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REVIEW

Lactobacilli and Klebsiella: Two Opposites in the Fight for Human Health

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Abstract—The problem of antibiotic resistance is currently very acute. Numerous research and development of new antibacterial drugs are being carried out that could help cope with various infectious agents. One of the promising directions for the search for new antibacterial drugs is the search among the probiotic strains present in the human gastrointestinal tract. This review is devoted to characteristics of one of these probiotic strains that have been studied to date: *Limosilactobacillus reuteri*. The review discusses its properties, synthesis of various compounds, as well as role of this strain in modulating various systems of the human body. The review also examines key characteristics of one of the most harmful among the currently known pathogenic organisms, *Klebsiella*, which is significantly resistant to antibiotics existing in medical practice, and also poses a great threat of nosocomial infections. Discussion of characteristics of the two strains, which have opposite effects on human health, may help in creation of new effective antibacterial drugs without significant side effects.

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INTRODUCTION

According to the World Health Organization (WHO), probiotics are live microorganisms that provide health benefits for the host when consumed in adequate amounts. Although the idea of using probiotics to benefit the body is not new, recently interest in this subject has significantly increased [1]. This may be partially due to the increasing resistance of pathogens to traditional antimicrobial agents, particularly in the treatment of the disorders of gastrointestinal tract (GIT), as well as to the fact that more and more people strive for the natural ways to heal the body. Probiotic microorganisms that have been previously shown to have beneficial properties include *Lactobacillus* spp., *Bifidobacterium* spp., *Saccharomyces boulardii*, *Propionibacterium* spp., *Streptococcus* spp., *Bacillus* spp., *Enterococcus* spp., and some strains of *Escherichia coli* [2].

There are several criteria that a probiotic must meet to be considered effective. These include the ability to survive in GIT, high resistance to gastric juice, absence of any transferred antibiotic resistance genes, and ability to have a positive effect on the body [3]. There are several mechanisms for this positive effect. The widespread generalization describing common mechanisms among the studied probiotic genera includes resistance to colonization, production of acids and short-chain fatty acids, normalization of intestinal function, normalization of disturbed gut microbiota, increase in enterocyte turnover rate, and competitive displacement of pathogens [4]. Some types of probiotics (although it has not been widely studied) exert a lot of effects, and some of these effects are strain specific. For example, some probiotic microorganisms can improve digestion of a host by metabolizing bile salt or supplementing the functions of digestive enzymes being absent [5, 6].

Abbreviations: GIT, gastrointestinal tract; MUBs, mucus-binding proteins.

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Lactobacillus spp. is one of the most widely used probiotics and can be found in a wide variety of foods worldwide [7]. The genus *Lactobacillus* includes a large heterogeneous group of Gram-positive, non-spore-forming, facultatively anaerobic bacteria. This genus plays a very important role in food fermentation and can also be found in the human and animal GIT in different amounts depending on the species, host age, or location in the intestines [8]. The genus *Limosilactobacillus* separated from the genus *Lactobacillus* in 2020 included species such as *L. fermentum*, *L. pontis*, *L. reuteri*, *L. vaginalis*, etc. [9]. What all bacterial species in this genus have in common is that they are able to form mucus from exopolysaccharides synthesized from sucrose.

Animal studies and preclinical trials have shown that lactic acid bacteria can help prevent and treat numerous gastrointestinal diseases. These include intestinal infections, antibiotic-associated diarrhea, necrotizing enterocolitis in premature babies, inflammatory bowel disease, colorectal cancer, and irritable bowel syndrome [10]. Although lactobacilli are supposed to demonstrate the maximum benefit in gastrointestinal tract, it has also been reported that some probiotic lactobacillus strains exert their effects in other parts of the body. These include prevention and treatment of urogenital disorders and bacterial vaginosis in women, atopic diseases, food hypersensitivity, and prevention of dental caries [10].

One of the *Limosilactobacillus* species, *L. reuteri*, has many beneficial properties influencing host's health such as prevention and/or treatment of various diseases. *L. reuteri* was isolated for the first time in 1962. It was characterized as a heterofermentative species that grows in an oxygen-limited atmosphere and colonizes human and animal GI tract [11]. The fact that this strain commonly colonizes gastrointestinal tract may determine its probiotic properties. This organism can exist in a wide range of pH values of the environment, uses numerous mechanisms that allow it to successfully reduce activity of pathogens, and it has been shown to secrete antimicrobial mediators [12, 13].

It has been shown that *L. reuteri* is really one of native bacteria in the human GIT [14]. They enter the GIT early in life through breast milk [15]. These bacteria naturally inhabit a wide range of vertebrates including pigs, rodents, and chickens. In fact, they have undergone a long evolution to become the host-adapted lineages of bacteria [16, 17]. This organism is most commonly found in the upper digestive tract of the host [18]. Several studies were performed to assess safety of this organism in adults, children, infants, and even in HIV (human immunodeficiency virus)-infected population [13, 19, 20]. The results showed that a dose as high as $2.9 \cdot 10^9$ colony forming units (CFU) per day was still well tolerated, safe, and effective in humans. There are also the studies detailing the benefits of *L. reuteri* as a probiotic. These benefits include health promotion, reduction of occurrence of infections, improvement of feed tolerance in animals, increase in assimilation of nutrients, minerals, and vitamins, modulation of host immune responses, increase in intestinal mucosal integrity and decrease in bacterial translocation [21-23].

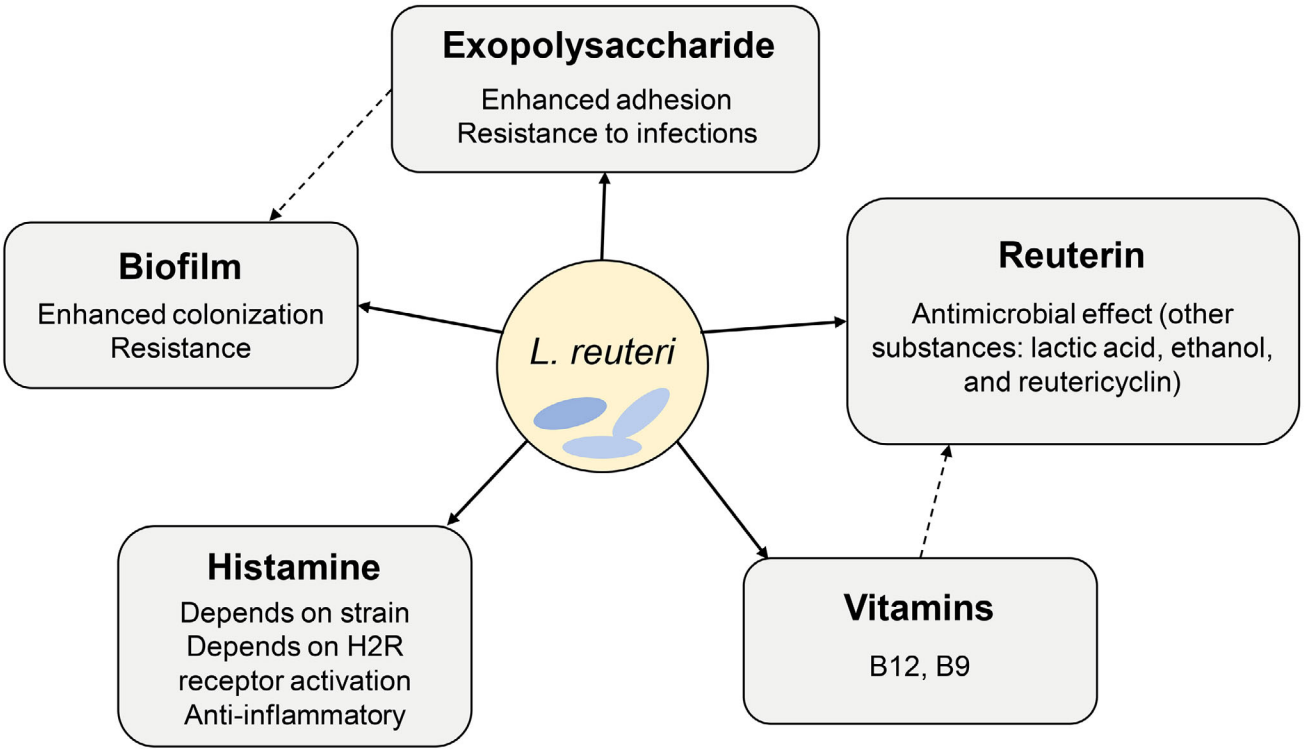
The hospital-acquired infections pose a serious problem, because many hospitalized patients are immunocompromised. In addition, the strains causing nosocomial infections are usually highly resistant to antibiotics. Bacteria of the genus *Klebsiella* are one of the causative agents of various dangerous diseases. These pathogens cause pneumonia, sepsis, urinary inflammation, liver and kidney problems, and their resistance to antibiotics increases from year to year [24]. In addition, it has been shown that bacteria of this genus, when affecting the body, take the form of biofilm and cannot be completely eliminated by the usual doses of "traditional" antibiotics and other antimicrobial drugs [25].

Recently it has been shown that some strains of *Lactobacillus* have a detrimental effect on bacteria of the genus *Klebsiella* [26]. Lactobacilli are contained in the intestines of healthy humans and, therefore, their administration does not induce an immune response. Proteomic analysis of some species of *Lactobacillus* bacteria was performed in the work [26]; it was shown that the studied strains synthesize a number of new enzymes when co-cultured with *Klebsiella*. These new enzymes can be roughly categorized into three main groups: (i) the enzymes hydrolyzing bacterial cell wall; (ii) the enzymes hydrolyzing nucleic acids; and (iii) the enzymes for cell metabolism. Altogether, these enzymes helped *Lactobacillus* to exert a bactericidal effect on the *Klebsiella* biofilms.

This review aims to highlight and analyze structural and metabolic features of *Klebsiella* and *Lactobacillus* (primarily *L. reuteri*) in order to explain potential antibacterial effect of the latter, to suggest the mechanism of this action, and to consider potential application of the complex of synthesized enzymes as an antibacterial agent against *Klebsiella*.

PROBIOTIC PROPERTIES OF *L. reuteri*

There are some basic factors for the strain under consideration to become a potential probiotic: survival in the environment with low pH in the presence of enzymes, ability to be attached to the epithelium for the host–probiotic interactions, and competition with pathogens. *L. reuteri* meets all these requirements. Additional probiotic properties of *L. reuteri*, which contribute to its diverse favorable effects on host health, as well as on disease prevention and/or improvement



Probiotic properties of *L. reuteri*

of condition of the body, should be also considered (figure).

Colonization of the intestine by *L. reuteri* bacteria. Some parts of the GI tract involved in digestion and absorption have very unfavorable conditions for colonization by microorganisms. For example, these include low pH values caused by stomach acids and bile salts in the upper part of the small intestine. Therefore, first of all, it is necessary to survive under such conditions to colonize the GI tract. Many *L. reuteri* strains are resistant to low pH values and bile salts [27, 28]. This resistance is thought to be dependent, at least partially, on the ability of these bacteria to form biofilms [29].

L. reuteri are able to attach to mucin and intestinal epithelium, and some strains can attach to intestinal epithelial cells in a number of vertebrate hosts [23]. A possible mechanism of adhesion is binding of bacterial surface molecules to the mucus layer. The mucus-binding proteins (MUBs) and MUB-like proteins encoded by the *Lactobacillales*-specific clusters of genes of the orthologous proteins serve as mediators of adhesion, or so-called adhesins [30, 31]. Considerable diversity of the MUBs in *L. reuteri* strains and differences in the abundance of MUBs on the cell surface correlate with the mucus-binding ability of these bacteria [32]. The strain-specific role of MUBs in the recognition of mucus elements and/or their ability to stimulate aggregation may explain contribution of MUBs to the ability of *L. reuteri* to bind to the intestine. The factors promoting attachment to the surfaces include numerous large surface proteins [33], MUB A [34], glucosyltransferase A (GtfA), and inulosucrase (Inu) [35], as well as D-alanine ester [36].

Since *L. reuteri* inhabiting GI tract of the host can form biofilms, some attempts were made to study regulation of the *L. reuteri* biofilm formation and its relationship with the attachment of bacteria to the host GIT epithelium. Analysis of the biofilm *in vitro* showed contribution of GtfA and Inu to formation of the *L. reuteri* TMW1.106 biofilm [35]. The *in vivo* biofilm formation of *L. reuteri* strains appears to depend on the host origin. In one study, nine *L. reuteri* strains isolated from different hosts (human, mouse, rat, chicken, and pig) were given to mice without intestinal microflora, and the resulting biofilms were evaluated after 2 days. It turned out that only the strains isolated from rodents were able to form biofilms and to adhere to the anterior gastric epithelium, although populations of the intestinal lumen were comparable among strains of different origin [18]. Another study showed that the specialized transport pathway (SecA2–SecY2 system) is unique in the strains isolated from rodents and pigs [37]. The rodent strain *L. reuteri* 100-23 was used to compare extracellular and cell wall-associated proteins between the wild-type strain and the secA2 mutant. Only one surface protein of *L. reuteri* 70902 was absent in the secA2 mutant. *In vivo* colonization studies showed that absence of *L. reuteri* 70902 resulted

in almost complete elimination of biofilm formation. This fact suggests that *L. reuteri* 70902 and the SecA2–SecY2 system are the key factors regulating *L. reuteri* 100-23 biofilm production in mice lacking these microorganisms [18]. Role of the bfrKRT and cemAKR two-component systems in the formation of *L. reuteri* 100-23 biofilm *in vitro* was also investigated [38]. Deletion of certain genes in the operons was found to enhance adhesion and biofilm formation. However, contribution of the bfrKRT and cemAKR systems to biofilm formation *in vivo* remains to be elucidated. The role of exopolysaccharide (EPS) in colonization was also investigated using *L. reuteri* 100-23. EPS expression was excluded due to mutation of the fructosyltransferase (FTF) gene [39]. Colonization of the FTF mutant in the anterior stomach and the blind gut was significantly impaired compared to the wild-type strain after administration to the mice lacking *Lactobacillus*. This fact indicates that EPS production may enhance colonizing ability of the strain 100-23 in the intestine. Interestingly, *L. reuteri* RC-14 is able to penetrate into the mature *E. coli* biofilm and to become part of it [40]. *L. reuteri* was also administered as a biofilm on a microsphere, and it was shown that such delivery promoted adhesion of *L. reuteri* to the intestinal epithelium and improved its probiotic properties [41, 42].

SYNTHESIS OF METABOLITES IN *L. reuteri* FOR HEALTH RECOVERY

Antimicrobial and immunomodulatory effects of *L. reuteri* strains are related to their metabolic profile. It is worth considering these metabolites and their probiotic effects in more detail.

Reuterin. Most of the *L. reuteri* strains of human and avian origin are capable of producing and secreting the well-known antimicrobial compound reuterin [43-45]. Reuterin is a mixture of different forms of 3-hydroxypropionaldehyde (3-HPA) [46]. It is known that *L. reuteri* can metabolize glycerol with formation of 3-HPA in the coenzyme B12-dependent glycerol-mediated dehydratase reaction [47, 48]. 3-HPA formation has also been demonstrated in several other bacterial species [49]. However, *L. reuteri* is unique with respect to its ability to produce and secrete more 3-HPA than the cell needs from the bioenergetics point of view [50]. Moreover, antimicrobial activity of reuterin seems to depend on spontaneous conversion of 3-HPA into a cytotoxic electrophile, acrolein [51]. Reuterin can inhibit a wide range of microorganisms, mainly Gram-negative microorganisms [52]. Obviously, most of the *Lactobacillus* bacterial species are resistant to reuterin; among them, *L. reuteri* strains are the most resistant [44]. In addition to its antimicrobial action, reuterin can conjugate heterocyclic amines, which also seems to depend on acrolein formation [51]. This fact suggests that acrolein is an important compound in the activity of reuterin.

In addition to reuterin, some other antimicrobial substances such as lactic acid, acetic acid, ethanol, and reutericycline have been identified as products of some *L. reuteri* strains [45]. Presence of these substances indicates that *L. reuteri* are effective against various bacterial infections of the GI tract. These infections include *Helicobacter pylori*, *E. coli*, *Clostridium difficil*e, and *Salmonella* [53, 54]. One of the most striking examples of the effectiveness of *L. reuteri* as a probiotic against infections is using *L. reuteri* to control *H. pylori*. *H. pylori* infection is the major cause of chronic gastritis and peptic ulcer disease, as well as a risk factor for gastric malignancies [55, 56]. The effect of *L. reuteri* on *H. pylori* has been investigated in many studies (Table 1). It has been suggested that *L. reuteri* competes with *H. pylori* and inhibits its binding to glycolipid receptors [57]. Competition reduces bacterial load of *H. pylori* and decreases the associated symptoms [58]. Some studies have shown that *L. reuteri* has a potential to completely eradicate *H. pylori* [59]. It should be noted that *L. reuteri* is well-suited to treat *H. pylori*, because these bacteria eliminate the pathogen without causing common side effects associated with antibiotic therapy [60].

Studies have also been conducted to determine beneficial effects of *L. reuteri* against viruses and fungi. There is evidence of the benefits of using *L. reuteri* against pneumoviruses, circoviruses, rotaviruses, Coxsackie viruses, and papillomaviruses [68-70]. Presumably, *L. reuteri* counteract viral infection by regulating microbiota and secreting metabolites that have antiviral components [71]. In addition, some studies show that *L. reuteri* may also have antifungal properties, because *L. reuteri* stops growth and eventually kill various *Candida* species [72].

Histamine. Some *L. reuteri* strains are able to convert amino acid L-histidine, a food component, into the biogenic amine histamine [45]. The human commensal bacterium *L. reuteri* 6475 was used as a model strain to study formation and role of histamine in *L. reuteri*. Histamine derived from *L. reuteri* 6475 was found to suppress production of tumor necrosis factor (TNF) by the stimulated human monocytes [73]. This suppression depended on activation of the histamine H_2 receptor, increase in the intracellular cAMP and protein kinase A, and inhibition of the MEK/ERK signal transduction cascade. Histamine synthesis and the subsequent suppression of TNF function *in vitro* are regulated by the complete chromosomal histidine decarboxylase (*hdc*) gene cluster containing the *hdcA*, *hdcB*, and *hdcP* genes [73]. It has also been shown that oral administration of *hdc*$^+$ *L. reuteri* can effectively suppress

Table 1. Clinical efficiency of *L. reuteri* against *H. pylori*

Strain	Therapy	Subjects	Result	References
L. reuteri DSM 17648	14 days	adults	reduced pathogenic load on GIT	[61]
L. reuteri DSM 17938	20 days	patients	successful elimination of the pathogen by 93% using the inhibitor tetracycline metronidazole – *L. reuteri* therapy	[62]
	8 weeks	patients	reduced urease activity in the pantoprazole therapy	[63]
L. reuteri ATCC 55730	10 days	sick children	improved symptoms of GIT infection	[64]
	7 days	patients	no improvement in the standard triple therapy	[65]
	4 weeks	patients	considerable reduction of pathogenic load and improved symptoms of dyspepsia	[58]
L. reuteri SD2112	4 weeks	patients	decreased amount of the pathogen and suppression of urease activity	[66]
L. reuteri DSMZ 17648	14 days	patients	reduced pathogenic load	[67]
L. reuteri DSM 17938, ATCC PTA 6475	during therapy	patients	reduced side effects of antibiotic therapy	[60]

intestinal inflammation in the trinitrobenzene sulfoxide (TNBS)-induced murine colitis model [74]. In addition, intraperitoneal injection of the *L. reuteri* 6475 supernatant into the mice previously exposed to TNBS resulted in comparable attenuation of colitis. These results indicate involvement of the *L. reuteri* metabolites, including histamine, in intestinal immunomodulation [75]. Further studies showed that the *rsiR* gene is required for expression of the *hdc* gene cluster in *L. reuteri* 6475 [76]. Inactivation of the *rsiR* gene led to the decrease in TNF inhibition *in vitro* and decrease of the anti-inflammatory function *in vivo*. In addition, both TNF inhibition *in vitro* and anti-colitis effects *in vivo* seem to be regulated by the *folC2* gene [75]. The *folC2* gene knockout resulted in suppression of the *hdc* gene cluster and reduced histamine production. Histamine production by *L. reuteri* is highly strain-dependent, and most studies have been focused on the strains of human origin [44].

Vitamins. There are 13 essential vitamins for humans, which cannot be synthesized in the human body [77]. Like many other *Lactobacillus* species, some *L. reuteri* strains are able to produce different types of vitamins, including vitamins B12 (cobalamin) and B9 (folate). As has been mentioned earlier, B12 is important for reuterin production, because conversion of glycerol to 3-HPA requires the B12-dependent coenzyme. To date, at least 4 strains of *L. reuteri* of different origins have been found to produce B12 [78]. Among them, the best-studied strains are *L. reuteri* CRL1098 and *L. reuteri* JCM1112 [79]. Administration of *L. reuteri* CRL1098 together with the diet deficient in vitamin B12 has been shown to improve pathology in pregnant female B12-deficient mice and in their offspring [80]. This fact indicates that administration of *L. reuteri* could be used for treatment of B12 deficiency. In addition to B12, folate can also be synthesized by some specific strains of *L. reuteri*, including *L. reuteri* 6475 and *L. reuteri* JCM1112 [75].

Exopolysaccharide (EPS). EPS produced by *L. reuteri* is important for biofilm formation and adhesion of *L. reuteri* to epithelial surfaces [29]. In addition, EPS synthesized by *L. reuteri* is able to inhibit adhesion of *E. coli* to pig epithelial cells *in vitro* [81]. More importantly, the EPS-mediated blockage of adhesion also suppresses expression of the genes of pro-inflammatory cytokines induced by *E. coli* infection, including IL-1β and IL-6. Further *in vivo* experiments on piglets showed similar results in that the EPS derived from *L. reuteri* prevented piglet diarrhea in the case of bacterial infection by reducing *E. coli* adhesion [82]. In addition, the EPS from *L. reuteri* was reported to suppress binding of enterotoxigenic *E. coli* to pig erythrocytes [83]. The EPS produced by *L. reuteri* 100-23 from rodents was also shown to induce the Foxp3$^+$ regulatory T cells (Treg) in the spleen [39]. In contrast, the strain

L. reuteri 100-23 with the *ftf* mutation, which blocks EPS production, did not induce splenic Treg cells. This fact suggests that EPS is required for the *L. reuteri*-mediated induction of Treg cells and indicates that the wild-type *L. reuteri* 100-23 can be used to treat Treg deficiency.

ROLE OF *L. reuteri* IN MODULATION OF VARIOUS BODY SYSTEMS

Modulation of the host microbiota by *L. reuteri* strain. Microbiota and immune system interact to maintain tissue homeostasis in the healthy individuals [84]. Many diseases are associated with the gut microbiota disruption [85], whereas restoration of the gut microbiota has been demonstrated to prevent or alleviate certain diseases [86]. *L. reuteri* can affect diversity, composition, and metabolic functions of the intestinal, oral, and vaginal microbiotas. These effects are highly strain-specific [87, 88].

Intestinal microbiota. The studies have shown the modulatory effect of *L. reuteri* on the microbiota of rodents, piglets, and humans. One of the studies was performed to assess oral administration of the human strain *L. reuteri* (DSM17938) to edematous mice with gut microbial dysbiosis as a result of mutation in the *foxp3* gene. The results showed that this *L. reuteri* strain was able to extend life span in the mice and to reduce inflammation in many organs while remodeling the gut microbiota [89]. Changes in the gut microbiota included increase in the phylum *Firmicutes* and in the genera *Lactobacillus* and *Oscilospira*. The disease-reducing effect of *L. reuteri* was determined by the altered gut microbiota, although the community composition was still different from the wild-type littermates. Further studies showed that inosine production by the gut microbiota increased upon the introduction of *L. reuteri*. When interacting with the A_{2A} adenosine receptor, inosine can repair the Th_1/Th_2 cells and associated cytokines. These results suggest that the axis of *L. reuteri* A_{2A} receptor – intestinal microbiota – inosine – adenosine could be a potential therapeutic target for the Treg-deficiency disorders. In addition, oral administration of *L. reuteri* 6475 resulted in a greater diversity of microbiota in both small intestine and ileum as was exemplified by the mice with ovariectomy-induced bone loss [90]. However, the question whether the altered gut microbiota is directly related to the prevention of bone loss needs further investigation. *L. reuteri* C10-2-1 has also been shown to influence the gut microbiota diversity in the rat ileum [91].

Compared to the infants after vaginal delivery, infants after cesarean delivery are characterized by the higher prevalence of enterobacteria and lower content of bifidobacteria in the gut microbiota [88]. Treatment of the infants after cesarean delivery at the age from 2 weeks to 4 months with *L. reuteri* DSM 17938 modulated development of the gut microbiota in a similar manner as in the infants after conventional delivery [88]. Composition of the gut microbiota in the infants after vaginal delivery remained unchanged upon the addition of *L. reuteri*. In another study, treatment of the children with the same strain of *L. reuteri* led to the decrease in anaerobic Gram-negative bacteria and increase in Gram-positive bacteria in the gut microbiota, whereas the abundance of Enterobacteriaceae and Enterococci significantly decreased after the treatment with *L. reuteri* [92]. Differences in the age of infants, duration of treatment, routes of administration and dosage may account for the differences in the results of the two studies.

In the adult humans, *L. reuteri* NCIMB 30242 administered as prolonged-release capsules for 4 weeks was able to increase the *Firmicutes* to *Bacteroidetes* ratio in the healthy individuals [93]. It is known that this strain of *L. reuteri* can activate bile salt hydrolase and thereby increase circulation of bile acids [94]. Upregulation of the circulating bile acid was suggested to be the cause of modulated gut microbiota [94]. The 3-month administration of *L. reuteri* DSM 17938 to the patients with type 2 diabetes mellitus did not significantly alter microbial composition of the intestine, however, the index of insulin sensitivity and the serum levels of secondary bile deoxycholic acid increased [95]. In addition, administration of the strain *L. reuteri* DSM 17938 to the patients with cystic fibrosis (CF) helped with gut microbiota dysbiosis by decreasing the content of *Proteobacteria* and increasing the relative abundance of *Firmicutes* [96]. However, the question whether the modulated gut microbiota improves gastrointestinal health in the CF patients treated with probiotics needs further investigation.

L. reuteri has a strain-specific effect on the gut microbiota of piglets. For example, oral administration of *L. reuteri* ZLR003 can alter both diversity and quantitative composition of the gut microbiota [97]. However, administration of the strain *L. reuteri* I5007 did not affect microbial composition of the colon in piglets [98]. The feed fermented by *L. reuteri* changed abundance of 6 different bacterial taxa, in particular, the family *Enterobacteriacae*, in the weanling piglets [99]. However, the major changes, including increase in *Mitsuokella* and decrease in the family of the phylum *Bacteroidetes*, could only be seen in the case of *L. reuteri* TMW1.656 but not *L. reuteri* LTH5794. TMW1.656 is a reutericyclin-producing strain, while LTH5794 is not, which is indicative of the potential contribution of reutericyclin to modulation of gut microbiota in piglets [99].

Oral microbiota. Bacteria of the phyla *Firmicutes*, *Bacteroidetes*, *Fusobacteria*, *Proteobacteria*, and *Actino-*

Table 2. Induction of Treg cells by *L. reuteri* in various communicable and non-communicable diseases

Health status	Organism	Tissue	Strain	References
Obesity associated with the “western” diet	mouse	MLN	ATCCPTA 6475	[115]
Wound healing	mouse	biopsy	ATCC PTA 6475	[116]
Systemic lupus erythematosus	mouse	kidneys	ATCC PTA 6475	[117]
Necrotizing enterocolitis	mouse	intestine, MLN	DSM 17938	[118]
Wild type	mouse	MLN, spleen	100-23	[39]
Wild type	mouse	spleen	ATCC 23272	[119]
Wild type, IBD, atopic dermatitis	mouse	MLN, colon, ear	ATCC 23272	[120]
IBD	human	peripheral blood	RC-14	[121]

Note. Designations: MLN, mesenteric lymph node; IBD, inflammatory bowel disease.

bacteria are most common in the human oral microbiome [100]. In the randomized controlled trial, 12-week daily consumption of two strains of *L. reuteri*, DSM 17938 and PTA 5289, resulted in the changes in composition of the oral microbiota, although diversity of the bacterial species did not change [100]. The changes disappeared 4 weeks after treatment termination, indicating rapid exchange in the oral microbiome. In another human study, oral treatment with *L. reuteri* decreased the number of periodontal pathogens in the subgingival microbiota, although no clinical impact was observed [101].

Vaginal microbiota. Lactic acid bacteria are predominant in the vaginal bacterial community in healthy women [102]. It has been shown that only 14 days of oral administration of *L. reuteri* RC-14 can restore normal vaginal microflora in the postmenopausal women [103]. Relative abundance of lactic acid bacteria is significantly reduced in the patients with bacterial vaginosis [102]. A total of 4 weeks of oral administration of capsules containing two strains, including *L. reuteri* RC-14, increased relative abundance of lactic acid bacteria. A similar increase in lactobacilli was observed when *L. reuteri* RC-14 was administered vaginally together with the strain of *L. rhamnosus* [104]. However, in pregnant women, the 8-week oral treatment with *L. reuteri* RC-14 did not result in effective restoration of the normal vaginal microbiota [105]. This fact suggests that *L. reuteri* RC-14 cannot work alone.

Role of *L. reuteri* in immunomodulation. *L. reuteri* can increase the levels of free secretory IgA (sIgA) in rats [106]. However, upregulation of sIgA was absent in the vitamin A-deficient rats, suggesting that the function of *L. reuteri* is vitamin A-dependent. In pregnant women, consumption of *L. reuteri* had no effect on the levels of total IgA or sIgA in breast milk [107]. In regard to the effect of *L. reuteri* on induction of the salivary IgA, the results are contradictory. Higher levels of IgA in human saliva in case of using the chewing gum with *L. reuteri* was reported [108]. However, another study has shown that *L. reuteri* have no effect on the concentration of salivary IgA [109]. The difference between the *L. reuteri* strains used in the studies may account for the different results. An important commonality is that the salivary *L. reuteri*-positive individuals have higher levels of the salivary IgA. Further research is needed to answer the question whether *L. reuteri* influences IgA levels by direct regulation of B cells.

It has been shown that *L. reuteri* can induce anti-inflammatory Treg cells, which probably contributes to the favorable effects of *L. reuteri* on a wide range of both communicable and non-communicable diseases (Table 2). The Treg-inducing property of *L. reuteri* is highly strain-dependent. However, anti-inflammatory effects of *L. reuteri* do not always depend on the induction of Treg cells. A good example is the *L. reuteri*-mediated suppression of the Th_1/Th_2 responses in the Treg-deficient mice [89]. Some strains of *L. reuteri* are able to reduce production of many pro-inflammatory cytokines. For example, *L. reuteri* GMNL-263 can reduce the serum levels of MCP-1, TNF, and IL-6 in the mice fed a high-fat diet [110]. Similar effects were observed in the mice treated with heat-killed GMNL-263. However, in some cases, the immunomodulatory effect of *L. reuteri* depends on its metabolites, in as much as the *L. reuteri* BM36301 culture supernatant can decrease TNF production in the human THP-1 myeloid cells [111]. *L. reuteri* tryptophan catabolites are ligands for the aryl hydrocarbon receptor (AhR).

By activating AhR, *L. reuteri* can stimulate local production of IL-22 by the innate lymphoid cells (ILC) [112]. In addition, tryptophan derivatives produced by *L. reuteri* can induce development of the regulatory $CD_4^+CD8\alpha\alpha^+$ double positive intraepithelial lymphocytes in an AhR-dependent manner [113]. Given that AhR is widely expressed, *L. reuteri* and their metabolites can affect many other types of immune cells, in addition to ILCs and T cells [114].

Role of *L. reuteri* in neuromodulation. Gut microbiota plays a role in functioning of the enteric nervous system (ENS) [122]. Subjects with depleted microbiota have an abnormal state of the ENS [122, 123]. Antibiotic treatment decreases the number of neurons in the ENS. This may be due to the decrease in the glial cell line-derived neurotrophic factor (GDNF), which can be restored by TLR_2 stimulation [123]. In addition, animals lacking microbes exhibit defective ENS morphology and excitability, which can be reversed through colonization of the microbiota [124]. *L. reuteri*, in particular, can prevent visceral pain response, mainly by reducing activity of the enteric nerve under the pressure of colorectal distension in mice [125]. Live, heat-killed, gamma-irradiated *L. reuteri*, or even the conditioned medium had similar effects [125]. *L. reuteri* can also produce gamma-aminobutyric acid (GABA), major inhibitory neurotransmitter in the central nervous system [126]. However, *in vivo* biological activity of the produced GABA has not been studied [122]. In addition, *L. reuteri* can increase excitability and number of action potentials in the rat colon sensory neurons [127]. These different effects of *L. reuteri* may be due to the differences in the target neurons [128].

Role of *L. reuteri* in the treatment of intestinal hyperpermeability. Physical, biochemical, and immunological barriers constitute the intestinal barrier function, which is necessary to block entry of the external antigens and toxins [129]. If the intestinal barrier is impaired, permeability may increase, which leads to the state of intestinal hyperpermeability. Various probiotics are known for their ability to enhance the mucosal barrier function, as is exemplified by *L. reuteri* [129]. In the DSS-induced colitis, administration of *L. reuteri* can reduce bacterial translocation from the gastrointestinal tract to the mesenteric lymph nodes (MLNs) [130]. In addition, treatment of the lupus-prone mice with a mixture of *Lactobacillus* species, including *L. reuteri*, resulted in the higher expression of tight junction proteins in the intestinal epithelial cells [117]. Subsequently, translocation of the proinflammatory molecules such as lipopolysaccharides was significantly suppressed, which correlated with attenuation of the disease. In addition to the studies in mice, it has been shown that several *L. reuteri* strains are able to modulate tight junction protein expression and to maintain the intestinal barrier integrity in pigs [91]. Moreover, the ability of *L. reuteri* to reduce intestinal permeability has been observed in humans. In children with atopic dermatitis, when there was a positive correlation between the impaired intestinal barrier function and pathogenesis of the disease [131], treatment with *L. reuteri* DSM 12246 (and *L. rhamnosus* 19070-2) significantly decreased the incidence of gastrointestinal symptoms with the reduced lactulose to mannitol ratio [132], which reflects improvement in the intestinal hyperpermeability [133].

BACTERIA OF THE GENUS *Klebsiella*

Klebsiellae were discovered more than 100 years ago by the German researcher E. Klebs, who discovered these microorganisms and described their pathogenic properties but failed to isolate the bacteria in pure culture [134]. It should be noted that up to date there has been no clarity on the issue of naming these bacteria, as the beginning of Klebsiellae discovery has long been associated with Friedländer [135]: he isolated typical microorganisms from the exudate of the pneumonic focus of a patient who died of pneumonia and described their properties. Therefore, Klebsiella can be found in the literature under the name of “Friedländer’s bacillus” [136, 137].

Klebsiellae are currently combined into the genus *Klebsiella*; they have been assigned to this genus according to all existing classifications of Enterobacteriaceae. Bergey’s Manual of Systematic Bacteriology (1974) [138] describes three species: *K. pneumoniae*, *K. phinoschleromatis*, and *K. oraenae*. To date, the genus *Klebsiella* is represented by twelve species [139]: *K. aerogenes*, *K. africana*, *K. granulomatis*, *K. grimontii*, *K. huaxiensis*, *K. michiganensis*, *K. oxytoca*, *K. pasteurii*, *K. pneumoniae*, *K. quasipneumoniae*, *K. spallanzanii*, and *K. variicola.*

Klebsiella spp. are widespread in nature. They are found in soil, fresh and sea water, flowers, grains, fruits and vegetables, industrial effluents, wood, etc. [140]. Infections of humans and animals by these bacteria are reported everywhere. Representatives of this genus are considered to be causative agents of the diseases of the respiratory tract, genitourinary tract, meninges (membranes of the brain), eyes, joints and spine, various purulent-septic complications, as well as acute gastrointestinal diseases of humans. It has been proposed to consider the acute sepsis-like diseases caused by Klebsiellae as an independent nosological entity: klebsiellosis [137, 141].

Klebsiella are also causative agents of the diseases in animals. Most often, animal diseases are caused by representatives of the species *K. pneumoniae*. Thus, its subspecies *K. pneumoniae*, similar to *E. coli*, being components of the permanent gut microflora, can play

Table 3. Differentiating features of some bacteria of the genus *Klebsiella* [147]

Test or substrate	*K. oxytoca*	*K. planticola*	*K. pneumoniae*			*K. terrigena*
			ozaenae	*pneumoniae*	*rhinoscleromatis*	
Indole production	+	±	–	–	–	–
Reaction with methyl red	+	+	+	± (more often –)	+	±
Voges–Proskauer test	+	+	–	+	–	+
Simmons citrate test	+	+	+	+	–	–
Urea hydrolysis	+	+	–	+	–	–
Malonate utilization	+	+	–	+	+	+
Dulcitol fermentation (A)*	+	± (more often –)	–	±	–	± (more often –)
Lactose fermentation (A)	+	+	±	+	–	+
Mucate fermentation (A)	+	+	± (more often –)	+	–	+
Lactose fermentation (G)**	–	–	+	+	+	–
Growth at 10°C	+	+	–	–	–	+

* Acid production.

** Gas production at 44°C.

the role of an etiologic factor in mastitis, pneumonia, septicemia of cows, pigs, horses, monkeys, and infectious diarrhea of young animals. These pathogenic bacteria have been found in gastrointestinal diseases of calves [142-144]. Various differentiating features of some *Klebsiella* spp. Bacteria are presented in Table 3.

Morphology. The genus *Klebsiella* includes immobile, capsular, Gram-negative, non-spore-forming bacteria with shape of irregular oval rods with their length and thickness varying from 0.6 to 6.0 μm and from 0.3 to 1.5 μm, respectively. They can be found as single cells, paired, less frequently chained. The characteristic feature of *Klebsiella* is the ability to form a capsule. *Klebsiella* were the first capsular microorganisms described among *Enterobacteriaceae*. The capsular variants of *Klebsiella* are usually isolated from human and animal pathological material. However, after cultivation on nutrient media, some strains lose the ability to form a capsule, while other strains, on the contrary, retain it for years. The capsule-less variants can restore the capsule on carbon-containing media. To obtain the pure capsular population, it is recommended [145] to use the technique of capsule selection by passaging on the carbon-containing media (glucose, sucrose), with control of the population purity and degree of dissociation in the obliquely incident light. The capsule can be restored when *Klebsiella* are passaged through the laboratory animals [146]. The capsule width and length can vary from 0.3 to 1.27 μm and from 0.6 to 6 μm, respectively [137]. During multiplication of *Klebsiella*, the capsule does not divide; therefore, several cells may share the same capsule. There are many staining methods for capsule detection. Best results for the negative staining of capsules are obtained by the simple method of staining preparations with ink.

Klebsiella are facultative anaerobes. All *Klebsiella* species grow well on simple nutrient media in a broad temperature range (from 4°C to 43°C); optimal temperature is 35-37°C, pH 7.2. A significant feature of *Klebsiella* is considered to be abundant growth and formation of large, convex, often merging colonies of slimy consistency on solid nutrient media. They often form red and pink slimy colonies with or without metallic glitter on Endo agar; red, pink, or colorless colonies on Ploskirev's agar; red or pink colonies on MacConkey agar; dark blue colonies with metallic glitter on EMS agar and Levin's medium [147].

Klebsiella are able to form smooth and rough colonies:

– Smooth forms (MKO-mucoid, capsular, with the O-antigen; KO-nonmucoid, capsular, with the O-antigen; MO-mucoid acapsular, with the O-antigen; O-nonmucoid, acapsular, with the O-antigen);
– Rough forms (MKR-mucoid, capsular, without the O-antigen; KR-nonmucoid, capsular, without the O-antigen; MR-mucoid, acapsular, without the O-antigen; R-nonmucoid, acapsular, without the O-antigen).

In the liquid media, growth of capsular variants is accompanied by uniform turbidity, slimy sediment, and a film on the broth surface. The acapsular R-forms of the bacteria form a granular precipitate with a clear and undisturbed supernatant. The bacteria can grow on the media with cyanide salts.

Biochemical properties. *Klebsiella* is one of the most enzymatically active members of the family *Enterobacteriaceae* and utilizes many substrates. The major differential feature is that *Klebsiella* utilize citrates as a sole carbon source. The bacteria ferment a large number of carbohydrates with the release of gasses, including lactose, glucose, sucrose, sedonite, inoside, and hydrolyze urea. Proteolytic activity of *Klebsiella* is weak: they produce neither hydrogen sulfide, nor indole, in contrast to *Escherichiae*. The exception is *K. oxytoca*, which forms indole. At the same time, they do not liquefy gelatin, cause gas production in the lactose-bile salt broth at 44°C, and use hydroxylbenzoic acid as a sole carbon source. There is a property specific to *Klebsiella* only: the color reaction with 5-aminosalicylic acid in a nutrient medium [148]. This reaction was positive in all *Klebsiella* species studied by the authors.

Pathogenicity. Epizootiological and epidemiological *Klebsiella* strains, especially of the respiratory origin, are highly virulent in mice, chicken embryos. Pathogenicity factors of the microorganisms are divided into three groups with respect to:

– Interaction between the pathogen and the epithelium, a “gateway for infection”;
– Resistance of microorganisms to humoral and cellular defense factors of a macroorganism;
– Ability to produce toxins and toxic products.

Adhesive properties of *K. pneumoniae* are associated with the presence of fimbrial structures, or cilia, in the bacteria [149, 150]. The presence of fimbriae often correlates with the hemagglutinating ability of bacteria. Different *Klebsiella* strains can synthesize four different types of hemagglutinins [150]. Fimbriae (cilia) are filamentous projections extending from the cytoplasm and located on the cell surface. There could be several hundreds of fimbriae on one bacterial cell [137]. The pathogenicity factor suppressing humoral and cellular host defense factors in *Klebsiella* is a polysaccharide capsule (more than 70 serovars have been identified on the basis of its antigenic composition), which protects them from the complement-binding substances and phagocytosis.

Thermolabile and thermostable toxins have been identified in different *Klebsiella* strains:

– The thermo- and acid-stable toxin, which activates the guanylate cyclase system, is similar in its structure and mechanism of action to the thermostable enterotoxin of *Escherichia*;
– The thermolabile toxin is inactivated at 100-120°C and has a cytotoxic effect promoting penetration of the pathogen into the bloodstream.

Antigenic structure and serological identification. *Klebsiella*, like other representatives of *Enterobacteriaceae*, have capsular K-somatic O- and R-antigens. In addition, some researchers consider mucosal formation of the cell, M-antigen, as an antigenic component in *Klebsiella* [151]. Presence of two distinguishable capsular antigens was demonstrated for the first time in 1915. Serological identification of *Klebsiella* is based primarily on the determination of K-antigens. This is due to the fact that the freshly isolated cultures have a capsule that completely screens bacterial O-antigen. Rough variants are often formed when obtaining the capsule-less forms for O-antigen detection [152, 153]. Currently, more than eighty K-antigens have been studied in *Klebsiella*. With respect to chemical composition, K-antigens are acidic polysaccharides constructed from individual sugars and interconnected hexuronic acids, mainly glucuronic acids, less frequently galacturonic acids [146]. Antigenic properties of the K-antigens are close to those of O-antigens in terms of heat resistance; their agglutinability and agglutinogenicity are impaired only by autoclaving at 120°C for 2.5 h, and their adsorption capacity is impaired by autoclaving at 121°C for the same period of time [137]. O-antigens are composed of a lipopolysaccharide-protein complex. The studies of *Klebsiella* O-antigens pose some challenges associated with the large number of K-antigens compared to O-antigens and capsule thermostability.

Resilience in the environment. When cultivated in a general nutrient medium, *Klebsiella*, in spite of certain resistance, are prone to dissociation and can die rather quickly; however, they are highly persistent in natural environment. *Klebsiella* have been found in desert soils, in the Antarctic Lake water, in timber, and textile effluents, in sugar cane, etc. Such widespread distribution of *Klebsiella* is referred to as an ecological mystery and seems to be due to peculiar biological properties of these microorganisms: presence of the capsule, which probably explains their resistance to many environmental factors. At room temperature,

Klebsiella persist for weeks and months. In dust samples taken at different levels of humidity, they persist for up to 2.5 years [154]. A shorter period of survival has been observed at constant temperature (25°C) and increased moisture content of dust (up to 53-86%). Heating at 65°C causes bacterial death within an hour. The resistance of *Klebsiella* to low temperatures is demonstrated by the fact that they, as the only representative of the family *Enterobacteriaceae*, were found in the Antarctic Lake water. *Klebsiella* strains isolated from the water and from the body of polar explorers with diarrhea could grow at the temperatures from 4°C to 45°C. At the same time, cultural and enzymatic properties of the above-mentioned cultures were equally manifested both at 37°C and 4°C. These features allowed considering *Klebsiella* as facultative psychrophilic bacteria. *Klebsiella* are more resistant than *Escherichiae* to some disinfectants and ultraviolet radiation. These bacteria are sensitive to chloramine, phenol, citral, and other disinfectants. Like other pathogenic enterobacteria, *Klebsiella* strains isolated from sick or dead animals are characterized by multidrug resistance [142, 147]. Some clinical strains of *Klebsiella* are resistant to penicillin, levomycin, tetracycline, erythromycin, carbecillin, and relatively sensitive to some glycoside drugs: gentamicin, thrombamycin, sisomicin, amikacin, neomycin, monomycin, rifampicillin (some strains are resistant to ampicillin) [137, 147]. The bacteria also show low sensitivity to polymyxin B, cephapotin, cephaloridine, and kanamycin. Antibiotic resistance of *Klebsiella* is attributed to the R-plasmid, loss of which could occur within a short period of passaging in broth.

CONCLUSIONS

The present review actually consists of two main parts, which, at first glance, are poorly related to each other. However, from the title it can be understood that the two genera under consideration: Gram-negative *Klebsiella* and Gram-positive *Lactobacillus*, in real life are in close contact with each other in the human body and have completely opposite effects on the latter. The former are very dangerous and harmful bacteria, and recently it has become very important to fight specifically *Klebsiella*, because they are currently one of the most dangerous threats to the human body, especially when the infection occurs with the development of pathogens as biofilms. Apparently, the evolutionary potential for antibiotic resistance in *Klebsiella* is one of the highest among the Gram-negative pathogens. Patients in hospitals, long-term care facilities, and in surgical units are particularly susceptible to such effects. For example, in transplantology, each 25th-30th surgery on average is accompanied by sepsis caused by pathogenic bacteria. Along with the well-known staphylococci (up to 40% of all infections), one of the genera of such dangerous bacteria is the genus *Klebsiella*. These bacteria not only show multiple drug resistance, but also could form biofilms, the state with much higher resistance to all impacts. Currently, there are several approaches to controlling pathogens, including bacteria of the genus *Klebsiella*. The broadest approach is to use combinations of different “classical” antimicrobial agents to enhance antibacterial action [155-159]. However, this approach has serious negative consequences and side effects for the body after therapy, which makes it not very attractive. A rather new and promising approach to controlling *Klebsiella* is the use bacteriophages [160-162]. However, what may be dangerous in this approach is that bacteriophages are in tight natural balance of the human microflora, which means that such therapy may cause a negative response of the immune system and other side-effects. Until recently, lactic acid bacteria have not been considered as a potential antipathogenic agent, but only as a probiotic. Although the beneficial effect of lactic acid bacteria on human body during and after antibiotic therapy, as well as for prevention and improvement of immunity, has been known for a long time, the studies of antipathogenic effect of lactobacilli started only recently [26, 163, 164]. One of the key species exhibiting activity against pathogens is the species *L. reuteri*. Lactobacilli are natural inhabitants of the healthy human microflora and, therefore, are devoid of proven and potential negative side effects of antibiotic and phage therapy. There are practically no studies on this subject in the world, but this area is very promising for the development of new antibacterial drugs based on the representatives of the beneficial intestinal microflora in a healthy person, including *L. reuteri*. The search of new ways to control pathogens, especially those with minimum of negative side effects, is still an important task for the world scientific community; therefore, we hope that this review devoted to the features of two bacterial genera with the opposite effects on human health will help researchers to find out the cause of the antagonistic effect of *L. reuteri* on *Klebsiella* and to use it for the development of antibacterial drugs.

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