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The Importance of Lactobacillus Reuteri for Women's and Infants' Health

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ABSTRACT: A probiotic with broad-spectrum antibacterial action is Lactobacillus reuteri. In addition to secreting enzymes and lactic acid, it possesses the traits of lactic acid bacteria and isalso capable of producing reuterin, a broad- spectrum antibacterial agent consisting of 3-hydroxypropionaldehyde(3-HPA).Because3-HPA may efficiently inhibit bacteria, yeasts, fungus, and pathogens, it is frequently used as an antiseptic and in the treatment of many diseases. Humans have L. reuteri in several body locations, such as the skin, gastrointestinal tract, urinary tract, and breast milk. various people have various levels of L. reuteri abundance. There have been several reported advantages of L. reuteri.

I. INTRODUCTION

A diverse assemblage of commensal bacteria makes up the human microbiota. The gut microbiota is more numerous and diversified in terms of metabolism and genetic makeup than the entire human body. The human microbiota, in particular the gut microbiota (which includes over 90% of all commensals), has profound effects on the host's body's growth and maintenance,including immunological control, metabolism, and neuronal function.(1). The gut microbiota coevolves with the host's metabolic and neurologicalprogrammingfrombirthonwards.The synergy between the infant's gut microbes is established from birth and forms throughout the earlyyears oflife. immune systemand prevents the colonization of pathogens (2). Environmental factors including diet and lifestyle have a complicated relationship with the host that affects the development of the gut microbiota. (3). Therefore, the dynamics of this community within the host and any potential links it may have with disease risks canbe illuminated bystudyingthe gut microbiota from infancy to old age. Probiotics are administered to alleviate a number of health issues, indicating the great potential of probiotic applications in disease cure, partially through gut microbialcompositionrebalancing.(4).Probiotics that produce lactic acid, such as various Lactobacillus species, have perhaps been thesubject of the most research, both in children and adults. Numerous gastrointestinal (GI) tract problems may be prevented and treated with lactobacilli, according to preclinical and animal research. Lactobacillus reuteri benefitsthe hostina number of ways. (4, 5).Since its initial isolation in 1962, L. reuteri has been described as a heterofermentative species that colonizes both human and animal gastrointestinal tracts and flourishes in environments with low oxygen levels. Its probiotic qualities might stem from the fact that it typically colonizes the GI tract. Humans have L. reuteri in several body locations, including as the skin,GItract,urinarytract,andbreastmilk. (5)The roleofLactobacillusreuetriinmaintainingmucosal homeostasis and controlling the gut microbiota has been investigated in a number of clinical investigations. In pathological situations, the metabolites generated by L. reuteri reduceintestinal inflammation and have an impact on the intestinal host immune system.This range of roles illustrates the dual benefit that L. reuteri providesto human immunity and intestinal health. (5)

For a probiotic strain to colonize, interact with host cells,suppresspathogenicgrowth,protectepithelial cells, or modify the immune system, it must adhere to the GI tract of the host.(6).The ability of L. reuteri to adhere to intestinal epithelial cells and colonizemucinhasbeendemonstratedinnumerous investigations.Surfaceproteins,exopolysaccharide, inulosucrase, mucus-binding protein, D-alanyl-LTA, and glucosyltransferase A have all been connected to the likely mechanism behindadhesion.(4). L. reuteri can adhere to intestinal epitheliaandmucininitshost withsuccess(7).The intestinal barrier is strengthened when L. reuteri colonizes an area because it reduces the amount of microbes that move from the gut lumen to the surrounding tissues. Inflammation may have originated from microbial translocation across the gut epithelium.

Probiotics:

According to the World Health Organization, probiotics are defined as "live microorganisms which, when administered in adequate amounts, confer a health benefit on the host". These probiotics, that have already been proven to exert a beneficial impact, include Saccharomyces boulardii, Lactobacillusspp., Bifidobacteriumspp., Propionibacteriumspp., Streptococcus spp., Bacillus spp., Enterococcus spp., and some specific strains of Escherichia coli etc, in which Lactobacillus spp. is the most widely used in human nutrition. Recently, numerousbodies of research demonstrated that probiotics are beneficial for various diseases, such as intestinal disorders, respiratory tract infections, vaginal diseases, and so on. With the development of the food and drug industries and the innovation of technology, an increasing number of emerging probiotic strains were developed and applied to different fields, including natural food preservatives, nutraceuticals, and so on. Somenovel technologies can also enhance probiotic products‟qualityandsensorycharacteristics,which can contribute to the extensive application of probiotics. Safety is also an essential issue during the process of investigating probiotics.An ocean of evidence indicated that the use of probiotics can cause some risks regarding systemic infections, deleterious metabolic activities, excessive immune stimulation in susceptible individuals, gastrointestinal side effects, and so on. Some probiotic microorganisms can even transfer resistance genes to protect against antibiotics,which may be responsible for the development of the antibiotic resistance crisis. Taken together, the application of probiotics is a double-edged sword. Before probiotics are used, we still need to carryoutenoughclinicaltrialsandanimalexperimentst o assess their benefits and harms. Lactobacillus spp., whichcanbefoundinvariousfoodproducts,isone of the most widely used probiotics, and includes Lactobacillus acidophilus, Lactobacillusrhamnosus, Lactobacillus bulgaricus, Lactobacillus casei, and Lactobacillus reuteri(L. reuteri). Lactobacillus reuteriis a gut symbiont mainly colonizedintheintestinesofhumans,rodents,pigs, and chickens. Since first isolated in 1962, there havebeenagreatnumberofstudiesconductedon

L. reuterito explore its functions and concrete mechanisms in different diseases, which cover gastrointestinal diseases, hypercholesterolemia,skin infection, allergic asthma, periodontitis, hand, foot, and mouth disease (HFMD), and so on. Amongthese,thereisanincreasinglyprevalent trend that the investigations of L. reuteriin terms of intestinal diseases are becoming far and away the best area, which mainly concentrates on inflammatory bowel disease (IBD), colorectal cancer(CRC),children‟sfunctionalboweldiseases, and so on. (2)

Probiotics are defined as "live microorganisms which, when administered in adequate amounts, confer a health benefit on the host"bytheWorldHealthOrganization(WHO)"

[8] Those probiotics having beneficial properties include Lactobacillus species pluralis (spp), bifid bacterium spp., Streptococcus spp., Bacillus spp., Enterococcus spp., and some strains of Escherichia coli. "Acommon mechanism in probiotics includes colonization, producing short chain fatty acid, regulating intestinal transit, normalizing perturbed microbiota and exclusion of pathogens. Some probiotic strains can improve host food digestionby metabolizing bile salt or supplementing the functions of missing digestive enzymes" [9]. "L. reuteriis a probiotic bacteria found in body sites, includingtheGItract,urinarytract,skin,andbreast milk. The L. reuteriinhibits the colonization of pathogenic microbes and remodel the microbiota composition in the host. The colonization of L. reuterimay decrease the microbial translocation from the gut lumen to the tissues" [10].

Infant colic is a distressing condition characterized by crying and/or fussing of unknown cause that afects up to 28% of infants under three months of age. etiology of infant colic is unclear and there is no widely accepted or effective treatment.Severalstudieshavefounddifferencesin gastrointestinal (GI) microbial diversity between infants with colic and healthy infants, suggesting that an aberrant microbial intestinal profile may cause or contribute to infant colic. Infants withcolic have higher rates and densities of Escherichia coli and other gas-producing coliforms and lower levels of Lactobacillus spp. compared with healthy infants, with some aerobic bacterial genera not detected in infants with colic. One study found that infantswithcolichadlower microbialdiversityand elevated fecal calprotectin (a marker of gut inflammation) compared with healthy infants. However, another study found no difference infecal calprotectin levels between healthy infantsand infants with colic. [4]

The immature neonatal fecal microbiota substantiallyimpactsthe development ofgut health and greatly increases the risk of disease.Developing effective strategies to modulate the development of neonatal fecal microbiota has great significance.Herein,weinvestigatedwhetherthe maternal dietary supplementation and oral administration of Lactobacillus reuteri could effectively promote the development and maturation of the fecal microbiome in piglets from birth to weaning. [5]

Tannock (11) proposed that the „ideal probiotic‟ should possess the following characteristics. It should persist for a long time in the GI tract and produce substances that inhibit gastrointestinalpathogensorstimulateimmunityso as to increase the host‟s resistance to intestinal infections. It should contribute to the host‟s nutrition by synthesizing essential nutrients and/or by digesting dietary substances (e.g., lactose) that the host may be physiologically ill-equipped to utilize. It should be amenable to large-scale commercial production, be safe and devoid of characteristics that could compromise the host‟s health, and it should exhibit stability in all theabove characteristics. He theorized, however, that attempts to isolate such an ideal probiotic strain would most likely fail, and that an alternative stratagem would be to derive such a strain by genetic manipulation. On a somewhat more optimistic note, (12) argued that it may be possible to isolate an „ideal probiotic‟, but only if proper screening methods are used to identify the above listed „ideal‟ traits. They suggested that in vivo efficacy testing be conducted only on strains thus selected to possess these „ideal‟traits. Barrow(13) on the other hand expressed concern about the high degree of variability observed when in vivo probiotic efficacy tests are conducted. How can probiotic efficacyofanystrainbe determined ifthe tests used to determine efficacy are unreliable owing to this high degree of variability? He attributes this variability, among other factors, to poor characterization of the strains used in the past and/or poor understanding of the microecology of the GI tract, positing that efficacy evaluations conducted using strains lacking either „ideal‟traits or host specificity are not likely to succeed in any event.And furthermore, that in too many instances, the occasional „positive‟results obtained are often over-optimistically, naively.

RoleofL.reuteriinGutHealthofInfants

From birth to six months of age, approximately one out of two infants develops at least one functional gastrointestinal disorder(FGID)orrelatedsignsandsymptoms.FGIDss uch as infantile colic, regurgitation, functionaldiarrhea, and functional constipation are commonworldwide, but their prevalence rates vary extensively(16).L.reuteriisbeneficialto the host‟s health as it enables the colonization of the gut with beneficial bacteria. This occurs because L. reuteristrains are resistant to low pH and bile salts. These strains can attach to mucin and intestinal epithelia because they can produce exopolysaccharides (EPS), which are important for biofilmformation.Theformationofbiofilmshelps L.reuetri to adhere to epithelial surfaces and enhancestheprobioticeffects of L.reuteri (15,17). Antimicrobial metabolites produced by L.reuteri such asreuterin inhibit a wide range of microorganisms, particularly gram-negative bacteria. Other metabolites such as lactic acid, acetic acid, ethanol, and reutericyclin are effective against numerous pathogenic bacteria. One of the key roles of the probiotic L. reuetristrain is to promote mucosal barrier functions by reducing bacterial translocation from the GI tract to the mesenteric lymph nodes. Apart from gut health, L. reuteriinteracts with the gut–brain axis and modulates the afferent sensory nerves thatinfluence gut motility (15, 18). The possible modes of action by which probiotic L. reuteri helps in the management of FGIDs are as follows (14,15, 18):

(i) L. reuteri improves gut motility, which reduces constipation and relieves functional abdominalpain. It also increases colonic contractility.

(ii) L. reuteri modulates the gut‟s immune and inflammatory responses, which reduces the incidence of infections such as diarrhea.

(iii) L.reuteriinhibits the visceralpainpathwayand thus may have a role in relieving functional abdominal pain.

(iv) L. reuteri reduces gastric distension and accelerates gastric emptying and thus helping reduce the frequency of regurgitation.

ProbioticPropertiesofL.reuteri

Therearesomeprerequisitesforbecoming 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. reuterimeets all ofthese requirements. Here, additional probiotic properties of L. reuteriare discussed that contribute to its diverse beneficial effects on host health and disease prevention and/or amelioration. [19]

GutColonizationofL.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 gastricacidsandbilesaltsinuppersmallintestine.

Thus,theveryfirststepofcolonizingtheGItrac tis to survive in such environments. Multiple L. reuteristains are resistant to low pH and bile salts. This resistance is believed to be at least partially dependent on its ability to form biofilms.L.reuteriis capable of attaching to mucin andintestinal epithelia, and some strains can adhere to gut epithelial cells in a range of vertebrate hosts. [19] Apossiblemechanismforadherenceisthe bindingofbacterialsurface moleculestothe mucus layer. Mucus-binding proteins (MUBs) and MUB-like proteins, encoded by Lactobacillalesspecific clusters of orthologous protein coding genes, serve as adherence mediators, or so-called adhesins. [20] The considerable diversity of MUBs among L. reuteristrains and the variation in the abundance of cell-surface MUBs significantly correlates with their mucus binding ability. [21]

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.[22]

As L. reuterithat has colonized to the host GI tract canform biofilms, efforts have been made to study the regulation of L. reuteribiofilmsecretion and its association with the adherence of bacteria to host GI epithelium. By doing in vitro biofilm assay, uncovered the contribution of GtfA and Inu in the biofilm formation of L. reuteriTMW1.106. [23]

The in vivo biofilm formation of L. reuteristrains seems to be dependent on the host origin of the strains. In one study, nine L. reuteristrains 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. [24]

Another study by the same authorsshowed that a specialized transport pathway (the SecA2-SecY2 system) was unique in the rodentand porcine strains. [25]

By using a rodent strain L. reuteri100-23, they compared extracellular and cell wall-associated proteins between the wild-type strainand the secA2 mutant. Only one surface protein, L. reuteri70902, was absent in the secA2 mutant. In vivo colonization studies showed that the absence ofL.reuteri70902leadstoalmostcompletely eliminated biofilm formation. This strongly suggeststhatL.reuteri70902andtheSecA2-SecY2 system are key factors regulating biofilmproduction from L. reuteri100-23 in germ-freemice. [26] Another group investigated the role oftwo-component systems bfrKRTand cemAKRin in vitro biofilm formation of L. reuteri100-23. They found the deletion of certain genes in the operons enhanced. [27]

Health-PromotingEffect

The antimicrobial and immunomodulatory effects of L. reuteristrains 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. reuteristrains of human and poultry lineage are able to produce and excrete reuterin, a well-known antimicrobial compound Apart from reuterin, several other antimicrobial substances, including lactic acid, acetic acid, ethanol, and reutericyclin, have been determined as products of some L. reuteristrains. With the synthesis of these substances, L. reuterihas been shown to be effective against a variety of GI bacterial infections. These infections include Helicobacter pylori, E. coli, Clostridium difficile, and Salmonella. One of the more notable illustrations of the efficacy of L. reuterias a probioticagainstinfectionsistheuseof L.reuterito 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. The use of L. reuteriagainst H. pylori has been explored in many studies. It has been suggested that L. reuteriworks by competing with H. pylori and inhibiting its binding to glycolipid receptors. The competition reduces the bacterial load of H. pylori anddecreases the related symptoms. Some studies have shown that L. reuterihasthe potentialto completely eradicateH.pylorifromtheintestine.Importantly, L. reuteriis advantageous in the treatment of H. pylori as the supplementation eradicates the pathogen without causing the common side effects associated with antibiotic therapy.

Histamine

The amino acid L-histidine, which is a dietary component, can be converted by certain strains of Lactobacillus reuteri into the biogenic amine histamine. The model strain for the investigationofhistamineinL.reuteriwasL. reuteri 6475, a human commensal bacterium. Histamine produced from L. reuteri 6475 was shown by J. Versalovic's group to inhibit the generation of tumour necrosis factor (TNF) in activated human monocytes. The histamine H2 receptor's activation, elevated intracellular cAMP and protein kinase A, and inhibition of MEK/ERK signalling were all necessary for this suppression. The entire chromosomal histidine decarboxylase (hdc) gene cluster, which consists of hdcA, hdcB, and hdcP, controls the synthesis of histamine and the ensuing in vitro TNF suppressing activity. Full chromosomal histidine decarboxylase (hdc) gene cluster, comprisinghdcA, hdcB, and hdcP, controls histamine production and, consequently, its ability to reduce TNF in vitro. In a mouse colitis model induced by trinitrobenzene sulfonic acid (TNBS), the same team of researchers also discovered that oral administration of hdc+ L. reuteri could successfully control intestinalinflammation. Furthermore,colitismitigationwasobservedwhen L. reuteri 6475 culture supernatant was injected intraperitoneally into mice treated with TNBS. These findings clearly demonstrate the role of histamine and other L. reuteri metabolites in intestinal immunomodulation.

Vitamins

Since the human body cannot synthesise any of the vitamins, there are thirteen that are vital to human health. Numerous L. reuteri strains, like many other Lactobacillus species, are capable of producing several vitamins, such as vitamin B9 (folate) and vitamin B12 (cobalamin). Because a B12-dependent coenzyme is needed for the reduction of glycerol to 3-HPA, as was previously indicated, B12 is essential for the synthesis of reuterin. Thusfar,B12hasbeendetectedin atleast 4 different origin L. reuteristrains.The two most researched strains of L. reuteri are L. reuteri JCM1112 and CRL1098. In one study, it was demonstrated that giving L. reuteri CRL1098 along with a diet deficient in vitamin B12 might improve pathologiesinpregnant female mice who wereB12 deficient, as well as in their offspring. This finding clearlyindicatesthepossible useofL.reuteriinthe treatment of B12 deficiency. Certain strains of Lactobacillusreuteri, suchasL.reuteri6475andL. reuteri JCM1112, have the ability to synthesisefolate in addition to B12.

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