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REVIEW

Harnessing postbiotics for liver health: Emerging perspectives

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Abstract

With emerging scientific breakthroughs, it has been established that gut microbiome dysbiosis has an undeniable correlation with hepatic diseases through complex interlinked metabolic pathways. There's always been a need for new therapeutic options to deal with the rising prevalence of metabolic dysfunction-associated steatotic liver disease, liver cirrhosis, alcoholic liver disease, hepatocellular carcinoma *etc.* Several researchers have studied the role of probiotics and prebiotics in altering gut microbiome to tackle microbial dysbiosis which has been proven to be the cause of several metabolic disorders. However, postbiotics remain an untapped potential due to the limited literature on their intake and associated benefits. These bioactive compounds include short chain fatty acids such as butyrate, propionate and acetate, exopolysaccharides, inactivated strains such as *Akkermansia muciniphila* and *Bacillus coagulans etc.*, have hepatoprotective effects which are highlighted in this article. This review aims to discuss the

findings of postbiotics research, their classification and their diverse role in serving as a therapeutic option for liver diseases.

Key Words: Liver; Prebiotics; Probiotics; Postbiotics; Gut dysbiosis; Short chain fatty acids

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Core Tip: Postbiotics, bioactive compounds produced by beneficial microbes, have emerged as promising therapeutic agents for liver diseases linked to gut microbiome dysbiosis. They offer anti-inflammatory, immunomodulatory, and antioxidant benefits, aiding in conditions like metabolic dysfunction-associated steatotic liver disease, liver cirrhosis, and hepatocellular carcinoma. Limited research underscores the need for extensive studies to unravel their classification, mechanisms, and potential in combating microbial and metabolic disorders.

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INTRODUCTION

Postbiotics are garnering significant attention in the nutritional research area due to their several advantages and therapeutic potential over prebiotics and postbiotics. International Scientific Association for Probiotics and Prebiotics define postbiotics as "a preparation of inanimate microorganisms and/or their components that confers a health benefit to the host"[1]. It encompasses a broad range of metabolites and components used such as inanimate cells and their components such as cell walls, membranes, exopolysaccharides (EPSs), anchoring protein with or without metabolites/end products such as proteins, enzymes, bacteriocins, peptides *etc.*[2]. The substances released from microbes denote the metabolic products produced during the life or after the death of the microbe whereas inanimate microbes are non-viable microbial cells or fragments of their physical structure which retains biologic activity. The diverse array of terminologies used to identify postbiotics in literature are proteobiotics, pharmabiotics, metabiotics, paraprobiotics, non-viable probiotics, inactivated probiotics, ghost probiotics or tyndallized probiotics. The liver and gut are interlinked through the portal circulation hence forming the gut-liver axis[3]. Gut dysbiosis has been associated with a breach in the intestinal barrier and translocation of bacterial endotoxins leading to immune dysregulation which forms the basis for various metabolic derangements[4]. In various pre-clinical and clinical trials postbiotics are effective in enhancing intestinal tight junctions, immunomodulation and altering gut microbiome either directly or indirectly. This review highlights the role of postbiotics in serving as a possible potent treatment modality in liver health.

MECHANISM OF ACTION OF POSTBIOTICS

Among the various beneficial interactions proposed by various studies, the primary mechanisms which play a valuable role in liver therapeutics are mentioned below (Figure 1).

Establishing gut eubiosis

It's established directly by the action of bacteriocins, known for their antibacterial properties derived from the supernatant of *Lactobacillus*. They act against pathogenic organisms and help in maintaining a healthy microbiome[5]. Similarly, reuterin, a potent postbiotic product derived from *Limosilactobacillus reuteri* prevents the growth of several pathogenic organisms[6]. In metabolic dysfunction-associated steatotic liver disease (MASLD), cirrhosis and hepatocellular carcinoma (HCC), gut dysbiosis is characterised by overrepresentation of pathogenic families such as *Prot-eobacteria*, *Enterobacteriaceae* and *Fusobacterium spp.*, *Bifidobacterium* (inactivated/products) can suppress these organisms through production of bacteriocins, alteration of pH and by competitive exclusion. Beyond pathogen elimination, products of Bifidobacterium serve as substrates for butyrate-producing bacteria, thus enhancing the anti-inflammatory milieu of the gut, maintenance of tight junction integrity as explained below and modulates immune responses. Dysbiosis can also be tackled in a different indirect approach where lactic acid-containing postbiotics serve as fermentable substrates for specific commensal gut bacteria, which convert them into short chain fatty acids (SCFAs) such as butyrate promoting a healthy gut microbiome[7].

Decreasing intestinal permeability

Injury by toxins from pathogenic organisms is usually prevented by the intestinal epithelial barrier comprising a mucous layer, gut epithelial layer and antimicrobial enzymes and peptides. Thus, breach in the barrier as a result of dysbiosis is

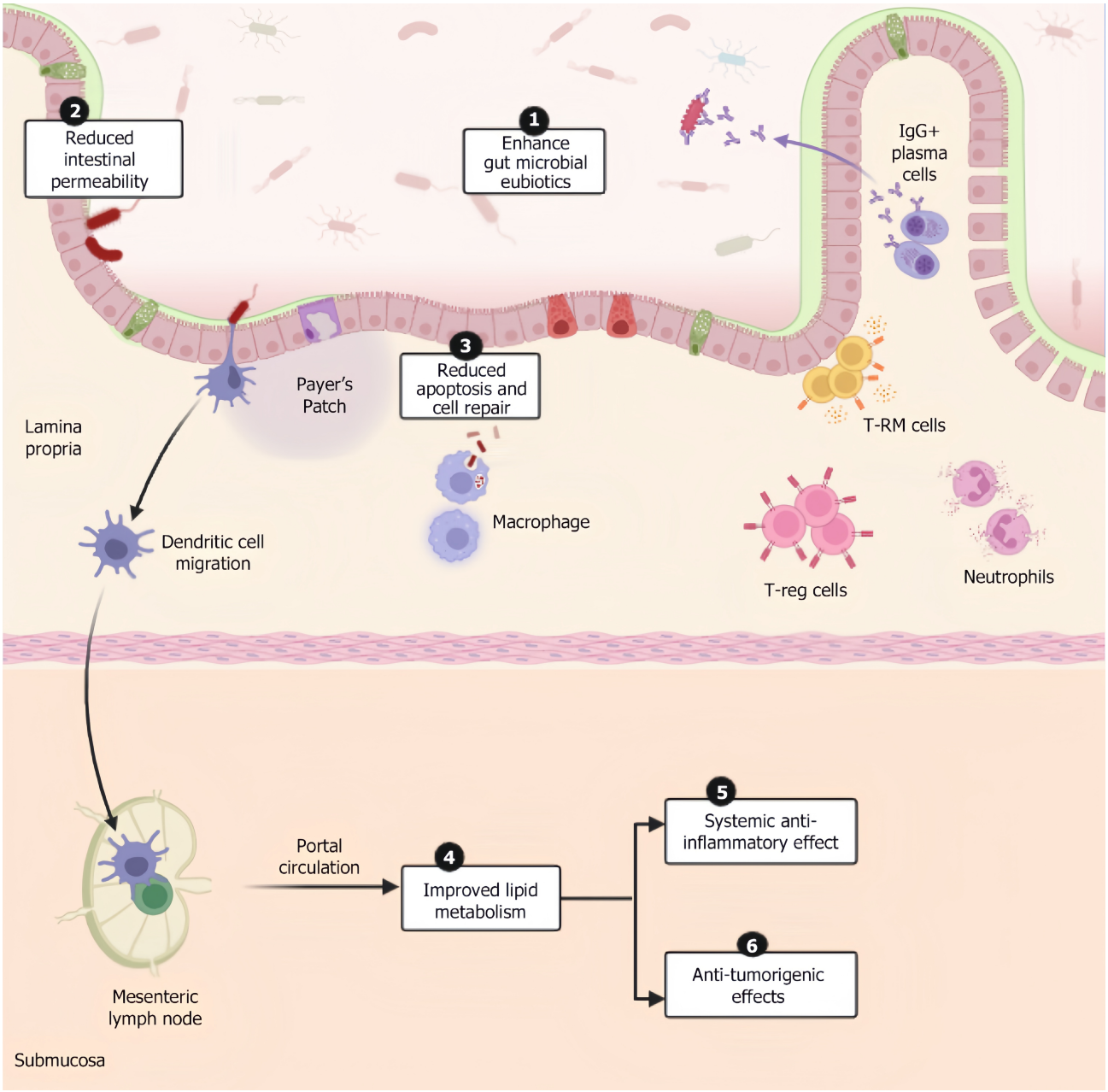


Figure 1 Mechanism of action of postbiotics. This includes (1) Enhancement of gut eubiosis, favouring commensal species while suppressing pathogenic strains; (2) Strengthening intestinal integrity by upregulation of occludins, tight junctions *etc.*; (3) Enhanced epithelial regeneration and mucosal healing promotes cell repair and reduces apoptosis; (4) Improved transit of lipid metabolites with enhanced processing at liver resulting in reduced pro-inflammatory lipid mediators; (5) Modulation of immune cells reduces excessive inflammation; and (6) Reduction of chronic inflammation and regulation of metabolism lowers the risk of malignant transformation. IgG: Immunoglobulin G; T-RM: Resident memory T.

rectified by stimulating mucosal excretion. In vivo, studies show that the supernatant of *Lactobacillus rhamnosus* (*L. rhamnosus*) consists of 2 components (HM0539 and p40), which promote mucin production *via* the epidermal growth factor receptor pathway through epithelial cells, which decreases intestinal permeability[8]. Similarly, *Lactobacillus plantarum* (*L. plantarum*) EPS stimulates mucin production by goblet cells and upregulate zonula occludens-1 and occludin through mitogen-activated protein kinases and phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT) pathways which ameliorates the permeability of the intestinal wall[9]. Generoso *et al*[10] demonstrated the role of cell wall structures of *Saccharomyces boulardii* in preserving intestinal permeability while limiting microbial product translocation. Similarly, postbiotic products of *Lactobacillus delbrueckii ssp. bulgaricus*, *Streptococcus thermophilus*, *Lactobacillus acidophilus* (*L. acidophilus*) inhibited breach in intestinal barrier by toxins from pathogenic bacteria by activating nitric oxide synthase (NOS), thereby counteracting the toxigenic effects[10].

Decreased apoptosis and cell repair

Postbiotics derived from *Lactobacillus* have been proven to enhance the healing of the lining epithelium of the gut and support tissue repair by increasing the expression of Cdc42 and Pak1[11].

Lipid metabolism and anti-oxidant effect

Microbe-derived SCFAs like propionate improve lipid metabolism *via* activation of GPR41 which leads to inhibition of PI3K/Akt/mammalian target of rapamycin (mTOR) pathway, resulting in reduced tumorigenesis and increased apoptosis and GRP43-mediated signalling causes downregulation of nuclear factor kappa B (NF-κB) leading to decreased transcription of pro-inflammatory and pro-tumorigenic genes like tumor necrosis factor (TNF)-alpha, cyclooxygenase-2 (COX-2) and interleukin (IL)-6. Activation of AMP kinase pathway (AMPK) causes mTORC1 suppression leading to inhibition of anabolic metabolism. They also enhance insulin sensitivity through increase in glucagon like peptide-1 (GLP-1) and peptide YY (PYY) secretion. Pasteurized *Akkermansia muciniphila* (*A. muciniphila*) supplementation has been shown to decrease markers of liver disease by reducing total cholesterol, serum lipopolysaccharides (LPS), fat mass, and insulin resistance in obese people[12]. In mice studies, downregulation of perilipin 2-associated protein in white and brown adipose tissue in mice was observed[13]. SCFAs like butyrate were found to increase glutathione levels in the colon, which reduced damage exerted by oxidative free radicals. Acetate has been shown to decrease lipolysis and increase fatty acid oxidation and energy expenditure. SCFAs have been shown to have anti-obesity effects on satiety, satiation, and energy expenditure by upregulating GLP-1 and PYY levels[14]. Such effects are produced through muramyl dipeptide which is a bacterial cell wall component by regulating GLP-1 secretion and insulin sensitivity[15].*In vitro* studies of Bhat and Bajaj[16] have shown the cholesterol-lowering effects of EPSs of *Lactobacillus paracasei* (*L. paracasei*) M7. EPSs of *Bacillus sp.*, *Lactobacillus delbrueckii*, *L. plantarum* exhibits anti-oxidant effects through AMPK/PI3K/Akt and NF-kB pathway and scavenges reactive oxygen species[17]. They exhibit anti-obesogenic effects through regulation of steroid response element binding protein-1C which is downregulated by farsenoid-X receptor (FXR) activation by postbiotic metabolites (indole derivatives), stearoyl-CoA desaturase 1, acetyl CoA carboxylase and fatty acid synthase and reduces very low-density lipoprotein, low density lipoprotein and triglyceride levels[18]. Vitamins obtained from *Bifidobacterium bifidum*, *Bifidobacterium breve*, *Bifidobacterium adolescents*, *Bifidobacterium longum*, *Bifidobacterium infantis* and *Bifidobacterium animalis subsp. Lactis* exhibit anti-oxidant effects through superoxide dismutase and catalase enzyme activity reduction and decrease in superoxide radicals production[19]. Although SCFAs have demonstrated hepatoprotective effects in general models of MASLD, studies that specifically evaluate their efficacy across histologically or metabolically distinct MASLD subtypes are currently lacking and represent a vital area for future research.

Anti-inflammatory effects

Postbiotic components are known to reduce oxidative stress and pro-inflammatory cytokines through various mechanisms. Each component has a unique anti-inflammatory property[20]. Peptidoglycan of *L. acidophilus* exhibits anti-inflammatory effects through inhibition of IL-12, C-Jun-N-terminal kinase pathway, extracellular signal regulated kinase pathway and through p38 kinase inhibition. They also decrease COX-2 and inducible NOS induction[20]. Teichoic acids of *L. plantarum*, *L. paracasei* and *L. rhamnosus* exhibits similar regulation along with reduction of IL-6, TNF-alpha and IL-1 Beta reduction[21]. Extracellular vesicles of *A. muciniphila*, *Propionibacterium freudenreichii* and *Lactobacillus spp.*, exhibit anti-inflammatory and anti-obesogenic effects through NF-κB modulation[21].

Role in HCC arising from MASLD

The protective component valeric acid, obtained from SCFAs of *L. acidophilus* exhibits anti-tumourigenic effects *in vivo* and *in vitro* by binding to GRP41/43 on liver cells to inactivate oncogenic pathways. Transcriptomic analysis done by Lau *et al*[22] and team revealed that several genes related to Rho GTPase pathway and cell cycle-RHOA, RAC1, ROCK1 and BUB1, CDC25C, CDC45, CDK1 had shown to be significantly downregulated in mouse NAFLD-HCC cells and liver cells after treatment with valeric acid. EPS-R1 increased cytotoxic T lymphocyte-associated antigen-4 and programmed death receptor-1 monoclonal antibodies against cysteine-cysteine motif chemokine ligand 20-exhibiting tumours by boosting antigen presentation and T-cell activation by stimulating dendritic cells and promoting major histocompatibility complex expression leading to increased infiltration of CD8+ T cells and as a result when such antibodies are administered, the immune system is already primed to exhibit a robust response in mice models[23]. Targeted supplementation with specific postbiotic types (*e.g.*, valeric acid for MASLD-HCC) holds greater promise when guided by metagenomic and metabolomic profiling[22,24,25].

Impact of phytochemicals on severe acute respiratory syndrome coronavirus 2 induced liver injury

Angiotensin convertase enzyme 2 is expressed in 60% of cholangiocytes and 3% of hepatocytes. The virus enters through these receptors and induce IL-6 and TNF-alpha mediated pro-inflammatory state, contributing to hepatocellular damage. In this study the anti-oxidant, anti-viral, and anti-inflammatory effects of various phytochemiucals were studied. Curcumin, a polyphenol, was found to possess anti-inflammatory effects through NK-κB inhibition thereby improving liver function and alleviation of liver inflammation in individuals with MASLD. Other phytochemicals like quercetin and resveratrol have anti-viral effects. Quercetin, apigenin, curcumin, resveratrol and carotenoids are known to have anti-oxidant effects which mitigates the damage induced by free radicals[26].

SYNTHESIS OF POSTBIOTIC COMPONENTS

Postbiotics are obtained from microorganisms in food or fermented foods. Essentially prebiotics from dietary sources such as fibres and oligosaccharides serve as substrates for gut microbes, which in turn metabolize them to produce bioactive compounds known as postbiotics which are either substances released from microbes or the inanimate microbes

themselves, comprising of cell wall constituents (peptidoglycans, teichoic acids), cell-free supernatants, bacteriocins, SCFAs, branched-chain fatty acids, polysaccharides, vitamins *etc*.[27]. Current innovations aim at isolating these postbiotics from supernatants and studying the effects of each component individually through pre-clinical trials. Other methods perform lysis of bacterial cells through thermal, enzymatic, chemical, sonification, hyperbaric, and solvent extraction. Several concentrating and purifying techniques are used to perform qualitative and quantitative analysis of the extracted metabolites. The extracted solutions underwent centrifugation, dialysis, lyophilization, and column purification to isolate postbiotics from bacterial cells. The obtained postbiotics undergo characterization as cell wall fragments, intracellular metabolites, and secreted metabolites by appropriate methods such as chromatography, spectrophotometry, and spectroscopy[28]. Such postbiotics obtained after undergoing treatment introduce several other intracellular substances and cell wall derived products, which when combined with the existing pool of postbiotics several new beneficial therapeutic functions can be obtained[7]. The effects of postbiotics on various liver disorders are tabulated in Table 1[8,16,29-67].

Table 1 Effects of postbiotics on various liver disorders

Ref.	Type of the study	Postbiotic involved	Mechanisms and outcomes
Inactivated bacteria			
Depommier *et al* [29]	*In vivo* in mice	*A. muciniphila*	Increased energy expenditure, obesity
Depommier *et al* [30]	Clinical trial	*A. muciniphila*	Improves obesity with insulin resistance
Andresen *et al* [31]	Clinical trial	*Bifidobacterium bifidum*	Improves symptoms of irritable bowel syndrome
Shin *et al*[32]	*In vivo*: Male rats	*B. longum* SPM1207	Decreases total and low-density lipoprotein cholesterol
Martorell *et al* [33]	*In vivo*: *Caenorhabditis elegans*. *In vitro*: Human colonic epithelial cells	*B. longum* CECT 7347	Alleviate gut barrier disruption by its anti-inflammatory properties
Nakamura *et al* [34]	*In vivo*: Male c57BL/6n mice	*Lactobacillus amylovorus* CP 1563	Treatment and prevention of dyslipidemia
Aiba *et al*[35]	*In vitro*	*Lactobacillus johnsonii*	Inhibits colonization of *Helicobacter pylori*
Miyauchi *et al* [36]	*In vitro*: Intestinal epithelial cells	*L. rhamnosus* OLL 2838	Intestinal barrier activity
Bacterial lysates			
Jensen *et al*[37]	*In vivo* in mice	*Methylcoccus capsulatus*	Enhance glucose regulation and decrease body and liver fat, MASLD
Mack *et al*[38]	Clinical trial	*Escherichia coli* DSM 17252 and *Enterococcus faecalis* DSM 16440	Improves diarrhoea-predominant irritable bowel syndrome by ameliorating endotoxin translocation and indirectly prevents the gut-liver translocation
Osman *et al*[39]	*In vivo*: Male rats	*L. paracasei*	Reduced lipids and triglycerides accumulation and significant reduction in elevated liver enzymes
Wang *et al*[40]	*In vivo*: Male mice	*L. rhamnosus* GG	Alcoholic liver disease prevention
Compare *et al* [41]	*Ex vivo*: Organ culture model	*Lactobacillus casei DG*	Alleviate inflammatory effects in intestinal mucosa
Gao *et al*[8]	*In vitro*: Intestinal epithelial cells (Caco-2). *In vivo*: Mice	*L. rhamnosus* GG	Ameliorates intestinal barrier dysfunction and protects intestinal epithelium thereby preventing translocation to liver
Mi *et al*[42]	*In vitro*: RAW264.7 cells. *In vivo*: Male mice. *Ex vivo*: Mouse splenocytes	*Bacillus velezensis* Kh2-2	Stimulate innate and adaptive immunity and regulate gut dysbiosis. Increase IL-2 secretion and inhibit IL-10 secretion in *ex vivo* model
Dinić *et al*[43]	*In vitro* study-HepG2 human hepatocyte cell line	*Lactobacillus fermentum* BGHV 110	Stimulation of PTEN-induced putative kinase 1-dependent autophagy in HepG2 cells and mitigation of hepatotoxicity induced by acetaminophen
Bacterial vesicles			
Hao *et al*[44]	*In vivo* mice	*L. plantarum*	Body weight loss and mitigate bleeding and colon shortening
Bacterial metabolites			

He *et al*[45]	*In vivo* mice and *in vitro* in tumour cells	Short chain fatty acid-butyrate	Improve CD8+ T cell immunity providing anti-tumour effects
Suez and Elinav [46]	*In vivo* in mice	Phytate and inositol triphosphate	Enhance gut epithelial proliferation and injury recovery
Ma *et al*[47]	*In vivo* in mice	Indole	Activate PFKFB3 expression and inhibit macrophage activation, MASLD
Li *et al*[48]	*In vivo* in mice and *in vitro* bacterial culture	Isoallolithocolic acid	Regulation of Treg cells by bile acid metabolites
Dahech *et al*[49]	*In vivo* in male Wistar rats	Polysaccharides of *Bacillus licheniformis*	Reduce glucose levels and hepatic and renal toxicity measured through thiobarbituric acid reactive substances
Ghoneim *et al* [50]	*In vivo* in male Sprague-Dawlwy rats	Polysaccharides of *Bacillus subtilis sp*	Reduce glucose levels and prevent complications of diabetes
Amaretti *et al* [51]	*In vitro*	The mixture of *Bifidobacterium*, *Lactobacillus*, *Lactococcus*, and *Streptococcus* thermophilus	Anti-oxidant properties
Segawa *et al*[52]	*In vitro*	Polyphosphates of *Lactobacillus brevis* SBC8803	Mediates epithelial barrier
Chen *et al*[53]	*In vivo: Mice*	SCFA of *Clostridium butyricum sp*	Regulate gut microbiome composition
Ticho *et al*[54]	*In vivo* in mice	Products of commensals after digestion of bile acids by *Bacteroides, Eubacterium* and *Clostridium*	Modulation *via* farsenoid-X receptor and GPCR5 which regulates lipid and lipoprotein metabolism
Rajakovich and Balskus[55]	*In vivo*	Products of *Lactocilli*, *Bifidobacterium* synthesize vitamins A, C, and B9	Enhance mucous secretion by epithelial cells and maintain the integrity of goblet cells
Noronha *et al* [56]	*In vivo*	Products of *Bacteroides* and thetaiotaomicron enhance angiogenin 4 expression	Angiogenin 4 has antibacterial activities
Other components			
Balaguer *et al* [57]	*In vivo* in *Caenorhabditis elegans*	Lipoteichoic acid of *Bifidobacterium animalis subsp. Lactis* CECT 8145	Anti-obesity as it reduces fat in nematodes
Schiavi *et al*[58]	*In vitro* in human peripheral blood mononuclear cells	EPS of *B. longum* W11	Regulates cytokine secretion and nuclear factor kappa B activation through anti-inflammatory properties
Bhat and Bajaj [16]	*In vitro*	EPS of *L. paracasei* M7	Decrease total cholesterol, immunomodulation
Kim *et al*[59]	*In vitro*: Human monocyte cells (THP-1)	Lipoteichoic acid of *L. plantarum*	Inhibits pro-inflammatory signaling in THP-1 cells
Matsuguchi *et al* [60]	*In vitro* in RAW264.7 cells of mouse	Lipoteichoic acid of *Lactobacillus acidophilus*, *Limosilactobacillus reuteri*, *L. plantarum*	Attenuate LPS-induced tumor necrosis factor-alpha production
Wang *et al*[61]	*In vivo* in male mice	Lipoteichoic acid of *L. paracasei* D3-5	Stimulate mucin production through its anti-inflammatory role and reduces systemic endotoxemia
Rahbar Saadat *et al*[62]	*In vivo* in mice	EPS of *L. paracasei*	Exhibits cholesterol lowering and metabolic regulation properties
Kareem *et al*[63]	*In vitro*	Cell free supernatant of *L. plantarum* RG11, RG14, RI11, UL4, TL1, RS5	Antimicrobial activity
Bali *et al*[64]	*In vitro*	Cell-free supernatant *Bifidobacterium sp*	Bacteriocin production against pathogenic organisms
Foo *et al*[65]	*In vivo* in mice	*L. plantarum* I-UL4, *Bacteriocin*	Significant reduction in total cholesterol concentrations in comparison to controls
Riaz Rajoka *et al* [66]	*In vitro*	Cell-free supernatant of *L. rhamnosus* SHA111, SHA112, and SHA113	Induces apoptosis by up-regulation of BAD, BAX, Caspase-3, Caspase-8, Caspase-9, and down regulation of *BCL-2* genes
Qi *et al*[67]	*In vitro* in RAW264.7 cells of mouse macrophages	Cell wall components of *L. rhamnosus* GG	Components protect macrophages from LPS-induced inflammation

A. muciniphila: *Akkermansia muciniphila*; *B. longum*: *Bifidobacterium longum*; EPS: Exopolysaccharide; *L. paracasei*: *Lactobacillus paracasei*; *L. plantarum*: *Lactobacillus plantarum*; LPS: Lipopolysaccharides; *L. rhamnosus*: *Lactobacillus rhamnosus*; MASLD: Metabolic dysfunction-associated steatotic liver disease.

SUMMARY OF HUMAN CLINICAL TRIALS

Fogacci *et al*[68] assessed the impact of butyrate-based formula on individuals with hepatic steatosis and metabolic syndrome. This supplementation was found to have improved fatty liver index, hepatic steatosis index, gamma-glutamyl transferase and lipid profiles[68]. A clinical trial assessing the impact of *A. muciniphila* supplementation in obese individuals with insulin resistance, dyslipidemia and elevated liver enzymes resulted in improved insulin sensitivity and decreased liver enzyme levels (Depommier *et al*[30]). However, in these studies the smaller sample size and limited duration of studies warrant for more large-scale and long-term clinical trials to translate these results into practical benefits. While studies assessing postbiotic supplementation in liver diseases are limited, it holds great potential to act as either an adjunct or a standalone therapy for liver diseases linked to gut dysbiosis[30].

BENEFITS OF POSTBIOTICS OVER PROBIOTICS

Postbiotics are resistant to digestive enzymes and are absorbed directly (SCFAs) or remain active at the site of administration (bacteriocins, cell wall components) without requiring further microbial fermentation or colonization unlike probiotics. Thus, postbiotics act rapidly after administration and prebiotics require time for fermentation and metabolite conversion. Postbiotics bypass the need for fermentation for gut bacteria, making them effective even in dysbiotic guts as seen in liver disorders[11,69]. Prebiotics require a functioning microbiome to yield therapeutic metabolites. In altered gut environment it may fail to reproduce such effects. Postbiotics are stable compounds with longer shelf life due to stability across wide range of temperature and pH and don't necessitate appropriate storage precautions. They don't require cold storage or encapsulation like prebiotics. Postbiotics can be precisely quantified, characterized and dosed whereas the effects of prebiotics are variable. Thereby, postbiotics can be precisely customized for individuals. For example, butyrate-based therapy can be administered for individuals deficient in SCFAs. Personalization becomes difficult with prebiotics as they produce diverse variable metabolites. Probiotics, being non-viable eliminate the risk of bacterial translocation causing bacteremia or sepsis as seen in some probiotics in immunocompromised hosts. They don't interfere with the antibiotics administered as they lack transmissible genetic material[27,70,71]. Their actions are similar to that of probiotics thus the risk of live microorganisms administered as probiotics to patients with compromised intestinal barrier and immune system can be avoided. Various possible properties of postbiotics[72-76] are noted like anti-inflammatory, anti-bacterial, anti-obesogenic, anti-carcinogenic, hypocholesterolemic, immunomodulatory, anti-oxidant, and anti-proliferative activities[77]. Postbiotics exhibit such pleiotropic effects that span several organ systems through their above effects. These are difficult to achieve with prebiotics alone without depending the host microbiota status. The risk of carrying antibiotic-resistant genes in probiotic strains is minimized through the use of postbiotics[69]. With respect to regulatory safety, postbiotics are easier to regulate than prebiotics as postbiotics are bioactive molecules with no live organisms unlike prebiotics. There are several possible delivery formats for postbiotics as discussed below but it's limited with prebiotics owing to their need for colonic ferementation. They have a role in treating a wide array of diseases which lacks definitive therapeutics.

PRECISION POSTBIOTICS

Patients with MASLD have shown in heterogeneity in clinical stages and histological diversity where certain population shows benign liver disease while others show extensive fibrosis and liver failure. This has been attributed to the individual baseline differences in gut microbiota composition which varies with age, geography, antibiotic exposure and disease state which determines the extent of postbiotic therapeutic efficacy. The composition of gut microbiome is determined by several factors such as genetics (polymorphisms in pattern recognition receptors like toll-like receptor 2, nucleotide-binding oligomerization domain 2 and metabolic regulators like FXR, peroxisome proliferator activated receptor alpha alter responsiveness to microbial metabolites), diet (dietary patterns influence bioconversion of prebiotics to postbiotics), physical activity, medications and geography[78-82]. The type of postbiotic to be administered to an individual with steatotic liver disease is determined after analyzing the extent of dysbiosis in a patient[69]. Thus, patients showing deficiencies in certain types of SCFAs might benefit from supplementation of that particular SCFAs. Similarly, the dosage and type of postbiotic to be administered should be adjusted as per the severity of patient's disease severity [24]. Advances in metagenomics and metabolomics allow for stratification of patients based on gut microbial signatures enable targeted selection of postbiotic selection. Postbiotics have targeted regulating effects not just confined to intestine but also includes skin, oral cavity, nasopharynx and other areas[9,83,84]. Due to gaining health consciousness and wellness among community, several industries have taken it upon themselves to research and develop postbiotics products. Certain products are used as metabolic support agents in nutraceuticals and functional foods, but not as prescription-based clinical therapies, as the concept of precision-postbiotics is still under research. HT-BPL1, LBiome, Viniflora, Lyofast LPR A, Totipro, Lacidophilin tablets *etc.*, are known to have anti-obesogenic and pro-gut health effects [11].

POTENTIAL IN-VIVO ROUTES OF DELIVERY OF POSTBIOTICS

Oral route

Oral route has been established as the superior mode of delivery due to its several advantages such as better adherence to treatment, conveniency for frequent administration, safety, low cost and better local and systemic effects where the latter is achieved through lymphatic absorption of postbiotics whose lipophilic nature enables them to bypass first pass metabolism. However, the ability to deliver the desired product to intestine is affected by several factors such as pH, transit time, nature of gut microbiome and the technology available for delivery which will be discussed below[85]. Oral postbiotics allows for local modulation of the gut microbiome, thereby reinforcing gut barrier function and reducing translocation of endotoxins *via* gut-liver axis. SCFAs and bacteriocins administered orally have shown to reduce liver fat, LPS and insulin resistance in metabolic associated fattly liver disease animal models[12,29].

The pH: The natural pH of the stomach is at 1-4 and that of small and large intestine are between 6 and 7.4. This natural pH should be kept in mind while designing the targeted delivery mechanisms. Thus, to achieve targeted delivery at the colon, methacrylic based polymers also known as enTRinsic capsules have shown to demonstrate resistance to gastric enzymes in the stomach and rapid release of postbiotics (SCFAs based) in intestine[86]. Puccetti *et al*[87] formulated a new local delivery technique using indole-3-aldehyde loaded gastro resistant spray dried microparticle for postbiotics to reach the targeted area of release. Innovations in pH-dependent delivery systems include methacrylic-acid based polymers (Eudragit), hydroxypropyl methylcellulose acetate succinate, cellulose acetate phthalate, Colopulse and enTRinsic capsules[88].

Gut microbiota: They have the potential to ferment prebiotics naturally through the use of their enzymes such as polysaccharides and azo-reductases. Thus, polysaccharide and azo coated preparations can be used for targeted delivery[89]. Recently double layered coating systems are used where the core layer has a chitosan based polymeric substance with citric acid and an outer enteric layer. This prevents release of postbiotics in stomach and intestine and on reaching the colon the layers dissolve under the action of chitosonase released by gut microbiota[90]. In patients with altered gut microbiome as a result of diarrhea or any inflammatory conditions, probiotics are co-administered to maintain eubiosis and targeted release of postbiotics. Current technologies using microbiota triggered delivery include COLAL, Phloral, COlon-targeted Delivery System, TARGIT *etc.*[91].

Time: The time of delivery has been correlated with the gastrointestinal transit times. But the high variability of transit times among individuals has hindered this concept. Thus, mesalamine based preparations (multimatrix) whose release are independent of time are utilized where they achieve maximum concentration in the colon[92]. Widely studied technologies using time dependent delivery include ChronoCap, Pulsnicap, Multimarix[93].

Osmotic pressure: Osmotic pressure-controlled delivery utilizes a double layered capsule where the outer enteric capsule made of gelatin is dissolved in the intestine and the inner core consists of push-pull osmotic units. The inner layer of enteric layer consists of a semi-permeable membrane which encompasses the osmotic and therapeutic unit. On dissolving the osmotic unit swells up leading to release of the therapeutic unit through the orifice[94]. These systems maintain consistent postbiotic release, improving systemic absorption of hepatoprotective metabolites and minimizing variability in gut fermentation times which is key in cirrhosis or MASLD patients with altered microbiota.

Nanoparticle delivery system: Among the various nanoparticle delivery systems, lipid or polysaccharide-based liposomes have proved to be effective to tide over inflammatory or neoplastic conditions. These coated liposomes are used to deliver several postbiotics such as vitamins and bacteriocins. Such delivery mechanisms prevent interaction of those nanoparticles with food and proteases of digestive tract. Hydrogels also serve as an effective nanoparticle carrying system as explained below. Promising potential of such delivery systems can be extrapolated to a large scale through more clinical trials. Some extensively studied systems include chitosan, poly (lactic-co glycolic acid), mesoporous silica nanoparticles, nanoparticle in microparticle oral delivery system, hydrogel microfibers and liposomes[95]. Such systems are highlighted for their potential to cross intestinal epithelium and enter systemic circulation, allowing targeted hepatic delivery.

INTRAVENOUS

Intravenous (IV) route is preferred for widespread systemic release of probiotics[96-98]. It has been discussed on lines on bypassing first pass metabolism, providing systemic hepatic access. However, IV postbiotic therapy for liver disease remains largely theoretical with no established large scale clinical evidence or regulatory approval. Among all of the above proposed modes, transport of postbiotics as nanoparticles are shown to be effective for *in vivo* infusion with persistent release. Such particles are transported through pulsatile delivery mechanisms to maintain a steady state plasma concentration for the desired duration. Such infusions have the benefit of limiting multiple doses, leading to improved patient's compliance[99].

Hydrogels also serve as an effective alternative owing to their one-of-a-kind properties, such as a three-dimensional polymeric structure with numerous micropores which enable them to disperse to their surroundings. They are also hydrophilic and thermo-responsive which enables them to change their size inside a capsule. Such heat-sensitive properties enable them to function as a flip switch by expansion and contraction[100].

However, IV administration has its own set of disadvantages such as infections through contaminated needles, improper patient adherence and lack of local effects. The major regulatory barriers include manufacturing purity, immunogenicity and lack of human dosing data.

By linking the above discussed delivery mechanisms to gut-liver signalling and hepatic pathophysiology, the translational potential of postbiotics could be enhanced.

Limitations on translation to clinical medicine

Postbiotics lack standardized definitions and criteria which makes it difficult to compare researchers and products. Thus, postbiotics currently fall into a regulatory gray zone with no dedicated regulatory category under Food and Drug Administration or World Health Organization frameworks. The variability in strain identity, culture medium, growth conditions, *etc.*, poses a major challenge in ensuring batch-to-batch consistency in bioactive content. The industrial processing of postbiotics from fermentation to inactivation and drying affects the yield and activity of the contents. Postbiotics cannot proliferate and thus require frequent dosing and non-adherence leads to diminished benefits[101]. As most human studies use food-based doses with no recording of dose-response data, the risk of overdosing or underdosing is concerning, especially in the vulnerable population. Exhaustive research on each component of postbiotics preparation and the concentration at which to be administered to elicit positive health results is required for understanding the role and quantity required of each component in halting liver diseases. Certain preparations consisting of LPS and teichoic acid have been shown to elicit immunogenic and inflammatory responses leading to sepsis, endocarditis, abscess formation *etc.* The interaction of postbiotics with conventional therapies should be studied extensively. At present only the safer and more effective native bacteria (*Lactobacillus*) is employed in development of postbiotics. Isolation of postbiotics requires advanced technologies which limits mass production[11].

CONCLUSION

The gut microbiome is considered as a virtual organ which has complex interlinked pathways with various metabolic processes. Postbiotics are an appealing therapeutic option due to their diverse pleiotropic efforts on several interlinked metabolic pathways and their beneficial properties. The active components of postbiotics with properties such as anti-inflammatory, anti-obesogenic, anti-oxidant, hypocholesterolemic and immunomodulation have diverse applications in serving as a treatment option for liver diseases as summarized above. Further research aimed at translating results in animal models to humans is required to analyze the beneficial and hazardous side effects before applying it clinically. This review calls for large scale human clinical trials, dose-response studies and development of targeted delivery systems while addressing regulatory challenges, safety profiling and translational gaps. With emerging cohorts and cross-sectional studies, we have progressed from learning correlations to understanding associations between gut microbiome and liver diseases.

FOOTNOTES

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