that are being selected also depend on the biosafety level, which means they should not be toxic or pathogenic [58]. They should be tested for safety parameters, including antibiotic susceptibility, antibiotic resistance gene, and hemolytic activity. Antimicrobial production is an important feature of probiotics against pathogens, but non-optimal antimicrobial activity will disrupt the healthy microbiota in the intestines and pose harmful effects [59]. Bile present in higher concentrations resulted in the lower growth of strains [60]. Probiotics can alter the pH of the surrounding environment, and hence they can compete with the pathogens present there.

In the same way, probiotics adhere to the adhesion sites on the mucosa, which decreases the chances of adhesion of pathogens and decreases the cases of probiotics being washed out [61]. Different tests are performed to identify the strain of bacteria, such as biochemical and molecular tests, then further techniques are used to differentiate between the strains of the same species, such as polymerase chain reaction (PCR) and gene sequencing tests [62,63]. Other tests are performed, such as hemolytic tests to determine whether the organisms are destroying red blood cells or not and platelet aggregation tests, which are crucial factors for pathogen activity [64]. Recommended storage temperature for probiotic foods is 4–5 °C, and the product must be used according to the information noted on the label, which should be clear [65].

2.1. Significant Effects of Probiotics on Oral Health Status

Probiotics primarily contribute to gastrointestinal health, but their diversity has been increasing and now they greatly contribute to oral health care [66]. Oral disease treatment is one of the most expensive health care treatments; that is why new approaches are being used to treat these infections, such as the use of probiotics [67]; in other words, oral lactic acid bacteria have been characterized after isolation and purification to use for oral health, especially to cure periodontal diseases, caries, and halitosis (bad breath) [19].

These ailments are some of the most widespread diseases throughout the world, but the treatment of these infections require potent antibiotics that cause severe side effects in the gastrointestinal tract. The use of probiotics as a relatively less harmful treatment has been advised to avoid such side effects [68].

Additionally, the buccal cavity is an excellent bacteriological medium, where micro-organisms can grow very easily if certain factors are out of balance due to poor oral health, poor diet, or immunodeficiency. These parameters alter the pH of the mouth and create a favorable environment for micro-biota growth. Micro-organisms are deposited on the oral cavity like biofilm and create a bacterial hold and aggressively colonize the buccal cavity [69].

Probiotic strains of *Bifidobacterium*, *Lactobacillus*, and *Streptococcus* are primarily used to prevent or cure oral infections. Plaque or dental biofilms in the buccal cavity leads to poor oral health, but lactic acid bacteria are probiotics that interact with that biofilm/plaque and destroy the causative agents with LAB's antimicrobial activity [70].

Indirectly, probiotics enhance immunity and strengthen the immune system by the interaction of lactic acid bacteria with immuno-competent cells, which leads to modification in the production of cytokines and ensuing effects on the overall immune system [71]. Lactobacilli used as a probiotic in mild gingival inflammation causes a great decline of Interleukin-8 discharge in the gingival crevicular fluid [72]. Probiotics have been used in the treatment of periodontitis and gingivitis: they modify the buccal cavity homeostasis, with possible numerous health benefits such as combatting dysbiosis and moderating inflammatory pathways to minimize the inflammation of periodontitis [73,74].

Probiotics are also being used in the treatment of halitosis; for this purpose, bacteriocins producing *Streptococcus salivarius* K12 strain were developed. This strain treats the mouth odor by actively helping de-colonize bacteria like *Solobacterium moorei*, *Parvimonas micra*, and *Eubacterium sulci*, which produce volatile sulfur compounds(VSCs) on the tongue [75,76].

A new study demonstrated the effects of widely commercially used chewing gum containing probiotic bacteria (xylitol), which greatly impacted plaque and gingival scores by reducing *Streptococcus mutants* counts in plaque and saliva [77]. Probiotics played an essential role in the clinical manifestation of dental disorders and periodontal diseases and perhaps impacted halitosis as well. Probiotics provide long and short-term therapeutic effects. Advance studies about particular strains and oral micro-biome transplants could also increase probiotics' role or efficacy in oral health, and probiotics consumed as part of the diet may also enhance oral health and strong oral immunity or hygiene [78,79].

2.2. Improvement of Intestinal Health through Probiotics

Probiotics are known as important micro-organisms that are used to improve intestinal health, including beneficial micro-organisms known to retard the production of bacterial enzymes that cause colon cancers [80]. Colonic microflora is very important for human health [81]. These bacteria promote the normal functioning in the intestine and maintain the host's health [82]. Consumption of pre and probiotics alters gut microbiota by facilitating or inhibiting microbe growth [83].

These bacteria first colonize the intestinal track and then help establish the immune system with balanced cell responses [84]. During pregnancy, prebiotics and probiotics are supplemented in pregnant females to protect the fetus from many autoimmune diseases and syndromes (AIDS). These supplements immunize the child and protect against AIDS [85]. Recent investigations have shown that human intestinal microbiota comprises over 1000 microbes [86]. In one study performed on obese and diabetic patients, scientists concluded that their gut microbiota differs from non-diabetic patients and this modification occurred as a result of dietary changes of diabetics versus non-diabetics [87]. Several studies have shown that the microbiota influences energy homeostasis and controls body weight [88].

Drug and probiotic interference are well known; studies have revealed the probiotics and warfarin interaction. Intestinal bacteria are well known for the production of vitamin K, but absorption of antibiotics disturb the gut flora and result in the deficiency of vitamin K [89]. According to the study, many external factors like medication, radiotherapy, stress, and infections disturb the gut microflora growth and their ratios [90]. Other essential functions played by probiotics include improvement in flu/influenza; protection from dental caries; prevention of tonsillitis, respiratory infections, and urogenital health problems; and help in wound healing and throat infection through immunomodulatory action. Currently, probiotics are being sold in markets as dietary supplements proven to be so-called standard drug therapy [91].

2.3. Role of Probiotics in Development of Immunity

Probiotics and prebiotics exert beneficial effects on humans' health, including immune modulating capacity, modulation of cellular metabolism, epithelial barrier functions, or proliferation [92]. The growth of the gut microbiome is a dynamic process, and early colonization of *Bacteroides* and *Bifidobacterium* species might play a crucial role in immune regulation. Factors that can affect the early colonization of gut microbes in neo-nates include the mother's diet, antibiotic treatments, method of delivery, and surrounding environment [93]. On the surface of immune cells, Toll-like receptors (TLR) behave differently depending on the immune system's response, which allows distinguishing between pathogenic and native gut microbiota. Probiotics and their effector molecules affect the gut barrier by different methods such as modulation of mucus production, reduction in bacterial adhesion, and induction of IgA [94].

3. Association of Probiotics in Prevention of Diseases

Probiotics are very helpful in preventing chronic diseases by mediating their effects. They show positive effects on gut health and help in skin-related problems such as burns, scars, infections, wounds. They increase the skin's innate immunity and help to regenerate healthy skin [95]. The action of Saccharomyces cerevisiae dressing improved burn skin healing significantly as demonstrated by [96], whereas a hypothetical model of intestinal microbiota influencing wound healing through gut-brain-skin axes explains damaged tissue repair [97]. The distinction in gut microbiota constitution and decreased levels of *Bifidobacteria* and *lactobacillus* in infants' guts leads to the onset of allergic symptoms. Both the reports of specific probiotic strains and their results indicate that they can be used in the prevention of eczema. Dysbiosis, also known as dysbacteriosis, is a term used for imbalance in microbes inside the body, such as impaired microbiota, which is often related to inflammatory bowel disease, colonic cancer, metabolic syndrome, and allergic reactions. Improving the gut microbiota balance by different nutritional concepts or by ingesting specific micro-organisms led to significant improvement in health and decreased the risk of diseases or changing treatment mode [98].

The development of irritable bowel syndrome is associated with deviation in intestinal homeostasis, whose outcome is the uncontrolled immune response to gut microbiota by intestinal immune cells and epithelial cells, which results in complications including ulcers and fibrosis. A prebiotic is a valuable food substance that can be used to facilitate the growth of beneficial bacteria that modifies intestinal microbiota. Both probiotics and prebiotics are helpful for irritable bowel syndrome [97].

Probiotics have been involved in the healing process of intestinal ulcers and infected cutaneous wounds. Skin microbiota acts as a defensive barrier and can regulate the skin's inflammatory response to minor epidermal injury by decreasing and promoting cytokine production to maintain healthy skin [99]. The process through which probiotics show positive effects includes directly killing the pathogen, increasing the epithelial barrier, competitive displacement of pathogenic bacteria, and induction of fibroblasts [100].

Probiotics are also very beneficial for burn patients; they can reduce the bacterial load on the ulcer area [101]. Skin injuries cause disturbance in microbiota levels and increase the prevalence of bacteria that exert adverse effects on wounds. Additionally, having a wound causes stress, which results in alterations of neuro-endocrinal responses and impairs wound healing [102]. Chronic wounds are those that are difficult to heal and can exert a burden not only on the patient but also on the health care system, for example, diabetic foot ulcers (DFU), venous leg ulcers (VLU), and decubitus ulcers (DU). In chronic wounds, polymicrobial biofilms that promote pathogenic microbial growth and interfere in the process of wound healing are abundant and play an important role in the development of impaired wounds [103].

Probiotics play an important role in the treatment of autism by affecting the microbiome, which is present in the gut and responsible for imbalanced neuro-developmental conditions, like autism. If gene *Shank*3 is disturbed by gut microbes, it affects a person's behavior and can lead to autism [104]. There are numerous medicines are available for treatment, but they have side effects; to avoid these side effects, probiotics are used as an alternative therapy. Probiotics alter the gene that is responsible for neurodevelopment and maintains the gut environment to treat this disease [105]. This bacterial disorder promotes different pathophysiological gastrointestinal syndromes like bowel syndrome, obesity, diarrhea, and food allergies [106].

Dietary biotic aid is used to maintain the GIT flora and relieve pain, vomiting, nausea, and bowel syndrome. The most potent probiotic strains used to treat GIT disorder are *L. rhamnosus GG*, *L. reuteri 17938, VSL #3*, and *Bifidobacteria* species [107]. With probiotic intake, stool PCR tests of autistic children indicated increased colony count of Bifidobacteria and lactobacilli with a major bodyweight loss and great progress in the severity of autism and gastrointestinal disorders [108]. In pregnancy, Interleukin-6, 17a cytokines prompt autism spectrum disorder. Probiotics play an important role in inhibiting the production of cytokines and preventing the autism spectrum disorder induced by maternal immune activation [109].

Osteoporosis is a disease that affects the skeletal system, manifesting as low bone mass density, deterioration of the skeletal system, and greater bone brittleness and sensitivity to crack. Most cracks are in the distal forearm, femur, and back. These cracks especially occur in postmenopausal women [110]. The cause of bone loss is due to the low level of the estrogen hormone because estrogen performs a significant role in developing and sustaining bones [111].

In America, many people face the problem of osteoporosis, and most people are at high risk of low bone mass. Osteoporosis can occur in males and females at any period of life, but it predominantly occurs in older females [112]. Probiotics act as a therapeutic agent that helps treat many bone diseases such as osteoporosis and rheumatoid arthritis [113]. There are many mechanisms of probiotics that affect bones; the most latent influence of probiotics on bone happens through the integration of vitamins. In the metabolism of calcium, vitamin D, C, K, and folate are linked and are necessary for bone development [114].

L. reuteri is a probiotic that plays an essential role in alleviating osteoporosis and improving bone density [115]. Osteocalcin serum (OC), osteoblasts, i.e., bone composition parameters, low serum C-terminal telopeptide (CTX) and osteoclasts, i.e., bone resorption parameters are increased by *B. longum* supplementation. *B. longum* changed the structure of the femur [116]. When bone loss in postmenopausal osteoporosis occurs due to the estrogen level being inadequate, intestinal and bacterial antigens traverse the arbitrated intestinal epithelium wall and inaugurate the immune response. Probiotics boost the intestinal epithelial wall, balance the deviant host immune responses, support intestinal calcium absorption, restore intestinal microbial diversity to prevent bone resorption, and help in the latest production of the estrogen-like substance [117]. Action and effects of probiotics on numerous diseases that have been reported by in vivo analysis are shown in Table 1.

Table 1. Effect and action mechanisms of probiotics to prevent diseases reported in various studies.

Probiotics	Type of Probiotics	Subjects of Administration	Duration of Intervention	Diseases	Potential Effects	Mechanism of Therapeutic Action	References
Lactobacillus	*L. acidophilus*	Humans	4 weeks	T2D	Improved the homoeostasis of glucose	Preservation and reduction of insulin sensitivity	[118]
	Limosilactobacillus reuteri	Ovx Mice	4 weeks	Menopausal bone loss	Loss in vertebral and femur bone was prevented, improvement in the density of bone	T-cells induced signals of osteoclast suppression by causing the reduction in osteoclastogenesis	[119]
	Lacticaseibacillus casei	Neonates	12 months	Enteric Colonization	Fungal diseases such as enteric colonization is preventable with the consumption of probiotic	Modification in the ecology of fungi carries out the application of mechanisms potentially by LCC in the gut. Increased mucosal responses of IgA include a significant fungi exclusion and reduction in colonization ability as well	[120]
	L. crispatus	Women	4 weeks	Recurrent UTI	Prevention of urinary tract infection such as vaginal flora infection and pregnancy issues due to urinary tract infection could be resolved	Probiotic was given as a vaginal suppository to indicate the reduction of infection in the urinary tract and enhanced the IgA	[121]
	L. gasseri	Rats	12 weeks	Obesity	Obesity and other weight gain problems could be resolved by oral uptake	Probiotic extracted from the milk of human breast effectively imposed influence on adipose tissues either by destroying cells or reducing their number	[122]
	Lactiplantibacillus plantarum	Mice	4 weeks	Spontaneous Colitis	Development of colitis due to the deficiency of IL usually under SPF conditions was prevented	Decrease the establishment of inflammatory colony inflammation due to mucosal IL	[123]
	Lacticaseibacillus rhamnosus	Epithelial cells	NR	Rotavirus	The development of an efficient immune system prevented rotavirus	Inoculation of IPEC-J2 cells with probiotics reduce the risk of rotavirus due to the anti-inflammatory properties	[124]

Table 1. *Cont.*

Probiotics	Type of Probiotics	Subjects of Administration	Duration of Intervention	Diseases	Potential Effects	Mechanism of Therapeutic Action	References
Bifidobacterium	*B. lactis*	Mice	12 weeks	Obesity	Reduced fat mass and weight gain	Significantly reduces adherence of mucosal bacteria in caecum and ileum	[125]
	B. bifidum	Mice	4 weeks	Inflammatory bowel disease	Assisted in controlling unusual responses of immunity in the tissues of intestine	Reduces lymphocyte infiltration and ameliorated the goblet cells reduction	[126]
	B. adolescentis	Cells	NR	Melanogenesis	Acted as antioxidant and inhibitory properties of melanoma made the *B. adolescentis*, a novel whitening agent for skin	Inhibition of tyrosinase action would lead to the reduction in melanogenesis, such as the melanoma process of cells	[127]
	B. infantis	Mice	7 days	Inflammatory bowel disease	The permeability of intestine could be reduced to treat IBD	The reduction in the infiltration of neutrophils and the inflammatory colon is reported	[128]
	B. breve	Mice	NR	Alzheimer's disease	Exhibit beneficial effects on peripheral tissues and the central nervous system and manages the neurodegenerative disorders	Non-viable bacterium metabolite or its components partially treat the cognitive decline while the specific probiotic suppresses the expressions and inflammation in the hippocampus	[129]
	B. longum	Mice	10 days	Gut derived sepsis	Treat opportunistic infection and significantly treat immunocompromised patients	Less *P. aeruginosa* viable count in the jejunum is reported and significantly repressed the *P. aeruginosa* adherence to the cell's monolayers	[130]
Other Species	*Escherichia coli*	Humans	12 weeks	Irritable bowel syndrome	Demonstrates beneficial effects to reduce the action of the syndrome of irritable bowel	Shows its action particularly in patients with enteric microflora having alteration, for instance, after antibiotics' administration or gastroenterocolitis	[131]
	Streptococcus thermophilus	Infants	5 months	Diarrhea	The formula that is obtained by fermentation can cause a reduction in the severe diarrhea	A combination of *Streptococcus thermophilus* and Bifidobacterium breve are fermented and interact with the immune system of the intestine to prevent acute diarrhea	[132]
	Bacillus subtilis	Rabbits	7 weeks	Immunodeficiency	Improvement in the mechanism of defense and immunity	Increases the weight of spleen and thymus prominently, provide innate immunity and induction of immunity on RK-13 cells	[133]
	Lactococcus lactis	Mice	5 days	Colitis	Acute and chronic colitis could be effectively managed to prevent damage to epithelial tissues	*L. lactis* which releases TFF are involved in the Intragastric administration at the colonic mucosa, in distinction to the administration of TFF which is purified, demonstrated to heal and prevent acute colitis induced by DSS	[134]

NR = not reported, EcN = Escherichia coli Nissle, Ovx = ovariectomized, RK-13 cells = rabbit kidney epithelial cell line, TFF = trefoil factors, DSS = dextran sodium sulfate, LCC = Lacticaseibacillus casei, IgA = Immunoglobulin A, UTI = urinary tract infection, IL = Interleukin, SPF = specific pathogen-free, IPEC-J2 = non-transformed porcine jejunum epithelial cell line, IBD = inflammatory bowel disease, AD = Alzheimer's disease.

3.1. Action Mechanism of Probiotics in Reduction of Obesity

Obesity is due to the union of microflora in the rectum area due to excessive absorption. Several new studies have confirmed that human intestinal micro-organisms play an important role in obesity through energy production and absorption of nutrients, and it has been shown that the duodenal microbiota is different in obese compared to lean persons. The upsurge of some gut microbial taxa such as *Escherichia coli*, *Staphylococcus aureus*, and other general bacterial gut fungi with *Bifidobacterium* has been shown to impact obesity [135].

Firmicutes are used directly as healing adjuvants, sold as named probiotics, prebiotics, or, usually, functional foods. In the United States, these products are characterized by the Food and Drug Administration and are generally recognized as safe. It is assumed that the gut of a fetus throughout the intrauterine period is deprived of any bacterial groups, i.e., it is thoroughly germ-free; however, during parturition, the transfer of micro-organisms from the mother to the fetus gut seems to occur and basic microbiota were found in it [136].

The mechanism credited with managing an upsurge in body fat was the capability of microbiota in extracting energy from food and controlling the host's energy balance. Deprivation of dietary polysaccharides and fiber by *Firmicutes* and *Bacteroides* in the gut resulted in the manufacture of SCFAs, such as acetate, propionate, and butyrate. Propionate is a significant energy source for the host from a mixture of glucose and lipids in the liver. A survey of 61 primary studies indicated differences in the microbial formation between overweight and non-obese subjects and the potential mechanisms involved [137].

Alterations are made homeostasis during the utility of dietary consumption and storehouse of lipids due to the balance of the abdominal microbiota. The microbiota is higher on metabolic pathways connected to obesity, including intonation with probiotics and prebiotics. This rise in *Bifidobacteria*, generally followed by weight gain and the increase in parameters linked to obesity [138].

Probiotics play a role in stopping the spread of bacteria and maintaining the gut environment to restore its normal flora. The ecology of the gut can be disturbed by numerous antibiotics plus some dietary products. Mostly probiotic strains come from gram-positive bacteria to treat gut disorders. To reduce tumor necrosis factor in the host, *L. reuteri* 6475 is important, and it also plays a vital role in promoting bone health and limiting bone absorption. Probiotic *Limosilactobacillus reuteri* has anti-inflammatory properties, particularly anti-TNFα properties [139].

Results demonstrated that these species reduce (LDL) low-density lipoprotein and (TC) total cholesterol, resulting in decreased coronary heart disease. A low level of leptin decreases obesity. LAB supplements also decrease LDL-C, aspartate aminotransferase (AST), alanine transaminase (ALT), high density lipoprotein (HDL), glucose, lipase, and triglycerides when a high fecal count is reported. LAB supplements also reduce intestinal microflora (tryptophanase, β-glucuronidase, and β-glucosidase). *Lactobacillus acidophilus* probiotics help ovariectomized subjects, intensify the microstructure of cortical and trabecular bone, expand the mineral density and diversity in bones, and prevent obesity [140].

Obesity levels has increased from 1980 to 2014 [141]. Obesity has an association with the high availability of energy and ambient temperature. An imbalance between intake and expenditure of energy is one of the significant causes of obesity. Gut microbiota influences the metabolism of the whole body by disturbing energy balance. They cause inflammation and barrier function in the gut, assimilating regulatory signals of central and peripheral food intake, thus enhancing body weight. Several physiologic functions are linked with probiotics that contribute to gut microbiota health and affect appetite, composition, food intake, metabolic functions, and body weight through gut bacterial community modulation and gastrointestinal pathways [142]. Figure 2 explains the anti-obesity mechanism of probiotic *bifidobacterium* spp., which is supplemented in the form of LAB supplement including *B. pseudocatenulatum* SPM 1204, *B. longum* SPM 1205, and *B. longum* SPM 1207.

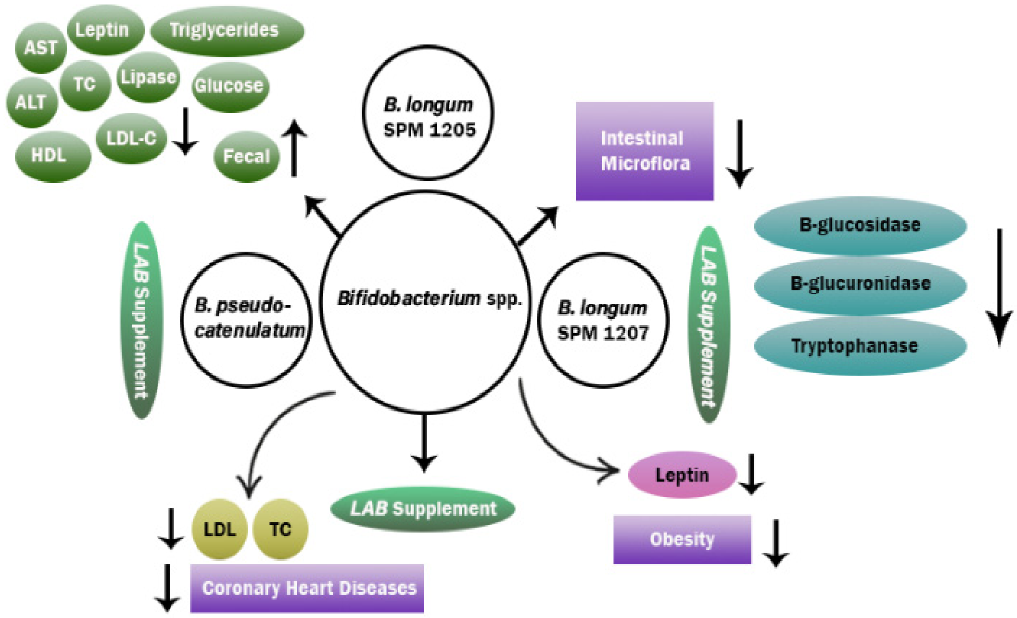

Figure 2. Probiotics (*Bifidobacterium* spp.) against obesity (adapted from [143]).

3.2. Action Mechanism of Probiotics in Minimizing T1D, T2D, GDM

A current major health problem is diabetes mellitus [144]. Failure in insulin secretion and insulin action leads to a state of hyperglycemia, which is a metabolic disease that ultimately results in diabetes mellitus [145]. Between 5 and 10% of people have type 1 diabetes, also known as term insulin-dependent diabetes or juvenile-onset diabetes, due to the cellular-arbitrated autoimmune disorder in these β-cells of the pancreas [146].

Diabetes mellitus type 2, also known as insulin resistance, is when the patient does not utilize the insulin correctly. As a result, the pancreas generates additional insulin to compensate, but it cannot impel the production of sufficient insulin to sustain the appropriate level of blood glucose. Gut-microbiota contours in diabetic patients are not regular. A spatial association of human metagenome investigation revealed an essential relationship between metabolic pathways in type 2 diabetes subjects, specific gut microbes, and bacterial genes the level of *Lactobacillus* spp. that were very different than that of the non-diabetic subject [147].

Glycated hemoglobin (HbA1c) values, fasting glucose level, and concentration of *Lactobacillus* species are positively correlated. *Clostridium* species concentration in the gut is positively correlated with high-density lipoprotein (HDL) cholesterol level and negatively related to fasting glucose, HbA1c, insulin concentration, C-peptide, and plasma triglyceride levels [148]. Gram-positive bacteria and coagulase-negative staphylococci were prevalent in diabetic subjects in higher proportions, primarily in diabetics with retinopathy [149].

In the development of T2D, many cytokines are included. In the intestinal immune system, there are fundamental signals that are involved in suppressing the physiological state of action in the gut and affect the probiotics in glucose metabolism [150]. There is enough research to recommend that focalization of diabetes plays an important role in oxidative damage and anti-oxidative ability. In diabetic rats, inhibition of lipid peroxidation and increases in the antioxidant content of glutathione, superoxide dismutase, catalase, and glutathione peroxidase due to probiotics decreases oxidative damage. Probiotics also can prevent insulin resistance due to their anti-diabetic properties, which, in turn, increases the liver's natural T killer cells [151].

Probiotics also can improve inflammation by accentuating TNF-α expression, insulin stability, and overcoming NF-kB tying activity. Probiotics increase the bioavailability of gliclazide, which improves glucose metabolism and also helps repress the intestinal assimilation of glucose and modulate the action of the autonomic nervous system. If the colonial microbial diversity increases, it helps with upholding the probity of the gastrointestinal lining, improving glucose homeostasis, reducing inflammation, sustaining insulin production, and accumulating nutrients from the diet [152].

Adverse effects are associated with gestational diabetes mellitus (GDM) for both mother and infant during pregnancy. It is difficult, but GDM can be prevented by adopting a healthy lifestyle. The bacteria composite, e.g., the gut microbiome is available in intestines that alter the pathways for glucose and lipid metabolism, and in some host-inflammatory settings, gut microbiome alteration was shown to affect responses. Probiotics are one of the ways to modify the gut microbiome. They cause alterations in the gut microbiome but also modify the pregnancy metabolic environment [153].

Lactobacillus has an immunomodulatory effect on the host immune system. Subdued expression of osteoclastogenic factors (IL-6, IL-17, TNF-α, and RANKL) and enhanced expression of anti-osteoclastogenic factors are due to the *Lactobacillus acidophilus*. *Lactobacillus acidophilus* also has therapeutic, osteo-protective action in bone well-being (via tweaking Treg-Th17 cell balance) in postmenopausal osteoporosis as well as preventing diabetes mellitus [154]. Figure 3 illustrates the mechanism action of probiotics (*Bacteroides dorei*, *Bifidobacterium*, and *Lactobacillus rhamnoses*) against type-1-diabetes (T1D), type-2-diabetes (T2D), and gestational diabetes mellitus (GDM).

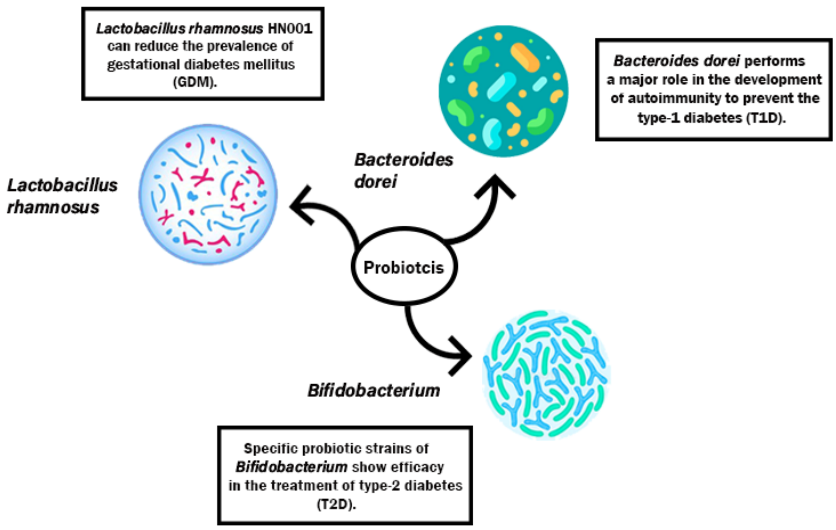

Figure 3. Mechanism action of probiotics (*Bacteroides dorei*, *bifidobacterium* and *Lactobacillus rhamnoses*) against type-1-diabetes, type-2-diabetes, and gestational diabetes mellitus adapted from [125,154–156].

3.3. Mechanism of Action of Probiotics against CKD

Probiotics play a vital role in reducing the risk and prevention of chronic diseases. There is an increasing concern in probiotics and prebiotics addition in the cases of chronic kidney disease (CKD) [157]. CKD increases at fluctuating rates, conditional on etiology and state of uremia. CKD is associated with consistent fatal disease build-up, and finally requires expensive treatments including peritoneal dialysis, kidney transplantation, and hemodialysis, which may prolong life [158].

The risk factor in the development of renal stones is known as hyperoxaluria, which can cause major damage to kidney function. The formation of oxalates primarily occurs. To ameliorate this condition, lactobacilli are given in the form of supplements that may decrease the formation of stones and reduce the chances of urolithiasis. *Lactobacillus casei* HY2743 and *L. casei* HY7201 may prevent the formation of oxalate [159].

Probiotics help the gut to maintain the luminal pH, produce antimicrobial peptides, influence function blockage by greater production of mucus and intonation of the host immune system, and transform the gut microflora. Gut microbiota plays an important role in the regulation of bone mass. The gut microbiota's effect on bone mass is propitiated through impacts on the immune system, whereas a change controls osteoclasto-genesis. In normal conditions bone-forming osteoblasts and bone-resorbing osteoclasts are constantly remodeled; when an imbalance occurs in this process, osteoporosis occurs [160]. Figure 4 represents the mechanism action of *Lactobacillus* spp. against oxalate stones.

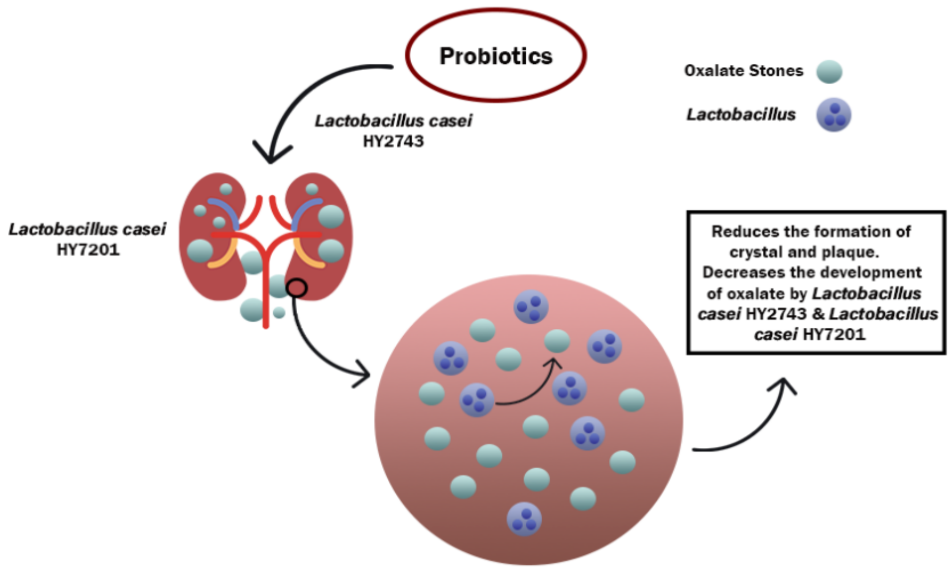

Figure 4. Prevention of kidney stones (oxalate) by probiotic (*Lactobacillus* spp.). Adapted from [161].

4. Probiotics for Animal Health

Sturdy pathogens such as Campylobacter and Salmonella can have a detrimental effect on the wellness and health of animals, as well as their development and reproductive abilities. These harmful bacteria can be transported via the food chain and into the human digestive organs, where they can cause serious human illnesses [162]. Numerous investigations on farm animals and normal or stressed humans have been conducted, which have proven the impact of various feed additives, and/or putative probiotics on good bacteria and decreased pathogen load in chickens, pigs, and ruminating animals [163].

5. Safety of Probiotics

A bacterial strain's safety, its source, antibiotic-resistant characteristics, and absolute lack of pathogenicity associated with virulent cultures all contribute to the safety profile's primary foundation; the rest is performance [164]. Probiotic performance promotes a variety of pathways, including adhesion to epithelial cells, decrease in gastrointestinal permeability, and immunoregulatory impacts [165]. Probiotics are not metabolized, have no potential for transference to animal-derived foods, and so do not result in the creation of residues. Due to the absence of their explicit and/or indirect transit from the gut into the animal body, they do not affect metabolic activities and therefore have no adverse effect [166].

6. Conclusions

Awareness regarding beneficial bacteria in the human gut originated in the 20th century, and by that time probiotics were considered an important player in intestinal and oral health. These gut microbes are associated with higher longevity. This associated effect between probiotics and long life is the basis of present research trends which are exploring the health-promoting properties and action mechanisms of gut microbes in cases of several prevalent diseases. Probiotics have anti-inflammatory properties because they can interfere with the working of cytokines and chemokines. Due to this vital property, they have been investigated in various diseases, especially in the case of chronic inflammatory diseases and GIT disorders. These gut microbes have a direct link with the overall nutritional status of a person as they help in the digestion and absorption of various nutrients, and therefore help regulate cholesterol levels and pancreatic functions. Due to their interference with cytokines and inflammation stimulation factors, they also tend to affect the immune system. Probiotics also tend to affect the gut barrier and thus also play a defensive role in human health.

7. Future Recommendations

More molecular studies are needed to ensure the safe use of some strains of bacteria, as insufficient data are available on the safety aspects of the probiotic strains. Not all microbes are beneficial and some of them can result in severe outcomes. A thorough study of the strain type used, its impact on health, and its interactions should be studied. Metabolomics exploration of human microbiome functionality with the involvement of bioinformatics may be a new horizon of research, without strong evidence the use of microbes as probiotics should not be encouraged.

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