Role of *Lactobacillus reuteri* in Human Health and Diseases

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*Lactobacillus reuteri* (*L. reuteri*) is a well-studied probiotic bacterium that can colonize a large number of mammals. In humans, *L. reuteri* is found in different body sites, including the gastrointestinal tract, urinary tract, skin, and breast milk. The abundance of *L. reuteri* varies among different individuals. Several beneficial effects of *L. reuteri* have been noted. First, *L. reuteri* can produce antimicrobial molecules, such as organic acids, ethanol, and reuterin. Due to its antimicrobial activity, *L. reuteri* is able to inhibit the colonization of pathogenic microbes and remodel the commensal microbiota composition in the host. Second, *L. reuteri* can benefit the host immune system. For instance, some *L. reuteri* strains can reduce the production of pro-inflammatory cytokines while promoting regulatory T cell development and function. Third, bearing the ability to strengthen the intestinal barrier, the colonization of *L. reuteri* may decrease the microbial translocation from the gut lumen to the tissues. Microbial translocation across the intestinal epithelium has been hypothesized as an initiator of inflammation. Therefore, inflammatory diseases, including those located in the gut as well as in remote tissues, may be ameliorated by increasing the colonization of *L. reuteri*. Notably, the decrease in the abundance of *L. reuteri* in humans in the past decades is correlated with an increase in the incidences of inflammatory diseases over the same period of time. Direct supplementation or prebiotic modulation of *L. reuteri* may be an attractive preventive and/or therapeutic avenue against inflammatory diseases.

**Keywords:** *Lactobacillus reuteri*, probiotic, microbiota, immune system, inflammatory diseases

**INTRODUCTION**

Probiotics are defined as “live microorganisms which, when administered in adequate amounts, confer a health benefit on the host” by the World Health Organization. While the idea to use probiotics for health benefits is not new, the interest has significantly increased in recent years (Islam, 2016). This may be due, in part, to the increase in antibiotic resistance particularly in the treatment of diseases in the gastrointestinal (GI) system, as well as an increasing desire by the public for natural health promotants. Those probiotic microorganisms that have been shown to have beneficial properties include *Lactobacillus* spp., *Bifidobacterium* spp., *Saccharomyces boulardii*, *Propionibacterium* spp., *Streptococcus* spp., *Bacillus* spp., *Enterococcus* spp., and some specific strains of *Escherichia coli* (Kechagia et al., 2013).

There are certain criteria that a probiotic must have to be considered efficacious. These include the capacity to survive in the GI tract, a high resistance to gastric acids, the lack of any transferable antibiotic resistance genes, and the capacity to exert clear benefits in the
host (Montalban-Arques et al., 2015). Probiotics promote a healthy body through diverse mechanisms. A widespread generalization describing common mechanisms among studied probiotic genera includes colonizing resistance, producing acid, and short chain fatty acid (SCFA), regulating intestinal transit, normalizing perturbed microbiota, increasing enterocyte turnover, and competitive exclusion of pathogens (Hill et al., 2014). Though not widely observed, there are a lot of effects among specific probiotic species, some being strain specific. For instance, some probiotic strains can improve host food digestion by metabolizing bile salt or complementing the functions of missing digestive enzymes (Amara and Shibl, 2015; Shi et al., 2016).

Lactobacillus spp. are one of the most widely used probiotics and can be found in a large variety of food products throughout the world (Giraffa et al., 2010). The genus Lactobacillus comprises a large heterogeneous group of Gram-positive, nonsporulating, facultative anaerobic bacteria which include L. acidophilus, L. rhamnosus, L. bulgaricus, L. casei, and L. reuteri. This genus plays a very important role in food fermentation and can also be found in the GI system of humans and animals in variable amounts depending on the species, age of the host, or location within the gut (Duar et al., 2017).

Animal studies and preclinical results have shown that Lactobacilli may help in the prevention and treatment of numerous GI tract disorders. Among these disorders are enteric infections, antibiotic-associated diarrhea, necrotizing enterocolitis in preterm neonates, inflammatory bowel disease, colorectal cancer, and irritable bowel syndrome (Lebeer et al., 2008). Although the GI tract is the site where Lactobacilli are believed to show the most benefits, probiotic applications of some Lactobacillus strains at other sites of the body have been reported. These include the prevention and treatment of urogenital diseases and bacterial vaginosis in women, atopic disease, food hypersensitivity, and the prevention of dental caries (Lebeer et al., 2008).

One species of Lactobacillus, L. reuteri has multiple beneficial effects on host health such as prevention and/or amelioration of diverse disorders. L. reuteri was first isolated in 1962. It has been characterized as heterofermentative species that grows in oxygen-limited atmospheres and colonizes the GI tract of humans and animals (Kandler et al., 1980). The fact that it normally colonizes the GI tract may be the reason it confers great probiotic properties. This organism can withstand a wide variety of pH environments, employs multiple mechanisms that allow it to successfully inhibit pathogenic microorganisms, and has been shown to secrete antimicrobial intermediaries (Jacobsen et al., 1999; Valeur et al., 2004).

L. reuteri has been shown to be one of the truly indigenous bacteria of the human GI tract (Sinkiewicz, 2010). It naturally colonizes a wide range of vertebrates, including pigs, rodents, and chickens. In fact, it has gone through long-term evolution to diversify into host-adapted lineages (Oh et al., 2010; Walter et al., 2011). This organism is most typically found in the proximal digestive tract of the host (Frese et al., 2013). Several studies have assessed the safety of this organism in adults, children, infants, and even in an HIV-infected population (Wolf et al., 1998; Valeur et al., 2004; Weizman and Alsheikh, 2006; Mangalat et al., 2012; Jones et al., 2012a,c; Hoy-Schulz et al., 2016). The results showed that a dose as high as $2.9 \times 10^9$ colony-forming units (cfu)/day was still well tolerated, safe, and efficacious in humans. There have also been numerous articles enumerating the benefits of L. reuteri as a probiotic. These benefits include promoting health, reducing infections, improving feed tolerance, enhancing the absorption of nutrients, minerals, and vitamins, modulating host immune responses, promoting gut mucosal integrity, and reducing bacterial translocation (Tubelius et al., 2005; McFall-Ngai, 2007; Indrio et al., 2008; Spinler et al., 2008; Hou et al., 2015). In the current review, we will focus on the particular probiotic, L. reuteri, and discuss its beneficial functions in promoting health and preventing infections and diverse diseases.

PROBIOTIC PROPERTIES OF L. reuteri

There are some prerequisites for becoming potential probiotics: to survive in low pH and enzyme-enriched environments, to adhere to epithelium for host-probiotic interaction, competition with pathogenic microorganisms, and most importantly, safety. L. reuteri meets all of these requirements. Here, additional probiotic properties of L. reuteri are discussed that contribute to its diverse beneficial effects on host health and disease prevention and/or amelioration (Figure 1).

Gut Colonization of L. reuteri

Built for digestion and absorption, some sites of the GI system have developed to be harsh for microorganism colonization. Examples of this can be seen in the low pH conditions caused by gastric acids and bile salts in upper small intestine. Thus, the very first step of colonizing the GI tract is to survive in such environments. Multiple L. reuteri stains are resistant to low pH and bile salts (Seo et al., 2010; Krumbeck et al., 2016). This resistance is believed to be at least partially dependent on its ability to form biofilms (Salas-Jara et al., 2016).

L. reuteri is capable of attaching to mucin and intestinal epithelia, and some strains can adhere to gut epithelial cells in a range of vertebrate hosts (Li et al., 2008; Hou et al., 2014, 2015). A possible mechanism for adherence is the binding of bacterial surface molecules to the mucus layer. Mucus-binding proteins (MUBs) and MUB-like proteins, encoded by Lactobacillales-specific clusters of orthologous protein coding genes, serve as adherence mediators, or so-called adhesins (Roos and Jonsson, 2002; Kleerebezem et al., 2010; Gunning et al., 2016). The considerable diversity of MUBs among L. reuteri strains and the variation in the abundance of cell-surface MUBs significantly correlates with their mucus binding ability (Mackenzie et al., 2010). The strain-specific role of MUBs in recognizing mucus elements and/or their capability of promoting aggregation can explain the contribution of MUBs on the adherence of L. reuteri. Factors that mediate the attachment to the surfaces include multiple large surface proteins (Walter et al., 2005; Wang et al., 2008; Frese et al., 2011), MUB A (Jensen et al., 2014), glucosyltransferase A (GtfA) and inulosucrase (Inu) (Walter et al., 2008), and D-alanyl ester (Walter et al., 2007).
As *L. reuteri* that has colonized to the host GI tract can form biofilms, efforts have been made to study the regulation of *L. reuteri* biofilm secretion and its association with the adherence of bacteria to host GI epithelium. By doing *in vitro* biofilm assay, Water, J. et al. uncovered the contribution of GtfA and Inu in the biofilm formation of *L. reuteri* TMW1.106 (Walter et al., 2008). The *in vivo* biofilm formation of *L. reuteri* strains seems to be dependent on the host origin of the strains. In one study, nine *L. reuteri* strains isolated from different hosts (human, mouse, rat, chicken, and pig) were given to germ-free mice and the biofilms were evaluated after 2 days. Interestingly, only rodent strains were able to form biofilms and adhere to the forestomach epithelium, although the luminal populations were comparable among strains of different origins (Frese et al., 2013). Another study by the same authors showed that a specialized transport pathway (the SecA2-SecY2 system) was unique in the rodent and porcine strains. In one study, nine *L. reuteri* strains isolated from different hosts (human, mouse, rat, chicken, and pig) were given to germ-free mice and the biofilms were evaluated after 2 days. Interestingly, only rodent strains were able to form biofilms and adhere to the forestomach epithelium, although the luminal populations were comparable among strains of different origins (Frese et al., 2013). Another study by the same authors showed that a specialized transport pathway (the SecA2-SecY2 system) was unique in the rodent and porcine strains. By using a rodent strain *L. reuteri* 100-23, they compared extracellular and cell wall-associated proteins between the wild-type strain and the secA2 mutant. Only one surface protein, *L. reuteri* 70902, was absent in the secA2 mutant. *In vivo* colonization studies showed that the absence of *L. reuteri* 70902 leads to almost completely eliminated biofilm formation. This strongly suggests that *L. reuteri* 70902 and the SecA2-SecY2 system are key factors regulating biofilm production from *L. reuteri* 100-23 in germ-free mice (Frese et al., 2013). Another group investigated the role of two-component systems bfrKRT and cemAKR in *in vitro* biofilm formation of *L. reuteri* 100-23 (Su and Ganzle, 2014). They found the deletion of certain genes in the operons enhanced the adherence and biofilm formation. However, the contribution of the bfrKRT and cemAKR to *in vivo* biofilm formation remains to be elucidated. The role of exopolysaccharide (EPS) in assisting colonization was also examined with *L. reuteri* 100-23. The production of EPS was eliminated due to a mutation of the fructosyl transferase (ff) gene (Sims et al., 2011). After administration to *Lactobacillus*-free mice, compared to the wild-type strain, the colonization of the ffr mutant in the forestomach and cecum was largely impaired. This indicates EPS production can enhance the colonizing ability of strain 100-23 in the gut. Interestingly, *L. reuteri* RC-14 has been demonstrated to be able to penetrate mature *E. coli* biofilm and become part of it (McMillan et al., 2011). Recently, *L. reuteri* was delivered as a biofilm on microsphere and such delivery was found to promote the adherence of *L. reuteri* to intestinal epithelium and enhance its probiotic property (Olson et al., 2016; Navarro et al., 2017).

**Production of Metabolites With Health-Promoting Effect**

The antimicrobial and immunomodulatory effects of *L. reuteri* strains are linked to their metabolite production profile. Here, we discuss a few well-studied metabolites with regard to the probiotic potential of *L. reuteri*.

**Reuterin**

Most *L. reuteri* strains of human and poultry lineage are able to produce and excrete reuterin, a well-known antimicrobial compound (Talarico et al., 1988; Talarico and Dobrogosz, 1989; Cadieux et al., 2008; Jones and Versalovic, 2009;
Mishra et al., 2012; Greifova et al., 2017). Reuterin is a mixture of different forms of 3-hydroxypropionaldehyde (3-HPA) (Talarico and Dobrogosz, 1989). It is known that L. reuteri can metabolize glycerol to generate 3-HPA via a coenzyme B12-dependent, glycerol dehydratase-mediated reaction (Talarico and Dobrogosz, 1990; Chen and Chen, 2013). The production of 3-HPA has also been demonstrated in a few other bacterial species (Zhu et al., 2002; Raynaud et al., 2003; Yang et al., 2007). However, L. reuteri is unique in its ability to produce and secrete 3-HPA in a manner more than its bioenergetics requirement (Stevens et al., 2011). Moreover, the antimicrobial activity of reuterin seems to rely on the spontaneous conversion of 3-HPA to acrolein, a cytotoxic electrophile (Stevens and Maier, 2008; Engels et al., 2016). Reuterin can inhibit a wide range of microorganisms, mainly Gram-negative bacteria (Cleusix et al., 2007). Not surprisingly, most Lactobacillus species are resistant to reuterin, among which L. reuteri strains exert the most resistance (Jones and Versalovic, 2009; Mishra et al., 2012). In addition to its antimicrobial property, reuterin is able to conjugate heterocyclic amines, which also seems to be dependent on the formation of acrolein (Engels et al., 2016). This suggests acrolein is an essential compound in the activity of reuterin.

Apart from reuterin, several other antimicrobial substances, including lactic acid, acetic acid, ethanol, and reutericyclin, have been determined as products of some L. reuteri strains (Gänzle and Vogel, 2003; Burge et al., 2015; Gopi et al., 2015; Yang Y. et al., 2015; Greifova et al., 2017). With the synthesis of these substances, L. reuteri has been shown to be effective against a variety of GI bacterial infections. These infections include Helicobacter pylori, E. coli, Clostridium difficile, and Salmonella (Reid and Burton, 2002; Cherian et al., 2015; Abhisintha et al., 2017; Genis et al., 2017). One of the more notable illustrations of the efficacy of L. reuteri as a probiotic against infections is the use of L. reuteri to treat H. pylori. H. pylori infection is a major cause of chronic gastritis and peptic ulcers, as well as a risk factor for gastric malignancies (Franceschi et al., 2007; Lesbros-Pantoflickova et al., 2007; Park et al., 2007). The use of L. reuteri against H. pylori has been explored in many studies (Table 1). It has been suggested that L. reuteri works by competing with H. pylori and inhibiting its binding to glycolipid receptors (Mukai et al., 2002). The competition reduces the bacterial load of H. pylori and decreases the related symptoms (Lionetti et al., 2006; Francavilla et al., 2008). Some studies have shown that L. reuteri has the potential to completely eradicate H. pylori from the intestine (Ojetti et al., 2012). Importantly, L. reuteri is advantageous in the treatment of H. pylori as the supplementation eradicates the pathogen without causing the common side effects associated with antibiotic therapies (Francavilla et al., 2014).

A considerable amount of research has been done to determine the beneficial effects of L. reuteri against viruses and/or fungi. There is evidence showing the benefit of L. reuteri against pneumoviruses, circoviruses, rotaviruses, coxsackieviruses, and papillomaviruses (Shornikova et al., 1997a, b; Freidis et al., 2012; Ang et al., 2016; Brenner et al., 2016; Piyathilake et al., 2016; Karafíva et al., 2017). It has been suggested that L. reuteri ameliorates viral infection by regulating the microbiota and secreting metabolites that have antiviral components (Ang et al., 2016). Furthermore, some studies suggest that L. reuteri may have antifungal properties as well, where L. reuteri antagonizes, stops the growth of, and eventually kills various species of Candida (Jorgensen et al., 2017).

Histamine
A few strains of L. reuteri are able to convert the amino acid L-histidine, a dietary component, to the biogenic amine histamine (Díaz et al., 2016; Greifova et al., 2017). A human commensal bacterium, L. reuteri 6475 was used as the model strain for studying histamine in L. reuteri. J. Versalovic’s group reported that L. reuteri 6475-derived histamine suppressed tumor necrosis factor (TNF) production from stimulated human monocytes (Thomas et al., 2012). This suppression was dependent on the activation of histamine H2 receptor, increased intracellular cAMP and protein kinase A, and the inhibition of MEK/ERK signaling. The production of histamine and subsequent in vitro TNF-suppressing function are regulated by a complete chromosomal histidine decarboxylase (hdc) gene cluster, which contains hdcA, hdcB, and hdcP (Rossi et al., 2011; Thomas et al., 2012). The same group of researchers also found that oral administration of hdc- L. reuteri could effectively suppress intestinal inflammation in a trinitrobenzene sulfonic acid (TNBS)-induced mouse colitis model (Gao et al., 2015). Moreover, intraperitoneal injection of L. reuteri 6475 culture supernatant to TNBS-treated mice resulted in similar colitis attenuation. These results strongly indicate the involvement of L. reuteri metabolites, including histamine, in intestinal immunomodulation (Thomas et al., 2016). Further investigations showed that a gene called rsiR was necessary for the expression of hdc gene cluster in L. reuteri 6475 (Hemarajata et al., 2013). Inactivation of rsiR gene led to reduced TNF inhibition in vitro and diminished anti-inflammatory function in vivo. Additionally, both the in vitro TNF suppression and the in vivo anti-colitis effects appear to be regulated by a gene named folC2 (Thomas et al., 2016). Inactivation of folC2 gene resulted in suppression of the hdc gene cluster and diminished histamine production. Notably, histamine production by L. reuteri is highly strain-dependent, and most studies have been focused on strains of human origin (Mishra et al., 2012).

Vitamins
There are 13 essential vitamins for humans due to the inability of the human body to synthesize them (Linares et al., 2017). Like many other Lactobacillus spp., several L. reuteri strains are able to produce different types of vitamins, including vitamin B12 (cobalamin) and B9 (folate). As mentioned earlier, B12 is vital in reuterin production because the reduction of glycerol to 3-HPA requires a B12-dependent coenzyme. Up to now, at least 4 L. reuteri strains with various origins have been found to produce B12 (Taranto et al., 2003; Santos et al., 2008b; Sriramulu et al., 2008; Gu et al., 2015). Among these strains, L. reuteri CRL1098 and L. reuteri JCM1112 are the most studied (Morita et al., 2008; Santos et al., 2008a, 2011). In one study, the administration of L. reuteri CRL1098 together with a diet lacking vitamin B12 was shown to ameliorate pathologies in B12-deficient pregnant
female mice and their offspring (Molina et al., 2009). This clearly points to the potential application of L. reuteri in treating B12 deficiency. In addition to B12, folate can also be synthesized by some specific L. reuteri strains, including L. reuteri 6475 and L. reuteri JCM1112 (Santos et al., 2008b; Thomas et al., 2016).

**Exopolysaccharide (EPS)**

The EPS produced by L. reuteri is important for biofilm formation and adherence of L. reuteri to epithelial surfaces (Salas-Jara et al., 2016). In addition, EPS synthesized by L. reuteri is able to inhibit E. coli adhesion to porcine epithelial cells in vitro (Ksonzekova et al., 2016). More importantly, EPS-mediated blocking of adhesion also suppresses gene expression of pro-inflammatory cytokines that are induced by E. coli infection, including IL-1β and IL-6. Further in vivo experiments in piglets showed similar results in that EPS originated from L. reuteri prevented piglet diarrhea in bacterial infection by reducing the adhesion of E. coli (Chen et al., 2014). In addition, EPS of L. reuteri origin has been reported to suppress the binding of enterotoxigenic E. coli to porcine erythrocytes (Wang et al., 2010). EPS produced by rodent L. reuteri 100-23 was also demonstrated to induce Foxp3+ regulatory T (Treg) cells in the spleen (Sims et al., 2011). In contrast, an L. reuteri 100-23 strain with the jff mutation that eliminates EPS production from L. reuteri did not induce splenic Treg cells. This suggests that EPS is required for the L. reuteri-mediated induction of Treg cells and indicates the potential of using wild-type L. reuteri 100-23 to treat Treg deficiency.

**L. reuteri-Mediated Modulation of Host Microbiota**

Emerging evidence suggests that the host microbiota and immune system interact to maintain tissue homeostasis in healthy individuals (Kamada et al., 2013; Bene et al., 2017). Many diseases have been associated with perturbation of the microbiota (Mu et al., 2015), whereas restoration of the microbiota has been demonstrated to prevent or ameliorate several diseases (Scott et al., 2015). L. reuteri is able to influence the diversity, composition and metabolic function of the gut, oral, and vaginal microbiotas. These effects are largely strain-specific (Yang Y. et al., 2015; García Rodenas et al., 2016; Galley et al., 2017; Su et al., 2017).

**Gut Microbiota**

Studies have shown the modulatory effects of L. reuteri on the microbiotas of rodents, piglets, and humans. One study assessed oral administration of a human-origin L. reuteri strain (DSM17938) to scurfy mice, which have gut microbial dysbiosis due to the foxp3 gene mutation. The results indicated that this strain of L. reuteri was able to prolong the lifespan of the mice and reduce multi-organ inflammation while remodeling the gut microbiota (He et al., 2017). Changes of gut microbiota included increases in the phylum *Firmicutes* and the genera *Lactobacillus* and *Oscilospira*. Notably, the disease-ameliorating effect of L. reuteri was attributed to the remodeled gut microbiota, though the community composition was still distinct from wild-type littermates. Further investigation showed that inosine production was enhanced by the gut microbiota upon L. reuteri administration. Through adenosine A₂A receptor engagement, inosine can reduce Th1/Th2 cells and their associated cytokines. These results suggested that the L. reuteri – gut microbiota – inosine – adenosine A₂A receptor axis serves as a potential therapeutic model for Treg-deficient disorders. Moreover, oral L. reuteri 6475 treatment led to a higher diversity of microbiota in both jejunum and ileum in an ovariectomy-induced bone loss mouse model (Britton et al., 2014). Specifically, there were more abundant *Clostridiales* but less *Bacteroidales*. However, whether or not the changed gut microbiota was directly associated with the prevention of bone loss requires further investigation. Furthermore, L. reuteri C10-2-1 has been shown to modulate the diversity of gut microbiota in the ileum of rats (Wang P. et al., 2016).

Compared to vaginally delivered infants, Cesarean (C)-section delivered infants display a higher abundance of *Enterobacter* but less *Bifidobacterium* in their gut microbiota (García Rodenas et al., 2016; Nagpal et al., 2016). In one study, treating C-section

**TABLE 1 | Clinical efficacies of L. reuteri against H. pylori.**

| Strain          | Treatment | Subjects          | Result                                                                 | Citation          |
|-----------------|-----------|-------------------|----------------------------------------------------------------------|-------------------|
| DSM 17648       | 14 days   | Adults            | Decrease in pathogen load in the stomach                             | Hołz et al., 2015 |
| DSM 17938       | 20 days   | Patients          | 93% successful eradication of the pathogen with inhibitor-tetracycline-metronidazole – L. reuteri therapy | Dore et al., 2016 |
| ATCC 55730      | 10 days   | Infected children | Improvement of GI symptoms                                           | Lionetti et al., 2006 |
| –               | 7 days    | Patients          | No improvement of the standard triple therapy                        | Scaccianocie et al., 2008 |
| ATCC 55730      | 4 weeks   | Patients          | Significant decrease of pathogen load and improvement of dyspeptic symptoms | Francavilla et al., 2008 |
| SD2112          | 4 weeks   | Patients          | Decrease of pathogen density and suppression of urease activity      | Imeh et al., 2007  |
| DSMZ 17648      | 14 days   | Patients          | Decrease in pathogen load                                            | Mehling and Busjahn, 2013 |
| DSM 17938, ATCC PTA 6475 | During therapy | Patients | Reduction of antibiotic-associated side effects in eradication therapy | Francavilla et al., 2014 |
| DSM 17938       | 8 weeks   | Patients          | Decrease of urease activity in pantoprazole therapy                  | Dore et al., 2014  |
with L. reuteri DSM 17938 from 2 weeks to 4 months of age modulated the development of gut microbiota toward the community pattern found in vaginally delivered infants (Garcia Rodenas et al., 2016). The gut microbiota structure of vaginally born infants remained unaltered upon L. reuteri supplementation. In another study, treating infants with the same L. reuteri strain resulted in decreased anaerobic Gram-negative and increased Gram-positive bacterial counts in gut microbiota, whereas the abundances of Enterobacteriaceae and Enterococci were lowered by L. reuteri treatment (Savino et al., 2015b). The differences in infant age, duration of treatment, route of administration, and dosage may explain the differences in results from the two studies.

For human adults, L. reuteri NCIMB 30242 administered as delayed release capsules for 4 weeks was able to increase the ratio of Firmicutes to Bacteroidetes in healthy individuals (Martoni et al., 2015). This strain of L. reuteri is known to be able to activate bile salt hydrolase and its effect in increasing circulating bile acid has been reported (Jones et al., 2012b). The upregulation of circulating bile acid has been proposed as a reason for the modulated gut microbiota (Jones et al., 2012b). In type 2 diabetes patients, although 3 months of L. reuteri DSM 17938 supplementation did not significantly change the gut microbial structure, the disease outcome of L. reuteri treatment was highly correlated with the baseline gut microbiota structure of individuals (Mobini et al., 2017). Furthermore, the administration of L. reuteri DSM 17938 in cystic fibrosis (CF) patients rescued gut microbiota dysbiosis by reducing Proteobacteria while also enhancing the relative abundance of Firmicutes (del Campo et al., 2014). However, whether or not the modulated gut microbiota contributed to improved GI health in probiotic-treated CF patients needs to be explored further.

L. reuteri influences the gut microbial community in piglets in a strain-specific manner. For instance, oral L. reuteri ZLR003 administration was able to change both the diversity and the composition of the gut microbiota (Zhang et al., 2016). However, treatment with the IS007 strain did not affect colonic microbial structure in piglets (Liu H. et al., 2017). In another study, fodder fermented with L. reuteri changed the abundances of 6 different bacterial taxa, particularly the family Enterobacteriaceae, in weanling pigs (Yang Y. et al., 2015). However, the major alterations including increased Mitsuokella and decreased a family under phylum Bacteroidetes could only be seen with L. reuteri TMW1.656 rather than L. reuteri LTH5794. TMW1.656 is a reutericyclin-producing strain while LTH5794 is not, suggesting the possible contribution of reutericyclin in modulating gut microbiota in piglets (Yang Y. et al., 2015).

**Oral Microbiota**

The phyla Firmicutes, Bacteroidetes, Fusobacteria, Proteobacteria, and Actinobacteria are most abundant in the human oral microbiome (Romani Vestman et al., 2015). In a randomized controlled trial, 12 weeks of daily consumption of two L. reuteri strains – DSM 17938 and PTA 5289 led to a shift in oral microbiota composition, though the bacterial species richness was not altered (Romani Vestman et al., 2015). The alterations disappeared 4 weeks after the treatments were terminated, suggesting the fast turnover of the oral microbiome. In another human study, oral L. reuteri treatment reduced the amount of periodontal pathogens in the subgingival microbiota, though no clinical impact was seen (Iniesta et al., 2012).

**Vaginal Microbiota**

Lactobacilli dominate the vaginal bacterial community in healthy women (Macklaim et al., 2015). One study showed that only 14 days of oral L. reuteri RC-14 administration could restore the normal vaginal flora in postmenopausal women (Petricevic et al., 2008). Interestingly, the relative abundance of Lactobacilli is largely decreased in bacterial vaginosis patients (Macklaim et al., 2015). A total of 4 weeks of oral capsule consumption of two Lactobacilli strains including L. reuteri RC-14 increased the relative abundance of Lactobacilli. A similar increase of Lactobacilli was seen when L. reuteri RC-14 was administered vaginally together with a rhamnosus strain (Bisanz et al., 2014). However, in pregnant women, 8 weeks of oral L. reuteri RC-14 treatment did not efficiently restore the normal vaginal microbiota (Gille et al., 2016). This suggests that L. reuteri RC-14 may not be able to act alone.

**Role of L. reuteri in Immunomodulation**

Lactobacillus reuteri is able to increase free secretory IgA (sIgA) levels in rats (Wang P. et al., 2016). However, the upregulation of sIgA was eliminated in vitamin A-deficient rats, suggesting that L. reuteri functions in a vitamin A-dependent manner. In pregnant women, the intake of L. reuteri did not alter the levels of total IgA or sIgA in breast milk (Bottcher et al., 2008). When it comes to the effect of L. reuteri in inducing salivary IgA, the results are controversial. Increased salivary IgA levels were reported in humans’ chewing gum containing L. reuteri (Ericson et al., 2013). However, other studies showed that L. reuteri did not affect IgA concentration in saliva (Garofoli et al., 2014; Jorgensen et al., 2016; Braathen et al., 2017). The difference in the strains of L. reuteri used in the studies may explain the difference in results. Notably, an important commonality is that salivary L. reuteri-positive individuals have higher salivary IgA levels. Whether L. reuteri affects IgA levels by directly regulating B cells requires further investigations.

Many studies have shown that L. reuteri can induce anti-inflammatory Treg cells, which likely contributes to the beneficial effects of L. reuteri in a wide range of diseased and non-diseased conditions (Table 2). The Treg-inducing property of L. reuteri is largely strain-dependent. However, the anti-inflammatory effect of L. reuteri does not always rely on the induction of Treg cells. A good example is L. reuteri-mediated suppression of Th1/Th2 responses in Treg-deficient mice (He et al., 2017). Certain L. reuteri strains are able to reduce the production of many pro-inflammatory cytokines. For example, L. reuteri GMNL-263 can reduce serum MCP-1, TNF, and IL-6 levels in mice fed with high fat diet (Hsieh et al., 2016). Similar effects were observed in mice treated with heat-killed
GMNL-263. However, in some cases, the immunomodulatory effects of *L. reuteri* appear to rely on its metabolites, as the culture supernatant of *L. reuteri* BM36301 could reduce TNF production from human myeloid THP-1 cells (Lee et al., 2016). Interestingly, tryptphan catabolites of *L. reuteri* have been recognized as ligands for aryl hydrocarbon receptor (AhR). Through activating AhR, *L. reuteri* can promote local IL-22 production from innate lymphoid cells (ILCs) (Zelante et al., 2013). In addition, the derivatives of tryptophan generated by *L. reuteri* can induce the development of regulatory CD4+CD25+ double-positive intraepithelial lymphocytes in an AhR-dependent manner (Cervantes-Barragan et al., 2017). Considering that AhR is ubiquitously expressed, *L. reuteri* and its metabolites may be able to influence many more types of immune cells beyond ILCs and T cells (Nguyen et al., 2013).

**Neuromodulatory Capability of *L. reuteri***

The intestinal microbiota plays a role in the functions of the enteric nervous system (ENS) (Yoo and Mazmanian, 2017). Subjects with microbiota depletion exhibit an abnormal ENS state (Anitha et al., 2012; Brun et al., 2013, 2015; Yoo and Mazmanian, 2017). Antibiotic treatment reduces the number of neurons in the ENS. This may be related to the decrease in Glial cell line-derived neurotrophic factor (GDNF), which can be restored by TLR2 stimulation (Brun et al., 2013). Moreover, germ-free animals show defective ENS morphology and excitability, which can be reversed by microbiota colonization (McVey Neufeld et al., 2010; Collins et al., 2014). *L. reuteri*, specifically, can prevent visceral pain response mainly by reducing the enteric nerve activity during the colorectal distension pressure in mice (Kamiya et al., 2006; Ma et al., 2009). Interestingly, live, heat-killed, gamma-irradiated *L. reuteri*, or even the conditioned media all had a similar effect (Kamiya et al., 2006). *L. reuteri* can also produce gamma-aminobutyric acid (GABA), the major inhibitory neurotransmitter in the central nervous system (Su et al., 2011; Barrett et al., 2012; Pallin et al., 2016). However, the *in vivo* bioactivity of the produced GABA has not been addressed (Yoo and Mazmanian, 2017). Furthermore, *L. reuteri* can increase the excitability and the number of action potentials in rat colonic sensory neurons (Kunze et al., 2009). These distinct effects of *L. reuteri* may be due to the difference in target neurons (Lai et al., 2017).

| Condition | Tissue | Strain | Citation |
|-----------|--------|--------|----------|
| Western-diet-associated obesity | MLN | ATCC PTA 6475 | Poutahidis et al., 2013b |
| Wound healing | Biopsy | ATCC PTA 6475 | Poutahidis et al., 2013a |
| Systemic lupus erythematosus | Kidney | ATCC PTA 6475 | Mu et al., 2017c |
| Necrotizing enterocolitis | Intestine, MLN | DSM 17938 | Liu et al., 2013, 2014 |
| Wild-type | MLN, Spleen | ATCC 23272 | Livingston et al., 2010; Sims et al., 2011 |
| Wild-type | Spleen | – | Karimi et al., 2009 |
| Wild-type, IBD, atopic dermatitis | MLN, Colon, Ear | – | Abediankenari and Ghasemi, 2009 |
| IBD | Peripheral blood | RC-14 | Lorea Baroja et al., 2007 |

**Role of *L. reuteri* in Reversing the Leaky Gut**

Physical, biochemical, and immunological barriers comprise the gut barrier function, which is required to block the entry of exterior antigens and toxins (Mu et al., 2017a). If any abnormalities occur in the intestinal barrier, the permeability may increase resulting in a leaky gut. Various probiotics are known for their abilities to enhance mucosal barrier function, of which *L. reuteri* is a well-known example (Mu et al., 2017a). In DSS-induced colitis, *L. reuteri* administration could reduce bacterial translocation from the GI tract to the mesenteric lymph nodes (MLN) (Dicksved et al., 2012). In addition, treatment of lupus-prone mice with a mixture of *Lactobacillus* species including *L. reuteri* led to a higher expression of tight junction (TJ) proteins in intestinal epithelial cells (Mu et al., 2017c). Subsequently, the translocation of pro-inflammatory molecules such as LPS was significantly suppressed, which correlated with attenuated disease. In addition to mouse studies, several strains of *L. reuteri* have been shown to possess the ability to modulate TJ protein expression and maintain intestinal barrier integrity in pigs (Yang F. et al., 2015; Wang Z. et al., 2016). Moreover, the ability of *L. reuteri* to decrease intestinal permeability has been seen in humans. In children with atopic dermatitis, where the impairment of intestinal barrier function has been positively correlated with disease pathogenesis (De Benedetto et al., 2011), treatment with *L. reuteri* DSM 12246 (and *L. rhamnosus* 19070-2) significantly reduced the frequency of GI symptoms while decreasing the lactulose to mannitol ratio (Rosenfeldt et al., 2004), which reflects the reversal of a leaky gut (Camilleri et al., 2010).

**L. reuteri ATTENUATE HUMAN DISEASES**

A growing body of evidences links microbiota and bacterial translocation with multiple diseases, including several autoimmune disorders (Mu et al., 2015, 2017a). Due to its strong modulatory effects on host microbiota and immune responses with almost no safety concerns, *L. reuteri* is a good candidate for disease prevention and/or treatment. Indeed, the therapeutic potential of various *L. reuteri* strains has been studied in diverse diseases and the results are promising in many cases.
### TABLE 3: Effects of *L. reuteri* on early-life diseases.

| Target                        | Strain       | Duration | Subjects   | Result                                                                 | Citation                  |
|-------------------------------|--------------|----------|------------|------------------------------------------------------------------------|---------------------------|
| Early caries lesions          | DSM 17938, ATCC PTA 5289 | 3 months | Adolescent | No significant change in fluorescence or lesion area                   | Keller et al., 2014       |
| Caries                        | ATCC 55730   | First year life | Infants | Reduced prevalence of caries and gingivitis score when the kids were 9 years old | Stensson et al., 2014     |
| FAP                           | DSM 17938    | 4 weeks  | FAP children | Significant decrease in the frequency and intensity of functional abdominal pain | Weizman et al., 2016      |
| FAP                           | DSM 17938    | 4 weeks  | FAP children | Significant reduction of pain intensity                               | Romano et al., 2014       |
| Infectious diarrhea           | DSM 17938    | 5 days   | Children  | Safe and well-tolerated; decreased duration of diarrhea                | Stensson et al., 2014     |
| Rotavirus diarrhea            | -            | Up to 5 days | Young children | Shortened diarrhea duration and large decrease in the occurrence of watery diarrhea | Shornikova et al., 1997a,b |
| Nosocomial diarrhea           | DSM 17938    | During hospital stay | Children | No effect on the overall incidence of diarrhea, including that related to rotavirus infection | Wanke and Szajewska, 2012 |
| Acute diarrhea                | DSM 12246 (with 19070-2) | 5 days   | Children patients | Decreased duration of diarrhea; decreased period of rotavirus excretion | Rosenfeldt et al., 2002a,b |
| Acute diarrhea                | DSM 17938    | 3 days   | Children  | Decrease in diarrhea frequency, duration, and relapse                  | Francavilla et al., 2012  |
| Acute diarrhea                | DSM 17938    | 5 days   | Hospitalized children | Effective decrease of the duration of acute diarrhea                  | Dinleyici et al., 2014    |
| Diarrhea                      | ATCC 55730   | 12 weeks | Infants   | Fewer and shorter diarrhea episodes                                     | Weizman et al., 2005      |
| Diarrhea                      | DSM 17938    | 6 months | Children  | Reduced incidence of diarrhea                                          | Agustina et al., 2012     |
| Diarrhea                      | DSM 17938    | 3 months | Children  | Decrease in diarrhea episodes and duration; Benefits against respiratory infection | Gutierrez-Castrellon et al., 2014 |
| Infant colic                  | DSM 17938    | 3 weeks  | Breastfed infants | Significant reduction in crying time                                 | Mi et al., 2015           |
| Infant colic                  | DSM 17938    | 3 weeks  | Breastfed infants | Reduction in crying and fussing time                                  | Chau et al., 2015         |
| Infant colic                  | DSM 17938    | 12 weeks | Newborns   | Effective preventive and protective action                             | Savino et al., 2015a      |
| Infant colic                  | ATCC 55730   | 28 days  | Breastfed infants | Significantly improvement of colicky symptoms compared with simethicone | Savino et al., 2007       |
| Infant colic                  | DSM 17938    | 21 days  | Breastfed infants | Improved symptoms; Increase of *Lactobacillus* increase and decrease of *E. coli* in the fecal microbiota | Savino et al., 2010       |
| Infant colic                  | DSM 17938    | 21 days  | Colicky infants | No effect on the global microbiota composition                         | Roos et al., 2013         |
| Infant colic                  | DSM 17938    | 21 days  | Breastfed infants | Higher rate of responders and reduced median crying time              | Szajewska et al., 2013    |
| Infant colic                  | DSM 17938    | 1 month  | Infants    | No effect on crying time                                              | Sung et al., 2014         |
| Infant colic                  | DSM 17938    | 90 days  | Infants    | Significant reduction of the mean crying time                         | Indrio et al., 2014       |
| Infant growth                 | DSM 17938    | 98 days  | Healthy infants | Well-tolerated but no improvement on growth                           | Cekola et al., 2015       |
| Atopic dermatitis             | DSM 122460 (with 19070-2) | 6 weeks | AD children | Improvement of eczema; more pronounced in allergic patients           | Rosenfeldt et al., 2003, 2004 |
| Atopic dermatitis             | ATCC 55730   | 8 weeks  | AD children | Positive modulation of cytokine pattern in the exhaled breath condensate | Minelli et al., 2010      |
| Eczema                        | ATCC 55730   | ~1 to 12 month old | Infants with family Allergic history | No protection of the general occurrence of eczema; Prevention of IgE-associated eczema | Abrahamsson et al., 2007  |

(Continued)
Early-Life Disorders

Taking advantage of the safety and tolerance of *L. reuteri* in infants and young children, a lot of efforts have been made to test the potential application of *L. reuteri* against disorders early in life (Table 3). In general, the results are promising. *L. reuteri* has been demonstrated beneficial in the prevention and/or treatment of many conditions including diarrhea, functional abdominal pain, colic, atopic dermatitis, allergy, feeding intolerance, and regurgitation. Infant colic, for example, has been the major therapeutic target of *L. reuteri* (Table 3). Infant colic is characterized by irritable crying and affects 10–30% infants (Mi et al., 2015). The exact cause and efficient treatment of this condition have remained elusive. The clinical efficacy of *L. reuteri* DSM 17938 has been demonstrated as most of the clinical trials were successful (Table 3). The failure of some studies may be explained by the differences in the dosage of *L. reuteri*, the infant age when the studies initiated, or the baseline microbiota structure. It is worth mentioning that *L. reuteri* is naturally contained in human breast milk (Soto et al., 2014), though inconsistencies exist among individuals. The presence of *L. reuteri* in milk may complicate the results of studies that involved breastfeeding. When given during pregnancy, *L. reuteri* did not show a significant effect on allergy and eczema in infants after they were born (Table 3).

### Systemic Lupus Erythematosus

The SLE is a multi-system autoimmune disease that involves both genetics and environment as the major disease causative factors (Tsokos, 2011; Edwards et al., 2017). The role of gut microbiota in SLE development was suggested by recent studies, and probiotics have been proposed as potential immunoregulators (Markle et al., 2013; Yurkovetskiy et al., 2013). Further investigation of this link is required. In another lupus mouse model, NZB/W F1, the administration of two *L. reuteri* strains, together with one *L. paracasei* strain, was shown to be effective in ameliorating lupus hepatitis (Hsu et al., 2017). Liver abnormalities, manifested as increased liver enzymes, portal inflammation and histopathological changes, have been observed in both lupus mouse models and SLE patients (Hsu et al., 2008; Grover et al., 2014). In this study, the oral *L. reuteri* treatment largely mitigated hepatic apoptosis and inflammation, suggesting a protective function of *L. reuteri* against lupus-associated liver disease (Hsu et al., 2017). The protection seems to rely on the capability of *L. reuteri* to increase antioxidant activity and reduce cytokines associated with more severe lupus.

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**Table 3** | Continued

| Target                  | Strain       | Duration | Subjects     | Result                                                                                      | Citation                       |
|-------------------------|--------------|----------|--------------|--------------------------------------------------------------------------------------------|--------------------------------|
| GI motility             | -            | 30 days  | Newborns     | Faster gastric emptying                                                                     | Indrio et al., 2009           |
| Respiratory allergy     | ATCC 55730   | –1 to 12 month old | Infants | No effect on the prevalence of asthma, eczema or other allergic diseases later in life       | Abrahamsson et al., 2013      |
| Feeding intolerance     | DSM 17938    | Until out of NICU | Preterm infants | Decrease in feeding intolerance and duration of hospitalization                              | Rojas et al., 2012            |
| Necrotising enterocolitis | DSM 17938  | Until discharge | Preterm infants | No effect on NEC rate; Decrease in feeding intolerance and duration of hospital stay         | Oncel et al., 2014            |
| Regurgitation           | DSM 17938    | 28 days  | Infants     | Prevention of regurgitation during the first month of life                                  | Garofoli et al., 2014         |
| Regurgitation           | DSM 17938    | 90 days  | Infants     | Significant reduction of the mean number of regurgitation                                   | Indrio et al., 2014            |

FAP, functional abdominal pain; NICU, neonatal intensive care unit; NEC, necrotising enterocolitis.
such as IL-6 and TNF (Tzang et al., 2017). Interestingly, within these two L. reuteri strains, only GMNL-263 can significantly promote the differentiation of Treg cells, again emphasizing the uneven immunoregulatory abilities of different L. reuteri strains.

**Obesity**
The correlation between gut microbiota and obesity is well documented (Okeke et al., 2014; Harakeh et al., 2016). The microbiota composition varies between lean and obese individuals, and a surprisingly high level of Lactobacillus spp. has been found in the microbiota of both obese adults and obese children (Armougom et al., 2009; Bervoets et al., 2013). Among different Lactobacillus spp., L. reuteri was specifically described to be associated with obesity (Million et al., 2012, 2013a). The association was further established when vancomycin-resistant L. reuteri in gut microbiota was determined as a body weight gain predictor during vancomycin treatment (Million et al., 2013b). However, in a randomized, double-blind and placebo-controlled clinical trial, the administration of L. reuteri JBD301 for 12 weeks significantly reduced body weight in overweight adults (Chung et al., 2016). Moreover, supplementation of infant formula with L. reuteri did not increase weight gain in infants (Braegger et al., 2011; Koleva et al., 2015). These conflicting results indicate that L. reuteri may influence the development of obesity in a strain-dependent manner. This hypothesis is partially verified in an animal study. In that study, three different strains of L. reuteri were used to test their influence on diet-induced obesity (Fåk and Bäckhed, 2012). It was demonstrated that only L. reuteri PTA 4659 efficiently reduced the body weight of mice fed with high-fat diet (HFD), whereas L. reuteri L6798-treated mice even gained some weight. The changes of adipose and liver weights were consistent with the body weight change.

In animal studies, several strains of L. reuteri have been reported to negatively regulate the development of obesity (Dahiya et al., 2017). In addition to the beneficial effect of L. reuteri JBD301 to human obese patients mentioned earlier, the favorable role of this strain of L. reuteri against weight gain was confirmed in HFD-fed mice (Chung et al., 2016). In HFD-induced obese mouse models, the beneficial role of L. reuteri GMNL-263 was also noted (Hsieh et al., 2016). Treatment with L. reuteri GMNL-263 reduced the body weight as well as the percentages of adipose tissue and liver to body weight. Interestingly, heat-killed GMNL-263 appeared to have a very similar beneficial function (Hsieh et al., 2016; Liao et al., 2016). L. reuteri 6475 has also been shown to be beneficial against obesity in mice (Porathidis et al., 2013b). The function of L. reuteri 6475 was suggested to be largely dependent on its capability to induce Treg cells without changing the gut microbiota ecology. Furthermore, the weight loss properties of some reagents have been attributed to their abilities to increase L. reuteri in mice. Polymannuronic acid, for example, was able to increase the relative abundance of L. reuteri and significantly reduce HFD-induced body weight gain (Liu F. et al., 2017). Whether the increase of L. reuteri is the cause of weight loss requires further investigation.

**Neurodevelopmental Disorder**
Exposure to maternal obesity in utero increases the chance of neurodevelopmental disorders, such as autism spectrum disorder, in children (Connolly et al., 2016). In a recent mouse study, maternal HFD (MHFD) was shown to induce social deficits in the offspring (Buffington et al., 2016). The impaired social ability in GF mice was restored by fecal microbiota transplantation from offspring with maternal regular diet (MRD) but not MHFD, suggesting a potential role of microbiota in this process. Further analysis showed that the abundance of L. reuteri was reduced more than ninefold in the gut microbiome of MHFD vs. MRD offspring. The social defects in MHFD offspring were rescued by direct L. reuteri administration, suggesting an effect of L. reuteri in regulating neurodevelopment in MHFD mice. This regulatory function of L. reuteri was attributed to its capability to increase the level of oxytocin (Poutahidis et al., 2013a; Buffington et al., 2016). The results of these studies suggest a potential application of L. reuteri in the treatment of patients who suffer from neurodevelopmental disorders.

**Stressor Exposure and Enteric Infection**
The composition of gut microbiota shift when the host is exposed to stressors (Bailey et al., 2010; Galley et al., 2014). In C57BL/6 males, social stressors led to an altered intestinal microbiota composition, though there was no significant change in community diversity (Galley et al., 2014). Further analysis showed stressor-induced reductions in the families Porphyromonadaceae and Lactobacillaceae, especially in the genus Lactobacillus. Among Lactobacillus spp., L. reuteri was specifically measured and a lower abundance of L. reuteri was evident in stressor-exposed CD-1 mice but not C57BL/6 mice. In fact, the level of L. reuteri in C57BL/6 male mice was below the detection limit with or without stressor exposure (Galley et al., 2014). It is important to note that stressor exposure increased the severity of Citrobacter rodentium-induced inflammation in the gut (Bailey et al., 2010; Mackos et al., 2016). The colonization of C. rodentium was promoted by stressor exposure, which subsequently resulted in more severe colonic pathology and increased production of inflammatory cytokines and chemokines (Mackos et al., 2016). Further studies revealed that stressor-induced C. rodentium colitis was C-C motif chemokine ligand 2 (CCL2)-dependent. Interestingly, administration of L. reuteri ATCC 23272 was able to reverse stressor-induced C. rodentium infection, which also relied on CCL2 (Mackos et al., 2013, 2016). However, L. reuteri was not able to restore the gut microbiota altered by social stressors. This indicates that the beneficial effect of L. reuteri on stressor exposure and subsequent enteric infection is not microbiota-dependent (Galley et al., 2017).

**CONCLUSION**
There has been a decrease in the abundance of L. reuteri in humans in the past few decades likely caused by the modern
lifestyle (Antibiotic use, western diet, improved hygiene). Such decrease coincides with higher incidences of inflammatory diseases over the same period of time. While evidence is lacking to establish the correlation, it may be helpful to increase L. reuteri colonization and/or facilitate its probiotic functions as a new and relatively safe strategy against inflammatory diseases. In addition, through direct regulation or indirect modulation via the host microbiota, L. reuteri plays an impressive role in eliminating infections and attenuating both GI diseases and diseases in remote tissues. The safety and tolerance of L. reuteri has been proven by the numerous clinical studies. There are multiple L. reuteri strains with different host origins, and many of the probiotic functions of L. reuteri are strain-dependent. Therefore, it may be advantageous to combine different strains of L. reuteri to maximize their beneficial effects.

AUTHOR CONTRIBUTIONS

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