J Food Sci Technol (January 2024) 61(1):1–15
https://doi.org/10.1007/s13197-022-05621-y

REVIEW ARTICLE

Synbiotics as potent functional food: recent updates on therapeutic potential and mechanistic insight

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Revised: 14 October 2022 / Accepted: 3 November 2022 / Published online: 14 November 2022

Abstract Synbiotics are the specific mixtures of prebiotics with probiotics intended to give health benefits to the host by stabilizing and supporting the gut microbiota.The prebiotic substance used in the synbiotics selectively favors the growth and metabolite production of probiotics. Gut microbiome dysbiosis may lead to generation and progression of various chronic diseases. Synbiotics act synergistically to modulate the gut ecosystem for improvement of metabolic health of the host. Probiotics have been found promising against various diseases being safer, effective, as an alternative or combinatorial therapy. Specific combinations of probiotics with suitable prebiotic substrate as synbiotics, may be the more effective therapeutic agents that can provide all benefits of probiotics as well as prebiotics. Though, effective combinations, dosage, mechanism of action, safety, cost effectiveness and other clinical investigations are required to be established along with other relevant aspects. Synbiotics have the potential to be functional food of importance in future. Present review summarizes the mechanistic overview of synbiotics related to gut microbiota, therapeutic potential and promising health benefits for human illnesses according to the available literature. In present scenario, synbiotics are more promising future alternatives as therapeutics to maintain healthy microbiota inside the host gut which directly affects the onset or development ofrelated disorders or diseases.

Keywords Synbiotics · Functional food · Gut microbiome · Intestinal health · Mechanism · Therapeutic potential

Abbreviations

CNS	Central nervous system
LBPs	Live biotherapeutic products
NGP	Next generation probiotics
GOS	Galacto-oligosaccharides
FOS	Fructo-oligosaccharides
XOS	Xyloseoligosaccharide
SCFAs	Short chain fatty acids
NK cells	Natural killer cells
GI Tract	Gastro-intestinal tract
BDNF	Brain-derived neurotrophic factor
IR	Insulin resistance
SES	Social andeconomic Status
TrkB	Tropomyosin receptor kinase B
IBD	Inflammatory bowel disease
UC	Ulcerative colitis
IHTG	Intra-Hepatic tri-acylglycerol
TNF-α	Tumournecrosis factor-α

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Introduction

Synbiotics are specific combinations of prebiotics and probiotics which collectively exert significant health benefits to the host by affecting the gut microbiota. Probiotics are living microbes having potential to exert health benefits when injected in the host in sufficient amounts (FAO/WHO 2001). Prebiotics are non-digestible food substances that can be utilized by selective host microbes and exert considerable health benefits (Gibson and Roberfroid 1995; Gibson et al. 2017). According to the Bindels et al. (2015), the prebiotics refer to "selectively fermented nondigestible food ingredients or substances that specifically support the growth and/or activity of health-promoting bacteria that colonize the gastrointestinal tract".It has been suggested that the focus should be towards the ecological and functional features of the microbiota more likely to be relevant for host physiology (Bindels et al. 2015).Appropriate combination of prebiotic and probioticas a single product ensures greater effects in comparison to the individual effect of prebiotic or probiotic as therapeutics. In present era, the gut microbiota is focused as a promising therapeutic target to treat several metabolism and neurological associated disorders or diseases. The gut microbiome constitutes abundant amount of genetic material and its contents can be easily modified as compared to the human genes. The microbial community inside the gut and their products influence the host functions in the gastrointestinal tract both locallyas well as systemically (Maftei 2019; Swanson et al. 2020). Gut microbes also affects the nutritional status of the host by several mechanisms such as; (a) fermentation of non-digestible food components, (b) *de novo* synthesis of micronutrients, (c) hunger stimulation due to interactions with central nervous system (CNS), and (d) alteration of host metabolism and nutrient assimilation. The promising synbiotics play a key role in improving host welfare by stimulating the metabolism and growth of good microbes which help to maintain favorable intestinal environment to promote host health (Gibson and Roberfroid 1995). Therefore, earlier studies suggested that the use of suitable prebiotics and probiotics in the form of synbiotics might play a significant role in prevention or treatment of present emerging health problemsat global level (Gurry 2017; Edwards et al. 2020).

The bacterial colonization in gut starts with the birth of new-borne and further exposure to a nonsterile environment. Infants may have different composition of gut microbiota depending on the mode of delivery i.e. vaginal delivery (VD) or cesarean delivery (Kim et al. 2020).It has been found that the maternal vaginal microbiome is an important source and plays an important role for infant gut microbiome development (Kim et al. 2020). On the other side, the infants delivered by Cesarean section (CS) do not make contact with the maternal vaginal microbiome and therefore, CS delivery method may affect the early establishment and development of the gut microbiome in a negative manner (Kim et al. 2020).Different studies have revealed higher *Enterobacteriaceae* and *Pseudomonas* levels in CS as compared to VD infants (Kim et al. 2020).Further, higher relative abundance of *Lactobacillus*, *Bifidobacterium*, and *Bacteroides* have been found in stools of VD infants as compared to CS infants (Kim et al. 2020).Usually, the composition of gut microflora remains same during the adulthood (Kerry et al. 2018). But the gut microbial composition may get changed and transformed over the lifetime of an individual. This transformation particularly depends upon multifaceted and dynamic interactions among the genome, lifestyle, diet, and antibiotic consumption of the host. Studies also reported age-specific remarkable variations in the gut microbiome including reduction in bifidobacteria population and the ratio of *Bacteroidetes/Firmicutes* in agedpeople (> 60 years) when their immunity becomes weak and continuously declines further. Probiotic microorganisms may belong to bacteria, yeast or mold which are also known as next-generation probiotics (NGPs) or live biotherapeutic products (LBPs) as per US Food and Drug Administration (EFSA 2017; Chang et al. 2018). Probiotics play significant role both in management of various contagious diseases, cardiovascular health problems, cholesterol reduction, lactose intolerance and digestion, allergic disease, urogenital disease, gastrointestinal disease, oral health, obesity and related disorders (Maftei 2019). These microbes also play a promising role in reduction of chronic inflammation in alimentary tract and management of specific cancers (Batista et al. 2020; Oh et al. 2020; Sehrawat et al. 2021; Sharma et al. 2021). Some selected probiotics along with NGPs are given in Table 1.

Besides the probiotics, the synbiotic formulations require the selection of suitable prebiotic compounds that can enhance the probiotics survival in gastrointestinal tract and provide great benefits to the host health (Gibson et al. 2017). Beside this, the selected prebiotics should possess some ideal characteristics such as (i) resistance towards the adverse effectsof acid present in the stomach, bile salts and intestinal hydrolyzing enzymes, (ii) should remain unabsorbed in the upper part of gastrointestinal tract, and (iii) should undergo fermentation easily by the intestinal beneficial microbes (Markowiak and Śliżewska 2017). The natural sources for prebioticsmay be fruits, vegetables, and grains which are generally consumed by the persons on routine basis.Moreover, intake of plants-based diet also provides flavonoids mediated significant health benefits. Various prebiotic sources suggested by earlier studies are breast milk, barley bran, wheat bran, soybeans, raw oat, yacon roots, non-digestible carbohydrates i.e., oligosaccharides, inulin and hydrolyzed products of inulin including galacto-oligosaccharides and oligo-fructose. But these can also be synthesized artificially such as lactulose, galacto-oligosaccharides

Table 1 List of commonly used probiotics microbes having therapeutic potential

Micro-organisms	Species	References	Broad applications
Yeast			Gut microbiota balance
Saccharomyces	*cerevisiae, bourlardii* and *boulardii*	EFSA 2017 and Justino et al. (2020)	Promotes growth of beneficial microbes
Candida	*pintolopesii*	EFSA (2017)	Inhibition of gut pathogens
Moulds			
Aspergillus	*niger* and *oryzae*	EFSA 2017	Treatment of several human diseases
Bacteria			
Lactobacillus	*plantarum, acidophilus, rhamnosus, sporogenes, delbrueckii, fermentum, reuteri, brevis, farciminis, casei, gasseri, paracasei, crispatus*	EFSA (2017) and Chang et al. (2018)	Treatment of intestinal mucositis Alteration of cell signaling pathways
Bifidobacterium	*longum, infantis, adolescentis, breve, thermophilum, lactis, bifidum,*	Kato et al. (2017) and Quaresma et al. 2020	Prevention or treatment of mucosal damage
Streptococcus	*lactis, cremoris, thermophilis, diacetylactis*	EFSA (2017)	Regulate or prohibit epithelial tissue injury in intestinal mucositis
Leuconostoc	*mesenteroides*	EFSA (2017)	Helps to raise the villus/crypt ratio
Enterococcus	*faecium*	EFSA (2017)	Decreases intestinal permeability & inflammatory parameters
Pediococcus spp.		Maftei (2019)	
Propionibacterium spp.		EFSA (2017) and Cordeiro et al. (2018)	Reduced weight loss and degeneration of goblet cells Reduced cells apoptosis Provide nutrition to the livestock Promising health benefits to the animals & livestock
Next generation probiotics (NGP)			
Bacteroides xylanisolvens DSM 23,964, *Akkermansia* spp., *Clostridium butyricum* MIYAIRI 588, *Bacteroides fragilis* strain ZY-312, *Faecalibacterium prausnitzii* and *Faecalibacterium* spp.		O'Toole et al. (2017)	Exerts beneficial health effects in humans Helps to re-establish gut microbiota homeostasis Prevention and treatment of diseases related to metabolism and inflammation

and fructo-oligosaccharides (Pandey et al. 2015). Prebiotics act as a potent energy source inside the host which results in significant health outcomes including; (a) restriction of pathogens development, (b) reduced occurrence and extent of diarrhoea, (c) increase in mineral absorption particularly Mg and Ca, (d) manage development of colon cancer, and (e) reduced inflammation and relief from related intestinal bowel disease or disorders (Maftei 2019; Li et al. 2020).

Salient features of synbiotics

Synbiotics are specific combination of probiotics and appropriate prebiotic substances. These have great potential to improve the survival of good microbes and implantation of live microbial dietetic supplements in gastrointestinal tract. Studies have also shown that probiotics and prebiotic substances act in synergy for the improvement of host health (Batista et al. 2020). Most commonly the probiotic species i.e. *Bifidobacteria* spp., *Lactobacillus* spp., *B. coagulans*, *S. boulardii* and prebiotic substrates i.e. Galacto-oligosaccharides (GOS), Fructo-oligosaccharides (FOS), and xyloseoligosaccharide (XOS) are utilized in synbiotic formulations (Pandey et al. 2015; Batista et al. 2020). Synbiotic are categorized in two groups: (a) complementary synbiotic and (b) synergistic synbiotic. The complementary synbiotics consist of probiotics and prebiotic which collectively exert health benefits without requirement of any co- dependent function. On the other hand, the synergistic synbioticsconstitute a substrate which is selectively consumed by the co-administered live microbial populations (Gibson et al. 2017; Swanson et al. 2020).

Synbiotics help to maintain the microbial population naturally residing in the gut and associated metabolic networks for beneficial health effects. These commensal microorganisms provide essential nutrients to the host, metabolize indigestible compounds, defend against colonization of pathogens, regulate gut barrier functions and improve the host immune system for maintaining the healthy status of the host.The fermentation of probiotic microbes produces lactic acid which provides health benefits by acting on the host's physiology. The prebiotic compounds act as a substrate for the production of physiologically active precursor or metabolite to be used by selective probiotics microbes present in infants' gut. These useful gut microorganisms play an important role to regulate health and provide protection against infectious conditions (Pandey et al. 2015). Hence, synbioticshave the immense potential to give protection against several human illnesses both in infants and adults. Several clinical studies also reported therapeutic potential of synbioticsto promote human health such as decrease in neonatal mortality, premature mortality due todevelopment of non-communicable diseases and improved mental health and well being (Gurry 2017; Singh et al. 2021).

Expansion of microbial research suggested that synbiotics significantly improve the human health due to symbiosis between probiotics microbes and prebiotic substrates. Some of the combinations of probiotics and prebiotics used in clinical trials are presented in Table 2. The potential benefits of synbiotics consumption in humans includes; (i) enhanced lactobacilli and bifidobacteria populations and maintain gut microbiota equilibrium, (ii) restrict bacterial translocation and decreases occurrences of nosocomial infections in patients due to surgery, (iii) Improved liver

Table 2 Combination of probiotics and prebiotics used as therapeutics in clinical studies

Probiotics	Prebiotics	Applications	References
Arginolytic bacteria	Arginine	To prevent and manage dental caries; Improve oral health	Zaura and Twetman (2019) and Bijle et al. (2020a)
Lactobacillus rhamnosus	L-arginine	Growth inhibition of pathogenic microbes i.e. *S. mutans;* Caries prevention	Bijle et al. (2020b)
Lactobacilli spp. *L. gasseri*, *L. paracasei*, *L. fermentum*, *Lb. plantarum*	Saccharides	Stimulated growth of beneficial probiotic microorganisms; Suppression of oral pathogens & improvement of mouth ecology; Affect cariogenic bacteria *Streptococcus mutans*	Nunpan et al. (2019)
L. acidophilus DSMZ 20079 or ATCC 4356	3% fructooligosaccharides; 3% galactooligosaccharides and 1% fructooligosaccharides	Reduced the growth rate of *S. mutans*	Nunpan et al. (2019)
Lactobacillus & Bifidobacterium species	Fructo-oligosaccharides (FOS)	Eradication of *Helicobacter pylori*	Sirvan et al. (2017)
Lactobacillus, Bacillus & Bifidobacterium species	GOS, FOS	Treatment of inflammation	Soleimani et al. (2019)
Lactobacillus species	Inulin	Treatment of dyslipidaemia & Diabetes	Asemi et al. (2017) andTajabadi-Ebrahimi et al. (2017)
Lactobacillus & Bifidobacterium species	Litesse Ultra polydextrose, FOS	Treatment of obesity and To treat metabolic syndrome (MS) and obesity associated problems	Hibberd et al. (2019) and Rabiei et al. (2019)
Lactobacillus species	Fructo-oligosaccharides (FOS)	To prevent sepsis in infants	Panigrahi et al. (2017)
L. bulgaricus and *L. rhamnosus*	XOS and RGE	Recoverey of intestinal microbiota	Li et al. (2020)
Lactobacillus gasseri 505	Cudraniatricuspidata leaf extract	Protection against colitis-related colorectal cancer	Oh et al. (2020)
Enterococcus faecium	Agave inulin	Improvement in learning and memory	Romo-Araiza et al. (2018)
L. bulgaricus and *L. rhamnosus*	Xylooligosaccharide and red ginseng extracts	Recovery of intestinal microbiota	Li et al. (2020)
Bifidobacterium longum UABl-14, Bifidobacterium lactis UABla-12, Bifidobacterium bifidum UABb-10, Lactobacillus acidophilus DDS-1	Trans-galactooligosaccharide (GOS)	Reduce obesity and associated symptoms	Sergeev et al. (2020)

function in cirrhotic patients and (iv) increased modulation of host immune system (Asemi et al. 2017; Markowiak and Śliżewska 2017).The applicability of synbiotics is not only restricted in humans but could also be valuable for animals and livestock nutrition (Malik et al. 2019; Swanson et al. 2020). Some promising synbiotics used in clinical studies are given in Table 3.

Mechanisms of action of synbiotics

Earlier clinical studies suggested that synbiotics exert synergistic effects by combining therapeutic potential of prebiotic and probiotic to treat several diseases or disorders caused by abnormal gastrointestinal flora or dysbiosis (Edwards et al. 2020; Swanson et al. 2020). Unbalanced gut microbiota negatively affects the intestinal health, metabolism and gut-brain axis results in irregular cell behavior and physiology. These changes later on result in development of metabolic, neurological, psychological, cardiovascular and inflammatory chronic diseases or disorders in the host (Bijle et al. 2020a; Sharma et al. 2021).In present scenario, the re-establishment of gut microbiota and its maintenance is a potential therapeutic target to treat the above said diseases. Use of synbiotics i.e. probiotics along with suitable prebiotics, is an efficient, more promising and cost-effective strategy to maintain microbiota homeostasis in gastrointestinal tract (Singh et al. 2021). The probiotics in synbiotic formulations helps in maintaining the balance of intestinal gut microflorawhich results inseveral health benefits to the host by producing antimicrobial compounds or antagonism, inhibiting bacterial toxin production, modulating host immune system and competing with the harmful microbes for nutrients and adhesion to the epithelium (Azad et al. 2018; Parada Venegas et al. 2019). On the other hand, the prebiotics have also been reported for beneficial effects on gut microbiota to maintain homeostasis. Fermentation of prebiotics by indigenous microbiota induces the production of functional compounds (Lactic acid; short chain fatty acids; SCFAs) which help in maintaining the intestinal environment more favorable for the beneficial microbes by reducing the intestinal pH. Lowering of pH also inhibits the growth and development of gastrointestinal pathogens. In addition, the prebiotics fermentation products include metabolites (folate riboflavin and vitamins) which show antimicrobial activity & maintains healthy gut barrier; mucin which decrease the frequency of bacterial translocation. Prebiotics and their fermented products also affect the immune cells (natural killer (NK) cells and phagocytes) via interaction with their receptor molecules (carbohydrate receptors) (Davani-Davari et al. 2019). Earlier studies suggested that synbiotics act in synergy as more powerful therapeutics where the probiotics support the growth of beneficial microbial population and the prebiotics stimulate the growth and metabolism of good microorganisms (i.e. *Lactobacillus, Bifidobacterium* and Saccharolytic bacteria) in the gut to maintain or re-establish homeostasis in gastrointestinal tract forpromising health effects (Enam and Mansell 2019; Swanson et al. 2020; Singh et al. 2021).

Hence, the synbiotics consumption as food or another form exert health promoting effects by increasing the probiotics viability in the gut. Intake of these compounds causes increase in methyl acetate, ketones, carbon disulfide and short chain fatty acids (SCFAs). These

Table 3 List of some available synbiotic and prebiotics formulations in the market

Synbionts	Application	References
Lactiv®	Increase of buffer capacity in persons affected with active tooth decay; Reduction of salivary viscosity	Hernandez et al. (2020)
Simbioflora®	Reduced intestinal permeability; Enhanced production of important short chain fatty acids SCFAs (acetate and butyrate) or extracellular factors; Improvement of intestinal mucosa at histological level, Preservation of epithelial architecture; Attenuated weight loss; Reduction of eosinophil infiltrate	Trindade et al. (2018)
Biomin®IMBO (ME BIOMIN GmbH); DigestAid™; PoultryStar® (ME BIOMIN GmbH)	Used for livestock nutrition	Markowiak and Śliżewska (2017)
Fermented Food (Sauerkraut and Kimchi)	Stimulate growth of favorable microbes in gastrointestinal (GI) tract	Park et al. (2017) and Shahbazi et al. (2021)
Prebiotics		
Mycostop (Extra-vit); Bacto CS1000; DOL-SORB DN (Dolfos); BionatStart	Provide nutrition for animals and livestock (Calves, Poultry, Pigs)	Markowiak and Śliżewska (2017)

compounds have been found to play important role in regulation of cellular metabolism and signaling pathways regulating cellular processes (Fig. 1) of the host organisms (Li et al. 2020; Peterson 2020). SCFAs have been reported to have anti-inflammatory, antimicrobial, antitumorigenic effects and also known to alter the gut integrity. But still, the previous studies are unable to give detailed knowledge about mechanism of action of synbiotics to treat, prevent or cure human diseases. The promising mechanisms of action for synbiotics may include; (i) modulation of the intestinal microbiota, (ii) make the intestinal environment more favorable by lowering of pH, (iii) improved survival of beneficial microbes in the gastrointestinal tract, (iv) elimination or growth inhibition of pathogenic microorganisms, (v) enhanced production of functional compounds (lactic acid; mucin, short chain fatty acids and metabolites) due to fermentation of prebiotics, (vi) Improved gut barrier functions and intestinal membrane integrity, (vii) Increased immune-modulation in host, and (viii) Reduced infection, inflammation and bacterial translocation.These mechanisms (shown in Fig. 1) collectively promotethe gut microbiota homeostasis which further helps in treatment or prevention of different diseases (Markowiak and Śliżewska 2017; Sergeev et al. 2020; Swanson et al. 2020).

Potential health benefits of synbiotics as therapeutics: recent trends

Synbiotics constitute appropriate combination of probiotics with their suitable prebiotic substrates that act in synergy and used as supplements to provide nutrition and associated health advantages. These have significant therapeutic potential as compared to the probiotics or probiotics alone. However, the determination or identification of specific combination of prebiotics and probiotics to exert the desired effect is itself a big challenge that varies according to the disease and person to person (Pandey et al. 2015; Markowiak and Śliżewska, 2017; Bijle et al. 2020a).Therapeutic efficacy of promising synbiotics have been reported as being anticarcinogenic, antiallergenic and antimicrobial effects, ant-diarrhealfeatures, prevention of osteoporosis, decrease in blood sugars and serum fats, immune system regulation and for aquaculture. Synbiotics are also helpful to treat ulcerative colitis, liver-related brain dysfunction and cardiovascular diseases (Gibson et al. 2017; Batista et al. 2020; Swanson et al. 2020) (Fig. 2). Some promising therapeutic applications and health benefits of synbiotics are as follows:

Effect on gut microbiota dysbiosis and homeostasis

Presently, the scientific community is considering the gut microbiota as a potential target due to its insightful effect

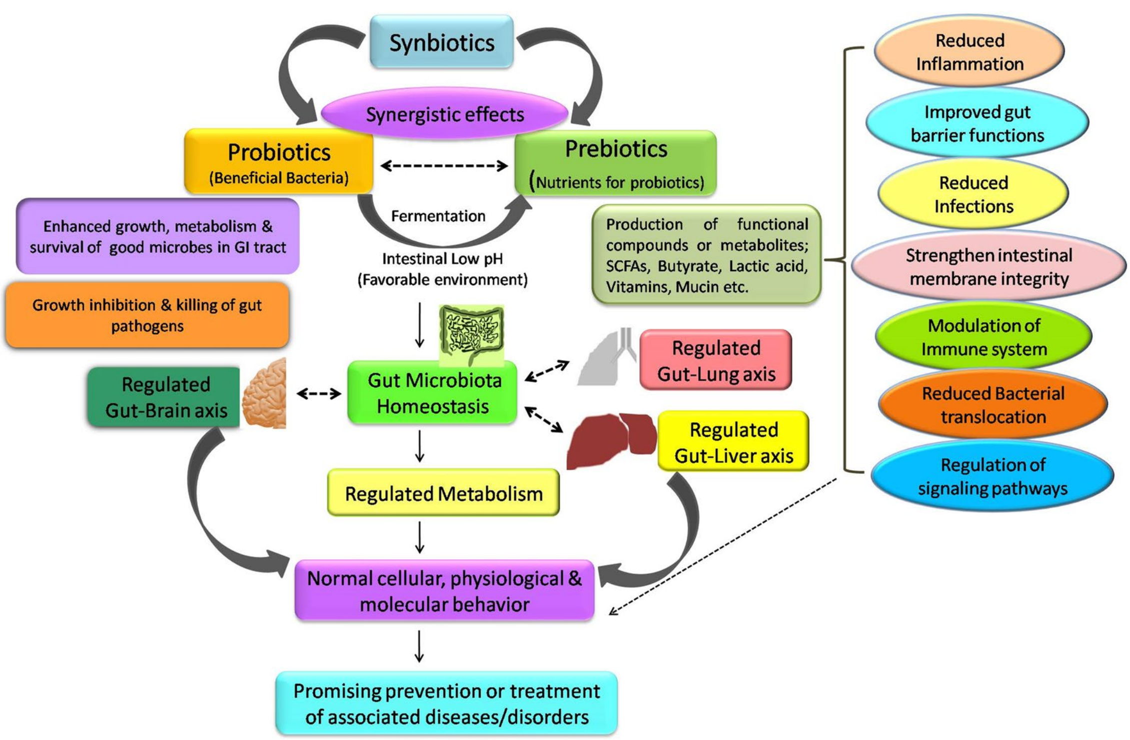

Fig. 1 Promising mechanistic overview for synbiotics to exert health benefits

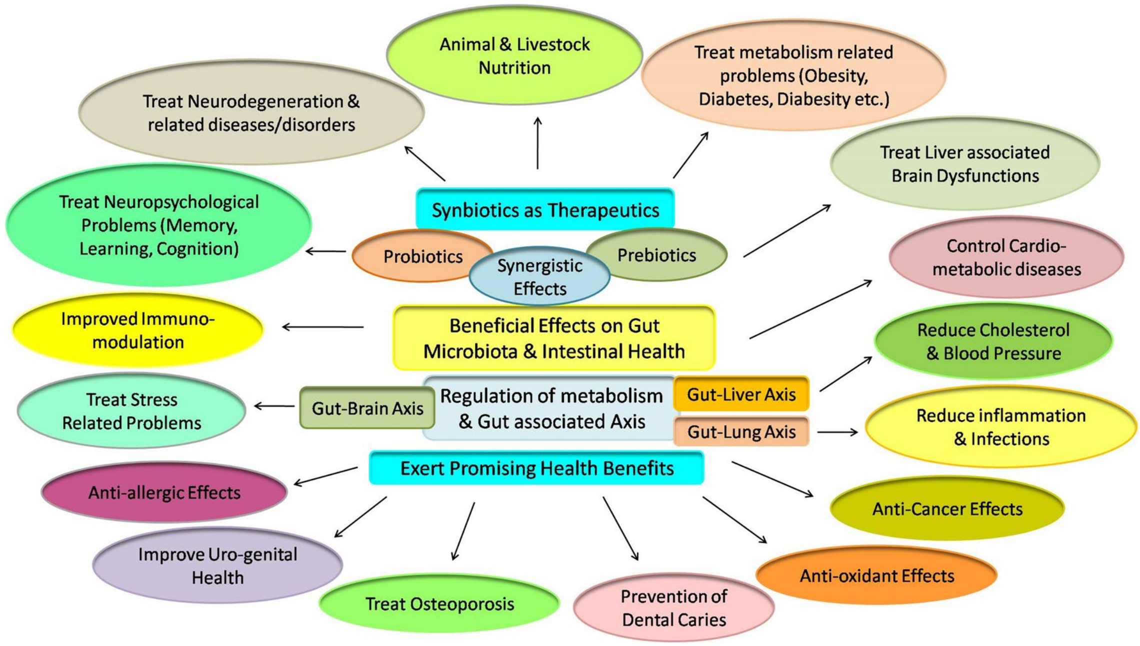

Fig. 2 Therapeutic potential and health benefits of synbiotics

on gut homeostasis and host health (Espírito Santo et al. 2021). Dysbiosis of microbial population in the gut is highly associated with on-set and progression of numerous chronic diseases such as obesity, diabetes, inflammatory bowel disease, and cancer (Fan et al. 2020). In view of these results, re-establishment of gut microbiome homeostasis is highly needed for good health (Fig. 2) and also, this is more efficient, promising and cost-effective therapeutic alternative in comparison to direct treatment of targeted illnesses. Alteration in gut microbiome composition and associated metabolism network could be achieved successfully in humans by several methods such as; (a) increase in implantation and survival of probiotics in colon, (b) growth stimulation of beneficial microbes in gut, (c) metabolism activation of good bacteria, (d) restoration of gut microbial composition, and (e) growth inhibition of pathogenic microbes as suggested by earlier case studies (Wu et al. 2020; Singh et al. 2021). Administration of synbiotics exerts great effects to reduce *Clostridium* and *Bacteroides* population and to increase in *Lactobacillus* population (Morshedi et al. 2020). It has also been suggested that selection of prebiotic substrate is very important to determinethe growth of desired bacteria. The population of useful microbes can be modulated by elimination of harmful microbes via competition and metabolite secretion having significant impact on physiology and metabolism of host. Appropriate probiotics along with its suitable prebiotic substrates can effectively eliminate or decrease the development of gastrointestinal diseases or associated microbial disorders resulted due to gut dysbiosis (Gurry, 2017). It has also been demonstrated that the synbiotics influence the microbial ecology in animals also. Administration of synbiotics in farm animals significantly improved the beneficial bacteria and decrease in pathogenic microbes but the knowledge about the effect of synbiotics on the host is still inadequate (Malik et al. 2016). Several strategies have been widely developed and studied as therapeutics by using prebiotics, probiotics or synbiotics in several clinical trials (da Silva et al. 2021). Recently, Singh et al. (2021) examined promising effects of prebiotics, probiotics and synbiotics on gut microbiome and related metabolism by analyzing specific gene sequences (16 S rRNA). Author's findings suggested that application of synbiotics as therapeutics contribute greater effects in comparison of prebiotics or probiotics application alone (Singh et al. 2021).

Improvement of intestinal health and Immuno-modulation

Dysbiosis in gut microbiota weaken the intestinal barrier which later on induces gastric inflammation and onset of chronic diseases. Moreover, the abnormalities in the intestinal microbiota can cause diarrhea, intestinal cancer and food allergies etc. Synbiotics increases the good bacteria and lactic acid production which helps in inflammation reduction in affected intestinal areas (Gurry 2017). Synbiotics application as novel biological prophylactics is mostly reported because of their promising antioxidant and anti-inflammatory potential (Fig. 2) (Chen et al. 2017). Earlier studies suggested the need of functional foods development usingsynbiotics supplements having capability to manage the intestinal micro-ecological environment to reduce the associated risks. Intake of these supplements causes inhibition of pathogenic microbes, decrease in ratio of Firmicutes/Bacteroidetes (i.e. *E. coli; Klebsiella*) and speed up revival of useful bacteria (i.e. *Lactobacillus*) inside the intestine. These are also capable to produce vital metabolites which improve gut health, regulate gut-brain axis, maintain barrier permeability and improve metabolic activity and cognition (Li et al. 2020; Arora et al. 2020).

Synbioticshave significant applicability for improvement of gut barrier function and stimulation of immune system in the host. Earlier, in vitro studies demonstrated the synergistic effects of synbiotics in the modulation of several immune-related genes at the transcriptional level that further results in enhanced anti-inflammatory behavior (Arena et al. 2016). Synbiotics make the intestinal environment more favorable for the survival and functions of good bacterial strains i.e. *Bifidobacterium* spp. and *Lactobacillus* spp. by lowering of pH and increasing bioactive compounds production (carbon disulfides; SCFAs; methyl acetates; ketones). This further restricts the pathogenic micro-organisms in the gut, reduces detrimental metabolites production and inactivates generation of nitrosamines and carcinogens. Increase in good microbial populations in GI tract and production of bioactive compounds results in immunomodulation and metabolic alterations in the host to exert potential health benefits (Fig. 2) (Maftei 2019; Ignacio et al. 2019; Edwards et al. 2020).

Effects on neurodegenerative disorders or diseases

The microbiome inside the GI tractaffects the host gut health and associated axis. These microbes also interact with several signaling pathways having role in central and enteric nervous system via gut-brain axis (Figs. 1 and 2). Recent data of human clinical trials and preclinical studies found that dysbiosis of gut microbiota is responsible for development or onset of neurodegenerative diseases. These findings also reveal exciting potential of synbiotics as therapeutics for treating health, aging and neurodegenerative disorders through modulation of gut microbiome (Arora et al. 2020; Peterson 2020). Wu et al. (2020) reviewed molecular mechanism for exhibiting significant interaction of gut microbes with brain by affecting gut–brain axis. Dysbiosis of these gut micro-organisms directly affect the regulation of gut-brain axis which later on results in onset of serious neurological disorders. Socala et al. (2021) summarized the involvement of microbiota and gut-brain axis in pathophysiology of neurological and neuropsychiatric disorders.

Treatment of memory impairments; dementia

Regulation of intestinal microflora is more promising strategy to treat or mitigate the diseases associated with nervous system because the gut microbiota directly or indirectly affects several physiological processes (Li et al. 2020). Dementia is a neurodegenerative disease characterized by behavioral changes, decrease in thinking, memory and every day activities. It also increases socio-economic burden worldwide. Earlier investigation found deep relation of memory with brain-derived neurotrophic factor and serotonin level inside the prefrontal cortex and hippocampus region. These findings also showed significant relation between the memory and microbiota of gastrointestinal region (Morshedi et al. 2020).The synbiotics have immense potential to control the level of neurotransmitters and proteins concentration, (i.e. serotonin, gamma-aminobutyric acid, brain-derived neurotrophic factor and glutamate). These substances are effective to maintain balance between excitatory-inhibitory signaling in neurons, control memory, mood, cognitive functions and learning processes (Peterson 2020). It has been reported earlier that intake of probiotics microbe, prebiotic and synbiotic (*L. paracasei* HII01; xylo-oligosaccharide) causes amelioration of learning and memory, attenuation of hippocampal oxidative stress and plasticity in rats treated with high fat diet (Chunchai et al. 2018). Similarly, another study demonstrated that consumption of synbiotics increased the butyrate production, brain-derived neurotrophic factor and reduction of pro-inflammatory cytokines which contributes towards improved cognition, memory and learning processes (Romo-Araiza et al. 2018). Li et al. (2020) summarized the role of prebiotics, probioticsand synbiotics in relation with psychological and behavioral indicators of dementia, cognition related functions, everyday activities, life quality and fulfillmentof safety in the patients suffering from dementia. The findings of Morshedi et al. (2020) suggested that the use of synbiotics as supplements reduces the population of *Clostridium* and *Bacteroides* and improves the cognitive impairment. Authors also found strong relation of increased population of *Lactobacillus* and reduced population of *Clostridium* with cognition and learning (Morshedi et al. 2020). These results suggested that synbiotics consumption could be a better alternate as therapeutics for mild cognitive impairment. But the exact mechanism behind the gut–brain interaction to improve behavioral or psychological disorders is still unavailable (Chunchai et al. 2018; Morshedi et al. 2020).

Reduction of diabetes mellitus (type 2)

Diabetes mellitus is a metabolism related disease characterized by hyperglycemia, insulin resistance (IR), and irregular antioxidant system which is further responsible for dysfunction in various body organs i.e. brain, heart, eyes and kidneys (Valenlia et al. 2018; Soleimani et al. 2019). T2DM induced oxidative strain in various brain region causes psychological and nervous system related disorders. Increases in levels of antioxidant enzymes are an efficient and promising alternative to treat or prevent such conditions. Earlier studies considered the microbiota of gut as a potential target for therapeutic developments because it links the gut with brain (Morshedi et al. 2020). Microbiota in the gut mainly composed of four phyla namely *Actinobacteria, Firmicutes*, *Proteobacteria* and *Bacteroidetes*. Any distortion in these commensal microorganisms (gut dysbiosis) causes alteration of behavioral mechanisms and similar cases have been reported in diabetic patients. Diabetic patients mostly showed reduced proportions of *Clostridia* and *Firmicutes*. Restoration of gut microbiota equilibrium may improve the brain development and function of nervous system (Hosseinifard et al. 2019). The communication between the hippocampus and prefrontal cortex regions of brain is specifically responsible for cognition response. But generation of oxidative stress disrupts the production of neurotransmitters, or their receptors, specific proteins and associated function in these two brain regions (hippocampus and prefrontal cortex) which results in severe damage to the nerves and cognitive abnormalities (Dumitrescu et al. 2018). In another study Asemi et al. (2017) investigated the effects of synbiotic intake on liver enzymes (AST, ALP and ALT), minerals and blood pressure in Iranian patients suffering from type-2 diabetes mellitus. Beside this, development of most of the behavioral and neurological disorders are associated with severe injury to specific protein, factors or kinases involved in the mechanisms or pathway regulating nervous system and behaviour pathway. These includetropomyosin receptor kinase B (TrkB), BDNF (brain-derived neurotrophic factor) and CREB (cyclic adenosine monophosphate responsive element-binding protein) pathway as reported in previous studies. The BDNF and serotonin are essential components thatact in synergy to maintain structure and function of the brain however, their concentration get decreased because of diabetes. Therefore, type-2 diabetes atrociously affects the cognitive activities (Dumitrescu et al. 2018; Socala et al. 2021). Morshedi et al. (2020) determined the effects of *Lb. plantarum* (probiotics) and inulin (prebiotics) as synbiotics intake on composition of gut microbiota, concentration of serotonin, BDNF, TrkB, CREB and oxidative stress markers in prefrontal cortex and hippocampus regions and cognitive function in male diabetic rats. Author's finding suggested that neuropsychological improvement is associated with balanced microbiota inside the host gut (Morshedi et al. 2020).

Reduction of obesity

Dysbiosis of gut microbiome is responsible for occurrence of metabolic disorders or diseases i.e.butyrate and propionate mediated activation of intestinal gluconeogenesis (Sergeev et al. 2020). In addition, increased production of acetate or its turnover causes activation of glucose mediated secretion of insulin and development of insulin resistance (IR) that finally results in obesity. Modification of existing microbial SCFA production profile (enhanced conversion of acetate to butyrate) of a suffering person may be helpful to reduce the occurrence of metabolic diseases at global level (Tajabadi-Ebrahimi et al. 2017). The microbes have been reported as promising therapeutic targets to treat metabolic disorders. Synbiotics intake may be a good alternate to reduce the frequency of metabolism related diseases having strong relations with social and economic status (SES) in developed as well as in developing countries. Later on, synbiotics were tested in a clinical trial in obese patients having type-2 diabetes as well as coronary heart disease. Authors determined the synbiotics effects on markers associated with lipid profiles and insulin metabolism (Tajabadi-Ebrahimi et al. 2017). Hence, appropriate synbiotics can be used as potent therapeutics to treat inflammation and metabolism related diseases or disorders and also to reduce the associated socio-economic burden significantly (Seergeev et al. 2020). However, the construction of novel synbiotic strategies depends upon good knowledge and clear understanding of the host physiology and how the microbial originated metabolome can affects it at molecular-level. Design of synbiotic strategy also keep in consideration various ecological factors and cross-feeding relationships holding microbial populations residing in the gut. Some of the bacterial species (e.g. *Anaerostipes caccae* and *Eubacterium hallii*) produce butyrate by using lactic acid as a substrate. Therefore, these bacteria depend upon the presence of lactic acid producing microbes (*Bifidobacterium adolescentis*) in culture media so that they can use their metabolite product (lactic acid) as a substrate. Therefore, the development of synbiotic therapy requires suitable probiotics and prebiotic pair that may yield a complex and novel discovery process to treat obesity in promising manner (da Silva et al. 2021). Beside this, the occurrence and burden of these metabolic diseases can be effectively reduced by following healthy life styles, physical activities, changes in dietary habits and increasing public awareness along with synbiotics based therapies (Gurry 2017; Sergeev et al. 2020).

Treatment of diabesity

Diabesity is presently a serious concern for increasing health burden at global level. It is a combination of type 2 diabetes and obesity. This disease has been found associated with dysbiosis of intestinal microbiome. Recently, Horvath et al. (2020) investigated the effects of multispecies synbiotic on gut microbiota, intestinal barrier strength and permeability, glucose metabolism, neutrophil function and life quality in treatment-experienced patients having diabesity. Authors found improved gut permeability and quality of life (secondary endpoints) in the patients under investigation but no any improvement in glucose metabolism in a six-month intervention. This study concluded that synbiotic supplementation could be a valuable treatment for diabesity (Horvath et al. 2020).

Treatment of metabolic syndrome & neuropsychological disorders

Poor dietary habits disturb the gut microflora which causes severe metabolic alterations resulted in Metabolic Syndrome. Gut microbiata can be a potent target to treat or prevent metabolic syndrome as suggested by previous studies. The synbiotic supplementation effects on metabolic syndrome were observed in earlier studies (Rabiei et al. 2019). Synbiotics generation may be an efficient and promising to improve several aspects of metabolic syndrome. But the availability of data and clinical trials relating the synbiotics effects on targeted metabolic syndrome is limited (Núñez-Sánchez et al. 2021).The microbiota in gut (i.e. Bacteroides and Firmicutes) affects the host through immune, neural, neuroendocrine and metabolism associated pathways. These microfloras help in maintaining the communication between brain and gut bi-directionally. These interactions further regulate neural development, influence the synthesis/metabolism of neurotransmitters, affect behavior and modulate transmission of neurons. These interactions further affect neuropsychiatric behavior, neuro-developmental, several neurological conditions and pathogenesis (Foster et al. 2017; Madan et al. 2020; Socala et al. 2021). Manipulation of the gut microbiome can also be a potent therapeutic target to cure neuropsychological and metabolic disorders (Morshedi et al. 2020). The neuropsychological and therapeutic effects of combination of *Lb. plantarum*and inulin were studied in diabetic rats recently by Morshedi et al. (2020). Authors found improved dysbiosis in gut and decline of oxidative stress due to administration of synbiotics (*Lb. plantarum*and inulin substrate). The used combination of prebiotic and probiotics as synbiotics also improved the serotonin concentration and associated signaling pathway (BDNF/TrkB). These findings concluded that the tested synbiotics considerably improved the composition of gut microbiota, levels of brain parameters and oxidative stress in investigated diabetic rats. These improved parameters exerted positive effects onmemory and learning impairments in diabetic rats. Author's findings suggested a powerful and significant relation between the changes in gut microbiota and cognition reactions (Morshedi et al. 2020).

Management of stress and related problems

Stress also affects the gut microbiota in the host. An alteration in gut micro biota disturbs the gut functions which results in decreased tolerance of stress, increased health risks and vulnerability towards several diseases (Li et al. 2020). The epithelium becomes compromised and permeable due to leaky gut stress. This later on causes translocation of lipopolysaccharide of Gram-negative bacteria, immune system activation and generation of pro-inflammatory cytokines. Higher concentration of pro-inflammatory cytokines along with environmental stress factors stimulate the limbic system which is involved in emotion,behavior and memory (Madan et al. 2020). Although many antidepressant drugs are available to overcome the depression but these are associated with severe side effects or adverse reactions in long term use. Applications of synbiotics may also improve or treat stress generated disorders including depression, memory loss and anxiety as well (Foster et al. 2017). In current scenario, understanding the pathway or mechanisms involved in communication between brain and intestinalcommensal microbes via gut-brain axis is focused to find out more useful, cost-effective and safer alternatives for currently used antidepressant therapy (Methiwala et al. 2021).

Management of aging

Synbiotics intake improve the population of beneficial microbes (*Lactobacillus* and *Bifidobacterium* species) inside the gut, enhance frequency of stool and mucosal membrane integrity, and increase lipid metabolism & butyrate production. Normally, the synbiotics constitute specific bacteria and oligosaccharides in combination and can be consumed either in tablets form, powder or capsules. Synbiotics were also found responsible for diminishing the pro-inflammatory response, occurrence of metabolic syndrome, reducing insulin resistance markers and cardiovascular risk factors in aged patients (Cicero et al. 2021). Coutts et al. (2020) evaluated the consequences of prebiotic substrates, probiotics and synbiotics (PPS) intake on functional outcomes in an elder population. Authors found that inadequate evidence or information are available till now that recommend use of PPS to alter gastrointestinal microbiome for exerting beneficial health effects, frailty, physical function, mortality, mood and duration of hospitalization among elder peoples (Coutts et al. 2020). It has been suggested by Ale and Binetti (2021) that functional food or food supplements (i.e.probiotics, prebiotics, or synbiotics) have great potential to change the gut microbiota in elderly patients. Hence, synbiotics applications can effectively counteract the aging related natural consequences. Moreover, these functional food products can be more suitable, economical and affordable to the aged people (Ale and Binetti 2021).

Protection from pathogenic and infectious diseases

The microflora of the intestinal region is a complex and dynamic ecosystem. It helps in production, growth and differentiation of epithelial cells to fight against infections and improve host immunity. The indigenous microbiota in the gut also prevents the invasion of foreign pathogenic microorganisms and associated diseases or infections (Markowiak and Śliżewska 2017). Synbiotics may also offer promise to treat non-communicable diseases related to metabolism and gastrointestinal inflammation in humans. Fermentation of dietary fibers by the good bacteria present in colon produces essential metabolites or short chain fatty acids (i.e. butyrate, propionate and acetate)which play critical role to maintain healthy gut (Arena et al. 2016). Among these microbial metabolites, butyrate significantly helps in modulation of intestinal inflammation andalteration in gene expression in cells of immune system. But decrease in butyrate producing micro-organisms results in development of inflammation related diseases (i.e. IBD). Ongoing studies found that development of inflammatory bowel disease may be associated with an infectious etiology. The pathogenic bacteria including various species of *Escherichia coli, Salmonella, Shigella, Yersinia, Clostridium, Campylobacter* and *Aeromonas* in the gut mucosa evoke an inflammatory response due to uncontrolled proliferation. Clinical studies have found that synbiotics-mediated therapies significantly reduce the inflammation in rectal mucosa, improve markers of inflammation and helps to regenerate epithelial tissue in colon (Arena et al. 2016). Therefore, use of synbiotichaving appropriate combination of butyrate-producing probiotics and easily fermentable prebiotic can be an excellent therapy to reduce inflammation of gastrointestinal regions and related disease (Parada Venegas et al. 2019). These diseases i.e. IBD are not only associated with high rates of mortality but also severely affect the individual's well-being and psychology. This further imposes public health burden and increases economic trouble on the population. These studies conclude that dietary intake of synbiotics helps in re-establishment of gut microbiota and treatment of microbiata associated infections or inflammatory diseases by altering the metabolism inintestinal regions (Chen et al. 2017; Li et al. 2020).

Prevention of Sepsis

Sepsis is a life-threatening disease. It occurs due to the host own body response towards an infection. Generally, the immune system responds against any infection in a regulated manner by secreting different types of chemicals and proteins. But when this response becomes out of control in any condition, then it triggers extensive inflammation and results in sepsis. And most of the infections that cause sepsis are bacterial. Globally, sepsis causes near about one million deaths annually in early infancy, particularly in developing countries. Currently, the effective strategy or method to prevent sepsis is not available. Panigrahi et al. (2017) investigated a double-blind, randomized and placebo-controlled trial of an oral synbiotic including *Lb. plantarum* (probiotics) and fructo-oligosaccharide (prebiotic) on rural newborns of India. Author's findings showed a considerable decrease in sepsis, fatality and respiratory tract infections. This study suggested that a major proportion of neonatal sepsis could be prevented efficiently using suitable synbiotics in developing countries (Panigrahi et al. 2017).

Treatment of hepatitis

Hepatitis is characterized by inflammation of liver that can be caused by viral infections, excessive alcohol consumption, autoimmunity and drugs reaction. This inflammation may cause less harm to the host or may lead to severe conditions as liver fibrosis, cirrhosis, or cancer development. Alteration of microbiota in gut and their metabolic products affect the gut-liver axis and causes intestinal inflammation which is responsible for disease pathogenesis and progression i.e. liver diseases. The disorder in the intestinal microbiota generates the proliferation of harmful bacteria and accumulation of toxic substances that increases the risk of liver damage by affecting the gut–liver axis (Konturek et al. 2018). But only few studies discussed the role of gut microflora in management of hepatitis and prevention of pathogenesis. Beside this, deep understanding about the role of dynamic alteration of gut microbiota in disease pathogenesis is still lagging behind (Mofidi et al. 2017; Sehgal et al. 2020). It has been demonstrated in a randomized study on adults with non-alcoholic steato-hepatitis that use of synbiotic products having five probiotics strains (*Lactobacillus delbrueckii* spp. *bulgaricus*, *Lb. plantarum*, *L. rhamnosus*, *L. acidophilus* and *Bifidobacterium bifidum)* along with the prebiotic inulin reduced the concentration of intra-hepatic tri-acylglycerol (IHTG) within a duration of 6 months (Markowiak and Śliżewska 2017). In recent times, synbiotics based functional foods research raised the awareness and commercial interest due to their effective role on gut health, prevention of disease and therapeutic potential. Therefore, the current investigations focused on designing new functional foods and screening of new microbial strains that can survive in gut and metabolize the specific prebiotic substrates efficiently in humans. Earlier studies (in vivo and *in vitro)* validated that combined use of prebiotics along with probiotic microbes as synbiotics are more beneficial for human health in comparison to their single use (Markowiak and Śliżewska 2017; Kerry et al. 2018). Hence, there is a great need to identify, make or design novel synbiotics as functional food supplements to attain more attractive opportunities for clinical and nutritional health improvement in near future (Maftei 2019; Sehgal et al. 2020).

Prevention of dental caries

Dental caries pessimistically affects the oral-health and associated psycho-social status of host life. The treatment methods of dental caries and subsequent maintenance further impose extra financial burdens which itself is a major problem. Previously, different probiotics strains and bacterial species mainly, bifidobacteria and lactobacilli have been widely used to prevent caries but the colonization of the probiotics is transient in the oral cavity. Therefore, more formulations are required for enhancing the probiotics survival to impart long-standing health benefits in clinical sector (Bijle et al. 2020a). Presently, two prebiotic compounds (N-acetyl-D-mannosamine and β-methyl-D-galactoside) were recognized as potential substrates for oral cavity microbes to maintain oral health. These prebiotics during in vitro study caused activation of commensal bacterial growth in oral cavity that resulted in biofilm shift and dominance of commensal microbes (Slomka et al. 2018). These studies suggested synbioticsapplication as a potential therapeutic andprophylactic agent to reduce the oral pathogens causing tooth decay and to enhance oral health. But thesepreliminary studies were unable to elaborate the mechanistic properties of the synbiotics for good oral health or caries prevention (Nunpan et al. 2019; Bijle et al. 2020a).

Conclusion and future aspects

The probiotics are now well known for various health benefits when consumed appropriately. Further, probiotics play a significant role in prevention and management of various diseases including cancers. Additionally, synbiotics present a key concept of providing probiotics and prebiotic together for better health benefits as compared to individual part. The use of synbioticsas therapeutics for beneficial health effects is presently an emerging, efficient and safe alternative to manage several diseases. Selection of suitable prebiotic and probiotic is very important. Therefore, identification or exploration of new probiotic strains and their specific prebiotics should be the priority of associated scientific community to design suitable synbiotics products and their effectiveness in nutritional, clinical or biomedical research. Extensive research on mechanism of action of synbiotics is required along with various other aspects including clinical trials and safety issues. In modern scenario, there is a strong need to generate low-cost next generation functional foods and food products having immense therapeutic value. Therefore, synbiotics may be more promising functional food to inhibit or cure severe human illnesses in future.

Acknowledgements Authors (MY, NS, AKS, SK) acknowledge the help and support by Head, Department of Biotechnology, Maharishi Markandeshwar (Deemed to be University), Mullana-Ambala, India.

Author contribution NS & MY contributed the basic theme of article (conceptualization) and also prepared the original draft-writing. Amit K & SK reviewed the therapeutic potential. Ashwani K & RS reviewed the mechanism of action. AKS was involved in reviewing the whole content and finalized the manuscript.

Funding Authors received no funding for this work.

Data Availability Not Applicable.

Code Availability Not Applicable.

Declarations

Ethical approval Not applicable.

Conflict of Interest The authors declare no conflict of interest.

Consent to participate Not applicable.

Consent for publication Not applicable.

Human and animal rights and informed consent This is a review article and does not contain any experimental studies involving use of animals or humans.

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