

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

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, phytochemicals, 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, lactacin 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 tract⁹³ 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
<i>Lactobacillus</i> Strains (<i>L. acidophilus</i> PBS066, <i>L. fermentum</i> PBS073, <i>L. plantarum</i> PBS067, <i>L. rhamnosus</i> PBS070, <i>L. reuteri</i> PBS072,) and <i>Bifidobacterium</i> Strains (<i>B. animalis</i> subsp. <i>Lactis</i> PBS075, <i>B. longum</i> subsp. <i>longum</i> PBS108)	G+ : <i>S. aureus</i> ATCC 6538, <i>E. faecalis</i> ATCC 29212, G- : <i>E. coli</i> ATCC 25922, <i>P. aeruginosa</i> ATCC 9027, fng : <i>C. albicans</i> ATCC 10231	Cell culture supernatants of the examined strains showed inhibition of the growth of the pathogen at different extents, especially for <i>P. aeruginosa</i> and <i>E. coli</i>	Agar well diffusion assay/paper disc assay	[24]
<i>L. salivarius</i> JM41, JK21V, JM31, JS2A, JM14, JK22, JM2A1 and JM32, <i>L. plantarum</i> PZ01, <i>P. acidilactici</i> JM241 and JH231, <i>P. pentosaceus</i> JS233, <i>E. faecium</i> JS11	G+ : <i>S. aureus</i> ATCC 29213, G- : <i>E. coli</i> K88, 25922 and 1569, <i>S. enteritidis</i> ATCC 13076, <i>S. typhimurium</i> ATCC 14082	Probiotic strains exert immunomodulation activity and efficiently inhibit adhesion and invasion of <i>Salmonella</i> to Caco-2 cells	Agar well diffusion assay/paper disc assay	[12]
<i>L. plantarum</i> FHI85	G+ : <i>S. aureus</i> , G- : <i>S. typhimurium</i>	Have a variable extent of growth Inhibition effect on <i>S. Typhimurium</i> and <i>S. aureus</i>	Co-culturing assay	[25]
<i>P. pentosaceus</i> KID7	G+ : (<i>S. aureus</i> KCCM11335, <i>S. aureus</i> KCCM40510 (Methicillin-resistant), <i>S. epidermidis</i> KCTC 1917, <i>L. monocytogenes</i> KACC10764, <i>B. cereus</i> KACC11240) G- : <i>S. Typhi</i> KCTC2514, <i>S. choleraesuis</i> KCTC2932, <i>S. gallinarum</i> KCTC2931, <i>S. boydii</i> KACC10792, <i>Y. enterocolitica</i> KACC15320, <i>E. coli</i> O138KCTC2615, O1KCTC2441, <i>P. aeruginosa</i> 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]
<i>L. fermentum</i> 907, <i>B. longum</i> 1011	G- : <i>E. coli</i> O157:H7, <i>E. coli</i> O86	The supernatant of both tested probiotics significantly inhibits the growth rates of both strains of <i>E. coli</i>	Co-culturing assay	[27]
<i>L. paraplantarum</i> FT259	G+ : <i>L. monocytogenes</i> IAL 633, <i>L. innocua</i> ATCC 3309	<i>L. paraplantarum</i> FT259 produces bacteriocins that inhibit the growth of <i>Listeria monocytogenes</i> , <i>Listeria innocua</i> , and several lactic acid bacteria	Spot-on lawn/agar spot assay	[15]
<i>Lactobacillus</i> MSMC64-I	G+ : MRSA DMST 20651, 20654, G- : <i>S. typhi</i> DMST 5784, <i>V. parahaemolyticus</i> DMST 5665, <i>S. dysenteriae</i> DMST 15111	<i>Lactobacillus</i> strain MSMC64-I produced reuterin that has potent antimicrobial activity against seven pathogenic indicator strains with very strong inhibitory activities against <i>S. typhi</i> DMST 5784 and MRSA DMST 20651.	Agar well diffusion or paper disc assay	[28]

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

(Continued)

Table 1 (Continued).

Probiotics with in vitro Antimicrobial Activity	Tested Pathogenic Microorganisms	Reported Result	In vitro Testing Method Employed	Ref
<i>L. casei</i>	G+ : <i>L. monocytogenes</i> , G- : <i>E. coli</i> C17, <i>S. enterica</i> ser Typhimurium	Twenty <i>Lactobacillus</i> strains were able to inhibit the enteropathogenic bacterium <i>Yersinia enterocolitica</i> , and two strains inhibit <i>Y. enterocolitica</i> , <i>S. serovar</i> Typhimurium, and <i>L. monocytogenes</i> . All acts by decreasing the Ph	Agar well diffusion or paper disc assay	[37]
<i>E. faecium</i> CV1, LPP29, <i>W. cibaria</i> P71, <i>L. lactis</i> subsp. cremoris SMF110, <i>Lc. mesenteroides</i> subsp. cremoris SMM69, <i>P. pentosaceus</i> SMM73, TPP3	G- : <i>T. maritimum</i> NCIMB2154, LL01.8.3.8, <i>V. splendidus</i> CECT528, DMC-I	Cell-free culture supernatants from all LAB but <i>Lb. curvatus</i> BCS35 inhibited the growth of <i>T. maritimum</i> NCIM2154 and <i>V. splendidus</i> CECT528.	Spot-on lawn/agar spot assay	[38]
13 strains of <i>Lactobacilli</i> (CM1, CM2, FS2, FM13, FM14, FM22, MF5, PM8, PS2, SP13, PSI1, SF6, FS10)	<i>S. aureus</i> ATCC 6538, <i>L. monocytogenes</i> DSM 12464, <i>E. faecalis</i> , <i>E. coli</i> ATCC 25922	All strains were effective against both <i>S. aureus</i> and <i>E. coli</i> , and variable activity versus <i>L. monocytogenes</i> and <i>E. faecalis</i> strains	Agar well diffusion or paper disc assay	[39]
<i>S. cerevisiae</i> JCM7255	G+ : <i>S. agalactiae</i>	Agar spot anti-streptococcal activity showed inhibition of 20 out of 30 strains of <i>S. agalactiae</i> .	Spot-on lawn/agar spot assay	[40]
<i>L. reuteri</i> , <i>B. subtilis</i> MA139	G- : <i>E. coli</i> K88	<i>Lactobacillus reuteri</i> alone as well as in combination with <i>B. subtilis</i> MA139 spores exerted strong inhibition against <i>E. coli</i> K88 under static conditions	Co-culturing assay	[41]
<i>L. acidophilus</i> JN188382, <i>L. fermentum</i> JN188383, <i>L. fermentum</i> JN188384, <i>L. buchneri</i> JN188385, <i>L. buchneri</i> JN188386, <i>L. buchneri</i> JN188387, <i>L. casei</i> JN188388, <i>L. casei</i> JN188389, <i>L. casei</i> JN188390	G+ : <i>E. faecium</i> ATCC 51558, <i>S. epidermidis</i> ATCC 12228, <i>P. acnes</i> ATCC 6919, <i>L. monocytogenes</i> , <i>S. aureus</i> S244; G- : <i>E. coli</i> ATCC 29181, <i>K. pneumoniae</i> K36, <i>E. doacae</i> , <i>S. sonnei</i> ATCC 25931, <i>H. pylori</i> ATCC 43579, <i>V. parahaemolyticus</i> , fng : <i>C. albicans</i> ATCC 44831	Nine of the <i>Lactobacillus</i> 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]
<i>L. paracasei</i> CNCM I_4034, <i>L. Bifidobacterium</i> breve CNCM I-4035 and <i>L. rhamnosus</i> CNCM I-4036	G- : <i>E. coli</i> ETEC CECT 501, <i>S. Typhimurium</i> CECT	Supernatants obtained from <i>L. paracasei</i> CNCM I-4034, <i>B. breve</i> CNCM I-4035 and <i>L. rhamnosus</i> CNCM I-4036 inhibit the growth of enterotoxigenic and enteropathogenic (EPEC) bacteria	Co-culturing assay	[43]

<i>L. casei</i> LC-01, <i>L. acidophilus</i> LA-5, <i>L. paracasei</i>	Fng: <i>A. niger</i> PTCC 5012, <i>A. flavus</i> PTCC 5004, <i>A. parasiticus</i> PTCC 5286, <i>P. chrysogenum</i> 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, <i>L. casei</i> being with the highest activity	Agar well diffusion or paper disc assay	[44]
<i>L. casei</i> PTCC 1608, <i>L. rhamnosus</i> PTCC 1637	G-: <i>P. aeruginosa</i> PTCC 1430	Cell-free supernatant (CFS) of probiotics could curtail the growth of <i>P. aeruginosa</i> . synergistic interactions were observed in the combination of CFS and aminoglycoside antibiotics	Agar well diffusion or paper disc assay	[45]
<i>L. mesenteroides</i> subsp. <i>mesenteroides</i> SD1, SD23, SF2, SF3	G+: <i>S. aureus</i> ATCC 25923, FRI 184, <i>L. monocytogenes</i> ATCC 19115, G-: <i>E. coli</i> ATCC43895, <i>S. enterica</i> ATCC 14028	The supernatant of the isolated showed inhibition to three enteropathogenic strains: <i>E. coli</i> ATCC43895 (EC), <i>S. enterica</i> ATCC 14028 (ST), and <i>L. monocytogenes</i> ATCC 19115 (LM) as well as two enterotoxigenic strains: <i>S. aureus</i> [ATCC 25923 (SA) and FRI 184 (SAI)]	Agar well diffusion or paper disc assay	[46]
<i>B. pumilus</i> B16, <i>B. mojavensis</i> J7	G-: <i>V. parahaemolyticus</i>	Twenty-four among 249 isolates displayed direct antimicrobial activity to <i>V. parahaemolyticus</i> with spot inoculation	Spot-on lawn/agar spot assay	[47]
<i>L. plantarum</i> S2	G+: <i>S. aureus</i> CMCC2607, G-: <i>E. coli</i> CMCC44825, <i>S. Typhimurium</i> CMCC50115, <i>S. flexneri</i> CMCC51061	<i>L. plantarum</i> S2 combined with xylooligosaccharides have enhanced antimicrobial activity against gastrointestinal pathogens	Agar well diffusion or paper disc assay	[48]
<i>L. rhamnosus</i> GR-I, <i>L. reuteri</i> RC-14	Fng: <i>C. glabrata</i>	Probiotic <i>Lact. rhamnosus</i> GR-I and <i>Lact. reuteri</i> RC-14 strains exhibited potent antagonistic activities against all of the tested <i>C. glabrata</i> strains causing cessation of growth and eventual cell death of <i>C. glabrata</i>	Co-culturing assay	[49]
<i>L. plantarum</i> CK06, CK19, B01, B07, K09, K10, K21, LM11, ZS07, ZS11 and ZS15	G+: <i>S. aureus</i> SSV25, <i>S. epidermidis</i> SSV30, <i>S. lentus</i> CCM 3472, <i>E. faecalis</i> V583, <i>L. monocytogenes</i> CCM 4699, G-: <i>A. calcoaceticus</i> CCM 4503; <i>S. paucimobilis</i> CCM 3293; <i>S. enterica</i> subsp. <i>enterica</i> TAI00 CCM 3812	When tested against indicator strains, the <i>Lactobacillus</i> 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)

Table 1 (Continued).

Probiotics with in vitro Antimicrobial Activity	Tested Pathogenic Microorganisms	Reported Result	In vitro Testing Method Employed	Ref
<i>L. helveticus</i> PJ4, <i>L. plantarum</i> PJ7	G+ : <i>S. aureus</i> MTCC737, G- : <i>E. coli</i> MTCC443, <i>S. Typhimurium</i> MTCC733, <i>S. flexneri</i> MTCC1457, <i>P. aeruginosa</i> MTCC1688	<i>L. helveticus</i> PJ4 and <i>L. plantarum</i> PJ7 exhibited strong antibacterial activities against the pathogens tested as assessed in neutral pH culture supernatants	Agar well diffusion or paper disc assay	[51]
<i>B. subtilis</i> JQ302302, <i>B. aerophilus</i> JQ312663	G- : <i>A. hydrophila</i> ATCC 49140, MTCC 1739, <i>Aeromonas</i> sp. JX136697, JX136698, <i>A. enteropelogenes</i> JX136699, <i>P. rettgeri</i> JX 136696	Isolates demonstrated significant antibacterial activity against the fish pathogens <i>A. hydrophila</i> ATCC 49140, <i>A. hydrophila</i> MTCC 1739, <i>A. enteropelogenes</i> JX136699, and <i>P. rettgeri</i> JX136696.	Agar well diffusion or paper disc assay	[52]
<i>L. rhamnosus</i> 204, <i>L. rhamnosus</i> 45B, <i>L. plantarum</i> N221-I, <i>L. rhamnosus</i> NI45-1A, <i>L. rhamnosus</i> QF60-2	G- : <i>H. pylori</i>	<i>L. johnsonii</i> NCC533 found to be the most efficient probiotic strain with anti- <i>H. pylori</i> activity compared with <i>L. rhamnosus</i> GG and <i>L. plantarum</i> 299v	Agar well diffusion or paper disc assay	[53]
<i>B. amyloliquefaciens</i> KATMIRA1933	Vir : Herpes simplex virus types 1 and 2	At high concentrations, subtilisin produced by <i>B. amyloliquefaciens</i> , has a virucidal effect against HSV-I. Subtilisin non-virucidal concentrations can inhibit wild-type HSV-I and acyclovir-resistant mutants in a dose-dependent manner	Agar well diffusion or paper disc assay	[54]
<i>B. subtilis</i> DCU, <i>B. pumilus</i> BP, <i>B. cereus</i> HL7	G- : <i>V. parahaemolyticus</i>	Of the 135 isolated strains three <i>Bacillus</i> 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]
<i>B. amyloliquefaciens</i>	G+ : <i>C. difficile</i>	After incubation with <i>B. amyloliquefaciens</i> supernatant growth inhibition were observed against all <i>C. difficile</i> ribotypes.	Agar well diffusion or paper disc assay	[56]
<i>L. fermentum</i> M059, <i>L. fermentum</i> F-6, <i>W. cibaria</i> 4213	G+ : <i>S. aureus</i> ATCC 6538, <i>B. cereus</i> NCIM 245, <i>B. subtilis</i> ATCC 6633, G- : <i>E. coli</i> ATCC 25922, <i>S. typhi</i> 25, <i>P. aeruginosa</i> 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]
<i>L. acidophilus</i> L-1, <i>L. bulgaricus</i> 6, <i>L. plantarum</i> 24-4B, <i>L. fermentum</i> 1, <i>L. brevis</i> , <i>B. animalis</i> subsp. <i>lactis</i> L-3	G+ : <i>S. aureus</i> , <i>B. cereus</i> G- : <i>E. coli</i>	Ten strains of <i>Lactobacillus</i> and <i>Bifidobacterium</i> showed promising antimicrobial activity against two pathogens or in both model systems (broth and milk)	Agar well diffusion or paper disc assay	[58]

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

(Continued)

Table I (Continued).

Probiotics with in vitro Antimicrobial Activity	Tested Pathogenic Microorganisms	Reported Result	In vitro Testing Method Employed	Ref
<i>L. acidophilus</i> ATCC3456, <i>L. casei</i> ATCC 39392, <i>L. rhamnosus</i> ATCC 7469	<i>S. aureus</i> ATCC 25923, <i>E. coli</i> ATCC 25922	All three <i>Lactobacillus</i> strains have inhibitory effects for <i>E. coli</i> , Cell-free supernatant of <i>L. casei</i> being the most effective probiotic	Microplate technique	[66]
<i>L. reuteri</i> (DSM17938), <i>L. acidophilus</i> (DSM), <i>B. coagulans</i> (DSM1), <i>L. plantarum</i> 299v (DSM9843), and <i>B. bifidum</i> (DSM20456)	<i>P. aeruginosa</i>	Combination of probiotic strains with antibiotics have enhanced inhibitory effect. <i>Lactobacillus plantarum</i> 299v had the highest effect.	Disk diffusion method.	[67]
<i>L. acidophilus</i> EMCC 1324, <i>L. helveticus</i> EMCC 1654, <i>L. plantarum</i> EMCC 1027, <i>L. rhamnosus</i> EMCC 1105 <i>B. longum</i> EMCC 1547 <i>B. bifidum</i> EMCC 1334	<i>E. coli</i>	All probiotic isolates exhibit strong antibacterial activity against all <i>E. coli</i> isolates and eradicated biofilms formed by multidrug-resistant <i>E. coli</i> .	Agar diffusion method	[68]
<i>L. paracasei</i> ABRIINW. F58	<i>S. aureus</i> , <i>P. aeruginosa</i>	Both MDR <i>E. coli</i> isolates and (9–12 mm), <i>Pseudomonas aeruginosa</i> isolates (7–10 mm) were sensitive to bacteriocins produced by <i>L. paracasei</i> ABRIINW. F58	Disc diffusion method	[69]
<i>L. acidophilus</i> and <i>S. cerevisiae</i>	<i>S. typhimurium</i>	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 (<i>L. animalis</i> , <i>L. gasseri</i> , <i>L. acidophilus</i> , <i>L. rhamnosus</i>)	<i>E. coli</i> , <i>K. pneumoniae</i>	Curd of lactobacilli alone or in combination with antibiotics had excellent antibacterial activities against <i>E. coli</i> and <i>K. pneumoniae</i> clinical isolates infection	Agar-overlay method	[71]
<i>L. reuteri</i> DSM 17938	<i>S. aureus</i> , <i>S. pyogenes</i> , <i>Cutibacterium acnes</i> , <i>P. aeruginosa</i> .	The probiotic decreased the inflammatory process and presented antimicrobial action against <i>S. aureus</i> , <i>S. pyogenes</i> , <i>Cutibacterium acnes</i> , and <i>P. aeruginosa</i> .	Agar well diffusion/ paper disc method	[72]
<i>B. longum</i> ATCC 15707, <i>L. brevis</i> ATCC 367, <i>L. delbrueckii</i> ATCC 9649, <i>L. fermentum</i> ATCC 23271, <i>L. paracasei</i> ATCC 335, <i>L. plantarum</i> ATCC 8014, and <i>L. rhamnosus</i> ATCC 9595	<i>C. butyricum</i> ATCC 860, <i>C. difficile</i> ATCC 9689, <i>C. perfringens</i> ATCC 12924	<i>L. plantarum</i> strain ATCC 8014 has probiotic potential, with antimicrobial activity against <i>C. butyricum</i> ATCC 860, <i>C. difficile</i> ATCC 9689, and <i>C. perfringens</i> 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
<i>L. paracasei</i>	<i>Galleria mellonella</i>	<i>L. paracasei</i> was able to modulate the immune system of <i>G. mellonella</i> and protect against candidiasis.	Clinical trial	[74]
<i>L. rhamnosus</i> , <i>L. acidophilus</i> , and <i>B. bifidum</i>	<i>Candida spp.</i>	Decrease in <i>Candida spp.</i> in individuals who used the probiotic formulation.	Randomized double-blind study	[75]
<i>L. salivarius</i> NK02	<i>Aggregatibacter actinomycetemcomitans</i>	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]
<i>L. casei</i>	<i>Cryptosporidium parvum</i>	Oral administration of the probiotic <i>L. casei</i> associated with albendazole reduced <i>Giardia</i> infection,	Murine model.	[77]
<i>B. animalis</i> subsp. <i>lactis</i> DN-173010	Periodontopathogens (<i>P. gingivalis</i> , <i>Fusobacterium nucleatum</i> , and <i>Aggregatibacter actinomycetemcomitans</i>)	<i>B. animalis</i> showed a positive effect against the accumulation of bacterial plaque and gingival inflammatory parameters.	Randomized controlled trial	[78]
<i>L. reuteri</i> CL9, K16, K67 and S33	G :- <i>E. coli</i> O149: K88 JG280	Isolates showed ≥50%protection from cell and worm death caused by enterotoxin expressed in <i>E. coli</i> . CL9promoted host defensive responses,	Porcine	[79]
<i>L. casei</i> B-7280, <i>B. longum</i> VK1, <i>B. bifidum</i> VK2	G +: <i>S. aureus</i> 8325-4	The number of colonies of <i>Staph. aureus</i> 8325-4 decreased significantly in infected mice that received probiotics compared to the mice that did not receive	Mice	[80]
Lb. FloraMax-B11 (<i>L. salivarius</i> , <i>L. Pediococcus parvulus</i>)	<i>S. enteritidis</i>	Administration of this probiotic significantly reduced <i>S. enteritidis</i> intestinal colonization in chickens	Broiler chickens	[81]
<i>Pseudoalteromonas sp.</i>	G :- <i>V. harveyi</i> ATCC 14126	Significant reduction in accumulated mortality of larvae in aquaculture system when supplemented with culture supernatant	Crustacean's larva	[82]
<i>L. salivarius</i> JM32, <i>L. plantarum</i> PZ01, <i>P. acidilactici</i> JH231	G :- <i>S. enteritidis</i> ATCC 13076	Lb strains reduced the number of <i>Salmonella</i> in intestinal content, spleen, and liver,	Broiler chicks	[12]
<i>B. amyloliquifaciens</i>	G +: <i>C. difficile</i>	An increase in <i>C. difficile</i> toxin A and B levels and a significant weight loss were seen in untreated and <i>S. boulardii</i> treated mic than in <i>B. amyloliquefaciens</i> treated mice	Mice	[56]
<i>L. acidophilus</i> CHI	Prs : <i>Enterocytozoon bienersi</i>	Anti-microsporidial effects of <i>L. acidophilus</i> CHI-derived bacteriocin in immunosuppressed mice were significantly potent.	Mice	[83]
Lb: <i>L. plantarum</i> LA5 and <i>L. paracasei</i> LA7	G :- <i>S. typhi</i>	LA5 or LA7 eradicate <i>S. Typhi</i> induced typhoid infection from infected mice due to antimicrobial, anti-inflammatory, and immunomodulatory activities	Mice	[84]

(Continued)

Table 2 (Continued).

Probiotics with Efficient in vivo Antimicrobial Activity	Tested Pathogenic Microorganisms	Finding	In vivo Testing Method Employed	Ref
<i>L. plantarum</i> LR/14	Ins: <i>Drosophila melanogaster</i>	At a concentration of 15 mg/mL, antimicrobial peptides from <i>L. plantarum</i> resulted in the deformity in cellular architecture, DNA fragmentation, premature apoptosis, and death of insects	<i>Drosophila melanogaster</i> fly	[85]
<i>L. plantarum</i> C014	G-: <i>A. hydrophila</i> TISTR 1321	Feeding the fish with the <i>L. plantarum</i> C014 supplemented diet for 45 days before challenging them with <i>A. hydrophila</i> 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]
<i>L. acidophilus</i> and <i>S. cerevisiae</i>	<i>S. typhimurium</i>	Oral administration of both probiotic isolates could decrease the counts of <i>S. typhimurium</i> in liver and spleen	Mice	[71]
<i>L. casei</i> , <i>L. acidophilus</i> , <i>L. rhamnosus</i> , <i>L. bulgaricus</i> , <i>B. breve</i> , <i>B. longum</i>	<i>K. pneumoniae</i>	Administration of Lactocare can reduce ICU and a hospital stays of patients	Randomized clinical trial	[86]
<i>L. plantarum</i> MTCC 1407, <i>L. acidophilus</i> MTCC 10307	Enteroaggregative <i>E. coli</i> and <i>E. coli</i> ATCC 25922	Probiotic strains can serve as a therapeutic agent against multi-drug-resistant <i>E. coli</i> .	Mice	[87]
<i>L. casei</i> (Shirota Strain)	<i>K. pneumoniae</i>	Oral administration of probiotic <i>L. casei</i> Shirota strain reduces the risk of Ventilator-associated pneumonia (VAP) in patients	Randomized, open-label controlled trial	[88]
<i>L. acidophilus</i> , <i>Pediococcus</i>	G-: <i>S. enteritidis</i> 13A	Probiotic treatment with <i>L. acidophilus</i> and <i>Pediococcus</i> significantly reduced <i>Salmonella</i> colonization in chicks	Birds	[89]
LactoLevure® (containing <i>L. plantarum</i> , <i>L. acidophilus</i> , <i>S. boulardii</i> and <i>B. lactis</i>)	<i>P. aeruginosa</i> and <i>E. coli</i>	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 <i>P. aeruginosa</i> , <i>E. coli</i> .	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	<i>Rotavirus</i>	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	<i>Bifidobacterium</i>	Increased <i>Bifidobacterium</i> , 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	<i>E. coli</i> , <i>C. perfringens</i>	Decreased in the population of pathogens	Broiler chickens	[110]
FOS and MOS	<i>C. perfringens</i> , <i>E. coli</i>	Decreased populations of <i>C. perfringens</i> and <i>E. coli</i>	Broiler chickens	[111]
Raffinose	<i>P. aeruginosa</i>	Inhibition <i>P. aeruginosa</i> 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	<i>Eubacteria</i> , <i>Lactobacillus spp.</i> , <i>Bifidobacterium spp.</i> , <i>Clostridium Cluster IV</i> , <i>Clostridium Cluster XIVa</i> ,	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 <i>Cynara cardunculus</i>	<i>L. acidophilus</i> and <i>Bifidobacterium</i>	The proliferation and growth of tested probiotic bacteria were greatly enhanced and aided in shifting toward the beneficial microbiota profile	Rats	[115]
Raffinose	<i>S. mutans</i>	Inhibit oral bacterial adhesion and biofilm formation and keep oral health by preventing bacterial-induced dental caries	In vitro culturing method	[116]
Raffinose	<i>P. aeruginosa</i> , <i>S. aureus</i>	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
<i>L. fermentum</i> 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]
<i>L. acidophilus</i> , <i>L. rhamnosus</i> , <i>B. bifidum</i> , <i>B. longum</i> , <i>E. faecium</i> , with FOS	Acute diarrhea	Duration of diarrhea and hospitalization was significantly shorter in children receiving the synbiotic group	Randomized controlled study	[133]
<i>S. thermophilus</i> , <i>L. rhamnosus</i> , <i>L. acidophilus</i> , <i>B. lactis</i> , <i>B. infantis</i> 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 <i>B. breve</i> 46, <i>B. lactis</i> 8:8, <i>B. longum</i> 6:18, <i>B. breve</i> CCUG 24611, <i>B. lactis</i> JCM 10602, <i>B. pseudocatenulatum</i> JCM 1200	<i>Clostridium difficile</i>	In the presence of such prebiotics, <i>Bifidobacterium breve</i> 46 and <i>Bifidobacterium lactis</i> 8:8 inhibited the growth and toxin production in four different strains of <i>Clostridium difficile</i> .	Agar plate assays	[135]
<i>B. lactis</i> B94 with inulin	<i>Rotavirus</i> , <i>Adenovirus</i> , <i>Entamoeba histolytica</i> , <i>Salmonella</i> , <i>Shigella</i> , <i>Campylobacter</i> , <i>Clostridium difficile</i> , <i>Cryptosporidium</i> , and parasites	Synbiotic treatment decreased the duration of diarrhea	Randomized controlled study	[136]
Garlic and basil as natural prebiotics with <i>Pediococcus acidilactici</i>	<i>E. coli</i> , <i>Salmonella</i> , <i>E. faecalis</i> and <i>S. aureus</i> .	The presence of prebiotics augments the antimicrobial activity of probiotic strains against tested pathogens.	Agar plate assays	[137]
<i>L. acidophilus</i> and FOS	<i>P. aeruginosa</i> , <i>E. coli</i> , <i>S. aureus</i> and <i>B. cereus</i>	Enhanced activity of the probiotic bacteria (<i>L. acidophilus</i>) and inhibited the pathogenic bacteria, where <i>E. coli</i> was more susceptible to inhibition, followed by <i>S. aureus</i> , <i>P. aeruginosa</i> , and <i>B. cereus</i> , respectively.	Agar plate assays	[138]
<i>L. rhamnosus</i> and <i>P. acidilactici</i> in combination with inulin-type fructans	<i>Candida albicans</i> .	The synbiotic combinations inhibit the growth and biofilm formation of <i>Candida albicans</i> and could be used as an alternative to antifungal drugs in candidiasis therapy.	Microtiter plates	[139]
<i>L. rhamnosus</i> with inulin or FOS	Vancomycin susceptible <i>Enterococcus faecalis</i> (VSEF) and clinical vancomycin-resistant <i>Enterococcus faecium</i> (VREF)	Synbiotic showed an inhibition effect on VREF growth, <i>Lactobacillus rhamnosus</i> 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
<i>P. pentosaceus</i> 5–33:3, <i>L. mesenteroides</i> 32–77:1, <i>L. paracasei</i> ssp. <i>paracasei</i> 19; and <i>L. plantarum</i> 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]
<i>L. plantarum</i> 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]
<i>L. acidophilus</i> 10, <i>L. rhamnosus</i> HS 111, <i>L. casei</i> 10, <i>B. bifidum</i> 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]
<i>B. breve</i> strain Yakult, <i>L. casei</i> 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]
<i>S. faecalis</i> T-110, <i>C. butyricum</i> TO- A, <i>Bacillus mesentericus</i> TO- A, <i>L. sporogenes</i>	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 antimicrobial 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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