MINIREVIEW

The Scientific Basis for Probiotic Strains of Lactobacillus

GREGOR REID*

Lawson Research Institute and Department of Microbiology and Immunology,
The University of Western Ontario, London, Ontario, Canada

The concept of using Lactobacillus species for disease treatment and prevention as well as health restoration and maintenance is not new. However, in recent times, there has been a renewal of interest in the use of probiotics (as distinct from antibiotics) (also termed biotherapeutic agents), driven in large part by consumers and the lay press. Probiotics have been used therapeutically to modulate immunity, lower cholesterol, treat rheumatoid arthritis, prevent cancer, improve lactose intolerance, and prevent or reduce the effects of atopic dermatitis, Crohn’s disease, diarrhea, and constipation as well as candidiasis and urinary tract infections (UTI).

There is no shortage of Lactobacillus products in health food stores in North America and in pharmacies and other distribution sites in Europe and Asia. Questions have been raised about reliability, viable content, and the general quality of many products. However, surely of greater importance is the question of which strains have any scientific evidence supporting their use in humans.

A review of the literature shows that there are hundreds of papers which report, in some shape or form, the use of various Lactobacillus strains as probiotic agents. The purpose of this review is to select and examine strains which have been tested thoroughly in vitro and in vivo, have substantial published data behind them, and have been shown to have real potential to maintain intestinal or urogenital health as well as reduce the risk of infection. It is my belief that such rigorous documentation should be required before wider human usage is considered.

PROPERTIES OF KEY IMPORTANCE AND IDENTIFICATION OF WELL-DOCUMENTED STRAINS

In general terms, a group of requirements have been identified as important properties for lactobacilli to be effective probiotic organisms (37, 41, 47). These include the ability to (i) adhere to cells; (ii) exclude or reduce pathogenic adherence; (iii) persist and multiply; (iv) produce acids, hydrogen peroxide, and bacteriocins antagonistic to pathogen growth; (v) resist vaginal microbicides, including spermicides; (vi) be safe and therefore noninvasive, noncarcinogenic, and nonpathogenic; and (vii) coaggregate and form a normal, balanced flora.

The strains listed in Table 1 represent those which fulfill the criteria established for discussion. Other strains, such as Lactobacillus plantarum 299V (product of Probi, Lund, Sweden), Lactobacillus acidophilus LA1, which has apparently been renamed Lactobacillus johnsonii L1 (marketed as LC1 by Nestle, Lausanne, Switzerland), L. acidophilus NCFB 1748, Lactobacillus crispatus CTV05 (product of Gynelogix, Boulder, Colo.), and Lactobacillus casei DN114 (Danone, Paris, France), either have shown promise in some human studies or have some in vitro data to support utility (such as LA1’s adhesion to intestinal cells and inhibition of pathogen invasion [3]).

Copyright © 1999, American Society for Microbiology. All Rights Reserved.
With respect to strain CRL431, the evidence for adhesion and competitive exclusion of pathogenic Escherichia coli, Listeria monocytogenes, Shigella sonnei, and Salmonella typhimurium comes from in vitro and animal studies (2, 25, 29) and therefore human studies may be necessary. Part of strain CRL431’s mode of action, and likely those of other strains delivered orally, appears to be an ability to increase phagocyte activity and secretary immunoglobulin A (27, 28, 30, 31). This ability to enhance the host’s immune function may have wide-ranging clinical usages.

While the expression of the factors listed above is likely important for probiotic activity, it is not easy to grade the extent to which any given property is essential or of greatest importance in vivo. Too few studies have investigated expression of these factors in humans, and none have proved cause and effect. It seems that adherence and expression of some antagonistic activity against pathogens, whether it be against their adhesion, growth, or ability to dominate the flora, are the most critical factors, but that fact does not exclude other properties. For example, if a Lactobacillus strain does not resist the action of spermicide in the vagina, it probably will not dominate in N-9 users, even if it does have probiotic properties.

**CLINICAL EVIDENCE OF USEFULNESS**

*L. rhamnosus* GG has perhaps been the most extensively studied probiotic in children and adults. Although not all studies have been ideally designed to include placebo control, there is strong evidence that GG, given orally at doses greater than 10^9 CFU/day, colonizes the intestine, at least temporarily, and reduces diarrhea (17–20, 26, 46). On the other hand, the application of GG to premature infants did not reduce pathogen load even when it colonized the intestine, giving rise to concerns that it might only poorly express its antagonistic capabilities in vivo (23).

The NCFM strain is able to survive stomach passage and colonize the intestine (7, 11). To date, its probiotic effects have been demonstrated in humans as reducing problems associated with lactose intolerance (24) and as reducing levels of free amines in the intestine, thereby decreasing the risk of colon cancer (12). These properties make this strain of potential value in several patient populations.

The Yakult Shirota strain, originally isolated from a human intestine in 1930, appears able to colonize the intestine (48, 52) and improve the recovery times of infants with rotavirus-induced gastroenteritis (50). While the strain appears to have potent antitumor and antimetastasis effects in mice (21), it did not stimulate any immune parameters in immunocompetent males, although increased counts of Lactobacillus and Bifidobacterium spp. were found in feces following its ingestion (49).

Strain MM53, also referred to as SD2112 (now ATCC 55730), isolated from breast milk, has been found to significantly prevent community-acquired diarrhea in Mexico (39) and to reduce the acute rotavirus-induced episodes of diarrhea in Finnish children (6). Much of the additional evidence for this strain’s probiotic activity comes from animal studies, but use in children with diarrhea has shown promise (44, 45). As there are few effective and nontoxic antiviral agents, it seems critical that probiotic organisms with proven antiviral effects be further examined and tested clinically.

There is mounting evidence that strain CRL431 may be an effective probiotic agent for stimulating immune responses, preventing infection by enteropathogenic bacteria, and treating and preventing diarrhea (13, 14). Further human trials along with a more in-depth examination of the mechanisms of action appear warranted.

The application of lactobacilli to the urogenital tract has almost exclusively been done with a select group of strains in Canada. Human trials with GR-1 and *L. fermentum* B-54, an isolate almost identical to RC-14, have shown that the vaginal microflora can be restored and the incidence of UTI be significantly reduced, following local instillation in a milk-based suspension (4) and in an encapsulated freeze-dried state (5, 32, 35). In addition, the patient groups investigated did not suffer any yeast infections, which are often a side effect of antibiotics. The potential exists for GR-1, B-54, and RC-14 to restore a normal urogenital flora and thereby reduce the risk of UTI, bacterial vaginosis, and yeast vaginitis. Given the properties of GR-1 and RC-14, it is possible that they may also act as intestinal probiotic strains. Studies to date have shown that they pass through the stomach and bile and colonize the intestine for several weeks (37b). Further studies are warranted.

Thus, application of properly selected probiotic strains to the vagina or the intestine is feasible and may provide a means to reduce antibiotic usage, thereby addressing the growing concern over multidrug resistance.

**SUMMARY**

While many *Lactobacillus* strains have been promoted as good probiotics for human usage, there are relatively few with substantial supporting in vitro and human data. Biotherapeutic properties and mechanisms of action are too often lacking, and arguably too many human studies are undertaken or contemplated with strains which have not been thoroughly characterized with respect to the intended site of insertion. There are a few notable exceptions, including those described in this review, which have been well studied, and the findings have been documented in peer-reviewed journals. With respect to site of action and speciation, it is premature to suggest that certain
species will function in only one site, although _L. reuteri_ is rarely found in the vagina and likely will be better suited to intestinal application. The challenge in the future will be to better understand how these seven organisms, and indeed other purported probiotic lactobacilli, interact within the microbial biofilms of the intestine and urogenital tract and how they and indigenous members of the normal flora restore and maintain health. Recent advances in the study of biofilms, such as use of confocal microscopy and the discovery of cell-to-cell signaling, will provide useful road maps for investigating the interactions between exogenous and indigenous lactobacilli and intestinal and urogenital biofilms. With the increased evidence of multidrug resistance among pathogens and a continued failure to manage gastrointestinal virus infections, plus a desire by consumers to use natural methods for health maintenance rather than long-term chemotherapeutic agents, the time is right for probiotics to be taken seriously. It is also time for scientists to provide the data which give a basis and mechanism of action for the human utilization of well-studied organisms.

ACKNOWLEDGMENTS

The cooperation and input of Mary Ellen Sanders and Andrew W. Bruce are much appreciated.

REFERENCES

children fed a beverage with a mixture of \textit{Lactobacillus} sp. Pediatr. Res. 39:104A.


