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Importance ofprobioticsforhumanhealth:Acritical reviewB

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Abstract

Probiotics,prebiotics,andsynbioticshavebeenstudiedfordecadesfortheirhealthbenefits.Probiotics arelivemicroorganismsknowntoconferahealthbenefitwhenadministeredinadequateamounts.The most commonprebiotics are FOS, GOS, XOS, Inulin, and fructans. Synbiotics, nondigestible fibres, selectivelyincreaseparticularmicrobespecies'growthandactivity,improvinghosthealth.Postbiotics arebeneficialmicrobesormetabolitesthatinduceTregulatorycelldifferentiationandsynthesizeanti-inflammatory cytokines, killing bacteria chemically and mechanically. Probiotic strains must pass multiple testing rounds to prove pathogen causation and monitor and investigate the illness. In vitro investigationsforstomachacidity, bileacidresistance,antibacterialactivity,andpathogen adhesionare recommended. Manufacturing and storage should include quality control and assurance, and effectivenessstudiesshouldfocusonhumans.Thesebeneficialgroupsofmicroorganismsareagreat boon to human health and are recommended for use in various prophylactic measures. This paper discussestheuses,properties,andfunctionsof someprobioticstrainsusedwidelyafter confirmation withclinicaltrials.Next-generationprobioticsproductionisoneofthefewadvancementsinthefield of biology and has significant prospects.

Introduction

Thehealthadvantagesofprobiotics,prebiotics,andsynbioticshavebeenextensivelyresearchedover thelastfewdecades.Thesedietarysupplements,functionalmeals,havebeenshowntochange,modify, andrestore pre-existing gutflora(Pandeyet al., 2015).They alsohelpthedigestive environmentrun smoothly. Bifidobacterium, Lactobacilli, S. boulardii, and Bifidobacterium coagulans are the most often utilized probiotic strains. Prebiotics such as FOS, GOS, XOS, Inulin, and fructans are the most frequentlyusedfibresthat,whencombinedwithprobiotics,arereferredtoassynbioticsandcanboost probioticviability(Pandeyetal.,2015).Thecurrentreviewconcernsthecompositionandfunctionsof Probiotics,Prebiotics, andSynbiotics in humanhealth.Additionally, additional health advantages such as immunological modulation, cancer prevention, inflammatory bowel disease, and so on are highlighted.

Probioticshavebeenutilizedtoaidinthepreventionandtreatmentofvariousmedicaldisorders.Some of their health benefits have been validated, while insufficient data back others. Probiotic effects are strain-specific, and probiotic products may differ, with more advantages found with one lot of probiotics vs.anotherduetothechallengeofqualitycontrolwithlivingmicroorganisms(Figure1).Furthermore, combination agents might make it difficult to assess specific therapeutic advantages (Senok et al., 2005; Surawicz,2008;Wald&Rakel,2008).Probioticshavetraditionallybeenusedtotreatgastrointestinal disorders,owingtotheirantimicrobialpropertiesandcapacitytorepairgutflora.Themostcompelling evidence for probiotic usage is treating certain diarrheal illnesses, particularly rotaviral diarrhea in children.Clinicalresearchhasalsoshownprobioticstobeeffectiveintreatingpouchitis(Phametal., 2008; Vanderhoof &Young, 2008). Data on the effectiveness of probiotics for antibiotic-associated diarrhea (AAD) and travellers'diarrhea are inconclusive (Pham et al., 2008; Senok et al., 2005). Despite inconsistent clinical trial outcomes, probiotic medication may effectively treat Crohn's disease, ulcerativecolitis(UC),irritablebowelsyndrome(IBS),andHelicobacterpyloriinfection(Macintyre & Cymet, 2005; Pham et al., 2008; Santosa et al., 2006; Scarpellini et al., 2008).

Prebioticsareprimarilynondigestiblefibresthatbenefitthehost'shealthbyselectivelyboostingcertain microbe species' developmentand activity(Figure1)(Gibson & Roberfroid, 1995). Lactobacilliand bifidobacteriaarecommonlyfound inthe colon(Gibson& Roberfroid,1995).Anexcellentprebiotic

shouldberesistanttotheeffectsofstomachacids,bilesalts,andotherhydrolyzingenzymesinthegut; the upper gastrointestinal system should not absorb it and be readily fermentable by intestinal microorganisms (Gibson & Roberfroid, 1995). WHO defines Prebiotics as a non-viable dietary component that confers health benefits to the host through microbiota regulation. Prebiotics are a varied category of substances like carbohydrate components with unknown origins, fermentation characteristics, and dosesnecessaryfor healtheffects.Prebioticscanbefoundinbreast milk,soybeans, raw oats, unprocessed wheat, unrefined barley, bacon, non-digestible carbs, and especially non-digestible oligosaccharides. However, only bifidogenic, non-digestible oligosaccharides (especially inulin, its hydrolysis product oligofructose, and (trans) galactooligosaccharides (GOS)) meet all prebiotic categorization requirements (Gibson & Roberfroid, 1995). Prebiotics such as inulin and pectin providesvarioushealthadvantages,includingreducingthefrequencyandlengthofdiarrhea,relieving inflammation, and alleviating other symptoms linked with diarrhea, intestinal bowel disease, and preventive properties against colon cancer (Gibson & Roberfroid, 1995). They are also related to improvedmineralbioavailabilityandabsorption,decreasedriskfactorsforcardiovasculardisease,and promoted satiety and weight reduction, hence avoidingobesity (Pokusaeva et al., 2011).

A synbiotic product benefits the host by increasing the survival and implantation of live microbial dietary supplements in the gastrointestinal tract by selectively expanding the development and activatingthemetabolismofoneorasmallnumberofhealth-promotingbacteria(Figure1).Because synbiotics imply synergism, they should be reserved for products in which the prebiotic compounds specificallybenefittheprobioticorganisms(Cencic& Chingwaru,2010).Synbiotics werecreatedto help probiotics survive. The justification for using synbiotics is based on findings demonstrating improvedprobioticbacteriasurvivalduringtransitthroughtheupperdigestivesystem.Moreefficient embeddinginthecolonandastimulatinginfluenceonthegrowthofprobioticsandubiquitousbacteria help maintain intestinal homeostasis and a healthy body (Peña, 2007).

Postbiotics areeithermetabolitesorfragmentsofmicroorganismsthatpositivelyaffectthehost (Figure 1).Thestructuralvariabilityofpostbioticssuggestsaplethoraofapproachesforpostbioticacquisition. Chemicalandmechanicalapproachescanbeusedtokillbacterialcells.Enzymaticextraction,solvent extraction, sonication, and heat are examples of these procedures. Extraction, dialysis, and chromatography isolate and identify desired compounds (Zolkiewicz et al., 2020). SCFA stands for short-chain fatty acids.

Postbioticsexhibitpleiotropiccharacteristics.Postbioticsrestorethebalancebetweenthetwoprimary arms oftheimmunesystem,represented byTh1andTh2, byinducing differentiation ofTregulatory cells and synthesizing anti-inflammatory cytokines (Zolkiewicz et al., 2020). Th2 lymphocytes are whitebloodcells.ThebalanceofTh1andTh2cellsiscriticalforimmunoregulation,anditsdisruption causesvariousimmunologicalillnesses,includingatopicdermatitis.Antibacterialactionismostlikely mediated by postbiotics' influence on the molecular structure of enterocytes, which results in the intestinal barrier being sealed. Postbiotics' "statin-like" action and potential therapeutic use in metabolic and associated illnesses are significantly expected (Zolkiewicz et al., 2020).

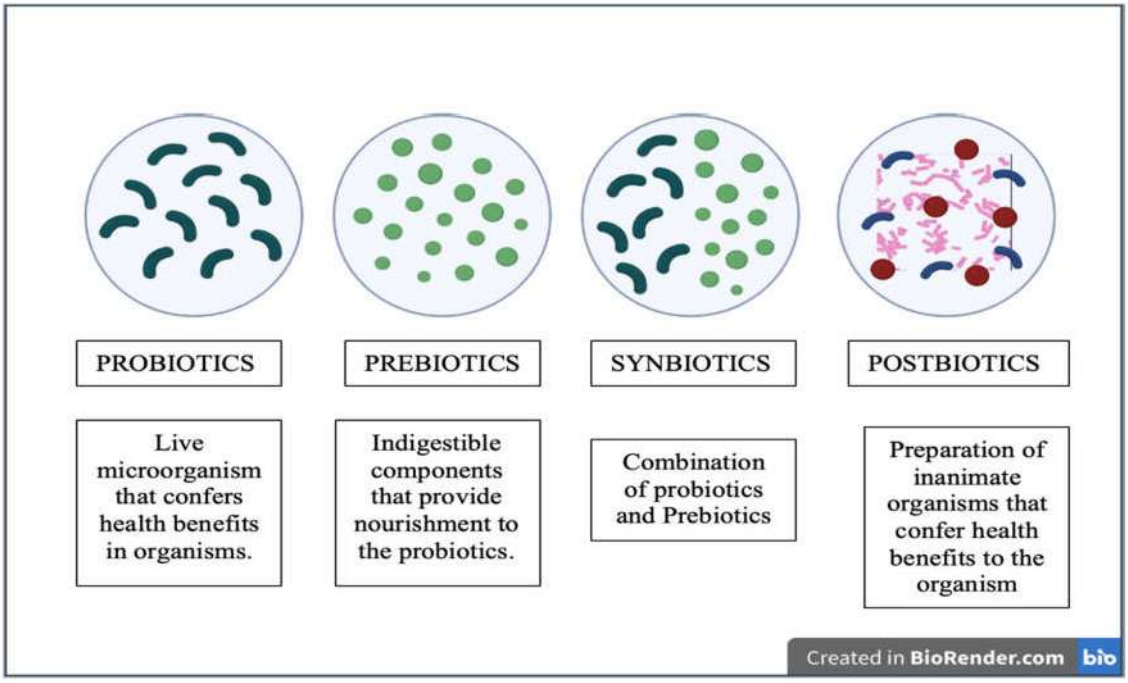

Figure1:DiagrammaticrepresentationofProbiotics,Prebiotics,SynbioticsandPostbiotics(Using BioRender).

Requirementsforastraintoqualifyasasourceofprobiotics

Thetestprobioticstrainhastoundergovariouslevelsoftestingtoqualifyasapotentialprobioticstrain; theseareachievedinmultiplesteps,whichincludecharacterizationofthestrain,safetyleveltestsfor intended use, usage of clinical trials on humans, delivery requirements to enter into the host, determining the dosage and also enhancement of the shelf life. In case the probiotic stain stands out with the characteristics mentioned. It is safe for humans and a prophylactic element for preventing many health conditions. ICMR-DBT has incorporated several guidelines to satisfy the above screenings, which are discussed below (Council & Icmr, 2015);

- Identification of the strain is crucial for establishing causality between a pathogen and a particular health outcome and for conducting effective monitoring and investigations of the spread of disease (epidemiological). Phenotypic and genetic testing should adhere to established protocols.
- PCR-basedmethods,16SrRNAsequencing,andDNAfingerprintingarecurrentlyemployed molecular approaches for identification, including ribotyping and PFGE (pulsed-field gel electrophoresis).
- In vitro tests are recommended to screen potential probiotic strains for resistance to gastric acidity,bile acid resistance,antimicrobial activity,andabilityto reducepathogenadhesion.
- These in vitro assays are predicated on the idea that the circumstances in the gut are unfavorable.Thesetests,takentogether,determinewhich cultures areeffectiveintheroleof probiotics.Andshouldbetestedfirstonsuitableanimalmodelstoensuresafetybeforebeing tried on humans in clinical trials.
- Evaluation of the acute, subacute, and chronic toxicity of exceptionally high doses of probiotics should be conducted for all possible strains. This evaluation may not be essential for strains with a documented usage history. This category comes under the in vivo tests dealing with safety levels.

- To verify in vitro effects, proper, validated animal models must be utilized before human testing.This category deals with the in vivo tests to determine the efficacy level.
- Probiotics for human use should be evaluated with the following tests: determination of antibioticresistancepatterns,assessmentofundesirableside-effects,andassessmentoftoxin production and hemolytic activity.Assessment of lack of infectivity by a probiotic strain in immunocompromised individuals is also an added measure.
- Humansshouldbetheprimaryfocusofprobioticefficacyresearchbecauseofthepotentialfor similarhealthbenefits.Improvementsincondition,symptoms,signs,health,orqualityoflife; decreased risk of disease; an increased time before the subsequent incidence of sickness; or accelerated recovery from illness, all of which are statistically and clinically significant in studies. Every metric must be statistically significant while testing probiotics.
- The probiotic strain's cfu/ml/day minimum effective dosageor quantity of viable cells in the carrier. Foods that exhibit functions that promote general health, overall wellness or specific health claims in the target group should be clearly labeled.
- Essential details on a label (Gregor Reid et al., 2001; Saldanha, 2008)should be the genus, species, and strain names, minimum viable numbers of each probiotic strain, health claims, recommendedservingsize,andproperstorageconditions.Thesedetailsshouldbeincludedin addition to the general information required by food legislation.
- Qualitycontrolandassurancemeasuresshouldbeinplacethroughoutproductionandstorage. It is recommended that all factories follow GMPs. Guidelines for using hazard analysis and criticalcontrolpoints(HACCP),asoutlinedbytheCodexGeneralPrinciplesofFoodHygiene, should be implemented.

Probioticsusedasanaidforirritablebowelsyndrome

Irritable bowel syndrome (IBS) is the most common digestive tract disease caused by an altered intestinalflora,theso-calleddysbiosis.Theintestinalfloraconsistsofmorethan2000differenttypes of bacteria belonging to the four main strains *Bacteroides, Firmicutes, Actinobacteria*, and *Proteobacteria*(Qinetal.,2010).Environmentalandgeneticfactorsdeterminetheproperfunctioning oftheintestinalflora(Wilsonetal.,2019).Ithasvariouseffects,suchasabdominalpainandbloating, and is caused by loose stools accompanied by diarrhoea and/or constipation, ranging from mild to severe (El-Salhyetal.,2014;Schuster,2001).Althoughirritablebowelsyndromedoesnotresultinincreased mortality(Wuetal.,2022),itdoeshaveseveralextraintestinalsymptoms,includingheadache,fatigue, fibromyalgia, poor social functioning, and emotional well-being (Böhn et al., 2013). This can sometimesleadtoareductioninaperson's qualityoflifeindailywork,leadingtoafinancial burden onsociety(Hahnetal.,1999;Patricketal.,1998).Themainchallengeinchoosingaprobioticstrainis the lack of clarity about the pathogenesis of IBS; However, several factors are responsible for the pathogenesis of IBS, mainly altered gut microbiota (dysbiosis) (Hong & Rhee, 2014), alternative enteroendocrine cells, previous infections, genetics, and diet (Mazzawi, 2022).

Probioticsareessentialinmaintaininggutdysbiosis(Tambolietal.,2004).IBDpatientshaveincreased intestinalpermeability,whichcausestheinvasionofpathogenicbacteria.Adefectivemucosalbarrier promoteslightexposureandtriggersasustainedimmuneactivation(Cain&Karpa,2011;Gersemann etal.,2012;Seksiketal.,2008).Thisleadstoadecreaseinprotectivebacteria,suchas*Bifidobacterium* and*Lactobacillus,*andanincreaseinthenumberofpathogenicbacteria,suchas*Escherichiacoli*and *Clostridium* species (Di Cagno et al., 2011; Macfarlane et al., 2004). It also reduces the synthesis of short-chain fatty acids (acetates, butyrate, and propionates)(Cain & Karpa, 2011). It increases the synthesis of toxins and the production of pro-inflammatory cytokines that cause inflammation and symptoms. On the contrary, probiotics offered a therapeutic treatment for these enteropathies (Vanderpooletal.,2008).Themechanismbywhichprobioticsalterthegutmicrobiotaincludesa

reduction in luminal pH, competitive adhesion, secretion and induction of antimicrobial compounds (bacteriocinsanddefensins),changesinnitrogenmetabolism,andcellularavoidance(Ngetal.,2009; Scott et al., 2015). The significant effect of these probiotics are analysed in the table 1. Pharmacological treatment of IBS has been observed as predominantly symptomatic and short-lived(Rao & Weber, 2014; Tack et al., 2016). Therefore, researchers have focused on nutritional management and probiotics to treat IBS over the past decade.

Table1:Multivariantprobioticsstrainsanditsmodeofaction.

Strains	**Mechanism ofaction**	**Reference**
Lactobacillusparacaseisubsp. Paracasei B21060	Inhibiting blood $CD4^{+}$T-cell proliferation inpatientswithIBD.	(Pelusoetal.,2007)
*B.breve*and*Bifidobacterium bifidum strains*	Reduction of proinflammatory cytokines (IL-8). IncreasestheIL-10synthesisin peripheral bloodmononuclearcells.	(Imaokaetal.,2008)
*B.breve,B.longum*and*L.casei*	Improvementofsymptoms,such as diarrhoea and abdominal pain.	(Fujimorietal.,2007)
*L.salivarius,L.acidophilus*and *B.bifidumstrain* *BGN4.*	Disease activity index improvement. Reductionintherecoverytime.	(Palumboetal.,2016)
Lactobacillus delbruekii and *Lactobacillusfermentum*	Improvement of mucosal inflammation and lesion.	(Hegazy&El-Bedewy, 2010)

ProbioticsusedasanaidforAlzheimer'sandParkinson'sDisease

Neurogenerative disorders have proven to spread widely throughout the world (Bulck et al., 2019). Some of them are curable, while certain disorders remain to be uncured. Multiple factors lead to the development of such disorders. Environmental, genomic, and metabolic are some of the factors that leadtothedevelopmentofthesedisorders.Thetwomostcommonneurogenerativedisordersinclude Alzheimer's and Parkinson's disorder (Bulck et al., 2019). Alzheimer's is usually characterized by memory impairment, primarily due to the presence of neurofibrillary fibers andAß (Naomi et al., 2022). Modern-day treatments use probiotics to treat this disorder in humans, and it has been observed that changes in gut microbial diversity also adversely affectAlzheimer's in humans (Naomi et al., 2022). Parkinson's is the second stage ofAlzheimer's. It is progressive and has been characterized by both motor and non-motor nerves (Gazerani, 2019).

Among the reports made, certain strains of probiotics, such as **SLAB51** (Bonfili et al., 2018), which containsspeciesofLactobacillusandStreptococcus,regulatedglucoseandbrainmetabolismwhenit wasinjectedintoananimalmodel.Thetable2listsotherprominentstrainsandtheirmechanismofthe action below.

Table 2:ProbioticsstrainsanditsmodeofactionforAlzheimer'sandParkinson'sdisease.

Strains	Mechanism ofaction	Reference
Lactobacillusplantarum	Regulatesbrainandglucosemetabolism. Regulates neuronal activity. Regulatesbrainmetabolism. Promotes the production of neurotransmitterslikeacetylcholineand acetylcholinesterase. Activates immune cells that leadsto the stimulationofmicrobiota-gut-brainaxis.	(Bonfilietal.,2018)
Bifidobacteriumlongum	Regulatesmetabolicabnormality. Regulatesmetabolicabnormalityand oxidative stress. Regulatespresynapticneurotransmitters in the brain. Regulates brain metabolites. Regulatesserummetabolites.	(RezaeiAsl et al., 2019; Rezaeiasl et al., 2019)
Lactobacillusacidophilus	Regulatesbrainandglucosemetabolism. Regulates neuronal activity. Activatesimmunecellsleadingto stimulationofmicrobiotagutbrainaxis. Regulatesbrainmetabolismandthe intestinal microbiome. Regulatespresynapticneurotransmitters in the brain.	(Abraham et al., 2019; Leblhuber et al., 2018; Rezaeiasl et al., 2019)
Clostridium butyricumWZMC1016	Regulatesbrainmetabolites.	(Bonfilietal.,2018)
Lactobacillus helveticusIDCC3801	Regulatesbrainmetabolites.	(Bonfilietal.,2018)

Tosummarize,thisstudyshowsvariousevidence-basedstudiesthathaveproventohelpeffectivelyin treatingneurogenerativedisordersinhumans.Clinicaltrialsassociatedwithhumanshaveshownthat Alzheimer'sandParkinson'scanbetreatedbytheusageofprobiotics(Figure2).Inaddition,various other clinical trials are being conducted to detect the specific changes in the gut flora. This interdisciplinaryapproachcaneffectivelyhelptreatandpreventvariousneurogenerativedisordersin humans.

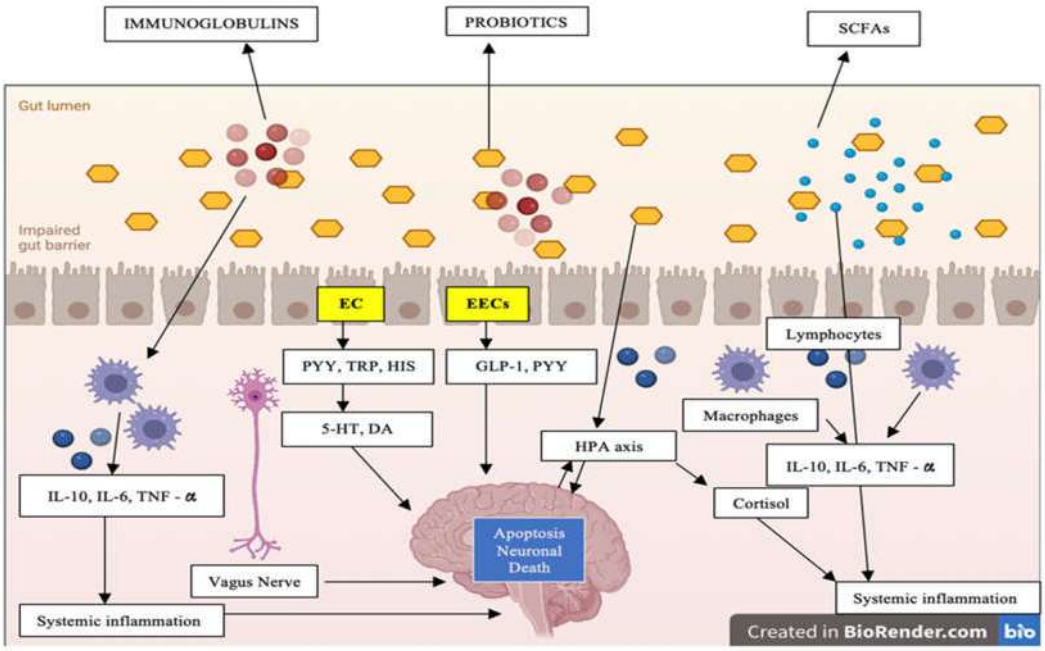

Figure2:ModeofactionofProbioticsinAlzheimer'sdisease(UsingBioRender).

ProbioticsusedasanaidforfoodHypersensitivity

Theingestionofaparticularfoodorfoodadditivethatcausesanimmunogenicresponseinthebodyis knownasfoodhypersensitivityorfoodallergy(Isolaurietal.,2002).Thisismainlycausedduetothe releaseofIgEandotherchemicalmediatorsinthebodythatmightleadtoaclassicallergicreactionor allergicanaphylaxisinthebody.Allergiesareprimarilyconcernedwithsmallchildren,andithasbeen noted that the gut flora of typical children is different from that of an allergic child (Isolauri et al., 2002). Most commonly, *Lactobacillus* and *Bifidobacterium* are the genera highly concentrated in humans' guts. Afterthe firstweekofbirth,infantscompromiseonvariousprobiotics. Probioticsaremaintainedinthe bodywiththehelpofprebiotics,theindigestiblefibresthathelpnourishprobiotics.Breastmilkissaid to be loaded with many prebiotics (Isolauri et al., 2002). Food hypersensitivity can be very well controlled by certain strains which are listed below in table 3.

Table3:Probioticsstrainsanditsmodeofactionforfoodhypersensitivity.

Strains	Mechanism ofaction	Reference
Lactobacillus rhamnosus + *Bifidobacterium lactis*	Helps in decreasing atopic dermatitisoreczemainchildren with food allergy.	(Santosetal.,2020)
LactobacillusrhamnosusGG	Decreases allergicasthma IncreasesfecalIgAlevels	(Pessietal.,2000)
Lactobacilluscasei	Decreases allergicrhinitis	(Santosetal.,2020)
Lactobacillusreuteri	Increases the Th1 and Th2 balanceinthebodyandtheTh2 cytokines	(Santosetal.,2020)

Bifidobacteriumlongum	DecreasesIL10productionin the body	(Santosetal.,2020)

This topic remains controversial as few clinical trials have been conducted to check the probiotic's action in treating food hypersensitivity. Mixing one strain of probiotics with either a prebiotic or a mixtureofwheycanalsoaffectthemodeofactionoftheseprobioticsinthebody.Probioticsmustnot besuppliedtoimmunocompromisedchildren,eventhoughtheyarepronetospecificfoodallergiesand atopicdermatitis(Kilpietal.,2002).Toconclude,thereisnotmuchevidencetoprovethatprobiotics help effectively treat and prevent food allergies in humans.

ProbioticsusedasanaidforOralHealth

Oralhealthhasgottenmuchattentioninthelastdecades.Apleasantandvaluabledentalstructurethat enablesanindividualtoleadafulfillingsociallife(Meurman&Stamatova,2007).Ontheotherhand, oral health is the state of being comfortable and pain-free, having a socially acceptable dentofacial profile, being able to chewand eat a wide variety of diet-related foods, speaking clearly, and having freshbreath(Meurman&Stamatova,2007).Oralhealthcanbecontrolledbycertainstrainswhichare listed below in table 4.

Table4:ProbioticsstrainsanditsmodeofactionforOralhealth.

Strains	Mechanism ofaction	Reference
Lactobacillusrhamnosus GG+Lactobacilluscasei	Hamperthegrowthof *Streptococcus* which are associated with the development of dental caries in the mouth.	(Aholaet al., 2002; Busscher et al.,1999;Hatakkaetal.,2001; Meurman et al., 1994)
S. salivarius	Reduction in volatile sulphur compounds	(Burtonetal.,2005)
Lactobacillussp	Helps to form a barrier to stop the colonization of pathogens due to the production of inhibiting substances	(Boriset al.,1997;G Reid et al., 1988)
Lactobacillus reuteri ATCC55730	Reduction in the level of *Streptococcus mutans*	(Caglaretal.,2006)
W.cibaria	Reduction in volatile sulphur compounds	(Kangetal.,2006)

Ithasbeendemonstratedthattheoralcavitycontainsstrainsspecificallydesignatedasprobioticswith itsdiverse microbial species (Meurman et al.,1994).Moreresearchisneeded toidentifythemouth's resident probiotics,delineatetheprocesstheycolonize, anddeterminehowtheyultimatelyaffect the oralenvironment.Moreresearchwouldbeneededtodeterminehowprobioticsaffectthe harmonyof theoralecosystem.Studiesonthecombinedeffectofmultipleprobioticsusedconcurrently,examining the potential additive, cumulative, or competing modes of action in the oral environment may be of particularinterest.Thestudiesonthesafetyofprobioticsmentionedherecanbeused as astartingpoint for further, in-depthresearch.The basic requirementsfor a strain to be classified as an oral probiotic mayalsochangedependingonitsintendedindications.Comparedtothestandardsappropriateforthe relevant strains in other regions of the gastrointestinal system, oral applications may need to be adjusted (Meurman et al., 1994). In other words, requirements for an oral probiotic may differ from those for other health purposes. To find the best candidate probiotics for oral and dental illnesses, systematic screeningandidentificationoflatentorresidentprobioticmicrobesisrequired.Investigatingprobiotic

therapy'srolein managingoralsymptoms of various diseases,such as cutaneousdisorders,iscritical forunderstandingthemechanismsbywhichprobioticspeciesmodifyoralimmunity(Meurmanetal., 1994). There is no evidence that probiotics have any effect on autoimmune disease oral symptoms. Studies on people with lichen planus, pemphigus vulgaris, cicatricial pemphigoid, or aphthous stomatitis may be useful in this area. Probiotics have traditionally been administered through dairy products, the vast majority of which are produced through lactic acid fermentation. Species that ferment sugar and reduce oral pH harm the teeth (Meurman et al., 1994).

Probioticsasanaidforchildhealth

Probiotics are bacteria that are advantageous to the host's health. Hypothesized processes include raising themucosalbarrier'sresistancetothemigrationofbacteriaandtheirtoxinsbystrengtheningintestinal cell junctions, modifying the host's response to microbial products, and boosting immunoglobulin levels. A mucosal response, enteral nutrition improvement to avoid pathogen growth, Competitive exclusionofpotentialpathogens,andantimicrobial proteinproduction.Inpublishedmeta-analysesand systematic reviews, the effects of probiotics on essential neonatal clinical outcomes are discussed (Szajewska, 2016). Human health and the activity and makeup of the gut microbiota are becoming increasinglylinkedtointestinalandsystemicillnesses.Infull-termnewbornswithmildhypoxiaonthe firstdayoflife,LachnospiraceaeandClostridiapredominate,relatedtodecreasedbraindevelopment and communication at 6 months(Szajewska, 2016).Antibiotic-resistant bacteria in preterm neonates increasetheriskofinfectionandnegativelyimpactneonatalgrowthanddevelopment(Bresestietal., 2022).ProbioticshaveincreasedintestinalBifidobacteriaandthefunctionalcapacitytoutilizehuman milk oligosaccharides whilereducingenteric inflammationand antibiotic resistance.To investigategut microbiota as a predictive biomarker and develop targeted therapies, it must be known if dysbiosis causes or results from significant disorders. Probiotic strains such as lactobacillus rhamnosus GG, saccharomycesboulardii,lactobacillusreuteriDSM17938,Bifidobacteriumanimalissubsp.BB12,E coli nissle 1917, and Bifidobacterium lactis DN173, along with rehydration therapy, are used frequently in neonatal treatments and for the prevention of conditions like acute gastroenteritis, antibiotic-associated diarrhea, nosocomial diarrhea, allergies, inflammatory bowel disease in the children (Szajewska, 2016).

Probioticsasanaidforcancer

Probiotics improve apoptosis in cancer patients (Śliżewska et al., 2020). In mouse andhuman colon cancer, HGC-27 and colitis Lactobacillus rhamnosus GG suppresses proliferation and promotes apoptosisinCaco-2,DLD-1,andHT-29cells(Orlandoetal.,2012).Probioticsandtheirmetabolites, suchasbutyrateandpyridoxine,mayfightcancerinpreclinicaltrials(figure3).SCFAsprovidecolon cellswithenergy,keepthegutacidic,restrictsecondarybileacidgeneration,andpromotecancercell acidosis and death (Kahouli et al., 2013). Butyric acid balances colon cell growth, division, and apoptosis. Colorectal cancer patients have lower stool butyrate levels than healthy persons because colon cell metabolism produces 70%–90% of itc(Macfarlane & Macfarlane, 2003).

Duetoindividualvariances,gutfloramaynotcreateenoughSCFAstopreventcolorectalcancer.Thus, probiotics boost SCFAproduction. SCFAs suppress pathogen development. In vitro, propionic acid and butyricacidpreventedSalmonellatyphimuriumfromattackinghealthycellsbyinhibitingitsinvasive genes (Gantois et al., 2006). SCFAs also modulate systemic and intestinal immunity. SCFAs cause intestinal epithelial cells to generate antimicrobial peptides and tight junctions to sustain intestinal barrier function.SCFAsinteractwithintestinal Gprotein-coupledreceptorstobalance inflammation and immunological response (Soel et al., 2007). Both conjugated linoleic acid (CLA) and LA can stimulate apoptosis genes, including Bcl-2, caspase 3, and caspase 9, preventing colon cancer cell spread(Luetal.,2021).Accordingtopreviousresearch,Lactobacillus,Bifidobacterium,Streptococcus salivarius, and Propionibacterium freudenreichii subspecies can create CLA in the terminal ileum, whichcoloniccellscanabsorborinteractwithtobenefit(Śliżewskaetal.,2020).Thesestrainscanbe

used alone or alongside cancer drugs. Immune surveillance against cancer achieved therapeutic goals(Zhangetal.,2019).ItisalsoobservedthatTGF-breceptorblockersandprobioticsenhancedthe antitumor immune response, decreasing tumor development (Shi et al., 2019). Probiotics' anticancer mechanismsincludepositivecontrolofintestinalflora,metabolicactivity,bindinganddegradationof carcinogenic chemicals, immunomodulation to reduce chronic inflammation, decreasing intestinal pH, andinhibitingenzymesthatcreatepotentialcarcinogens(Molska&Reguła,2019;Reisetal.,2019).In animalmodels,probioticscurecancers(Lietal.,2016;Ranjietal.,2019).Abnormalgutfloraincreases colorectalcancerrisk(Fongetal.,2020).Colorectalcancerpatientshavemoregutbacteriathatinduce gastrointestinal inflammatory disorders and create toxins and carcinogenic compounds (Yang et al., 2017). SCFA-producing bacteria andprobiotics decrease. Inflammationincreases cancer risk. Under thecolonmucuslayer,Clostridiumspp.invadedthe submucosaandcausedchronic localinflammation (Molska & Reguła, 2019). Colorectal cancer tissues had elevated Clostridium spp. and a profile of inflammation-related genes and proteins, such as COX-2, NF-kB,TNF-a, IL-6, IL-8, and IL-12, and matrixmetalloproteinases 3 and9, which contributed to tumordevelopment andtransfer (Reis et al., 2019).It'sbeendiscoveredthatLactobacillusrhamnosusGG,acidophilus,orcelecoxibdecreasedNF-kB,COX-2,b-catenin,andK-rascarcinogenicindicatorsinacolorectalcanceranimalmodel(Chandel et al., 2019). Colorectal cancer patients have a distinct microbial structure and lower diversity than noncancer individuals. Probiotics boosted mucosal bacteria diversity and structure. Pyrosequencing showed that probiotics reduced Fusibacter genus abundance, previously linked to cancer. Another preclinicalinvestigationsuggestedthatBifidobacteriumbifidumandL.acidophilusmightchangegut microorganismstopreventcoloncancer.Probioticsmaypreventortreatcolorectalcancerinhigh-risk individuals (Lu et al., 2021).

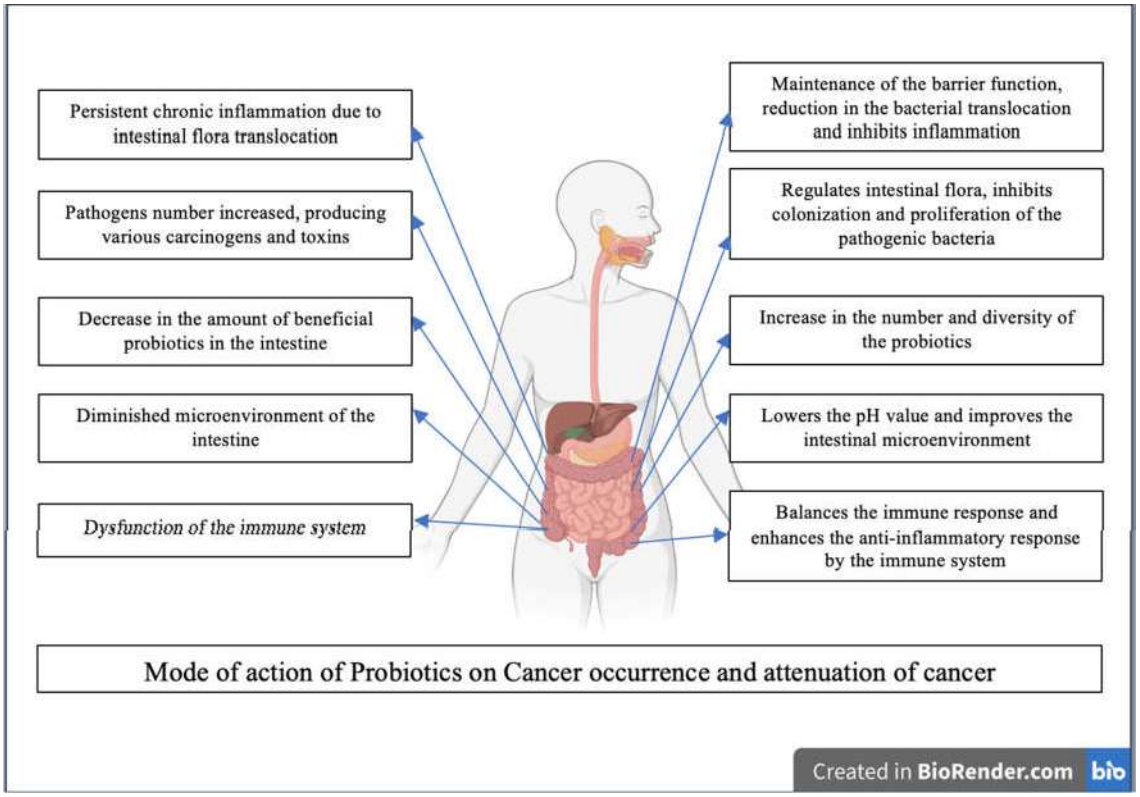

Figure3:Modeofactionofprobioticsoncanceroccurrenceandattenuationofcancer.

Nextgeneration probiotics

Over the past decade, gut commensal bacteria research has outpaced pathogen research. Many researchers have examined gut microbiota dysbiosis. Chronic inflammation causes intra- and extra-intestinal chronic inflammation-related illnesses, including colitis, obesity/metabolic syndromes, diabetes mellitus, liver diseases, cardiovascular diseases, cancer, and neurodegenerative diseases (Changetal.,2019).Alteringgutmicrobiotastructurehasbeenextensivelyinvestigatedtoovercome thesehurdles.Ithasrevealedmoreabouttreatinginflammation-relatedillnesses(Changetal.,2019). Next-generation probiotics are showing promise as preventive and therapeutic agents, whereas conventional probiotics frequently have relatively moderate advantages. Prevotella copri and Christensenella minuta regulate insulin resistance. Parabacteroides Goldstein, Akkermansia muciniphila,and Bacteroides thetaiotaomicron reverseobesityandinsulinresistance, Faecalibacterium prausnitzii protects mice from intestinal diseases, and Bacteroides fragilis reduces inflammation and fights cancer (Chang et al., 2019). New anti-inflammatory drugs will be released soon. Intestinal integrity and homeostasis depend on next-generation probiotics and gut microbiota necrobiosis.

Oneofthebestwaystotreatdiseasescausedbyleakygutsyndromesiswiththehelpofprobioticdrugs. Themainreasonswhyprobioticsaregivenmayincludemakingtheintestinalepitheliallayerstronger, boostingIgAproductiontoitshighestlevel,controllingtheproductionandreleaseofhomeostaticbile acids,andmakingmoreantimicrobialpeptides(Olveira&González-Molero,2016).Generally,well-known conventional probiotics like Bifidobacterium spp., Lactobacillus spp., and many others were chosenbychanceorbyputtingtogetherpersonalexperiences.Buttheoveralleffectsandfunctionson improvingillnessarestatisticallyinsignificant,evenifmostaresafeforbiologicaluse.Somemaywork toimprovethecondition.Traditionalprobiotics,however,don'ttreatanyparticulardiseases.Because ofthis,itisessentialtofindanddescribenewNGPsspecifictothedisease(Bottacinietal.,2017).In additiontosafetyconcerns,theNGPwillneedtoknowalotabouttheconditionstheyaretryingtotreat andthegeneticandphysiologicalaspectsofbacteria,suchashowtheygrowandrespondtoantibiotics.

Also,it'sessentialtounderstandthemolecularpathwaysthatleadtoimprovement.Todothis,cutting- edge NGS (next-generation sequencing) and bioinformatics technology platforms must be used to screenandisolatetheNGPandthendostrictfunctionalvalidationofthenovelprobiotics.Intermsof how they work, these methods are very different from those usually used alone or with traditional probiotics. To choose good probiotics, it would be necessary to do cross-sectional (or even longitudinal) studiesandmorein-depthbioinformaticsanalysisofthemicrobiotacomposition,metagenomics,and thehost'sresponses,suchasthemetabolites/metabolomesthataremade.Afterthat,potentialprobiotics ortheconsortiumcouldbechosenbasedontheanalysisdonebythemanymulti-omicsbigdatagroups. Afterthat,theselectedprobioticsaretestedtomakesuretheywork.Thiscanbedonewithinvitrocell lines, ex vivo animal models, in vivo animals, or even clinical trials with people. Also, it may be necessary to improve the quality of the samples to be analyzed to get more valuable and relevant results. Thesesamplescouldcomefromnearbymucosalociorfecesthatareeasytoget.Itisimportanttostress that strict design and execution of standardized processing processes for sample collection, ideal storage conditions,andcompletesequencingandbioinformaticsanalysiswillbeneeded.Togetabiochemical result that looks at the big picture, different extensivedata findings from studies of large amounts of blood/serum,tissues,urine,andfecessamplesunderotherenvironmentalconditions,suchasdifferent dietsanddrugtreatments,mustbecombined.Then,theseresultscanbeusedtoshowhowthehostand bacteria interact in more realistic ways (Hiippala et al., 2018).

Some of the prominent examples suitable for next-gen probiotics include Bacteroides fragilis. Faecalibacterium prausnitzii (Duncan et al., 2002; Park et al., 2018; Wrzosek et al., 2013),Akkermansia muciniphila(PDCanietal.,2014;PatriceDCani&deVos,2017;Everardetal.,2013;Plovieretal., 2017;Wangetal.,2018),Prevotellacopri(Fuetal.,2005;Huetal.,2009),Bifidobacteriumspp(Bilen etal.,2018;Delcenserieetal.,2007;Russelletal.,2011).Severaltechniques,suchasbioinformatics,

computational biology, 16srna sequencing, biochemical characterization, strain improvement techniques, and genetic engineering, could be followed and practiced to work the next generation of probiotics successfully.

Riskfactorsinvolvedintheuseofprobioticsashealthsupplements

Probiotics are widely considered to be safe (GRAS) and are added to a variety of meals, primarily yoghurts, as well as beverages and other common food supplements (Floch, 2013). They are often offeredoverthecounterandarenotregulatedbeyondthecontrolofmarketingclaims.However,there arepotentialinfectionriskfactorsthatshouldbeconsideredpriortoprobioticadministration,suchas immunocompromisedandpreterm infants(Floch, 2013).Minorriskfactorsforheart valvedysfunction includethepresenceofcentralvenouscatheters,impairedintestinalepithelialbarriers,administration of probiotics via jejunostomy, concurrent administration of broad-spectrum antibiotics to which probiotics are resistant, properties of high mucosal adhesion of known pathogens, and cardiac valve disease. Boyle et al., 2006and his colleagues found that these risk variables were substantial despite their limited prevalence. Whelan & Myers, 2010 conducted a systematic analysis of case reports, randomisedcontrolledtrials,andnonrandomizedstudies,andfoundthattheextremelylowfrequency of problemsinindividualsreceivingnutritional assistance didnotconstitute acontraindication fortheir usage. Prior to administration, probiotics should be subjected to a risk-benefit analysis and regular adverseeventmonitoringshouldbeperformed.Thereisalonghistoryofsafeuseofprobioticsinmeals and as supplements, and theFood and DrugAdministration and EFSAgenerally considerthem to be safe (Ferreira et al., 2010).

Conclusion

Probiotics, prebiotics, and synbiotics have been studied for their health benefits, and this paper discusses theuses,properties,andfunctionsofsomeprobioticstrains.Next-generationprobioticsproductionis one of the few advancements in biology and has significant prospects. Probiotics are GRAS and are often offered over the counter, but there are potential infection risk factors such as immunocompromised and preterminfants. Risk factorsforheartvalvedysfunction includecentral venous catheters, impaired intestinal epithelial barriers, administration ofprobiotics via jejunostomy, concurrent administration of broad-spectrum antibiotics, and cardiac valve disease. Prior to administration, probiotics should be subjected to a risk-benefit analysis and regular adverse event monitoring.

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