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Postbiotics: A New Post in Biotics and Its Prospective Role in Human Health and Diseases

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ABSTRACT:
Postbiotics is a cluster of biomolecules in the contemporary field of "biotics" matrix. It is presently classified as a collection of healthful by-products of the probiotic metabolism as well as active biomolecules produced by bacterial fermentation. The postbiotics prevalently consist of proteins, saccharides, short-chain fatty acids, microbial cell fragments, and inanimate microbial cells. They provide therapeutic effects such as anti-microbial, anti-carcinogenic, and lowering of blood pressure by modulating gut microbiota and strengthening the intestinal barrier. It has also been noted that in the transition phase of the COVID-19 pandemic, postbiotics could potentially boost the treatment efficacy against SARS-CoV-2 by inhibiting angiotensin-converting enzyme 2 activity.

Nowadays, postbiotics potentially offer a safer and more effective alternative to traditional synbiotics, a combination of probiotics and prebiotics, in cases where microorganisms and spores cannot be safely administered to the patient for the betterment of health. The unique characteristics like thermostability, high shelf life, and absence of living bacteria of postbiotics elevate their disease-curing efficiency. However, the universal acceptance of the beneficial effects of postbiotics is still an active area of future investigation. This review article narrates an insight into the mechanism of action, genesis, and possible application of postbiotics in the design of therapeutics in conjunction with the upliftment of the pharmaceutical industry for the management of diversified health complications.

KEYWORDS: Postbiotics,Biomolecules,Probiotics ,Prebiotics,Therapeutics

RUNNING TITLE: Beneficial Aspects of Postbiotics

HIGHLIGHTS:

- Postbiotics, the beneficial byproduct of probiotics, play an essential role in maintaining health.
- Components of postbiotics include short-chain fatty acids, bacteriocins, and lipopolysaccharides.
- Postbiotics have diversified beneficial effects on the gastrointestinal system, immune system, and other systems.
- They are emerging as potential alternatives to synbiotics because of their unique biochemical and physical properties.

I. INTRODUCTION:

Postbiotics, components of microorganisms or innate microorganisms like mixtures of cellular structures or metabolites produced by the cell, such as short-chain fatty acids, thechoic acid, and exopolysaccharides, confer health benefits to humans (1). Emerging studies suggest that inactive microorganisms maintain and reset gut homeostasis by enhancing the functionality of the gut microbiome in an individual (1). Emerging studies suggest that postbiotic administration plays a significant role in maintaining mental and physical health by modulating the brain-gut axis. Postbiotics primarily modulate immunity, provide protective modulation to infections, and have demonstrated significant benefits in the fight against obesity (1). Several

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components of postbiotics, like cell-free supernatant (CFS), bacteriocins show anti-cancer properties mainly via their immunomodulatory activities. They are also being considered as a therapeutic strategy for SARS-CoV-2 infection and hypertension (2). Substantial research and data indicate that postbiotics in conjugation with probiotics and prebiotics can potentially decrease the severity of various life-threatening diseases (3). A jointly released report by the World Health Organization (WHO) and the Food and Agriculture Organization (FAO) of the United Nations in 2002 states that "probiotics may theoretically be responsible for four types of side effects: systemic infections from undesired pathogens present in probiotic culture cause deleterious metabolic activities. In allergic people, excessive immune stimulation can occur. "Gene transfer" and some symptoms related to the gastrointestinal system are also reported (4). A prebiotic is a substrate that is selectively utilized by host microorganisms, conferring a health benefit (5). The adverse effects of prebiotics, primarily linked to their osmotic effect, are bloating, diarrhoea, cramps, and flatulence (6). Although antibiotics are used for the treatment of infectious diseases, they harm the gut microbiota, along with a consequential enhancement in susceptibility to diseases associated with the microbiota.

To mitigate this complication, modern-era products such as postbiotics have been shown to be more stable and effective in the gut environment. Additionally, because postbiotics are heat-killed microorganisms or their metabolites, they have a better effect on immunocompromised individuals and infants and reduce the risk of infection or microbial translocation, making them safer to use.This article reviews the potential applications of postbiotics to reduce the severity of several health complications. Additionally, the future prospects of postbiotics in the food industry were summarised for the promotion of innovation and accurate market positioning.

II. MATERIALS AND METHODS

The databases of PubMed, PMC, and ScienceDirect were searched for published articles in English from October 1997until May2024 for this review article. Terms including "Postbiotics, Components of Postbiotics, Mechanism of Action of Postbiotics, Potential Biological Activities of Postbiotics, Future Scope of Postbiotics" were used in the search (**Figure 1**).

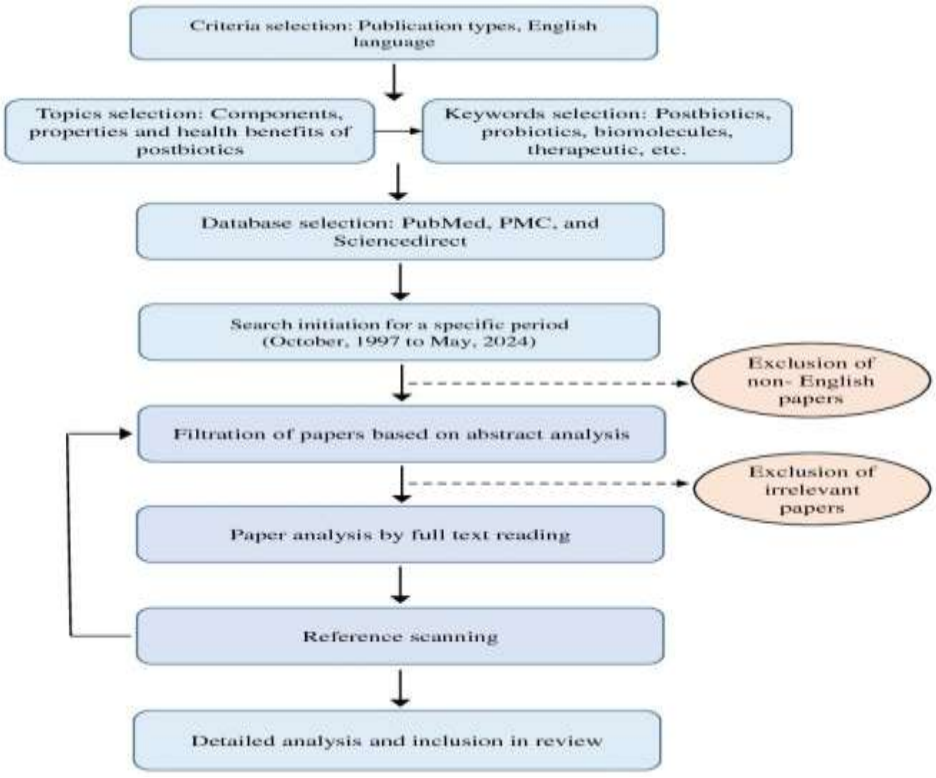

Figure 1: Materials and methods

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III. RESULTS AND DISCUSSIONS:

Postbiotics are composed of certain parts of fermented bacterial products. Each having their own unique characteristics and effects on the consumer's body. Commonly available postbiotics' components have been enlisted and designated with their known functions.

3.1 Postbiotics: properties and role

Postbiotics, being by-products of probiotic fermentation, are more thermostable and can withstand adverse processing and storage conditions, which usually degrade probiotics. This makes postbiotic options suitable for use in the food and pharma industries. They do not require heavy refrigeration and can be stored for longer periods before retail, making them more convenient and cost-effective. In certain situations, such as immune-compromised individuals or sensitive manufacturing processes, the presence of live organisms in probiotics may not be desirable or feasible, causing detrimental effects on individual health. Postbiotics provide an alternative to this by offering similar health benefits and eliminating the need for live organisms. The efficacy of live bacteria or spores is highly variable, but postbiotic compounds are stable (7). Unlike probiotics, where different strains and individual patients can have different effects, postbiotics offer a standardised and consistent composition of bioactive compounds. Their effects, in general, are the same for all individuals. Postbiotics can be more easily formulated into various products like supplements, functional foods, and topical applications, making them more accessible for different purposes (**Figure2**).

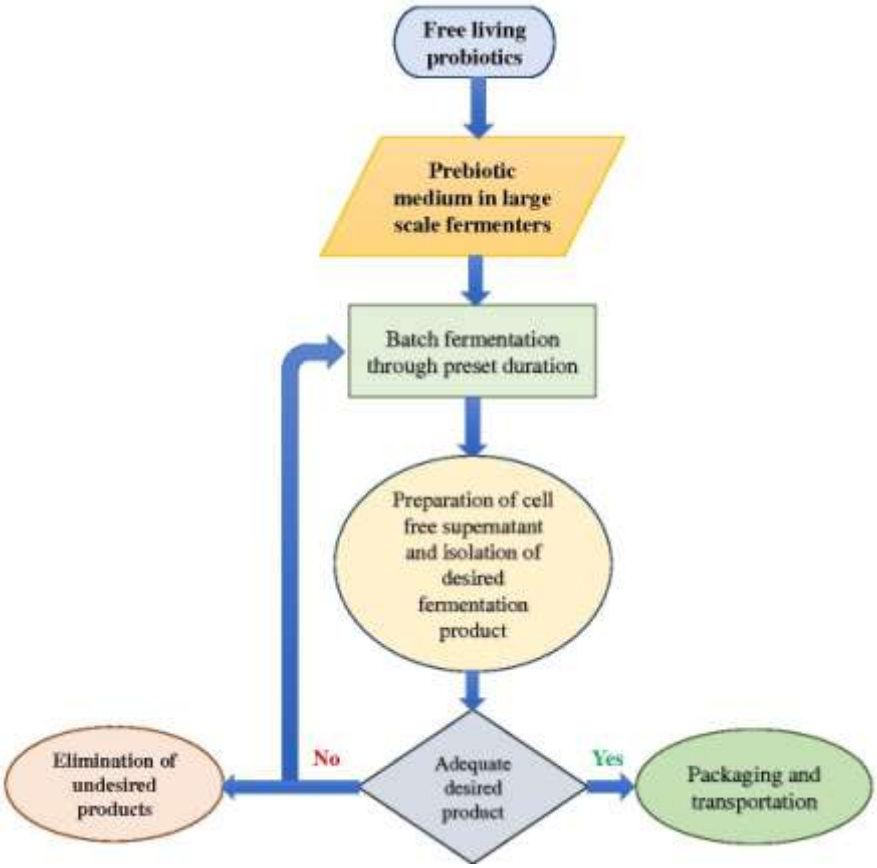

Figure2: Preparation of postbiotics

Short-chain fatty acids (SCFAs), derived from the fermentation of dietary fibres, have emerged as vital energy sources for colonic cells. They also exhibit diverse effects on the gut-brain axis, influencing appetite regulation and exerting epigenetic roles. They exhibit the multifaceted functions of SCFAs in maintaining gut integrity, modulating immune responses, and impacting systemic metabolism. Polyamines help in promoting homeostasis and modulating epigenetic processes, apoptosis, and cell proliferation. Polyamines interact with proteins and nucleic

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acids, and those interactions impact cellular functions and human health. Bile acids not only participate in the digestion of lipids but also play a role in signalling molecules regulating glucose metabolism and immune responses. P-cresols are derived from tyrosine fermentation. They show antimicrobial and antioxidant properties. It may also be associated with enteric pathogens, autism, and kidney diseases. Trimethylamine N-oxide (TMAO) may have a role in cardiovascular diseases. Bacteriocins are antimicrobial peptides or host defence peptides produced by certain bacteria and have antibiotic properties. They play an important role in shaping the gut microbial composition and help in the maintenance of gut health (**Figure 3**) (8).

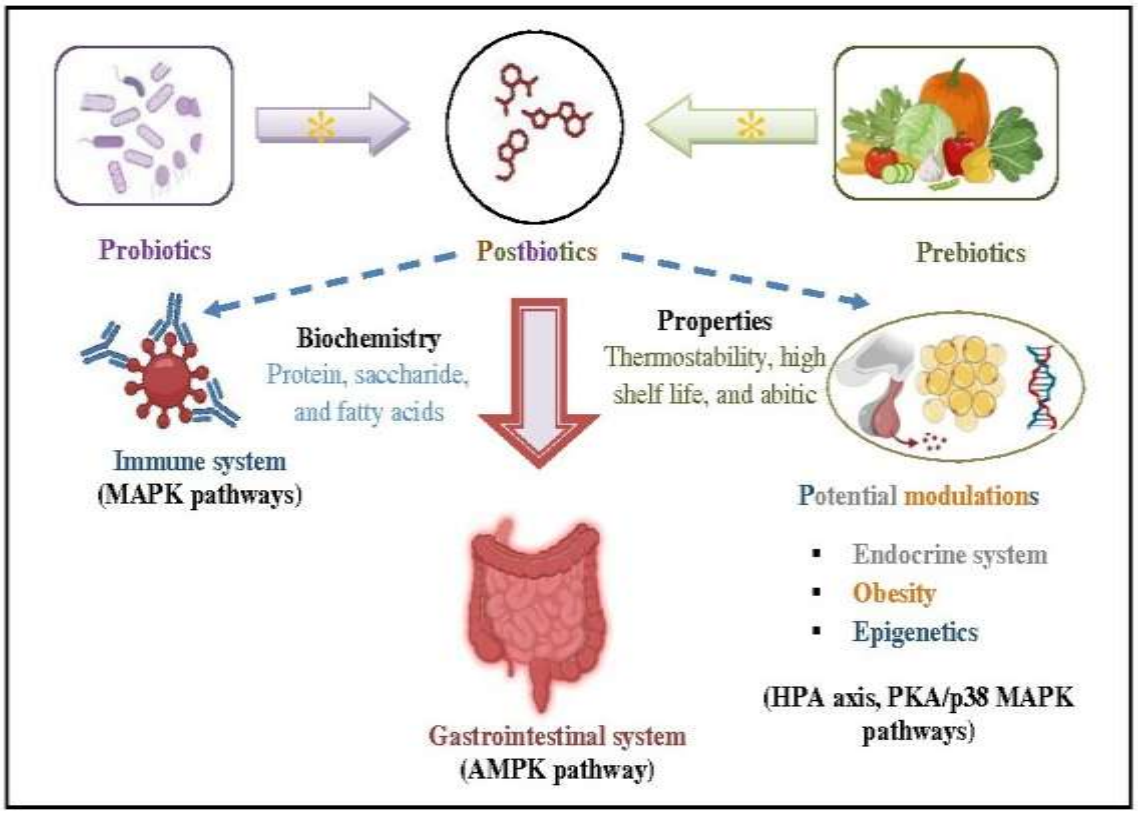

Figure3: Quartile effect of postbioticson various biological activities. MAPK=mitogen-activated protein kinase, HPA=hypothalamic-pituitary-adrenal, PKA=protein kinase A.*=combination

3.2Effects of postbiotics on gastrointestinal system

Postbiotics impact the gut microbiome and also enhance the barrier property of the gut by stimulating more tight junction protein formation and increased mucous secretion (9). Various postbiotic components, such as branched fatty acids, cell wall components, and SFA, show various influences on immune responses. SFA shows immunomodulatory effects by modifying the barrier function and also protects against lipopolysaccharide (LPS)-induced disruption by inhibiting the LPS action on the NLRP3 inflammasome (10). Theoic acid produced by different bacteria, specifically Lactobacillus strains, has shown an inhibitory effect on the formation of biofilm, which is the main cause of the pathogenicity imparted by harmful microorganisms (11). Another antimicrobial component of postbiotics is bacteriocin, which prevents the formation of biofilm in the gut. Bacteriocins are ribosomally synthesized, low-molecular-weight, membrane-active cationic bacterial peptides secreted by gram-positive bacteria like lactic acid bacteria (LAB) (12).

The AMP-activated kinase (AMPK) pathway is a cellular effector of postbiotics. This AMPK is linked with postbiotics via the phosphoinositide-3-kinase/protein kinase B (PI3K/PKB) pathway. Postbiotics such as butyrate and the CSF of L. plantarum RG14 act via activating protein kinase B (PKB/Akt) to enhance the synthesis of claudins-3 and 4, which are tight junction proteins. This pathway is also utilized for

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enhancing the production of mucin or expression of the muc2 gene as a response to butyrate and the purified protein HM0539 from Lactobacillus rhamnosus GG (LGG) and thus stimulating the intestinal cell to secrete mucins, which has an effect on increased intestinal permeability (13). Many postbiotics derived from Lactobacillus promote the growth of epithelial cells in the gut and also inhibit cell death. It has been observed that some components promote goblet cell differentiation,thus increasing mucus secretion by them, and protecting the intestinal epithelial cells (14). Lactate is known to promote the migration rate of epithelial cells of the intestine by enhancing mitochondrial ATP production and ameliorating colitis by stimulating the upregulation of expression of Cdc42 and Pak1, two factors associated with healthy intestinal epithelial cell migration (15).

Mitogen-activated protein kinase (MAPK) activation by postbiotics like E. coli, LPS, and conditioned media from Lactobacillus GG induces heat shock protein (HSP) expression (HSP25 and HSP72) in epithelial cells of the intestine (16,17). MAPKs are protein kinases that are serine/threonine-specific protein kinases and have three subfamilies: extracellular signal-regulated kinases (ERKs), c-Jun N-terminal kinases (JNKs), and p38 mitogen-activated protein kinases (p38s). The MAPK pathway involves a series of phosphorylations leading to the activation of MAPK. Activated Ras protein, receptors like receptor tyrosine kinase (RTKs), and G-protein-coupled receptors (GPCR) activate MAP kinase kinasekinase (MAPKKK), which in turn leads to phosphorylation of MAPKKK. This phosphorylates MAP kinase effector kinases, which include ERK, JNK, and p38. Phosphorylated MAPKs exert several cellular effects by acting through effectors like transcription factors and other kinases (14). In cultured young adult mouse colon (YAMC) cells, E. coli LPS stimulated the p38 and ERK1/2 pathways but did not stimulate the stress-activated protein kinases/Jun amino-terminal kinases(SAPK/JNK)pathway, whereas Lactobacillus GG acts via the p38 and JNK pathways to induce HSP expression. These cytoprotective HSPs positively influence gut epithelial barrier integrity and provide the host with improved protection against infection. Some microbial postbiotic bacteria produce bifidocin, which has a wide spectrum of action against both gram-negative and gram-positive bacteria (18). Moreover, postbiotics also help to maintain a balance of gut microorganisms.

3.3Effect of postbiotics on immune system

Postbiotics exert modulatory effects on the immune response by regulating how the immune cells act. The immunomodulatory activity of postbiotics can aid in the regulation of inflammatory action and apoptosis, increasing immune defence and decreasing hypersensitivity reactions like allergies or autoimmune diseases. Cytokines are important signalling molecules that play an important role in the regulatory pathway of immune responses, whose production can be stimulated by postbiotics by influencing the NF-κB and MAPK pathways (19). The advantage is that a lack of live microorganisms in postbiotic preparation eliminates the probability of adverse effects (20).

Postbiotics are being considered as a potential tool for adjunct therapy in cancer patients (21). Postbiotics like exopolysaccharides (EPS), cell-free supernatant (CFS), and bacteriocins can bring about the apoptosis of cancer cells. EPS of Lactobacillus spp., including L. plantarum GD2, L. rhamnosus E9, L. brevis LB63 isolated from healthy infant faeces, L. delbrueckii subsp., and L. bulgaricus B3 isolated from yoghurt, increases the expression of BCL-2-associated X (BAX) genes and decreases the level of expression of B-cell lymphoma 2 (BCL-2). This prevents the pro-apoptotic factors from being bound by anti-apoptotic factors, thus allowing them to reach the mitochondrial membrane and induce apoptosis in colon cancer cells (HT-29). It also induces apoptosis by activating caspases 3 and 9 and reducing survivin protein, as well as inhibiting the expression of the survivin gene. The potential of the EPSs to induce apoptosis could be dependent on the composition of sugar in the EPS, with glucose and mannose being the main components. Low glucose and a high mannose content can be related to B3EPS being able to strongly induce apoptosis (22). CFS of a liquid culture of strains of Lactobacillus rhamnosus SHA111, SHA112, and SHA113, which were isolated from human breast milk, showed a significant anticancer effect on cervix cancer cells (HeLa) by mediating cytotoxicity and inducing apoptosis by up-regulating the BAD, BAX, caspases-3,8 and 9, and down-regulating the BCL-2 genes (23). CFS of Lactobacillus fermentum also induces apoptosis of colorectal cancer cells by increasing the expression

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of caspase-3 and mRNA for Bax, Bak, Bid, and Noxa in HCT-116 and HT-29 cells (24).

Postbiotics from CFS and heat-killed bacteria (HKB) exert anti-inflammatory effects largely by attenuating the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway. NF-κBβ, a family of transcription factors, is known for playing an important role in both innate and adaptive immunity. There are 5 members in the mammalian NF-κB family: c-Rel, RelB, RelA (p65), NF-κB1 (p105 and p50), and NF-κB2 (p100 and p52). In two pathways for NF-κB activation,the classical pathway is triggered by microbial and viral infections or by proinflammatory cytokines, mostly targets dimers of p50:RelA and p50:c-Rel, and is dependent mainly on IκB kinase (IKK) activity. The second pathway, called the alternative pathway, is triggered by the members of the TNF cytokine family via selective activation of IKKα homodimers and induces the processing of NF-κB2/p100 precursor protein that mostly exists as a heterodimer with RelB in the cytoplasm, resulting in selective activation of p52:RelB dimers. The classical pathway is involved in the inhibition of apoptosis under most conditions. On the other hand, the alternative pathway is essential for premature B-cell survival and the development of secondary lymphoid organs. Under most conditions, dominance of survival signals prevails, but under circumstances in which IKKβ or NF-κB activities have been compromised, receptor activation results in cell death (25).

The mechanisms of the attenuation of this pathway by CFS and HKB involve the inhibition of nuclear translocation of NF-κB by inhibiting IκB phosphorylation and by hindrance of its degradation by the proteasome. The CFS of L. rhamnosus CNCMI-4036 enhances IκB subunit expression and therefore tightens the sequestering of NF-κB in the cytoplasm (24).

The CFS of Lactobacillus casei ATCC334 has a significant anti-tumor effect on colon cancer cells. Ferrichrome, a molecule for tumor suppression, is produced by L. casei ATCC334. Treatment of cells with ferrichrome induces apoptosis via the activation of the c-jun N-terminal kinase-DNA damage-inducible transcript 3 (JNK-DDIT3)-mediated apoptotic pathway. The molecules related to the endoplasmic reticulum (ER) stress response, including transcription factor DDIT3 and glucose-regulated generic binding protein of 78 kDa, showed remarkable upregulation under the effect of ferrichrome (26).

Secondary metabolite products of Lactobacillus plantarum significantly reduce the expression of the BCL-2 gene in the human breast cancer MCF-7 cell line. It also reduces the expression of the anti-apoptotic gene BUFFY and increases the expression of the apoptotic genes DECAY, FADD, and RAS64B in Drosophila sp. There is also a reduction in the expression of the apoptotic genes APAF-1 and TP53 in human beings and DARK and DEBCL in Drosophila (27).

The butyrate-producing bacterium Clostridium butyricum causes suppression of the development of intestinal tumor.C. butyricum supernatant results in remarkable repression of the proliferation of intestinal tumor cells and stimulation of their apoptosis. One of the mechanisms by which the anticancer effect is exerted is by downregulating theWnt/β-catenin pathway (28).

The Wnt/β-catenin signaling pathway belongs to a group of signalling pathways called Wntsignaling pathways. There are three well-characterized Wnt signalling pathways: the canonical Wnt pathway, the noncanonical planar cell polarity pathway, and the noncanonical Wnt/calcium pathway (29). The canonical pathway that involves the transcriptional coactivator β-catenin, hence called the Wnt/β-catenin signaling pathway, is one of the primary mechanisms that modulate embryonic development and tissue homeostasis. Mutations in this pathway are associated with serious diseases, including cancer. Phosphorylation or degradation of β-catenin and its control by Wntare at the core of this signalling pathway. When Wnt is absent, cytoplasmic β-catenin forms a complex with axin, adenomatosis polyposis coli (APC), glycogen synthase kinase 3 (GSK3), and casein kinase 1α (CK1α). β-catenin undergoes phosphorylation by CK1 and GSK3 and is subsequently targeted for ubiquitination by the E3 ubiquitin ligase b-Trcp, which sends it to the proteosome for degradation. When Wnt ligand is present, Wnt, Fz, and LRP5/6 form a complex that recruits scaffolding protein dishevelled (Dvl), resulting in phosphorylation of LRP5/6 and axin recruitment. This inhibits axin-mediated phosphorylation or degradation of β-catenin, which permits β-catenin to travel to the nucleus, where it acts as a coactivator for T-cell factor/lymphoid enhancing factor (TCF/LEF) transcription factors to activate Wnt-target genes, including oncogenes cyclin D1 and c-Myc(27). HCT116 cells treated with C. butyricum showed a reduction in the expression of β-catenin in the nucleus and lowered

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expression of Wnt-target genes ofcyclin D1 andc-Myc (27).

Treatment with heat-killed, isolated strains of LAB, including L. salivarius MG242, L. plantarum MG989,and also Bifidobacterium bifidum MG731 and Bifidobacteriumlactis MG741, inhibits the production of nitric oxide (NO) via the suppression of inducible nitric oxide synthase (iNOS) and cyclooxygenase 2 (COX-2) and tumour necrosis factor-α (TNF-α) in LPS-stimulated RAW 264.7 cells. LPS activation of RAW 264.7 macrophage cells results in the induction of inflammatory mediators such as NOS, COX-2, and the proinflammatory cytokine TNF-α, which induces massive production of nitric oxide, leading to inflammation (30).

Various types of bacteriocins, like nisin, enterocin, and plantaricin, exert inhibitory effects on different cancer cell lines in different ways. Head and neck squamous cell carcinoma (HNSCC) cells, on being treated with bacteriocinnisin, exhibit an enhanced apoptosis rate via alteration of membrane phospholipids and calcium ion influx into the cells, which is needed for apoptosome formation. Nisin from Lactococcuslactis also decreases matrix metalloproteinase 2 and 9 (MMPs) and carcinoembryonic antigen (CEA) gene expression in HT-29, Caco-2, LS180, and SW48 cells. MMP-2 and MMP-9 are involved in lymph node metastasis. Enterocin, produced by Enterococcus sp., is a broad-spectrum bacteriocin (31). Al-Madbolyet al. reported increased apoptosis in the G0 phase of the cell cycle and a significant decrease in the expression of CD surface markers in HepG2 cells in the presence of enterocin LNS18 (32).

3.4 Postbiotics in weight management

Some postbiotics have been shown to regulate metabolism and promote weight loss, making them potential tools for fighting obesity. There is growing evidence that postbiotics play an important role in supporting weight management and preventing obesity. Postbiotics, particularly SCFAs such as acetate, propionate, and butyrate, have been shown to affect health and energy balance. They stimulate the release of hormones such as glucagon-like peptide-1 (GLP-1) and peptide YY (PYY), which increase satiety and reduce food intake. They help to control overeating and weight gain by regulating hormones (33). Yoon et al. observed that on administration of postbiotics derived from heat-killed Lactobacillus plantarum and Lactobacilluscurvatus, there is a reduction in the accumulation of adipose (34). Youn et al. observed that there is an increased level of Hesperetin and thus a reduction in body weight (35). Osman et al. observed that postbiotics obtained from Egyptian cheese cell-free extract showed a significant increase in lipid metabolism and also enhanced anti-oxidant enzyme activity (36). Rahman et al. observed that after the administration of postbiotics, there is a reduction in weight gain and ependymal fat accumulation(37). It also shows improved insulin sensitivity and glucose use. The anti-obesity effect was exerted via the PKA/p38 MAPK signaling pathway (37). Sugawara etal.also found that postbiotics improved the gut microbial condition and reduced fat in the abdominal region of the body (38).

3.5 Postbiotics and cardiovascular health

Studies have indicated that postbiotics can help decrease cholesterol levels, indicating a potential role in managing cardiovascular health. Postbiotics have been shown to improve the expression of genes involved in lipid oxidation; thereby, they can increase fat production and reduce fat storage (39). Additionally, postbiotics can inhibit the activity of enzymes involved in fat synthesis, thus potentially preventing excess fat. Studies have shown that postbiotics can improve insulin sensitivity, glucose homeostasis, and lipid profile, all of which are important in obesity and metabolic syndrome. Postbiotics may aid weight control and reduce the risk of obesity by improving the body's response to insulin and overall metabolic activity (40).Some postbiotics show antihypertensive effects. SCFAs like acetate, propionate, and butyrate are signaling molecules and can act mainly via specific GPCRs. Postbiotics may also exhibit a blood pressure-lowering effect by regulating the renin-angiotensin-aldosterone system (RAAS), a hormonal system that plays an important role in the regulation of blood pressure. Postbiotics are capable of inhibiting the production of angiotensin-converting enzyme (ACE). ACE is involved in the conversion of the hormone angiotensin I to angiotensin II, which increases the blood pressure by constricting the veins and arteries and also mediates aldosterone secretion from the adrenal cortex. Chronic low-grade inflammation has been implicated in the pathogenesis of hypertension, and postbiotics can help to dampen this inflammatory response, thereby decreasing high blood pressure. Gurunathan et al. suggest that postbiotic supplements, primarily produced by

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Bifidobacterium andLactobacillus spp., have been shown to reduce blood pressure, indicating their potential for treating hypertension (41).

3.6 Postbiotics and nervous system

The mechanism by which postbiotics affect the nervous system is not yet fully understood. But there are some postulated means through which this may occur, and they are vagus nerve stimulation, production of neurotransmitter, modulation of inflammation, and immune response. Apart from this, SCFAs, like acetate, propionate, and butyrate, can cross the blood-brain barrier (BBB) to interact with neuronal receptors, thus affecting the functions of the brain(42). Postbiotics can regulate the production and release of gastrointestinal hormones, which serve as signaling molecules to influence the activity of the neurons, those are part of the gut-brain axis(42).

3.7 Postbiotics and SARS-CoV-2

SARS-CoV-2 infection adversely impacts the respiratory organs mainly due to its inflammatory effect on airways, which is accompanied by increased release of proinflammatory cytokines like IL-1B, IL-6, IL-17, IL-15, IFN-γ, and TNF-α, resulting in the onset of a cytokine storm. The inflammatory stimulus-response is caused by the activation of the response of the TH1 cell. Gut dysbiosis and the associated decrease in the production of bacterial metabolites cause an imbalance of TH1 or TH2 cells, which results in the secretion of proinflammatory cytokines in the lungs. Postbiotics, in the case of SARS-CoV-2 disease, act by modulating the intestinal microbiota, causing a balance between TH1 or TH2 cells and thus reducing the cytokine storm. This decreases inflammation of the airways (43).

Postbiotics is an umbrella term for all synonyms and related terms of these microbial fermentation components.They include many different constituents, including metabolites, microbial cell fractions, SCFAs, functional proteins, extracellular polysaccharides (EPS), cell lysates, teichoic acid, peptidoglycan-derived muropeptides, and pili-type structures, which can potentially modify the composition or functions of the host microbiota (**Table 1**).

Table 1. Potential biological activities of several postbiotics

Source	Component	Outcome
Plantaricin BN, Plantaricin JLA-9, Plantaricin W, Plantaricin D along with RNA-dependent RNA polymerase (RdRp) (44)	Plantaricin metabolites	Anti viral effect
W. cibaria and W. confuse (45)	Phenolic and flavinoid components	Anti-microbial and anti oxidant
Lactic acid bacteria (Lactobacillus plantarum and Lactobacillus curvatus) (41)	bioactive components, S-layer proteins (SLPs, LPSLP, and LCSLP).	Anti- adipogenic effect
Lentilactobacillus kefiri from Kefir (35)	bioconversion of whey (WHE) and polyphenol-rich citrus pomace extract (CPX) by using kefir lactic acid bacteria (LAB)	Anti-obesity effect
Lactobacillus paracasei (cell-free extract) (36)	superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GSH-px)	Lipolytic effect
Bifidobacterium bifidum DS0908 and Bifidobacterium longum DS0950 (37)	bacterial culture supernatant	Lipolysis
Lactobacillus amylovorus CP1563 (38)	fragmented CP1563	reduction in abdominal fat area, body weight, and BMI

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Pediococcus pentosaceus LP28 (46)	Heat killed bacteria	Reduction in BMI, body fat and also the waist circumference reduces.
Lactobacillus bulgaricus (47)	DEODAN, an oral preparation from lysozyme lysates	Increased WBC count in patients with leukopenia
Lactobacillus rhamnosus strains isolated from human breast milk (23)	cell-free supernatant of a liquid culture	Anti cancer activity
Lactobacillus fermentum (24)	cell-free supernatant (CFS)	Induction of apoptosis
Lactobacillus casei ATCC334 strongly supresses colon cancer cells (25)	Cell free supernatant (CFS), ferrichrome	Ferrichrome treatment induced apoptosis andstrongly supresses colon cancer cells.
Bifidobacterium spp. and Lactobacillus spp. (48)	Cell free supernatant (CFS)	Inhibition of the growth of colon cancer cells through the intestinal microflora balance
Lactobacillus spp. (22)	lyophilized exopolysaccharides (EPSs)	induction of apoptosis of colon cancer cells (HT-29)
Faecalibacterium prausnitzii (49)	supernatant and EVs	Upregulate anti-inflammatory cytokines
Lactobacillus paracasei (50)	cell wall proteins	anti-proliferative effect on cancer cell line
Lactobacillus plantarum (27)	cell free supernatant	Reduced expression of anti-apoptotic genes
Clostridium butyricum (28)	Supernatant	Inhibit intestinal tumor development
Lactiplantibacillus plantarum (51)	cell-free supernatant	used as an alternative to antibiotics
Lactic acid bacteria (52)	Compounds of the cell walls of 17 strains heat-killed lactic acid bacteria	immunomodulatory properties and anti-inflammatory
Lactobacillus paraplantarum SC61 (53)	heat killed isolation technique	antioxidant and immunostimulatory activity
Lactobacillus plantarum KU15149 (54)	Lactobacillus plantarum KU15149	Antioxidant activity, anti-inflammatory activity
Gut microbial-derived SCFAs (54)	gut microbial-derived SCFAs acetate and butyrate [acetylated and butyrylated high amylose maize (HAMSAB)]	Lowered blood pressure
Lactobacillus acidophilus (55)	lyophilized and inactivated culture	improved the efficacy of a standard anti-H. pylori therapy

3.8Future scope in food and nutraceutical industry

Postbiotics can be used in the production and improvement of many consumer goods due to the superior quality of the fermentation products. Therefore, the application area of postbiotics is very wide and can be utilized in many industries, such as food, beverages, supplements, cosmetics, medical products, and certain non-clinical products (**Figure 4**). These bioactive compounds play an essential role in maintaining and restoring hosts' health (56).

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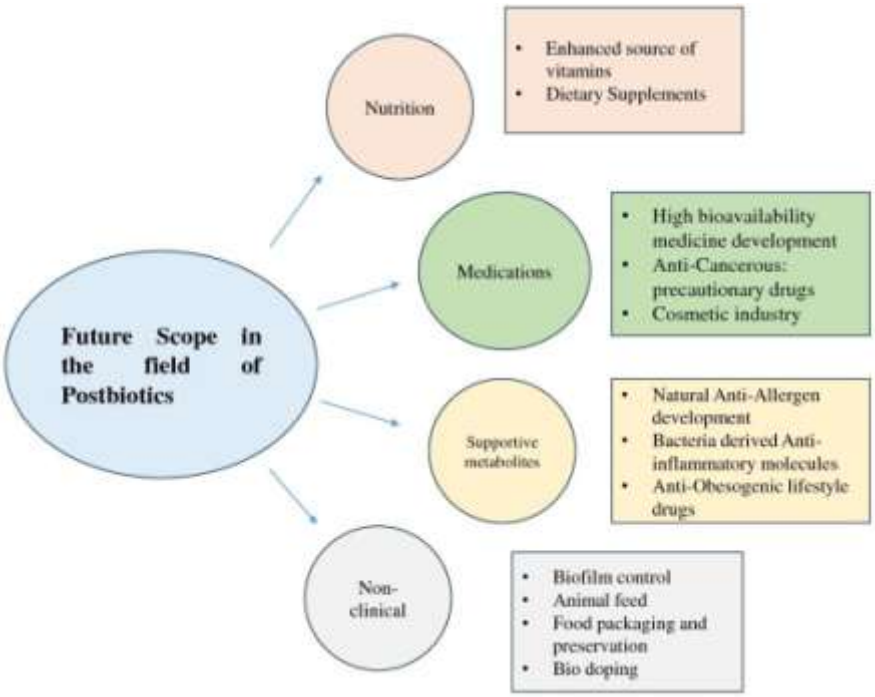

Figure4: Future scope in the field of postbiotics

Driven by the advancement of people's knowledge of health care and healthy food needs, large companies have to devote themselves further to the research and production of postbiotic-related products. In this context, the demand for postbiotics containing healthy foods such as fortified yoghurt, kombucha, pre-canned pickled consumables like packed kimchi, and daily food substitutes such as bread and snacks has caught on. A rise in consciousness regarding physique and improved access to diet planning led to a demand for postbiotic supplement capsules. Previously, they were used only by people undergoing chemotherapy, radiation therapy, or high-dose antibiotic treatment, compromising the action of natural gut flora. We now see such products on the market in various degrees of quality and dosage control. With the advent of lab applications on foods like yogurt, kombucha, etc. on an industrial scale, many of the problems associated with access to postbiotics will be erased (57).

Adolescence is a transitional stage of physical and behavioural characteristics that occurs during the period from puberty to adulthood. They constitute around 21% of the Indian population and more than 1.2 billion worldwide (58). Numerous grave illnesses stem from adolescent preferences for hazardous lifestyles and unhealthy diets and a lack of awareness and knowledge regarding their physiological alternation, which facilitatesto morbidity and mortality during this stage and further life (58). Seeding the plants for thedevelopment of postbiotic care and medication will prove to be a great boon for upcoming adults (59). The importance of the use of epigenetics in medicine has brought postbiotics to new light. It has the potential to serve as a constituent of nutritional strategies to modulate the microbiome where and when needed, as well as an alternative to traditional antibiotics (8). The evidence shows that postbiotics are effective and safe for healing health issues related to stomach/diarrhoea, immunity, allergies,hypersensitivity, cancer, neurodegenerative diseases, and so on (8). However, extensive scientific research and evidence are awaited to reach the destination for disease, individual health profile, and dose-specific, tailored application of postbiotics (8).

IV. CONCLUSIONS:

In the twenty-first century, postbiotics have progressively drawn the attention of the scientific and nutrition communities from a rising number of individuals in an effort to eradicate sub-health complications. The evolving scientific evidence indicates that the metabolites help host health by fortifying and regulating a range of biological processes, such as the digestive system and immunity, and boosting the pharmaceutical industry. These contemporary molecules serve their

protective roles by strengthening the gut microbiota, modulating the various cell signaling pathways, including NF-κB, MAPK, and PI3K/AKT, and targeting pathogen-associated molecular patterns (PAMPs) and toll-like receptors (TLRs). The narrative literature review focuses on the modulatory role of postbiotics on diversified biological activities, including the gastrointestinal system and immunity. However, compensatory mechanisms for the non-proliferative activity, as well as the dosage and route of supplementation, still need to be determined. Furthermore, indicators for figuring out the threshold concentration of postbioticsare hidden. Further research is necessary by counteracting the existing missing links to establish the pleotropic effect of postbiotics in the biological matrix.

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VI. STRENGTHS AND LIMITATIONS:

This enlightens the reader on the mechanism of action of the components as well as the future application of the same in the body system. A tabulation of the purpose, source, and function of specific bacterial metabolites gives a quick view of the current status of the application of probiotic-applied medicines. This paper is unique in highlighting the pharmaceutical-marketing approach of postbiotics. In the past, postbiotics were shown only as gut flora modulators by the pharma industry. Our focus has mainly been on bacterial postbiotic metabolites, leaving out any elaborations on plant- and algae-based ones.We shed light on the multiple new microbe metabolites that have emerged, allowing targeted medication.

Every attempt has been made to review the article data from relevant and credible sources; however, it must be acknowledged that scientific consensus on the application of postbiotics is evolving; new data may provide alternate mechanisms of activity for the same metabolite or disprove association with the same. Errors in data interpretation by authors from original material may occur despite cross-verifications from alternate articles. The paper fails to elaborate on certain mechanisms mentioned, which are available in the source reference. Segments beyond the scope of our paper include industrial standards for postbiotic production, results from trials of metabolites, and a review of available postbiotics on the market.

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CONFLICT OF INTEREST:

Authors have no conflict of interest.

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