Infection and Drug Resistance

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REVIEW

Novel Dietary Approach with Probiotics, Prebiotics, and Synbiotics to Mitigate Antimicrobial Resistance and Subsequent Out Marketplace of Antimicrobial Agents: A Review

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Abstract: Antimicrobial resistance (AMR) is a significant public health concern worldwide. The continuous use and misuse of antimicrobial agents have led to the emergence and spread of resistant strains of bacteria, which can cause severe infections that are difficult to treat. One of the reasons for the constant development of new antimicrobial agents is the need to overcome the resistance that has developed against existing drugs. However, this approach is not sustainable in the long term, as bacteria can quickly develop resistance to new drugs as well. Additionally, the development of new drugs is costly and time-consuming, and there is no guarantee that new drugs will be effective or safe. An alternative approach to combat AMR is to focus on improving the body's natural defenses against infections by using probiotics, prebiotics, and synbiotics, which are helpful to restore and maintain a healthy balance of bacteria in the body. Probiotics are live microorganisms that can be consumed as food or supplements to promote gut health and improve the body's natural defenses against infections. Prebiotics are non-digestible fibers that stimulate the growth of beneficial bacteria in the gut, while synbiotics are a combination of probiotics and prebiotics that work together to improve gut health. By promoting a healthy balance of bacteria in the body, these can help to reduce the risk of infections and the need for antimicrobial agents. Additionally, these approaches are generally safe and well tolerated, and they do not contribute to the development of AMR. In conclusion, the continuous development of new antimicrobial agents is not a sustainable approach to combat AMR. Instead, alternative approaches such as probiotics, prebiotics, and synbiotics should be considered as they can help to promote a healthy balance of bacteria in the body and reduce the need for antibiotics.

Keywords: antimicrobial resistance, probiotics, prebiotics, synbiotics

Introduction

The continual emergence of antimicrobial resistance (AMR) from unchecked and unregulated antimicrobial usage has posed a higher influence on the world population's health and development plan. Drug-resistant pathogens have a multifaceted problem and could result in prolonged illness, disability, and death, as well as worldwide economic loss. Globally, there is an estimated annual death rate of 700,000 people from antimicrobial-resistant infections. Antimicrobial-resistant infections have become a major source of worldwide economic loss in searching for more expensive medicines. The consequences and burdens of these drug-resistant pathogens are particularly significant in developing nations where poor sanitation, inadequate infection prevention and control, and sophisticated healthcare problems are dominated.[1–3]

An increase in the occurrence of infections with increased morbidity, mortality, and readmissions is the common fearful consequence of multidrug-resistant pathogens as compared to susceptible ones. The insusceptibility of these pathogenic microbes to the currently available antimicrobial agents calls many researchers to stand for action for

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searching non-antimicrobial therapeutic alternatives which is useful for preventing and treating infectious disease conditions from those resistant pathogens. Many of the non-antibiotic therapeutic options explored include the use of probiotics, prebiotics, synbiotics, phytocompounds, vaccines, Clustered Regularly Interspaced Short Palindromic Repeats-Cas (CRISPR-Cas), nucleic acid-based anti-bacterial treatments, bacteriocins, antimicrobial peptides, phage therapy, immunostimulants, cytokines, Quorum Quenchers (QQ) or Quorum Sensing Inhibitors (QSI), feed enzymes, Nanoparticles (NPs), and Chicken Egg Yolk Antibodies (IgY).[4–6]

Of these various approaches, the probiotics, prebiotics, and synbiotics dietary-based non-antibiotic alternative approach is by far the most promising ones due to their convenient availability as a dietary supplement, their ability to mitigate the risk of antimicrobial resistance in the natural way of living making them host and environmentally friendly approaches, their ability to replenish washed-out endogenous gut flora associated with antibiotic treatment, their antagonistic activity against a varied number of resistant strains and their several mechanisms involved in the prevention of emergence of antimicrobial resistance and infections, their applicability as prophylactic and therapeutic approaches, and their wider applicability to improve general health beyond their antagonistic activity on pathogens.[4,7]

However, other approaches like Clustered Regularly Interspaced Short Palindromic Repeats-Cas (CRISPR-Cas) are associated with many drawbacks like higher cost and time-consuming to formulate these novel methods, probability of off-target effects, lack of on-target editing efficiency, incomplete editing (mosaicism), Cas9 toxicity, difficulty of targeting intracellular infections with this technology, genome instability which may not be an effective barrier to plasmid and drug resistance spread, delivery inefficiency and inability to use conventional approaches like nanoparticles when phages are non-symmetrical and large.[4,6]

The probiotics, prebiotics, and synbiotics dietary-based non-antibiotic alternative approach aimed to switch the intestinal bacterial makeup of humans, involving the replacement of important beneficial bacteria by out-competing colonization of harmful pathogenic bacteria to regrow and establish a healthy microbiome.[7] In this approach, clinically important established promising outcomes were observed when these products are incorporated as a formulation into our day-to-day life helping in modulating an optimal balance of the human gut microbiome and possibly preventing the development of AMR.

Probiotics

Probiotics are live microbial species of bacteria or yeasts that resemble important functional microorganisms residing inside the human intestine. Under properly controlled studies, these live microbial species have been shown to have a health-promoting property for humans when taken in sufficient quantity as dietary supplements or found in foods.[8] Broad-spectrum antagonistic activity on the vast majority of microbes is especially an important health-promoting benefit of probiotics. Probiotics (yeasts or bacteria) are becoming the most popular, less expensive, and environmentally friendly novel therapeutic options to antibiotics to overcome the problems of antimicrobial resistance by direct inhibition of drug resistance pathogens or indirectly by reducing the risk of infections.[9,10]

The most common and well-investigated probiotics include many bacterial species of *Bifidobacterium* (ie, *B. longum, B. animalis* subsp. *lactis, B. infantis*, etc.) and *Lactobacillus* (ie, *L. plantarum, L. casei, L. acidophilus, L. rhamnosus* etc.). Some other bacterial species like *Lactococcus lactis* subsp. *lactis, Pediococcus acidilactici, Streptococcus thermophilus, Leuconostoc mesenteroides, Bacillus subtilis, Escherichia coli* Nissle 1917, *Enterococcus faecium*, etc.), and yeasts (*S. boulardii)* are also probiotics.[9–11]

Mechanism of Actions of Probiotics Against Antimicrobial-Resistant Pathogens

Probiotics have an enormous function for humans, mainly in the improvement of the intestinal microflora, making sure stability between harmful pathogens and bacteria essential for everyday functioning. The antagonistic activity of probiotics against antimicrobial-resistant pathogens can be by competitive exclusion through the creation of a hostile environment, blocking harmful pathogens from their adhesion sites,[12] toxin receptor blockage and degradation, out-competing pathogenic microbes for nutrients, modulating the host immunity and expression of genes,[13,14] and producing

substances (H2O2, bacteriocins, organic acids, and antioxidants) with inhibitory and antagonistic potential against the vast majority of pathogenic microbes.[15–20]

Substances like benzoic acid, formic acid, lactic acid, phenylacetic acid, acetic acid, carbon dioxide, hydrogen peroxide, acetoin, short-chain fatty acids, diacetyl, acetaldehyde, and bacteriocin substances of enterocin, enterolysin, lacticin plantaricin, nisin pisciolin, lactocin, reuterin, and pediocin are among the commonest chemical substance with the antimicrobial property.

These usually produced bacteriocins can effectively improve the host mucosal integrity by disrupting surface-associated microbial cells and decreasing the number of harmful microorganisms residing at the intestinal epithelium. This can further aid to reduce the pathogenic bacterial population and promote "colonization resistance".[21]

Probiotics at the intestinal epithelial cells can initiate cells in producing mucus and antimicrobial substances and thereby aid in improving intestinal barrier functions.[22] Production of immunoglobulins, macrophages, lymphocytes, and γ- interferon can also be their mechanism of improving mucosal immunity which could possibly reduce and eradicate harmful pathogenic microorganisms and opportunistic microbes in the human gut.[23] Probiotic microorganisms can efficiently protect the adhesion and colonization of pathogenic microbes to the surface of intestinal epithelial cells. They can also trigger and illicit a series of signaling pathways that can activate the various immunological cells which aid in preventing infectious diseases.

Several ex vivo and in vivo testing approaches have been employed for investigating the potential effects of probiotics as an alternative antimicrobial agent against harmful pathogens. The ex vivo (in-vitro) testing method uses different assay techniques like agar well diffusion/paper disc, microtiter plate, co-culturing, cell-line assays, and spot-on lawn/agar spot for determining antimicrobial activity.[11] Table 1 shows many established antimicrobial activities of many investigated probiotics against harmful microbes. The in vivo method uses animal studies, placebo-controlled human trials, and randomized double-blind studies to investigate the apparent ability of probiotic formulations against other microorganisms (Table 2).

Prebiotics

Prebiotics are carbohydrate-based polysaccharide food components that are selectively utilized by human or animal hosts. They are known for providing health-promoting effects to the host.[91] Carbohydrate-based glucans and fructans are known for their proven prebiotic potentials from other substances like starches, glucose, pectin, oligomers of mannose, human milk, xylose, and polyphenols.[91,92] In common practice, prebiotics are given to the host through orally,[91] however, direct application of the products to other microbially colonized body sites is also investigated as a possible method of administration. For instance, they can be directly applied to the vaginal tract[93] and skin.[94] Studies have outlined numerous investigated health benefits of prebiotics, including defending microbes,[95,96] modulating immunity,[97,98] absorbing minerals,[99–101] proper bowel functioning,[102,103] cardiovascular disease,[104,105] and assuring satiety.[106,107]

Mechanism of Action of Prebiotics in Defense Against Antimicrobial-Resistant Pathogens

Colonic bacteria utilize prebiotics as substrates of their fermentation products, resulting in the production of short-chain fatty acids (ie propionic acid, butyric acid, and lactic acid) which decreases pH in the colon. This lowering in colonic pH level will create acidic surroundings that are less suitable for the existence of harmful and pathogenic microorganisms which could result in the reduction of their numbers.[23,108] This change in the composition of the intestinal microbiome is helpful in reducing the risk of antimicrobial resistance. Moreover, the reduction in the pH of the colon can aid calcium and other minerals absorption, which can in turn help in limiting the growth of yeasts, and other harmful microorganisms.[19]

Prebiotics may also act by aiding epithelial cells functioning and supporting the gut microbiota by providing metabolic energy and thereby affecting the composition and function of these beneficial microorganisms. Establishing an optimal balance of beneficial microorganisms will help in reducing the availability of nutrient food components for the invading pathogenic microbes, and therefore inhibit epithelial invasion and colonization.[92,108] Moreover, prebiotics may also affect the intestinal epithelial absorption of nutrients and the level of host immune system efficiency.[102] Table 3

Table 1 Current Evidence Revealing in vitro Antimicrobial Activity of Probiotics

Probiotics with in vitro Antimicrobial Activity	Tested Pathogenic Microorganisms	Reported Result	In vitro Testing Method Employed	Ref
Lactobacillus Strains (L. acidophilus PBS066, *L. fermentum* PBS073, *L. plantarum* PBS067, *L. rhamnosus* PBS070, *L. reuteri* PBS072,) *and Bifidobacterium Strains (B. animalis* subsp. *Lactis* PBS075, *B. longum* subsp. *longum* PBS108)	**G+**: *S. aureus* ATCC 6538, *E. faecalis* ATCC 29212, **G-**: *E. coli* ATCC 25922, *P. aeruginosa* ATCC 9027, **fng**: C. *albicans* ATCC 10231	Cell culture supernatants of the examined strains showed inhibition of the growth of the pathogen at different extents, especially for *P. aeruginosa* and *E. coli*	Agar well diffusion assay/paper disc assay	[24]
L. salivarius JM41, JK21V, JM31, JS2A, JM14, JK22, JM2A1 and JM32, *L. plantarum PZ01, P. acidilactici* JM241 and JH231, *P. pentosaceus* JS233, *E. faecium JS11*	**G+**: *S. aureus* ATCC 29213, **G-**: *E. coli* K88, 25922 and 1569, *S. enteritidis* ATCC 13076, *S. typhimurium* ATCC 14082	Probiotic strains exert immunomodulation activity and efficiently inhibit adhesion and invasion of *Salmonella* to Caco-2 cells	Agar well diffusion assay/paper disc assay	[12]
L. plantarum FH185	**G+**: *S. aureus*, **G-**: *S. typhimurium*	Have a variable extent of growth Inhibition effect on *S. Typhimurium* and *S. aureus*	Co-culturing assay	[25]
P. pentosaceus KID7	**G+**: (*S. aureus* KCCM11335, *S. aureus* KCCM40510 (Methicillin-resistant), *S. epidermidis* KCTC 1917, *L. monocytogenes KACC*10764, *B. cereus* KACC11240) **G-**: *S.* Typhi KCTC2514, *S. choleraesuis* KCTC2932, *S. gallinarum* KCTC2931, *S. boydii* KACC10792, *Y. enterocolitica* KACC15320, *E. coli* O138KCTC2615, O1KCTC2441, *P. aeruginosa* KCCM 11802,	The concentrated culture filtrate of the tested probiotic showed a broad-spectrum antimicrobial activity against both gram-positive and gram-negative pathogenic bacteria	Agar well diffusion or paper disc assay	[26]
L. fermentum 907, *B. longum* 1011	**G-**: *E. coli* O157:H7, *E. coli* O86	The supernatant of both tested probiotics significantly inhibits the growth rates of both strains of *E. coli*	Co-culturing assay	[27]
L. paraplantarum FT259	**G+**: *L. monocytogenes* IAL 633, *L. innocua* ATCC 3309	L. paraplantarum FT259 produces bacteriocins that inhibit the growth of Listeria monocytogenes, Listeria innocua, and several lactic acid bacteria	Spot-on lawn/agar spot assay	[15]
Lactobacillus MSMC64-1	**G+**: MRSA DMST 20651, 20654, **G-**: *S. typhi* DMST 5784, *V. parahaemolyticus* DMST 5665, *S. dysenteriae* DMST 15111	Lactobacillus strain MSMC64-1 produced reuterin that has potent antimicrobial activity against seven pathogenic indicator strains with very strong inhibitory activities against S. typhi DMST 5784 and MRSA DMST 20651.	Agar well diffusion or paper disc assay	[28]

Lb: L13, L18, S30, S49, *L. plantarum* L14, *L. fermentum* L32, *L. pentosus* L45	*V. cholera* strain 0139 MTCC 3906, *Salmonella enterica Typhimurium* MTCC 733, *Listeria monocytogenes* MTCC 657, *Escherichia coli* MTCC 119, *Shigella flexneri* MTCC 1457, *V. parahaemolyticus* MTCC 451, and *Staphylococcus aureus* MTCC 96.	The culture supernatant (CS) of all seven isolates of Lactobacillus spp. used in the study inhibited the biofilm formation of V. cholerae by more than 90%.	Agar well diffusion assay	[29]
L. helveticus KLDS 1.8701	**G+** (*S. aureus* ATCC 25923, *L. monocytogenes* ATCC 19115), and **G-**: (*E. coli* O157:H7 ATCC 43889, *S. typhimurium* ATCC 14028)	Cell-free supernatants of KLDS1.8701 exhibited a higher inhibition of food-borne pathogens	Co-culturing assay	[30]
L. plantarum (P6)	*S. aureus* ATCC 25923, *E. coli* ATCC 25921, *B. cereus, P. aeruginosa, V. cholerae, L. ivanovii* ATCC 19119 and *S. enterica*	Neutralized free-cell supernatant from the culture of the Lb. plantarum (P6) inhibited the growth of all pathogenic indicators	Spot-on lawn/agar spot assay	[31]
L. viridescens NRRL B-1951	**G+**: *L. monocytogenes* CWD 1002, CWD 1198	Lactobacillus viridescens NRRL B-1951 could produce an inhibitory compound with a proteinaceous nature that is active against L. monocytogenes CWD 1002 and CWD 1198	Agar well diffusion or paper disc assay	[16]
L. acidophilus La-5,: *B. longum* ATCC 15707	**G+**: *S. aureus, L. monocytogenes;* **G-**: *E. coli* O157:H7	Probiotics in yoghurt inhibit the growth of S. aureus, E. coli O157:H7, and L. monocytogenes in vitro	Spot-on lawn/agar spot assay	[32]
L. acidophilus P106, *L. plantarum* P164	**Prs**: *Giardia lamblia*	L. acidophilus bacteriocin showed in vitro activity against G. lamblia trophozoites	Co-culturing assay	[33]
L. plantarum C014	**G-**: *A. hydrophila* TISTR 1321	The bacterial strain isolated from the intestines of hybrid catfish exhibited an in vitro inhibitory effect, *Aeromonas hydrophila* TISTR 1321	Co-culturing assay	[34]
FloraMax®-B11 containing LAB 18, LAB 48	**G-**: *S. enterica* serovar *enteritidis*, *E. coli* O157:H7, *C. jejuni*	Both strains showed in vitro antibacterial activity against *S. enterica* serovar *enteritidis*, *E. coli* (O157:H7), and *C. jejun*	Spot-on lawn/agar spot assay	[35]
L. plantarum WCFS1, *L. plantarum* NA7	**G+**: *L. monocytogenes* CIP 81.3 ILSI NA 39, **G-**: *E. coli* O157:H7 ATCC 43888, *S. enterica* ser *enteritidis* CIP 81.3	Supernatants from different Lactobacillus could produce food pathogen inhibitory molecules and inhibit TNF-α production	Agar well diffusion or paper disc assay	[36]

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Table 1 (Continued).

Probiotics with in vitro Antimicrobial Activity	Tested Pathogenic Microorganisms	Reported Result	In vitro Testing Method Employed	Ref
L. casei	**G+**: *L. monocytogenes*, **G-**: *E. coli* C17, *S. enterica* ser *Typhimurium*	Twenty Lactobacillus strains were able to inhibit the enteropathogenic bacterium Yersinia enterocolitica, and two strains inhibit Y. enterocolitica, S. serovar Typhimurium, and L. monocytogenes. All acts by decreasing the Ph	Agar well diffusion or paper disc assay	[37]
E. faecium CV1, LPP29, W. cibaria P71, L. lactis subsp. cremoris SMF110, Lc. mesenteroides subsp. cremoris SMM69, P. pentosaceus SMM73, TPP3	**G-**: *T. maritimum* NCIMB2154, LL01.8.3.8, *V. splendidus* CECT528, DMC-1	Cell-free culture supernatants from all LAB but Lb. curvatus BCS35 inhibited the growth of T. maritimum NCIM2154 and V. splendidus CECT528.	Spot-on lawn/agar spot assay	[38]
13 strains of Lactobacilli (CM1, CM2, FS2, FM13, FM14, FM22, MF5, PM8, PS2, SP13, PS11, SF6, FS10)	*S. aureus* ATCC 6538, *L. monocytogenes* DSM 12464, *E. faecalis, E. coli* ATCC 25922	All strains were effective against both *S. aureus* and *E. coli*, and variable activity versus L. monocytogenes and E. faecalis strains	Agar well diffusion or paper disc assay	[39]
S. cerevisiae JCM7255	**G+**: *S. agalactiae*	Agar spot anti-streptococcal activity showed inhibition of 20 out of 30 strains of *S. agalactiae*.	Spot-on lawn/agar spot assay	[40]
L. reuteri, B. subtilis MA139	**G-**: *E. coli* K88	*Lactobacillus reuteri* alone as well as in combination with B. subtilis MA139 spores exerted strong inhibition against E. coli K88 under static conditions	Co-culturing assay	[41]
L. acidophilus JN188382, *L. fermentum* JN188383, *L. fermentum* JN188384, *L. buchneri* JN188385, *L. buchneri* JN188386, *L. buchneri* JN188387, *L. casei* JN188388, *L. casei* JN188389, *L. casei* JN188390	**G+**: *E. faecium* ATCC 51558, *S. epidermidis* ATCC *12228, P. acnes ATCC 6919, L. monocytogenes, S. aureus* S244; **G-**: *E. coli ATCC 29181, K. pneumoniae* K36, *E. cloacae, S. sonnei ATCC 25931, H. pylori ATCC 43579, V. parahaemolyticus*, **fng**: *C. albicans* ATCC 44831	Nine of the Lactobacillus strains exhibited good antimicrobial activities and a good ability to attach to intestinal epithelial cells with no resistance to the tested antibiotics	Spot-on lawn/agar spot assay	[42]
L. paracasei CNCM I_4034, *L. Bifidobacterium breve* CNCM I-4035 and *L. rhamnosus* CNCM I-4036	**G-**: *E. coli* ETEC CECT 501, *S. Typhimurium* CECT	Supernatants obtained from L. paracasei CNCM I-4034, B. breve CNCM I-4035 and L. rhamnosus CNCM I-4036 inhibit the growth of enterotoxigenic and enteropathogenic (EPEC) bacteria	Co-culturing assay	[43]

L. *casei* LC-01, *L. acidophilus* LA-5, *L. paracasei*	**Fng**: *A. niger* PTCC 5012, *A. flavus* PTCC 5004, *A. parasiticus* PTCC 5286, *P. chrysogenum* PTCC 5035	Both liquid culture and supernatant of probiotic bacteria strains have the ability to prevent the growth of pathogenic and mycotoxigenic fungi as antifungal agents, L. case being with the highest activity	Agar well diffusion or paper disc assay	[44]
L. casei PTCC 1608, *L. rhamnosus* PTCC 1637	**G-**: *P. aeruginosa* PTCC 1430	Cell-free supernatant (CFS) of probiotics could curtail the growth of P. aeruginosa. synergistic interactions were observed in the combination of CFS and aminoglycoside antibiotics	Agar well diffusion or paper disc assay	[45]
L. *mesenteroides* subsp. *mesenteroides* SD1, SD23, SF2, SF3	G+: *S. aureus* ATCC 25923, FRI 184, *L. monocytogenes* ATCC 19115, G-: *E. coli* ATCC43895, *S. enterica* ATCC 14028	The supernatant of the isolated showed inhibition to three enteropathogenic strains: E. coli ATCC43895 (EC), S. enterica ATCC 14028 (ST), and L. monocytogenes ATCC 19115 (LM) as well as two enterotoxigenic strains: S. aureus [ATCC 25923 (SA) and FRI 184 (SAI)]	Agar well diffusion or paper disc assay	[46]
B. pumilus B16, *B. mojavensis* J7	**G-**: *V. parahaemolyticus*	Twenty-four among 249 isolates displayed direct antimicrobial activity to V. parahaemolyticus with spot inoculation	Spot-on lawn/agar spot assay	[47]
L. plantarum S2	**G+**: *S. aureus* CMCC2607, **G-**: *E. coli* CMCC44825, *S. Typhimurium* CMCC50115, *S. flexneri* CMCC51061	L. plantarum S2 combined with xylooligosaccharides have enhanced antimicrobial activity against gastrointestinal pathogens	Agar well diffusion or paper disc assay	[48]
L. rhamnosus GR-1, *L. reuteri* RC-14	**Fng**: *C. glabrata*	Probiotic Lact. rhamnosus GR-1 and Lact. reuteri RC-14 strains exhibited potent antagonistic activities against all of the tested C. glabrata strains causing cessation of growth and eventual cell death of C. glabrata	Co-culturing assay	[49]
L. plantarum CK06, CK19, B01, B07, K09, K10, K21, LM11, ZS07, ZS11 and ZS15	**G+**: *S. aureus SSV25, S. epidermidis SSV30, S. lentus CCM 3472, E. faecalis* V583, *L. monocytogenes* CCM *4699*, **G-**: *A. calcoaceticus* CCM *4503; S. paucimobilis* CCM *3293; S. enterica subsp. enterica* TA100 CCM 3812	When tested against indicator strains, the *Lactobacillus* isolates demonstrated different inhibitory activities with a zone of inhibition ranging from 1mm to 5mm by the production of organic acids,	Spot-on lawn/agar spot assay	[50]

(*Continued*)

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Probiotics with in vitro Antimicrobial Activity	Tested Pathogenic Microorganisms	Reported Result	In vitro Testing Method Employed	Ref
L. helveticus PJ4, *L. plantarum* PJ7	**G+**: *S. aureus* MTCC737, **G-**: *E. coli* MTCC443, *S. Typhimurium* MTCC733, *S. flexneri* MTCC1457, *P. aeruginosa* MTCC1688	L. helveticus PJ4 and L. plantarum PJ7 exhibited strong antibacterial activities against the pathogens tested as assessed in neutral pH culture supernatants	Agar well diffusion or paper disc assay	[51]
B. subtilis JQ302302, *B. aerophilus* JQ312663	**G-**: *A. hydrophila* ATCC 49140, MTCC 1739, *Aeromonas* sp. JX136697, JX136698, A. *enteropelogenes* JX136699, *P. rettgeri* JX 136696	Isolates demonstrated significant antibacterial activity against the fish pathogens A. hydrophila ATCC 49140, A. hydrophila MTCC 1739, A. enteropelogenes JX136699, and P. rettgeri JX136696.	Agar well diffusion or paper disc assay	[52]
L. rhamnosus 204, *L. rhamnosus* 45B, *L. plantarum* N221-1, *L. rhamnosus* N145-1A, *L. rhamnosus* QF60-2	**G-**: *H. pylori*	L. johnsonii NCC533 found to be the most efficient probiotic strain with anti-H. pylori activity compared with L. rhamnosus GG and L. plantarum 299v	Agar well diffusion or paper disc assay	[53]
B. amyloliquefaciens KATMIRA1933	**Vir**: Herpes simplex virus types 1 and 2	At high concentrations, subtilosin produced by B. amyloliquefaciens, has a virucidal effect against HSV-1. Subtilosin non-virucidal concentrations can inhibit wild-type HSV-1 and acyclovir-resistant mutants in a dose-dependent manner	Agar well diffusion or paper disc assay	[54]
B. subtilis DCU, *B. pumilus* BP, *B. cereus* HL7	**G-**: *V. parahaemolyticus*	Of the 135 isolated strains three Bacillus strains (BP, DCU, HL7) showed strong inhibition against the pathogen, causing a clear zone of about 15–20 mm in the agar spot assay	Spot-on lawn/agar spot assay	[55]
B. amyloliqufaciens	**G+**: *C. difficile*	*After incubation with B. amyloliquefaciens* supernatant growth inhibition were observed against all *C. difficile* ribotypes.	Agar well diffusion or paper disc assay	[56]
L. fermentum M059, *L. fermentum* F-6, *W. cibaria* 4213	**G+**: *S. aureus* ATCC 6538, *B. cereus* NCIM 245, *B. subtilis* ATCC 6633, G-: *E. coli* ATCC 25922, *S. typhi* 25, *P. aeruginosa* ATCC 27853	The selected strains exhibited varied inhibitory effects against each indicator bacterium and inhibited both Gram-positive and Gram-negative pathogens	Agar well diffusion or paper disc assay	[57]
L. acidophilus L-1, *L. bulgaricus* 6, *L. plantarum* 24-4B, *L. fermentum* 1, *L. brevis, B. animalis* subsp. *lactis* L-3	G+: *S. aureus, B. cereus* G-: *E. coli*	Ten strains of Lactobacillus and Bifidobacterium showed promising antimicrobial activity against two pathogens or in both model systems (broth and milk)	Agar well diffusion or paper disc assay	[58]

L. casei	**G-: S**. *flexneri, S. sonnei*	L. casei strongly inhibits the development of MDR Shigella pathogenic strains	Agar well diffusion or paper disc assay	[59]
L. brevis DT24	**G-**: *E. coli* MTCC 729	Expression of E. coli colicin E2 (ColE2) into Lactobacillus showed increased expression of colicin E2 at the extracellular level to inhibit the infectious disease that occurred by uropathogenic E. coli. Antimicrobial properties of transformed L. brevis DT24-ColE2 showed a higher zone of inhibition (56 mm) compared to Wild Type L. brevis DT24 (23 mm)	Agar well diffusion or paper disc assay	[60]
B. amyloliquefaciens FPTB16	*E. tarda, A. hydrophila, V. harveyi, V. parahaemolyticus*	Dietary supplementation of 109 CFU/g B. amyloliquefaciens significantly improves health status and resistance of catla against bacterial challenge	Agar well diffusion or paper disc assay	[61]
L. plantarum DK211, DK303; *L. paracasei* DK215, L. *sakei* DK301	*S. aureus* KCTC 3881, *E. faecalis* KCTC 2011, *B. cereus* KCTC 3624	DK211, DK215, DK301, and DK303 had effective inhibitory activity against all pathogens tested except E. coli. This suggests a potential probiotic	Agar well diffusion or paper disc assay	[62]
L. plantarum, L. salivarius, L. johnsonii, L. ingluviei, L. agilis, L. kitasatonis, L. mucosae, and L. oris	*S. aureus* ATCC 6538S, *C. perfringens* ATCC 13124, *E. coli* ATCC 8734, *S. enteritidis* ATCC 13311, *R. anatipestifer* ATCC 11845, *P. multocida* ATCC 43137	The selected Lactobacillus strains show strong inhibition against the growth of pathogenic bacteria due to lactic acid production and can potentially restore the balance of intestinal microflora in geese and could offer an alternative to antibiotic therapy	Agar well diffusion or paper disc assay	[63]
L. salivarius K35, K43	**G+**: *S. mutans* ATCC 25175	K35 and K43L. Salivarius strains, significantly inhibited S. mutans biofilm formation and possessed a stronger bactericidal activity against S. mutans on Spot assay	Agar well diffusion or paper disc assay	[64]
L. mesenteroides MTCC 5442, *B. subtilis*	**G-**: *V. cholerae*	*L. mesenteroides* or *B. subtilis*, is able to produce an inhibitory effect on the growth of V. *cholerae* and had a synergistic effect when used in combination	Agar well diffusion or disc assay	[65]
L. acidophilus P106, *L. plantarum* P164	Prs: *Giardia lamblia*	L. acidophilus bacteriocin showed in vitro activity against G. lamblia trophozoites	Agar well diffusion or paper disc assay	[33]

(*Continued*)

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Table 1 (Continued).

Probiotics with in vitro Antimicrobial Activity	Tested Pathogenic Microorganisms	Reported Result	In vitro Testing Method Employed	Ref
L. acidophilus ATCC3456, *L. casei* ATCC 39392, *L. rhamnosus* ATCC 7469	*S. aureus* ATCC 25923, *E. coli* ATCC 25922	*All three Lactobacillus strains have inhibitory effects for E. coli, Cell-free supernatant of L. casei being the most effective probiotic*	*Microplate technique*	[66]
L. reuteri (DSM17938), *L. acidophilus* (DSM), *B. coagulans* (DSM1), *L. plantarum* 299v (DSM9843), and *B. bifidum* (DSM20456)	*P. aeruginosa*	Combination of probiotic strains with antibiotics have enhanced inhibitory effect. Lactobacillus plantarum 299v had the highest effect.	*Disk diffusion method.*	[67]
L. acidophilus EMCC 1324, *L. helveticus* EMCC 1654, *L. plantarum* EMCC 1027, *L. rhamnosus* EMCC 1105 *B. longum* EMCC 1547 *B. bifidum* EMCC 1334	*E. coli*	All probiotic isolates exhibit strong antibacterial activity against all E. coli isolates and eradicated biofilms formed by multidrug-resistant E. coli.	Agar diffusion method	[68]
L. paracasei ABRIINW. F58	*S. aureus, P. aeruginosa*	Both MDR E. coli isolates and (9–12 mm), Pseudomonas aeruginosa isolates (7–10 mm) were sensitive to bacteriocins produced by L. paracasei ABRIINW. F58	Disc diffusion method	[69]
L. acidophilus and *S. cerevisiae*	*S. typhimurium*	Increased concentration of probiotic filtrate could increase the inhibition zone due to the increased concentration of inhibitory compounds especially the bacteriocins	Agar well diffusion method	[70]
Curd lactobacilli (*L. animalis, L. gasseri, L. acidophilus, L. rhamnosus*)	*E. coli, K. pneumoniae*	Curd of lactobacilli alone or in combination with antibiotics had excellent antibacterial activities against *E. coli* and *K. pneumoniae* clinical isolates infection	Agar-overlay method	[71]
L. reuteri DSM 17938	*S. aureus, S. pyogenes, Cutibacterium acnes, P. aeruginosa.*	The probiotic decreased the inflammatory process and presented antimicrobial action against *S. aureus, S. pyogenes, Cutibacterium acnes*, and *P. aeruginosa.*	Agar well diffusion/ paper disc method	[72]
B. longum ATCC 15707, *L. brevis* ATCC 367, *L. delbrueckii* ATCC 9649, *L. fermentum* ATCC 23271, *L. paracasei* ATCC 335, *L. plantarum* ATCC 8014, and *L. rhamnosus* ATCC 9595	*C. butyricum* ATCC 860, *C. difficile* ATCC 9689, *C. perfringens* ATCC 12924	*L. plantarum* strain ATCC 8014 has probiotic potential, with antimicrobial activity against *C. butyricum* ATCC 860, *C. difficile* ATCC 9689, and *C. perfringens* ATCC 12924	Agar spot test	[73]

Abbreviations: G+, Gram-positive; G−, Gram-negative; fng, fungi; prs, parasite; Vir, Virus.

Table 2 Current Evidence Revealing in vivo Antimicrobial Activity of Probiotics

Probiotics with Efficient in vivo Antimicrobial Activity	Tested Pathogenic Microorganisms	Finding	In vivo Testing Method Employed	Ref
L. paracasei	*Galleria mellonella*	*L. paracasei* was able to modulate the immune system of *G. mellonella* and protect against candidiasis.	Clinical trial	[74]
L. rhamnosus, L. acidophilus, and B. bifidum	*Candida spp.*	Decrease in *Candida spp.* in individuals who used the probiotic formulation.	Randomized double-blind study	[75]
L. salivarius NK02	*Aggregatibacter actinomycetemcomitans*	The results suggest that the mouthwash containing probiotics were healthy for daily use as an alternative to maintaining dental and periodontal health.	Randomized double-blind study	[76]
L. casei	*Cryptosporidium parvum*	Oral administration of the probiotic *L. casei* associated with albendazole reduced Giardia infection,	Murine model.	[77]
B. animalis subsp. lactis DN-173010	Periodontopathogens (*P. gingivalis, Fusobacterium nucleatum*, and *Aggregatibacter actinomycetemcomitans*)	*B. animalis* showed a positive effect against the accumulation of bacterial plaque and gingival inflammatory parameters.	Randomized controlled trial	[78]
L. reuteri CL9, K16, K67 and S33	**G-**: *E. coli* O149: K88 JG280	Isolates showed ≥50%protection from cell and worm death caused by enterotoxin expressed in E. coli. CL9promoted host defensive responses,	Porcine	[79]
L. casei B–7280, *B. longum* VK1, *B. bifidum*VK2	G+: *S. aureus*8325–4	The number of colonies of Staph. aureus 8325–4 decreased significantly in infected mice that received probiotics compared to the mice that did not receive	Mice	[80]
Lb. FloraMax-B11 (*L. salivarius, L. Pediococcus parvulus*)	*S. enteritidis*	Administration of this probiotic significantly reduced *S. enteritidis* intestinal colonization in chickens	Broiler chickens	[81]
Pseudoalteromonas sp.	**G-**: *V. harveyi* ATCC 14126	Significant reduction in accumulated mortality of larvae in aquaculture system when supplemented with culture supernatant	Crustacean's larva	[82]
L. salivarius JM32, *L. plantarum* PZ01, *P. acidilactici* JH231	**G-**: *S. enteritidis* ATCC 13076	Lb strains reduced the number of Salmonella in intestinal content, spleen, and liver,	Broiler chicks	[12]
B. amyloliqufaciens	**G+**: *C. difficile*	An increase in C. difficile toxin A and B levels and a significant weight loss were seen in untreated and S. boulardii treated mic than in *B. amyloliquefaciens* treated mice	Mice	[56]
L. acidophilus CH1	**Prs**: *Enterocytozoon bieneusi*	Anti-microsporidial effects of *L. acidophilus* CH1-derived bacteriocin in immunosuppressed mice were significantly potent.	Mice	[83]
Lb: *L. plantarum* LA5 and *L. paracasei* LA7	**G-**: *S. typhi*	LA5 or LA7 eradicate *S. Typhi* induced typhoid infection from infected mice due to antimicrobial, anti-inflammatory, and immunomodulatory activities	Mice	[84]

(*Continued*)

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Table 2 (Continued).

Probiotics with Efficient in vivo Antimicrobial Activity	Tested Pathogenic Microorganisms	Finding	In vivo Testing Method Employed	Ref
L. plantarum LR/14	**Ins**: *Drosophila melanogaster*	At a concentration of 15 mg/mL, antimicrobial peptides from *L. plantarum* resulted in the deformity in cellular architecture, DNA fragmentation, premature apoptosis, and death of insects	Drosophila melanogaster fly	[85]
L. plantarum C014	**G-**: *A. hydrophila* TISTR 1321	Feeding the fish with the *L. plantarum* C014 supplemented diet for 45 days before challenging them with *A. hydrophila* at the dose of LD50 enhances innate immune response, and reduces the mortality rate of the fish from 50% (in the control group) to 0% (in treated group)	Hybrid Catfish	[34]
L. acidophilus and *S. cerevisiae*	*S. typhimurium*	Oral administration of both probiotic isolates could decrease the counts of *S. typhimurium* in liver and spleen	Mice	[71]
L. *casei, L. acidophilus, L. rhamnosus, L. bulgaricus*, B. *breve, B. longum*	*K. pneumoniae*	Administration of Lactocare can reduce ICU and a hospital stays of patients	Randomized clinical trial	[86]
L. plantarum MTCC 1407, *L. acidophilus* MTCC 10307	Enteroaggregative *E. coli* and *E. coli* ATCC 25922	Probiotic strains can serve as a therapeutic agent against multi-drug-resistant E. coli.	Mice	[87]
L. casei (Shirota Strain)	*K. pneumoniae*	Oral administration of probiotic *L. casei* Shirota strain reduces the risk of Ventilator-associated pneumonia (VAP) in patients	Randomized, open-label controlled trial	[88]
L. acidophilus, Pediococcus	**G-**: *S. enteritidis* 13A	Probiotic treatment with L. acidophilus and Pediococcus significantly reduced Salmonella colonization in chicks	Birds	[89]
LactoLevure® (containing *L. plantarum, L. acidophilus, S. boulardii and B. lactis*)	*P. aeruginosa and E. coli*	Pretreatment with these probiotics products could increase the survival rate and levels of cytokine eg, TNF and IL-10 of mice under infection conditions with MDR P. aeruginosa, E. coli.	Mice	[90]

Abbreviations: G+, Gram-positive; G−, Gram-negative; Prs, parasite; Ins, insect; MDR, multidrug-resistant.

Table 3 Current Evidence Revealing Antimicrobial Activity of Selected Prebiotics

Prebiotics with Reported Antimicrobial Activity	Target Pathogenic Microorganisms	Reported Results	Testing Method Employed	Ref
Combination of GOS and FOS	*Rotavirus*	Increased levels of SCFAs, decreased incidence of stools, improved stool consistency, a significant reduction in viral shredding, improved immune system, reduced effects of rotavirus-induced gastroenteritis	Suckling rat rotavirus infection model	[108]
GOS	*Bifidobacterium*	Increased *Bifidobacterium*, improving the immune system of the host due to the interaction of immune cells and host epithelium with colonic microbiota, reducing the risk of infections	Double-blind, controlled trial, formula-fed infants	[109]
MOS and FOS	*E. coli, C. perfringens*	Decreased in the population of pathogens	Broiler chickens	[110]
FOS and MOS	*C. perfringens, E. coli*	Decreased populations of *C. perfringens* and *E. coli*	Broiler chickens	[111]
Raffinose	*P. aeruginosa*	Inhibition *P. aeruginosa* biofilm formation	In vitro agar plates	[112]
Lactosucrose	Influenza A virus	Provide enhanced innate immune responses and aid in suppressing influenza A virus infection which increased the overall survival rate of tested mice	Mice	[113]
Casein, fiber-rich soybean meal	*Eubacteria, Lactobacillus spp., Bifidobacterium spp., Clostridium Cluster* IV, *Clostridium Cluster* XIVa,	Enhanced fecal counts of tested beneficial bacterial groups which could out-compete and potentially prevent invasion with pathogenic microbes	Pigs	[114]
Whey peptide extract from Cynara cardunculus	*L. acidophilus* and *Bifidobacterium*	The proliferation and growth of tested probiotic bacteria were greatly enhanced and aided in shifting toward the beneficial microbiota profile	Rats	[115]
Raffinose	*S. mutans*	Inhibit oral bacterial adhesion and biofilm formation and keep oral health by preventing bacterial-induced dental caries	In vitro culturing method	[116]
Raffinose	*P. aeruginosa, S. aureus*	It effectively reduces the biofilm formation of tested pathogens in a dose-dependent manner	In vitro co-culturing	[117]

Abbreviations: FOS, Fructooligosaccharide; GOS, Galactooligosaccharide; MOS, Mannan-oligosaccharide.

summarizes the currently available evidence on the antimicrobial activity of prebiotics through these different proposed mechanisms of action.

Synbiotics

Synbiotics are a combination product of live microorganisms and substrate(s) that are selectively taken and utilized by human or animal hosts to impart a health-promoting benefit. Those products can be complementary synbiotics where they are selectively used by either the endogenous microbiota or synergistic types where they are utilized by the live microorganism in the formulation, and therefore having proof of conferring health benefit is not merely sufficient to prepare and formulate a synbiotic product. As for probiotics, the application of synbiotics inside or outside the intestine is also possible and promising. Synbiotics might be formulated into a variety of suitable and convenient products, such as drugs, foods, or nutritional supplements.[118]

Table 4 Current Evidence Revealing in vivo or ex vivo Antimicrobial Activity of Synbiotics

Synbiotics	Target Infectious Diseases/ Microorganisms	Reported Results	Study Undertaken	Ref
L. fermentum CECT5716 with GOS	Gastrointestinal and respiratory infection	Synbiotic administration has marked inhibition on rotavirus and prevented community-acquired gastrointestinal infections in infants	Randomized controlled study	[132]
L. acidophilus, L. rhamnosus, B. bifidum, B. longum, E. faecium, with FOS	Acute diarrhea	Duration of diarrhea and hospitalization was significantly shorter in children receiving the synbiotic group	Randomized controlled study	[133]
S. thermophilus, L. rhamnosus, L. acidophilus, B. lactis, B. infantis with FOS	Acute diarrhea of likely infectious origin	Synbiotics could shorten the duration of diarrhea and reduce the number of additional medications (antipyretics, antiemetics, antibiotics) used	Randomized, controlled clinical trial	[134]
Non-digestible oligosaccharides (GOS, FOS, XOS, IMOS, and lactulose) with *B. breve* 46, *B. lactis* 8:8, *B. longum* 6:18, *B. breve* CCUG 24611, *B. lactis* JCM 10602, *B. pseudocatenulatum* JCM 1200	*Clostridium difficile*	In the presence of such prebiotics, Bifidobacterium, breve 46 and Bifidobacterium lactis 8:8 inhibited the growth and toxin production in four different strains of Clostridium difficile.	Agar plate assays	[135]
B. lactis B94 with inulin	*Rotavirus, Adenovirus, Entamoeba histolytica, Salmonella, Shigella, Campylobacter, Clostridium difficile, Cryptosporidium, and parasites*	Synbiotic treatment decreased the duration of diarrhea	Randomized controlled study	[136]
Garlic and basil as natural prebiotics with *Pediococcus acidilactici*	E. coli, Salmonella, E. faecalis and S. aureus.	The presence of prebiotics augments the antimicrobial activity of probiotic strains against tested pathogens.	Agar plate assays	[137]
L. acidophilus and FOS	*P. aeruginosa, E. coli, S. aureus* and *B cereus*	Enhanced activity of the probiotic bacteria (*L. acidophilus)* and inhibited the pathogenic bacteria, where E. coli was more susceptible to inhibition, followed by *S. aureus, P. aeruginosa*, and *B. cereus*, respectively.	Agar plate assays	[138]
L. rhamnosus and *P. acidilactici* in combination with inulin-type fructans	*Candida albicans.*	The synbiotic combinations inhibit the growth and biofilm formation of *Candida albicans* and could be used as an alternative to antifungal drugs in candidiasis therapy.	Microtiter plates	[139]
L. rhamnosus with inulin or FOS	Vancomycin susceptible Enterococcus faecalis (VSEF) and clinical vancomycin-resistant Enterococcus faecium (VREF)	Synbiotic showed an inhibition effect on VREF growth, Lactobacillus rhamnosus with inulin being the most effective	Agar well diffusion method	[140]

(*Continued*)

Table 4 (Continued).

Synbiotics	Target Infectious Diseases/ Microorganisms	Reported Results	Study Undertaken	Ref
P. pentosaceus 5–33:3, *L. mesenteroides* 32–77:1, *L. paracasei ssp. paracasei* 19; and *L. plantarum* 2362; and inulin, oat bran, pectin, and resistant starch	Critically ill, mechanically ventilated, multiple trauma patients	Symbiotic treatment in critically ill, mechanically ventilated, multiple trauma patients improve the patient's response by reducing infection and sepsis rates and	Randomized Controlled Trial	[141]
L. plantarum ATCC-202195 plus FOS	Sepsis in infants	The synbiotic combination reduced culture-positive and culture-negative sepsis and lower respiratory tract infections.	Randomized, controlled trial	[142]
L. acidophilus 10, *L. rhamnosus* HS 111, *L. casei* 10, *B. bifidum* plus FOS	Surgical infections and complication prevention	Synbiotic administration significantly decreases the incidence of postoperative infection and also shortens the duration of antibiotic therapy	Randomized, Clinical Trial	[143]
B. breve strain Yakult, *L. casei* strain Shirota plus GOS	Postoperative infections	Synbiotics reduce the number of harmful bacteria, and post-operative infection complications, and enhanced beneficial bacteria and organic acids	Randomized, controlled trial	[144]
S. faecalis T-110, *C. butyricum* TO-A, *Bacillus mesentericus* TO- A, *L. sporogenes*	Postoperative infectious complications	Synbiotics significantly reduce septic complications, hospital stay, and antibiotic requirements in patients undergoing pancreatic surgery for chronic pancreatitis.	Randomized Control Trial	[145]

Abbreviations: FOS, fructooligosaccharides; GOS, galactooligosaccharides; IMOS, isomaltooligosaccharides; XOS, xylooligosaccharides.

Species from the genera *Lactobacillus, Bifidobacterium*, and *Streptococcus* with variable doses of either galactooligosaccharides, inulin, or fructo-oligosaccharides are the most commonly used to test live microorganisms and substrate components in synbiotic formulations, respectively.[11]

Many trials have claimed the potential health benefits of synbiotics in preventing and treating various infectious disease conditions like eradicating infection induced by *Helicobacter pylori* bacteria,[119,120] and preventing the occurrence of surgical site infections.[121–125] The result reported from various systematic review and meta-analysis studies done at different times also revealed the effectiveness of synbiotics in reducing surgery-related complications like sepsis, diarrhea, urinary tract infection, pneumonia, abdominal distention, duration of postoperative fever, surgical site infection, and duration of antimicrobial therapy and subsequent duration of hospitalization.[126,127]

Mechanism of Actions of Synbiotics in Defense Against Antimicrobial-Resistant Pathogens

There are many proposed mechanisms of action for synbiotics in defending against many harmful resistant pathogens. The presence of substrate components in a synbiotic formulation provides a favorable condition for living microorganisms to help in competing with the pathogenic microorganisms inside the gut environment and thereby improving the growth and number of useful microflora which supports intestinal homeostasis.[128] Host immune system modulation and microbial toxin neutralization through the production of metabolites like short-chain fatty acids are also their mechanisms to fight against resistant pathogens.[126] Synbiotics-based natural way inhibition of such pathogenesis can significantly

reduce the high burden of antimicrobial pills use and subsequent antimicrobial resistance resulting from antimicrobial-induced selection pressure.[128] Some studies[129–131] have established the potential of synbiotics for restoring unbalanced gut microbiome by enhancing the growth and number of gut-useful microbes which can serve as a promising option for the antimicrobial treatment of various infectious diseases. Table 4 summarizes the currently available evidence on the in vivo and in vitro antimicrobial potential of synbiotics.

Summary and Future Prospects of Probiotics, Prebiotics, and Synbiotics as Alternative Sources for Antimicrobial Agents and Prevention of Antimicrobial Resistance

The potential benefits of using probiotics, prebiotics, and synbiotics as alternative therapies to combat antimicrobial-resistant infections are promising. These natural agents have been shown to have antimicrobial properties and can help to restore and maintain a healthy balance of bacteria in the body, which can reduce the risk of infections and minimize the need for antimicrobial agents. However, the effective means of administering these natural agents to the site of action is still a topic of investigation. Nanotechnology formulations with a biocompatible matrix encapsulation of probiotics with polysaccharide prebiotics can be a promising approach to delivering these agents to the site of action. The use of polysaccharides with prebiotics potential as a matrix polymer is an innovative approach that can provide a dual benefit as a delivery agent and an effective synbiotics formulation. It is also important to note that probiotics, prebiotics, and synbiotics should be used as adjuvants or synergistic agents to conventional antimicrobial therapies, rather than a replacement. This approach can aid in fostering healing and eradication rates of pathogenic microbial infections, reduce the cumulative dose and side effects of conventional antimicrobials, and minimize the development of anti-microbial resistance. It is crucial for stakeholders and government health policies to give special emphasis to formulating individualized dosage forms with established safety and efficacy of these therapeutic biologic agents, taking into account various factors like the disease condition, ways of administration/delivery, storage conditions, and facilities, and host innate and physiologic conditions. All these factors need to be considered and standardized. Furthermore, the theoretical side effects from the consumption of probiotics, such as transferring antimicrobial-resistant genes to pathogens, should be considered. An investigation of antimicrobial susceptibility of the strains to identify potential drug-resistant plasmids and assure that no transferable antimicrobial-resistant gene is present should also be performed to ensure safety and efficacy. Efforts should be put in to assure market availability of these products in the most cost-effective manner so that every society across the world can get benefited. Like the conventional pharmaceutical products being marketed, these products should also be procured at each distribution and retail outlet and should be advertised through television, radio, newsletters web banners, social media, email, blogs, public gatherings, conferences, and pay per click ads for assuring products continual future utilization.

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References

1. Karbalaei M, Keikha M. Probiotics and intestinal decolonization of antibiotic-resistant microorganisms; A reality or fantasy? *Ann Med Surg*. 2022;31(80):104269. doi:10.1016/j.amsu.2022.104269
2. Nureye D, Salahaddin M, Woldeselassie W. One health approach and antimicrobial resistance: from global to Ethiopian context. *EC Pharmacol Toxicol*. 2020;8:59–75.
3. Reygaert WC. An overview of the antimicrobial resistance mechanisms of bacteria. *AIMS Microbiol*. 2018;4(3):482–501. doi:10.3934/microbiol.2018.3.482
4. Sharma C, Rokana N, Chandra M, et al. Antimicrobial resistance: its surveillance, impact, and alternative management strategies in dairy animals. *Front Vet Sci*. 2018;4:237. doi:10.3389/fvets.2017.00237

5. Sannathimmappa MB, Nambiar V, Aravindakshan R. Antibiotics at the crossroads - Do we have any therapeutic alternatives to control the emergence and spread of antimicrobial resistance? *J Educ Health Promot*. 2021;30(10):438. doi:10.4103/jehp.jehp_557_21
6. Tao S, Chen H, Li N, Liang W. The application of the CRISPR-cas system in antibiotic resistance. *Infect Drug Resist*. 2022;15:4155–4168. doi:10.2147/IDR.S370869
7. Feehan A, Garcia-Diaz J. Bacterial, gut microbiome-modifying therapies to defend against multidrug resistant organisms. *Microorganisms*. 2020;8(2):166. doi:10.3390/microorganisms8020166
8. Hill C, Guarner F, Reid G, et al. Expert consensus document. The international scientific association for probiotics and prebiotics consensus statement on the scope and appropriate use of the term probiotic. *Nat Rev Gastroenterol Hepatol*. 2014;11(8):506–514. doi:10.1038/nrgastro.2014.66
9. Figueroa-González I, Quijano G, Ramírez G, Cruz-Guerrero A. Probiotics and prebiotics--perspectives and challenges. *J Sci Food Agric*. 2011;91(8):1341–1348. doi:10.1002/jsfa.4367
10. Hernandez-Patlan D, Solis-Cruz B, Hargis BM, Tellez G. The use of probiotics in poultry production for the control of bacterial infections and aflatoxins. *Prebiotics Probiotics*. 2020;4:217–238.
11. Fijan S. Antimicrobial effect of probiotics against common pathogens. *Probiotics Prebiotics Human Nutr Health*. 2016;13(10):5772.
12. Feng J, Wang L, Zhou L, Yang X, Zhao X. Using in vitro immunomodulatory properties of lactic acid bacteria for selection of probiotics against salmonella infection in broiler chicks. *PLoS One*. 2016;11(1):e0147630. doi:10.1371/journal.pone.0147630
13. Panggabean LS. A naturally-stabilized-and-balanced synbiotics as a catalyst to aid in healing anti-microbial-resistance-induced communicable and non-communicable diseases; 2019.
14. Plaza-Diaz J, Ruiz-Ojeda FJ, Gil-Campos M, Gil A. Mechanisms of action of probiotics. *Adv Nutr*. 2019;10(suppl_1):S49–S66. doi:10.1093/advances/nmy063
15. Tulini FL, Winkelströter LK, De Martinis EC. Identification and evaluation of the probiotic potential of Lactobacillus paraplantarum FT259, a bacteriocinogenic strain isolated from Brazilian semi-hard artisanal cheese. *Anaerobe*. 2013;22:57–63. doi:10.1016/j.anaerobe.2013.06.006
16. Ünlü G, Nielsen B, Ionita C. Production of antilisterial bacteriocins from lactic acid bacteria in dairy-based media: a comparative study. *Probiotics Antimicrob Proteins*. 2015;7(4):259–274. doi:10.1007/s12602-015-9200-z
17. Sikorska H, Smoragiewicz W. Role of probiotics in the prevention and treatment of methicillin-resistant Staphylococcus aureus infections. *Int J Antimicrob Agents*. 2013;42(6):475–481. doi:10.1016/j.ijantimicag.2013.08.003
18. Dinev T, Beev G, Tzanova M, Denev S, Dermendzhieva D, Stoyanova A. Antimicrobial activity of Lactobacillus plantarum against pathogenic and food spoilage microorganisms: a review. *Bulgarian J Vet Med*. 2018;21(3):253–268. doi:10.15547/bjvm.1084
19. Saville BA, Saville SH. Functional attributes and health benefits of novel prebiotic oligosaccharides derived from xylan, arabinan, and mannan. In: *Prebiotics and Probiotics-Potential Benefits in Nutrition and Health*. IntechOpen; 2019.
20. Maldonado J. Probiotics and prebiotics in infant formulae. In: *Prebiotics and Probiotics-Potential Benefits in Nutrition and Health*. IntechOpen; 2019.
21. Hills RD, Pontefract BA, Mishcon HR, Black CA, Sutton SC, Theberge CR. Gut microbiome: profound implications for diet and disease. *Nutrients*. 2019;11(7):1613. doi:10.3390/nu11071613
22. Isacco CG, Ballini A, De Vito D, et al. Probiotics in health and immunity: a first step toward understanding the importance of microbiota system in translational medicine. In: *Prebiotics and Probiotics-Potential Benefits in Nutrition and Health*. IntechOpen; 2019.
23. Panesar PS, Anal AK. *Probiotics, Prebiotics and Synbiotics: Technological Advancements Towards Safety and Industrial Applications*. John Wiley & Sons; 2022:18.
24. Presti I, D'Orazio G, Labra M, et al. Evaluation of the probiotic properties of new Lactobacillus and Bifidobacterium strains and their in vitro effect. *Appl Microbiol Biotechnol*. 2015;99(13):5613–5626. doi:10.1007/s00253-015-6482-8
25. Park SY, Lim SD. Probiotic characteristics of lactobacillus plantarum FH185 isolated from human feces. *Korean J Food Sci Anim Resour*. 2015;35(5):615–621. doi:10.5851/kosfa.2015.35.5.615
26. Damodharan K, Lee YS, Palaniyandi SA, Yang SH, Suh JW. Preliminary probiotic and technological characterization of Pediococcus pentosaceus strain KID7 and in vivo assessment of its cholesterol-lowering activity. *Front Microbiol*. 2015;6:768. doi:10.3389/fmicb.2015.00768
27. Likotrafiti E, Tuohy KM, Gibson GR, Rastall RA. Development of antimicrobial synbiotics using potentially-probiotic faecal isolates of Lactobacillus fermentum and Bifidobacterium longum. *Anaerobe*. 2013;20:5–13. doi:10.1016/j.anaerobe.2013.01.002
28. Chimchang J, Theparee T, Ladda B, Tanasupawat S, Wongsatayanon BT, Taweechotipatr M. Antimicrobial properties of a potential probiotic lactobacillus from Thai newborn feces. *J Med Assoc Thai*. 2015;98(Suppl 9):S116–S122.
29. Kaur S, Sharma P, Kalia N, Singh J, Kaur S. Anti-biofilm properties of the fecal probiotic lactobacilli against *Vibrio* spp. *Front Cell Infect Microbiol*. 2018;8:120. doi:10.3389/fcimb.2018.00120
30. Bian X, Evivie SE, Muhammad Z, et al. In vitro assessment of the antimicrobial potentials of Lactobacillus helveticus strains isolated from traditional cheese in Sinkiang China against food-borne pathogens. *Food Funct*. 2016;7(2):789–797. doi:10.1039/c5fo01041a
31. Anas M, Ahmed K, Mebrouk K. Study of the antimicrobial and probiotic effect of Lactobacillus Plantarum isolated from raw goat's milk from the region of Western Algeria. *World Appl Sci J*. 2014;32(7):1304–1310.
32. El-Kholy AM, El-Shinawy SH, Meshref AMS, Korny AM. Screening of antagonistic activity of probiotic bacteria against some food-borne pathogens. *J Appl Environ Microbiol*. 2014;2(2):53–60.
33. Amer EI, Mossallam SF, Mahrous H. Therapeutic enhancement of newly derived bacteriocins against Giardia lamblia. *Exp Parasitol*. 2014;146:52–63. doi:10.1016/j.exppara.2014.09.005
34. Butprom S, Phumkhachorn P, Rattanachaikunsopon P. Effect of Lactobacillus plantarum C014 on innate immune response and disease resistance against Aeromonas hydrophila in hybrid catfish. *Sci World J*. 2013;2013:392523. doi:10.1155/2013/392523
35. Menconi A, Kallapura G, Latorre JD, et al. Identification and characterization of lactic Acid bacteria in a commercial probiotic culture. *Biosci Microbiota Food Health*. 2014;33(1):25–30. doi:10.12938/bmfh.33.25
36. Aoudia N, Rieu A, Briandet R, et al. Biofilms of Lactobacillus plantarum and Lactobacillus fermentum: effect on stress responses, antagonistic effects on pathogen growth and immunomodulatory properties. *Food Microbiol*. 2016;53(Pt A):51–59. doi:10.1016/j.fm.2015.04.009
37. Bujalance C, Jiménez-Valera M, Moreno E, Ruiz-López MD, Lasserrot A, Ruiz-Bravo A. Lack of correlation between in vitro antibiosis and in vivo protection against enteropathogenic bacteria by probiotic lactobacilli. *Res Microbiol*. 2014;165(1):14–20. doi:10.1016/j.resmic.2013.10.006
38. Muñoz-Atienza E, Araújo C, Magadán S, et al. In vitro and in vivo evaluation of lactic acid bacteria of aquatic origin as probiotics for turbot (Scophthalmus maximus L). farming. *Fish Shellfish Immunol*. 2014;41(2):570–580. doi:10.1016/j.fsi.2014.10.007

39. Caggia C, De Angelis M, Pitino I, Pino A, Randazzo CL. Probiotic features of Lactobacillus strains isolated from Ragusano and Pecorino Siciliano cheeses. *Food Microbiol*. 2015;50:109–117. doi:10.1016/j.fm.2015.03.010
40. Pinpimai K, Rodkhum C, Chansue N, Katagiri T, Maita M, Pirarat N. The study on the candidate probiotic properties of encapsulated yeast, Saccharomyces cerevisiae JCM 7255, in Nile Tilapia (Oreochromis niloticus). *Res Vet Sci*. 2015;102:103–111. doi:10.1016/j.rvsc.2015.07.021
41. Yang JJ, Niu CC, Guo XH. Mixed culture models for predicting intestinal microbial interactions between Escherichia coli and Lactobacillus in the presence of probiotic Bacillus subtilis. *Benef Microbes*. 2015;6(6):871–877. doi:10.3920/BM2015.0033
42. Shokryazdan P, Sieo CC, Kalavathy R, et al. Probiotic potential of Lactobacillus strains with antimicrobial activity against some human pathogenic strains. *Biomed Res Int*. 2014;2014:927268. doi:10.1155/2014/927268
43. Muñoz-Quezada S, Bermudez-Brito M, Chenoll E, et al. Competitive inhibition of three novel bacteria isolated from faeces of breast milk-fed infants against selected enteropathogens. *Br J Nutr*. 2013;109(Suppl 2):S63–S69. doi:10.1017/S0007114512005600
44. Abbaszadeh S, Tavakoli R, Sharifzadeh A, Shokri H. Lactic acid bacteria as functional probiotic isolates for inhibiting the growth of Aspergillus flavus, A. parasiticus, A. Niger and Penicillium chrysogenum. *J Mycol Med*. 2015;25(4):263–267. doi:10.1016/j.mycmed.2015.10.011
45. Aminnezhad S, Kermanshahi RK, Ranjbar R. Evaluation of synergistic interactions between cell-free supernatant of lactobacillus strains and amikacin and gentamicin against Pseudomonas aeruginosa. *Jundishapur J Microbiol*. 2015;8(4):e16592. doi:10.5812/jjm.8(4)2015.16592
46. Diana CR, Humberto HS, Jorge YF. Probiotic properties of leuconostoc mesenteroides Isolated from Aguamiel of Agave salmiana. *Probiotics Antimicrob Proteins*. 2015;7(2):107–117. doi:10.1007/s12602-015-9187-5
47. Liu XF, Li Y, Li JR, et al. Isolation and characterisation of Bacillus spp. antagonistic to Vibrio parahaemolyticus for use as probiotics in aquaculture. *World J Microbiol Biotechnol*. 2015;31(5):795–803. doi:10.1007/s11274-015-1833-2
48. Yu X, Yin J, Li L, et al. Prebiotic potential of xylooligosaccharides derived from corn cobs and their in vitro antioxidant activity when combined with lactobacillus. *J Microbiol Biotechnol*. 2015;25(7):1084–1092. doi:10.4014/jmb.1501.01022
49. Chew SY, Cheah YK, Seow HF, Sandai D, Than LT. Probiotic Lactobacillus rhamnosus GR-1 and Lactobacillus reuteri RC-14 exhibit strong antifungal effects against vulvovaginal candidiasis-causing Candida glabrata isolates. *J Appl Microbiol*. 2015;118(5):1180–1190. doi:10.1111/jam.12772
50. Belicová A, Mikulášová M, Dušinský R. Probiotic potential and safety properties of Lactobacillus plantarum from Slovak Bryndza cheese. *Biomed Res Int*. 2013;2013:760298. doi:10.1155/2013/760298
51. Jena PK, Trivedi D, Thakore K, Chaudhary H, Giri SS, Seshadri S. Isolation and characterization of probiotic properties of Lactobacilli isolated from rat fecal microbiota. *Microbiol Immunol*. 2013;57(6):407–416. doi:10.1111/1348-0421.12054
52. Thankappan B, Ramesh D, Ramkumar S, Natarajaseenivasan K, Anbarasu K. Characterization of Bacillus spp. from the gastrointestinal tract of Labeo rohita--towards to identify novel probiotics against fish pathogens. *Appl Biochem Biotechnol*. 2015;175(1):340–353. doi:10.1007/s12010-014-1270-y
53. Gotteland M, Cires MJ, Carvallo C, et al. Probiotic screening and safety evaluation of Lactobacillus strains from plants, artisanal goat cheese, human stools, and breast milk. *J Med Food*. 2014;17(4):487–495. doi:10.1089/jmf.2013.0030
54. Torres NI, Noll KS, Xu S, et al. Safety, formulation, and in vitro antiviral activity of the antimicrobial peptide subtilosin against herpes simplex virus type 1. *Probiotics Antimicrob Proteins*. 2013;5(1):26–35. doi:10.1007/s12602-012-9123-x
55. Wu HJ, Sun LB, Li CB, et al. Enhancement of the immune response and protection against Vibrio parahaemolyticus by indigenous probiotic Bacillus strains in mud crab (Scylla paramamosain). *Fish Shellfish Immunol*. 2014;41(2):156–162. doi:10.1016/j.fsi.2014.08.027
56. Geeraerts S, Ducatelle R, Haesebrouck F, Van Immerseel F. Bacillus amyloliquefaciens as prophylactic treatment for Clostridium difficile-associated disease in a mouse model. *J Gastroenterol Hepatol*. 2015;30(8):1275–1280. doi:10.1111/jgh.12957
57. Gomathi S, Sasikumar P, Anbazhagan K, et al. Screening of indigenous oxalate degrading lactic acid bacteria from human faeces and South Indian fermented foods: assessment of probiotic potential. *ScientificWorldJournal*. 2014;2014:648059. doi:10.1155/2014/648059
58. Georgieva R, Yocheva L, Tserovska L, et al. Antimicrobial activity and antibiotic susceptibility of Lactobacillus and Bifidobacterium spp. intended for use as starter and probiotic cultures. *Biotechnol Biotechnol Equip*. 2015;29(1):84–91. doi:10.1080/13102818.2014.987450
59. Mirnejad R, Vahdati AR, Rashidiani J, Erfani M, Piranfar V. The antimicrobial effect of lactobacillus casei culture supernatant against multiple drug resistant clinical isolates of Shigella sonnei and Shigella flexneri in vitro. *Iran Red Crescent Med J*. 2013;15(2):122–126. doi:10.5812/ircmj.7454
60. Trivedi D, Jena PK, Seshadri S. Colicin E2 expression in Lactobacillus brevis DT24, A vaginal probiotic isolate, against uropathogenic Escherichia coli. *ISRN Urol*. 2014;2014:869610. doi:10.1155/2014/869610
61. Das A, Nakhro K, Chowdhury S, Kamilya D. Effects of potential probiotic Bacillus amyloliquefaciens [corrected] FPTB16 on systemic and cutaneous mucosal immune responses and disease resistance of catla (Catla catla). *Fish Shellfish Immunol*. 2013;35(5):1547–1553. doi:10.1016/j.fsi.2013.08.022
62. Baick SC, Kim CH. Assessment of characteristics and functional properties of lactobacillus species isolated from kimchi for dairy use. *Korean J Food Sci Anim Resour*. 2015;35(3):339–349. doi:10.5851/kosfa.2015.35.3.339
63. Dec M, Puchalski A, Urban-Chmiel R, Wernicki A. Screening of Lactobacillus strains of domestic goose origin against bacterial poultry pathogens for use as probiotics. *Poult Sci*. 2014;93(10):2464–2472. doi:10.3382/ps.2014-04025
64. Wu CC, Lin CT, Wu CY, Peng WS, Lee MJ, Tsai YC. Inhibitory effect of Lactobacillus salivarius on Streptococcus mutans biofilm formation. *Mol Oral Microbiol*. 2015;30(1):16–26. doi:10.1111/omi.12063
65. VidyaLaxme B, Rovetto A, Grau R, Agrawal R. Synergistic effects of probiotic Leuconostoc mesenteroides and Bacillus subtilis in malted ragi (Eleucine corocana) food for antagonistic activity against V. cholerae and other beneficial properties. *J Food Sci Technol*. 2014;51(11):3072–3082. doi:10.1007/s13197-012-0834-5
66. Naderi A, Kasra-Kermanshahi R, Gharavi S, Imani Fooladi AA, Abdollahpour Alitappeh M, Saffarian P. Study of antagonistic effects of Lactobacillus strains as probiotics on multi drug resistant (MDR) bacteria isolated from urinary tract infections (UTIs). *Iran J Basic Med Sci*. 2014;17(3):201–208.
67. Moghadam SS, Khodaii Z, Zadeh SF, Ghooshchian M, Aghmiyuni ZF, Shabestari TM. Synergistic or antagonistic effects of probiotics and antibiotics-alone or in combination-on antimicrobial-resistant Pseudomonas aeruginosa isolated from burn wounds. *Arch Clin Infect Dis*. 2018;13(3):e63121.
68. Abdelhamid AG, Esaam A, Hazaa MM. Cell free preparations of probiotics exerted antibacterial and antibiofilm activities against multidrug resistant *E. coli*. *Saudi Pharm J*. 2018;26(5):603–607. doi:10.1016/j.jsps.2018.03.004
69. Gomaa EZ. Synergistic antibacterial efficiency of Bacteriocin and silver nanoparticles produced by probiotic Lactobacillus paracasei against multidrug-resistant bacteria. *Int J Pept Res Ther*. 2019;1(25):1113–1125. doi:10.1007/s10989-018-9759-9

70. Ibraheem SK, Alshaibani AB, Ad'hiah AH. Protective effect of Lactobacillus acidophilus and Saccharomyces cerevisiae against multi-drug resistant Salmonella enterica serovar typhimurium in vitro and in vivo. *World J Pharm Res*. 2014;28(3):193–203.
71. Halder D, Mandal S. Antibacterial potentiality of commercially available probiotic lactobacilli and curd lactobacilli strains, alone and in combination, against human pathogenic bacteria. *Transl Biomed*. 2016;7(2):1–7. doi:10.21767/2172-0479.100061
72. Khmaladze I, É B, Fabre S, Gillbro JM. Lactobacillus reuteri DSM 17938-A comparative study on the effect of probiotics and lysates on human skin. *Exp Dermatol*. 2019;28(7):822–828. doi:10.1111/exd.13950
73. Monteiro CRAV, Do Carmo MS, Melo BO, et al. In Vitro antimicrobial activity and probiotic potential of Bifidobacterium and Lactobacillus against species of Clostridium. *Nutrients*. 2019;11(2):448. doi:10.3390/nu11020448
74. Rossoni RD, Fuchs BB, de Barros PP, et al. Lactobacillus paracasei modulates the immune system of Galleria mellonella and protects against Candida albicans infection. *PLoS One*. 2017;12(3):e0173332. doi:10.1371/journal.pone.0173332
75. Ishikawa KH, Mayer MP, Miyazima TY, et al. A multispecies probiotic reduces oral Candida colonization in denture wearers. *J Prosthodont*. 2015;24(3):194–199. doi:10.1111/jopr.12198
76. Sajedinejad N, Paknejad M, Houshmand B, et al. Lactobacillus salivarius NK02: a potent probiotic for clinical application in mouthwash. *Probiotics Antimicrob Proteins*. 2018;10(3):485–495. doi:10.1007/s12602-017-9296-4
77. Helmy YA, Krücken J, Nöckler K, von Samson-Himmelstjerna G, Zessin KH. Comparison between two commercially available serological tests and polymerase chain reaction in the diagnosis of Cryptosporidium in animals and diarrhoeic children. *Parasitol Res*. 2014;113 (1):211–216. doi:10.1007/s00436-013-3645-3
78. Kuru BE, Laleman I, Yalnızoğlu T, Kuru L, Teughels W. The influence of a bifidobacterium animalis probiotic on gingival health: a randomized controlled clinical trial. *J Periodontol*. 2017;88(11):1115–1123. doi:10.1902/jop.2017.170213
79. Zhou M, Zhu J, Yu H, et al. Investigation into in vitro and in vivo models using intestinal epithelial IPEC-J2 cells and Caenorhabditis elegans for selecting probiotic candidates to control porcine enterotoxigenic Escherichia coli. *J Appl Microbiol*. 2014;117(1):217–226. doi:10.1111/jam.12505
80. Lazarenko L, Babenko L, Sichel LS, et al. Antagonistic action of lactobacilli and bifidobacteria in relation to Staphylococcus aureus and their influence on the immune response in cases of intravaginal Staphylococcosis in mice. *Probiotics Antimicrob Proteins*. 2012;4(2):78–89. doi:10.1007/s12602-012-9093-z
81. Prado-Rebolledo OF, Delgado-Machuca JJ, Macedo-Barragan RJ, et al. Evaluation of a selected lactic acid bacteria-based probiotic on Salmonella enterica serovar Enteritidis colonization and intestinal permeability in broiler chickens. *Avian Pathol*. 2017;46(1):90–94. doi:10.1080/03079457.2016.1222808
82. Morya VK, Choi W, Kim EK. Isolation and characterization of Pseudoalteromonas sp. from fermented Korean food, as an antagonist to Vibrio harveyi. *Appl Microbiol Biotechnol*. 2014;98(3):1389–1395. doi:10.1007/s00253-013-4937-3
83. Mossallam SF, Amer EI, Diab RG. Potentiated anti-microsporidial activity of Lactobacillus acidophilus CH1 bacteriocin using gold nanoparticles. *Exp Parasitol*. 2014;144:14–21. doi:10.1016/j.exppara.2014.06.002
84. Mazaya B, Hamzawy MA, Khalil MA, Tawkol WM, Sabit H. Immunomodulatory and antimicrobial efficacy of Lactobacilli against enteropathogenic infection of Salmonella typhi: in-vitro and in-vivo study. *Int J Immunopathol Pharmacol*. 2015;28(4):469–478. doi:10.1177/0394632015592099
85. Gupta R, Sarkar S, Srivastava S. In vivo toxicity assessment of antimicrobial peptides (AMPs LR14) derived from Lactobacillus plantarum strain LR/14 in Drosophila melanogaster. *Probiotics Antimicrob Proteins*. 2014;6(1):59–67. doi:10.1007/s12602-013-9154-y
86. Mahmoodpoor A, Hamishehkar H, Asghari R, Abri R, Shadvar K, Sanaie S. Effect of a probiotic preparation on ventilator-associated pneumonia in critically ill patients admitted to the intensive care unit: a prospective double-blind randomized controlled trial. *Nutr Clin Pract*. 2019;34(1):156–162. doi:10.1002/ncp.10191
87. Kumar M, Dhaka P, Vijay D, et al. Antimicrobial effects of Lactobacillus plantarum and Lactobacillus acidophilus against multidrug-resistant enteroaggregative Escherichia coli. *Int J Antimicrob Agents*. 2016;48(3):265–270. doi:10.1016/j.ijantimicag.2016.05.014
88. Rongrungruang Y, Krajangwittaya D, Pholtawornkulchai K, Tiengrim S, Thamlikitkul V. Randomized controlled study of probiotics containing Lactobacillus casei (Shirota strain) for prevention of ventilator-associated pneumonia. *J Med Assoc Thai*. 2015;98(3):253–259.
89. Gonzalez-Gil F, Diaz-Sanchez S, Pendleton S, et al. Yerba mate enhances probiotic bacteria growth in vitro but as a feed additive does not reduce Salmonella Enteritidis colonization in vivo. *Poult Sci*. 2014;93(2):434–440. doi:10.3382/ps.2013-03339
90. Machairas N, Pistiki A, Droggiti DI, et al. Pre-treatment with probiotics prolongs survival after experimental infection by multidrug-resistant Pseudomonas aeruginosa in rodents: an effect on sepsis-induced immunosuppression. *Int J Antimicrob Agents*. 2015;45(4):376–384. doi:10.1016/j.ijantimicag.2014.11.013
91. Gibson GR, Hutkins R, Sanders ME, et al. Expert consensus document: the International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of prebiotics. *Nat Rev Gastroenterol Hepatol*. 2017;14(8):491–502. doi:10.1038/nrgastro.2017.75
92. Sanders ME, Merenstein DJ, Reid G, Gibson GR, Rastall RA. Probiotics and prebiotics in intestinal health and disease: from biology to the clinic. *Nat Rev Gastroenterol Hepatol*. 2019;16(10):605–616. doi:10.1038/s41575-019-0173-3
93. Coste I, Judlin P, Lepargneur JP, Bou-Antoun S. Safety and efficacy of an intravaginal prebiotic gel in the prevention of recurrent bacterial vaginosis: a randomized double-blind study. *Obstet Gynecol Int*. 2012;2012:147867. doi:10.1155/2012/147867
94. Kano M, Masuoka N, Kaga C, et al. Consecutive intake of fermented milk containing bifidobacterium breve strain yakult and galacto-oligosaccharides benefits skin condition in healthy adult women. *Biosci Microbiota Food Health*. 2013;32(1):33–39. doi:10.12938/bmfh.32.33
95. Vulevic J, Drakoularakou A, Yaqoob P, Tzortzis G, Gibson GR. Modulation of the fecal microflora profile and immune function by a novel trans-galactooligosaccharide mixture (B-GOS) in healthy elderly volunteers. *Am J Clin Nutr*. 2008;88(5):1438–1446. doi:10.3945/ajcn.2008.26242
96. Vulevic J, Juric A, Walton GE, et al. Influence of galacto-oligosaccharide mixture (B-GOS) on gut microbiota, immune parameters and metabonomics in elderly persons. *Br J Nutr*. 2015;114(4):586–595. doi:10.1017/S0007114515001889
97. Moro G, Arslanoglu S, Stahl B, Jelinek J, Wahn U, Boehm G. A mixture of prebiotic oligosaccharides reduces the incidence of atopic dermatitis during the first six months of age. *Arch Dis Child*. 2006;91(10):814–819. doi:10.1136/adc.2006.098251
98. Ivakhnenko OS, Nyankovskyy SL. Effect of the specific infant formula mixture of oligosaccharides on local immunity and development of allergic and infectious disease in young children: randomized study. *Pediatr Pol*. 2013;88(5):398–404. doi:10.1016/j.pepo.2013.07.002

99. Abrams SA, Griffin IJ, Hawthorne KM, Ellis KJ. Effect of prebiotic supplementation and calcium intake on body mass index. *J Pediatr*. 2007;151(3):293–298. doi:10.1016/j.jpeds.2007.03.043
100. Abrams SA, Griffin IJ, Hawthorne KM. Young adolescents who respond to an inulin-type fructan substantially increase total absorbed calcium and daily calcium accretion to the skeleton. *J Nutr*. 2007;137(11Suppl):2524S–2526S. doi:10.1093/jn/137.11.2524S
101. Whisner CM, Martin BR, Schoterman MH, et al. Galacto-oligosaccharides increase calcium absorption and gut bifidobacteria in young girls: a double-blind cross-over trial. *Br J Nutr*. 2013;110(7):1292–1303. doi:10.1017/S000711451300055X
102. Collado Yurrita L, San Mauro Martín I, Ciudad-Cabañas MJ, Calle-Purón ME, Hernández CM. Effectiveness of inulin intake on indicators of chronic constipation; a meta-analysis of controlled randomized clinical trials. *Nutr Hosp*. 2014;30(2):244–252. doi:10.3305/nh.2014.30.2.7565
103. Buddington RK, Kapadia C, Neumer F, Theis S. Oligofructose provides laxation for irregularity associated with low fiber intake. *Nutrients*. 2017;9(12):1372. doi:10.3390/nu9121372
104. Krumbeck JA, Rasmussen HE, Hutkins RW, et al. Probiotic Bifidobacterium strains and galactooligosaccharides improve intestinal barrier function in obese adults but show no synergism when used together as synbiotics. *Microbiome*. 2018;6(1):121. doi:10.1186/s40168-018-0494-4
105. Cani PD, Possemiers S, Van de Wiele T, et al. Changes in gut microbiota control inflammation in obese mice through a mechanism involving GLP-2-driven improvement of gut permeability. *Gut*. 2009;58(8):1091–1103. doi:10.1136/gut.2008.165886
106. Stoddart LA, Smith NJ, Milligan G; International Union of Pharmacology. LXXI. Free fatty acid receptors FFA1, −2, and −3: pharmacology and pathophysiological functions. *Pharmacol Rev*. 2008;60(4):405–417. doi:10.1124/pr.108.00802
107. Bolognini D, Barki N, Butcher AJ, et al. Chemogenetics defines receptor-mediated functions of short chain free fatty acids. *Nat Chem Biol*. 2019;15(5):489–498. doi:10.1038/s41589-019-0270-1
108. Rigo-Adrover M, Saldaña-Ruíz S, van Limpt K, et al. A combination of scGOS/lcFOS with Bifidobacterium breve M-16V protects suckling rats from rotavirus gastroenteritis. *Eur J Nutr*. 2017;56(4):1657–1670. doi:10.1007/s00394-016-1213-1
109. Nomayo A, Schwiertz A, Rossi R, et al. Infant formula with cow's milk fat and prebiotics affects intestinal flora, but not the incidence of infections during infancy in a double-blind randomized controlled trial. *Mol Cell Pediatr*. 2020;7(1):6. doi:10.1186/s40348-020-00098-1
110. Janardhana V, Broadway MM, Bruce MP, et al. Prebiotics modulate immune responses in the gut-associated lymphoid tissue of chickens. *J Nutr*. 2009;139(7):1404–1409. doi:10.3945/jn.109.105007 PMID: 19474157.
111. Kim GB, Seo YM, Kim CH, Paik IK. Effect of dietary prebiotic supplementation on the performance, intestinal microflora, and immune response of broilers. *Poult Sci*. 2011;90(1):75–82. doi:10.3382/ps.2010-00732 PMID: 21177446.
112. Kim HS, Cha E, Kim Y, et al. Raffinose, a plant galactoside, inhibits Pseudomonas aeruginosa biofilm formation via binding to LecA and decreasing cellular cyclic diguanylate levels. *Sci Rep*. 2016;6:25318. doi:10.1038/srep25318
113. Kishino E, Takemura N, Masaki H, Ito T, Nakazawa M. Dietary lactosucrose suppresses influenza A (H1N1) virus infection in mice. *Biosci Microbiota Food Health*. 2015;34(4):67–76. doi:10.12938/bmfh.2015-005
114. Rist VT, Weiss E, Sauer N, Mosenthin R, Eklund M. Effect of dietary protein supply originating from soybean meal or casein on the intestinal microbiota of piglets. *Anaerobe*. 2014;25:72–79. doi:10.1016/j.anaerobe.2013.10.003
115. Yu YJ, Amorim M, Marques C, Calhau C, Pintado M. Effects of whey peptide extract on the growth of probiotics and gut microbiota. *J Funct Foods*. 2016;1(21):507–516. doi:10.1016/j.jff.2015.10.035
116. Ham SY, Kim HS, Cha E, Lim T, Byun Y, Park HD. Raffinose inhibits Streptococcus mutans biofilm formation by targeting glucosyltransferase. *Microbiol Spectr*. 2022;10(3):e0207621. doi:10.1128/spectrum.02076-21
117. Kim HS, Jang Y, Ham SY, et al. Effect of broad-spectrum biofilm inhibitor raffinose, a plant galactoside, on the inhibition of co-culture biofilm on the microfiltration membrane. *J Hazard Mater*. 2021;402:123501. doi:10.1016/j.jhazmat.2020.123501
118. Swanson KS, Gibson GR, Hutkins R, et al. The International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of synbiotics. *Nat Rev Gastroenterol Hepatol*. 2020;17(11):687–701. doi:10.1038/s41575-020-0344-2
119. Ustundag GH, Altuntas H, Soysal YD, Kokturk F. The effects of synbiotic "Bifidobacterium lactis B94 plus inulin" addition on standard triple therapy of helicobacter pylori eradication in children. *Can J Gastroenterol Hepatol*. 2017;2017:8130596. doi:10.1155/2017/8130596
120. Islek A, Sayar E, Yilmaz A, Artan R. Bifidobacterium lactis B94 plus inulin for treatment of helicobacter pylori infection in children: does it increase eradication rate and patient compliance? *Acta Gastroenterol Belg*. 2015;78(3):282–286.
121. Komatsu S, Sakamoto E, Norimizu S, et al. Efficacy of perioperative synbiotics treatment for the prevention of surgical site infection after laparoscopic colorectal surgery: a randomized controlled trial. *Surg Today*. 2016;46(4):479–490. doi:10.1007/s00595-015-1178-3
122. Anderson AD, McNaught CE, Jain PK, MacFie J. Randomised clinical trial of synbiotic therapy in elective surgical patients. *Gut*. 2004;53 (2):241–245. doi:10.1136/gut.2003.024620
123. Rayes N, Seehofer D, Theruvath T, et al. Effect of enteral nutrition and synbiotics on bacterial infection rates after pylorus-preserving pancreatoduodenectomy: a randomized, double-blind trial. *Ann Surg*. 2007;246(1):36–41. doi:10.1097/01.sla.0000259442.78947.19
124. Reddy BS, Macfie J, Gatt M, Larsen CN, Jensen SS, Leser TD. Randomized clinical trial of effect of synbiotics, neomycin and mechanical bowel preparation on intestinal barrier function in patients undergoing colectomy. *Br J Surg*. 2007;94(5):546–554. doi:10.1002/bjs.5705
125. Usami M, Miyoshi M, Kanbara Y, et al. Effects of perioperative synbiotic treatment on infectious complications, intestinal integrity, and fecal flora and organic acids in hepatic surgery with or without cirrhosis. *JPEN J Parenter Enteral Nutr*. 2011;35(3):317–328. doi:10.1177/0148607110379813
126. Skonieczna-żydecka K, Kaczmarczyk M, Łoniewski I, et al. Meta-analysis, and meta-regression evaluating the efficacy and mechanisms of action of probiotics and synbiotics in the prevention of surgical site infections and surgery-related complications. *J Clin Med*. 2018;7(12):556. doi:10.3390/jcm7120556
127. Kasatpibal N, Whitney JD, Saokaew S, Kengkla K, Heitkemper MM, Apisarnthanarak A. Effectiveness of probiotic, prebiotic, and synbiotic therapies in reducing postoperative complications: a systematic review and network meta-analysis. *Clin Infect Dis*. 2017;64(suppl_2):S153–S160. doi:10.1093/cid/cix114
128. Elshaghabee FM, Rokana N. Dietary management by probiotics, prebiotics and synbiotics for the prevention of antimicrobial resistance. In: *Sustainable Agriculture Reviews 49: Mitigation of Antimicrobial Resistance*. Vol. 2. Natural and Synthetic Approaches; 2021:33–56.
129. Connolly ML, Lovegrove JA, Tuohy KM. Konjac glucomannan hydrolysate beneficially modulates bacterial composition and activity within the faecal microbiota. *J Funct Foods*. 2010;2(3):219–224. doi:10.1016/j.jff.2010.05.001

130. Jačan A, Kashofer K, Zenz G, et al. Synergistic and antagonistic interactions between antibiotics and synbiotics in modifying the murine fecal microbiome. *Eur J Nutr*. 2020;59(5):1831–1844. doi:10.1007/s00394-019-02035-z
131. Hammami R, Ben Abdallah N, Barbeau J, Fliss I. Symbiotic maple saps minimize disruption of the mice intestinal microbiota after oral antibiotic administration. *Int J Food Sci Nutr*. 2015;66(6):665–671. doi:10.3109/09637486.2015.1071340
132. Maldonado J, Cañabate F, Sempere L, et al. Human milk probiotic Lactobacillus fermentum CECT5716 reduces the incidence of gastrointestinal and upper respiratory tract infections in infants. *J Pediatr Gastroenterol Nutr*. 2012;54(1):55–61. doi:10.1097/MPG.0b013e3182333f18
133. Dinleyici EC, Dalgic N, Guven S, et al. The effect of a multispecies synbiotic mixture on the duration of diarrhea and length of hospital stay in children with acute diarrhea in Turkey: single blinded randomized study. *Eur J Pediatr*. 2013;172(4):459–464. doi:10.1007/s00431-012-1903-5
134. Vandenplas Y, De Hert SG. PROBIOTICAL-Study Group. Randomised clinical trial: the synbiotic food supplement Probiotical vs placebo for acute gastroenteritis in children. *Aliment Pharmacol Ther*. 2011;34(8):862–867. doi:10.1111/j.1365-2036.2011.04835.x
135. Kondepudi KK, Ambalam P, Nilsson I, Wadström T, Ljungh A. Prebiotic-non-digestible oligosaccharides preference of probiotic bifidobacteria and antimicrobial activity against Clostridium difficile. *Anaerobe*. 2012;18(5):489–497. doi:10.1016/j.anaerobe.2012.08.005
136. Işlek A, Sayar E, Yılmaz A, Bö B, Mutlu D, Artan R. The role of Bifidobacterium lactis B94 plus inulin in the treatment of acute infectious diarrhea in children. *Turk J Gastroenterol*. 2014;25(6):628–633. doi:10.5152/tjg.2014.14022
137. Koruri SS, Chowdhury R, Bhattacharya P. Potentiation of functional and antimicrobial activities through synergistic growth of probiotic Pediococcus acidilactici with natural prebiotics (garlic, basil). *Microbes Spotlight*. 2016;28:219–224.
138. Ibrahem AA, Al-Shawi SG, Al-Temimi WKA. The antagonistic activity of the synbiotic containing Lactobacillus acidophilus and pineapple residue FOS against pathogenic bacteria. *Braz J Biol*. 2022;84:e258277. doi:10.1590/1519-6984.258277
139. García-Gamboa R, Domínguez-Simi M, Gradilla-Hernández MS, et al. Anticandidal and antibiofilm effect of synbiotics including probiotics and inulin-type fructans. *Antibiotics*. 2022;11(8):1135. doi:10.3390/antibiotics11081135
140. Erginkaya Z, Konuray G, Harmanci M, Kesen G, Nagihan ME. Antibacterial effects of microencapsulated probiotic and synbiotics. *Çukurova Tarim ve Gida Bilimleri Dergisi*. 2019;34(1):27–36.
141. Kotzampassi K, Giamarellos-Bourboulis EJ, Voudouris A, Kazamias P, Eleftheriadis E. Benefits of a synbiotic formula (Synbiotic 2000Forte) in critically Ill trauma patients: early results of a randomized controlled trial. *World J Surg*. 2006;30(10):1848–1855. doi:10.1007/s00268-005-0653-1
142. Panigrahi P, Parida S, Nanda NC, et al. A randomized synbiotic trial to prevent sepsis among infants in rural India. *Nature*. 2017;548 (7668):407–412. doi:10.1038/nature23480
143. Sommacal HM, Bersch VP, Vitola SP, Osvaldt AB. Perioperative synbiotics decrease postoperative complications in periampullary neoplasms: a randomized, double-blind clinical trial. *Nutr Cancer*. 2015;67(3):457–462. doi:10.1080/01635581.2015.1004734 PMID: 25803626.
144. Kanazawa H, Nagino M, Kamiya S, et al. Synbiotics reduce postoperative infectious complications: a randomized controlled trial in biliary cancer patients undergoing hepatectomy. *Langenbecks Arch Surg*. 2005;390(2):104–113. doi:10.1007/s00423-004-0536-1
145. Rammohan A, Sathyanesan J, Rajendran K, et al. Synbiotics in surgery for chronic pancreatitis: are they truly effective? A single-blind prospective randomized control trial. *Ann Surg*. 2015;262(1):31–37. doi:10.1097/SLA.0000000000001077