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REVIEW



Potential *in vivo* delivery routes of postbiotics

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ABSTRACT

Bioactive micro- and macro-molecules (postbiotics) derived from gut beneficial microbes are among natural chemical compounds with medical significance. Currently, a unique therapeutic strategy has been developed with an emphasis on the small molecular weight biomolecules that are made by the microbiome, which endow the host with several physiological health benefits. A large number of postbiotics have been characterized, which due to their unique pharmacokinetic properties in terms of controllable aspects of the dosage and various delivery routes, could be employed as promising medical tools since they exert both prevention and treatment strategies in the host. Nevertheless, there are still main challenges for the *in vivo* delivery of postbiotics. Currently, scientific literature confirms that targeted delivery systems based on nanoparticles, due to their appealing properties in terms of high biocompatibility, biodegradability, low toxicity, and significant capability to carry both hydrophobic and hydrophilic postbiotics, can be used as a novel and safe strategy for targeted delivery or/and release of postbiotics in various (oral, intradermal, and intravenous) *in vivo* models. The *in vivo* delivery of postbiotics are in their emerging phase and require massive investigation and randomized double-blind clinical trials if they are to be applied extensively as treatment strategies. This manuscript provides an overview of the various postbiotic metabolites derived from the gut beneficial microbes, their potential therapeutic activities, and recent progressions in the drug delivery field, as well as concisely giving an insight on the main *in vivo* delivery routes of postbiotics.

KEYWORDS

Delivery routes; fecal microbial transplant; health benefits; microbiome-based therapies; postbiotic; probiotic

Introduction

The gastrointestinal tract acts as the principal immune organ, comprising approximately 70% of the human body's immune system (Wan et al. 2019). The surface area of the intestine is about 300 to 400 cm², which is covered by masses of living microorganisms. In particular, this surface is colonized by approximately 10¹⁴ bacteria across over 500 species (Hsiao et al. 2008). The gut microbiota significantly assists in numerous biological processes of the human, comprising immunomodulation and neuronal activity, nutritional and metabolic homeostasis (Figure 1) (Cheng et al. 2020). In turn, the host provides an optimal and stable platform for the growth, development, and activity of commensal microorganisms and guarantees a constant inflow of dietary nutrients. Through technological developments such as gnotobiotic models (the use of germ-free or gnotophoric organisms) and genome sequencing (metagenomics), the talent of the gut microbiome has become more apparent in promoting the health status of the host. Over the past decade, the emergence of these tools has enhanced our understanding and knowledge of host-microbiome interactions. Gut microbial imbalances (dysbiosis) in terms of ideal

number, composition, and function have been associated with a wide range of diseases as the molecular etiology. The results of clinical studies demonstrate that some issues such as the mother's gut microbiota composition, the type of birth, nurturing manner during infancy, under-treatment with various antibiotics, xenobiotics, low-fiber diet, chronic disorders, anxiety, and altered host genetics are important factors that can result in loss of microbial diversity and homeostatic function (Muñoz-González et al. 2015; Prato et al. 2019; Rad, Abbasi, Javadi, et al. 2020). Therefore, we will continue to see the goal of modifying the gut microbiome as an effective and accessible method to promote human health in future studies.

On the other hand, the results from recent investigations have demonstrated that some bioactive non-viable substances of gut microbial sources significantly mediating the regulation of host metabolic pathways and health status (Bäuerl et al. 2020; Chuah et al. 2019; Gao et al. 2019). These bioactive substances play a vital role in promoting growth/development, and reproduction of self/other beneficial organisms, communication between the cells, and preservation versus stress factors as they possess unique chemical

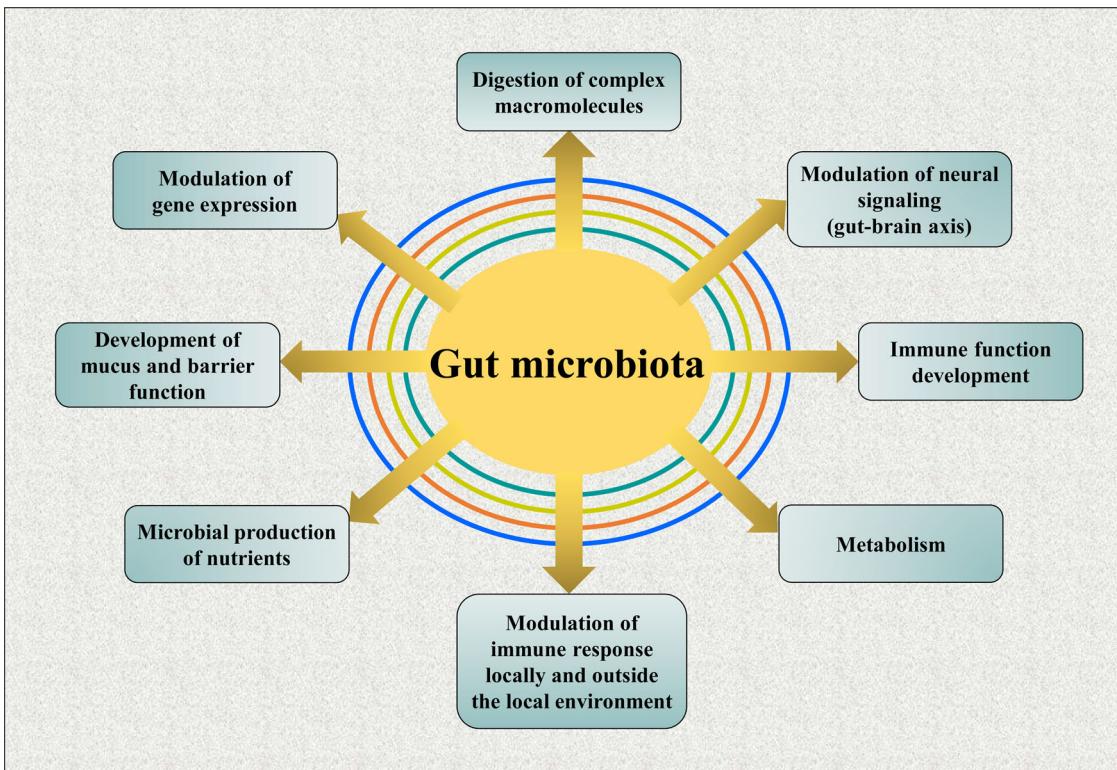


Figure 1. Main functions associated with gut microbiota.

characteristics, which have attracted the researchers to study the genuine potentials of these substances (Braga, Dourado, and Araújo 2016; Netzker et al. 2015; Oleskin and Shenderov 2019). Due to the unique characteristics of bioactive substances in terms of clinical, technological, and economic aspects, their large-scale employment in various fields of the food and pharmaceutical industry, medicine, veterinary, etc. has been studied (Rad, Abbasi, Kafil, et al. 2020). Currently, bioactive substances (postbiotics) derived from gut beneficial microbiome are considered as a new perspective, which can be applied as a promising tool in personalized medicine approach to reestablish gut eubiosis and relieve symptoms in the patient with microbial infections (Abramov et al. 2014; Reynés et al. 2019). Despite the inherent ability of bioactive substances to create positive effects in *in vitro* models, for its *in vivo* use, it is indispensable to design various efficient delivery approaches, which will enable the bioactive substances to cross biological barriers and reach the intended site and perform its therapeutic action. Investigators are always looking to discover new compounds with a natural origin that can use as an alternative to conventional drugs or for adjuvant treatment strategies. Computer-based instrumentation systems that include high-throughput screening (HTS) platforms, high-throughput chemistry, and robotics have created an impressive trend for affordable assessment and screening of an extensive range of bioactive substances. The performance success or failure of bioactive substances can be easily assessed *in vitro*, but their validation can be a major challenge when designing for an *in vivo* study. In *in vivo* investigations, the performance of bioactive substances can merely be determined if the bioactive substances reach their

targeted site of action in the body. Here we can refer to the targeted delivery strategy, which can possess a significant positive effect on the performance of bioactive substances, as a fundamental challenge. Following the discovery of nanoparticles and their acceptance as an effective delivery tool, they have been firstly under examination for their application in promoting targeted delivery systems. It is essential that bioactive substances are efficiently delivered to the target site before getting breakdown by digestive agents in the body. Numerous biodegradable nanoparticles such as lipids, lysosomes, and non-digestible prebiotic constituents are being investigated for their application in targeted delivery systems. Hence, this manuscript provides an overview of the various postbiotic metabolites derived from the gut beneficial microbes, their potential therapeutic activities, and recent progressions in the drug delivery field, as well as concisely giving an insight on the main *in vivo* delivery routes of postbiotics.

Gut microbiome-based therapies

In recent decades, due to the extensive functions, the gut microbiome possesses in various intra- and extra-gastrointestinal disorders, it has become a formidable tool for potential therapeutic strategies (Thaiss and Elinav 2017). Nevertheless, one of the major challenges in microbiome investigation is to specify the cause and effect associations and to design novel microbiome-based therapeutic strategies that are capable of conferring foreseeable effects on the gut microbial population and host's health status. The present microbiome-based therapeutic strategies target the gut microbiome by modifying the microbial composition

through the exogenous intake of living beneficial microbes. These approaches, communally denote probiotics. From the perspective of “therapeutic microbiology,” a probiotic strategy can signify an alternative therapy for an extensive variety of intra- and extra-gastrointestinal disorders, which have become increasingly popular in the last decade (Abbasi et al. 2020; Bozzi Cionci et al. 2018). However, notwithstanding the confirmed health-promoting benefits of living probiotic cells, no evidence from long-term clinical trials exists stating that intaking the products of probiotics is capable of promoting the health status in individuals who were formerly healthy (Cohen 2018). Besides the safety and efficacy issues regarding the consumption of probiotics in vulnerable and pediatric patients are still a matter of debate (Kothari, Patel, and Kim 2019; Rad, Aghebati-Maleki, et al. 2020). In this regard, some experts in this field believe that strengthening each individual’s probiotics can be more effective than getting new ones (Rad, Akbarzadeh, and Mehrabany 2012; Rad, Maleki, et al. 2020). One substitute approach to living probiotic cells is using the prebiotics. Prebiotics are characterized as non-digestible elements (oligofructose, oligosaccharides, inulin, raffinose, and stachyose) that are not affected by host digestive enzymes. Nonetheless, they are fermented via endogenous colonized probiotics in the large colon, stimulating the growth and development of beneficial microbiota and thus improving the health status of the host. The gut microbial ecosystem of each person pertains to several factors, such as the daily diet (nutritional pattern) and environmental factors that are specific to each individual. The gut ecosystem diversity has been described to differ by area, which is not at all unconventional. Thus, it seems reasonable to reinforce the endogenous probiotics of each host through feeding these bioactive substances, prebiotics, instead of introducing unfamiliar and non-native strains to the gut ecosystem by an extensive range of food supplements or pharmaceutical products (Cummings, Macfarlane, and Englyst 2001; Gibson and Roberfroid 1995; Karimi et al. 2020). However, it seems that prebiotics are a comparatively unspecific approach to microbiome-based investigations, and additional studies are required to completely describe the precise effects of prebiotics on various gut bacterial species.

Presently, an efficacious FDA-approved experimental therapy and the microbiome-based investigation is the fecal microbiota transplantation (FMT). FMT (stool transplant) is an infusion into the intestinal tract, or the intake of a homogenous liquid solution of fecal matter from a donor with an appropriate health status to a receiver with a characterized unhealthy gut microbiome-related disease (Carlson 2020). This microbiome-based therapy (FMT) has been shown to possess noteworthy efficiency in treating the infection mediated by *Clostridium difficile*, which most frequently occurs after antibiotic treatment (Quraishi et al. 2017). In this regard, a prospective cohort study by Ianiro et al. (2019) established that the individuals with *Clostridium difficile* infection (as the main risk factor for bloodstream infections [BSIs]) treated with FMT had a lower risk of BSI, fewer days of therapy in the hospital, and an added increase in

general survival rate in comparison with those treated with conventional antibiotics (Ianiro et al. 2019). The use of FMT for other disease statuses, such as inflammatory bowel disease (ulcerative colitis and, to some extent, Crohn’s disease), irritable bowel syndrome, and metabolic syndrome (insulin resistance) is currently being evaluated (Singh et al. 2014). However, in some cases, FMTs can be related to significant health threats for the receiver, such as the involuntary transplantation of pathogens/pathobionts, undesirable communications with the receiver’s gut microbial community, and the theoretically limited long-term maintenance of a foreign microbial configuration when introduced into a new host that harbors a unique nutritional milieu, metabolic, immune, and genetic (Alang and Kelly 2015; Moayyedi et al. 2015). Due to the extensive variability of the gut microbial community between persons and the confined long-dated sustainability of an extraneous microbial configuration, opportunities for comprehending the contribution of the gut microbiomes to the host’s health status are abundant through novel substitute approaches that are based on precise mechanisms (Wong and Levy 2019).

On the other hand, our current understanding of host-microbiome communications at the cellular/molecular levels has been developing from descriptive investigations toward ones aiming for mechanistic deciphering of the molecular nature of these relationships. A fundamental view that can be inferred from the interpretation of the results of these studies is that many of these interactions are carried out by various biomolecules (postbiotics), which are typically secreted, degraded, or adapted by the intestinal microbiome/host, thus establishing a strong network of signaling pathways that affect the host, microbiome, and inter-dependent functions. This view has led to the development of a microbiome-based therapeutic approach and involves the administration of microbiome-derived biomolecules. The microbiome-derived biomolecules therapy is aimed at influencing their downstream signaling pathways that are associated with the pathogenesis of the disease while prevailing the requirement of transplanting a whole or limited microbial population (by FMT or probiotic supplements) (Fattah, Heidari, and Khosroushahi 2020; Saadat et al. 2020; Wong and Levy 2019). Therefore, microbiome-derived biomolecules therapy may work straightly on host pathways that have been injured via microbial function; alternatively, the biomolecules’ influences on the host may modify the pathways that provide the development of pathogenic germs, hence assisting a change toward eubiosis conditions; or the therapy may synergistically induce both pathways. Besides, while a compositional investigation of the gut microbiome as a means of recognizing useful commensals or pathobionts is infrequently obtainable on a strain level specificity, intaking biomolecules rather than the live cells may facilitate to prevail this challenge with targeting downstream of the microorganisms, thereby overcoming interindividual strain-level variations in gut microbiome configuration (Plovier et al. 2017). Consequently, microbiome-derived postbiotics therapy may serve as a novel/an alternative approach to probiotic/FMT interventions, which has created many

opportunities to investigate the discovery of new postbiotics, assessment of their safe profiles, and precise mechanism of action as well as for their application in the prevention and control of a wide range of diseases.

Postbiotic-based therapeutics

Preclinical and clinical studies over the past decade have discovered that the gut microbial community represents much of its customary function on host physiology through the production of metabolites with low molecular weight (<50, 50–100, and 100< kDa) that regulate cellular processes (e.g., Anti-inflammatory, Anti-proliferative, Antimicrobial, Immunomodulation) and metabolic pathways (e.g., Anti-hypertensive, Anti-obesogenic, Hypocholesterolemic, Hepatoprotective) (Rad, Abbasi, Kafil, et al. 2020; Rad, Aghebati-Maleki, et al. 2020). These biomolecules work as novel effective tools for the promotion of growth, development, and reproduction of beneficial organisms of the gut, preservation when encountering stress factors, and communication between the cells (microbe-microbe or/and microbe-host interactions) (Netzker et al. 2015). Description of such low molecular weight metabolites has been performed by terms including “abiotic,” “biogenic,” “metabiotic,” “ghost probiotics,” “pseudoprobiotic,” and “postbiotic.” The most employed term in the literature, however, is “postbiotic” (de Almada et al. 2016; Homayouni Rad, Aghebati Maleki, Samadi Kafil, and Abbasi 2020; Rad, Maleki, et al. 2020). In gut dysbiosis conditions the dominant microbial community of intestines alters in favor of pathogenic germs, which not only secrete health-threatening metabolites (e.g., toxins) when they grow and occupy the surface of intestinal epithelial cells but also take away the opportunity to survive from the beneficial microbes, ultimately resulting in undesirable effects on host’s health status (Bajaj et al. 2014; Yasukawa et al. 2019; Homayouni Rad, Aghebati Maleki, Samadi Kafil, and Abbasi 2020). In this regard, from the perspective of “postbiotic-based therapeutics,” consuming postbiotic-based pharmaceutical or/and food products initially decelerates and halts the growth of pathogenic germs and successively decreases the secretion of health-threatening metabolites (cure gut dysbiosis) (Pérez-Sánchez et al. 2020; Rad, Aghebati-Maleki, et al. 2020). Also, postbiotics influence operation and downstream signaling pathways of the gut microbiome via alleviating the undesirable effects of a surplus, paucity, or imbalance of metabolites with the contribution to these pathways, as well as interacting with the eukaryotic cells of the host, modulating immune system’s function, and activating the related signaling pathways for the induction of gastrointestinal homeostasis (Cicenia et al. 2016; Dadi et al. 2020) (Figure 2).

Some main examples of potential postbiotic-based therapies that have been discovered in *in vitro* and *in vivo* models include short-chain fatty acids (SCFAs), which have been revealed to have significant anti-inflammatory properties and change in inflammatory bowel disease (IBD) patients (Butzner et al. 1996; Macia et al. 2015; Scheppach and Group 1996); exopolysaccharide, which exerts anticancer effects through inducing apoptosis by increasing the level of

the expression of Caspase-9, Bax, and Caspase-3, and reducing the level of the expression of Survivin and Bcl-2 (Tukmenmez et al. 2019); bacteriocin, which exerts significant anti-bacterial, anti-fungal and anti-viral (e.g., SARS coronavirus [COVID-19]) activities (Anwar et al. 2020; Juturu and Wu 2018); flavonoid compounds which are involved in therapies for metabolic diseases (Thaiss, Itav, et al. 2016); and the lipoteichoic acid (LTA), which is capable of modulating the immune functions that are mediated by cytokines and is a potential tool to preserve the homeostasis of the gut against extreme inflammation. *Lactobacillus plantarum*-derived LTA postbiotics downregulate TNF- α -driven transcription of the inflammatory cytokines under *in vitro* conditions (HT-29 cells) through a TLR-2-associated mechanism, leading to the inhibition of the signaling pathways of mitogen-activated protein kinase and NF- κ B (Kim et al. 2012) (Table 1).

A noteworthy number of scientific reports have been published in the literature on the confirmation of the health effects related to the intake of pharmaceutic or/and functional food products (Burta et al. 2018; Taverniti and Guglielmetti 2011; Vandenplas et al. 2017). In recent years, postbiotic-based therapies due to their unique features with regards to performance, safety, and economic aspects have gained much interest from researchers (Rad, Aghebati-Maleki, et al. 2020). These low molecular weight biomolecules are physiologically plentiful at high density, thus possessing low potential toxicity (Dinić et al. 2017; Homayouni Rad et al. 2021). Another important feature of postbiotics is the controllability of their dosage and the different routes of administration that follow the principles of pharmacokinetics. Furthermore, postbiotics prevail in most parts of the body and are therefore appropriate for various routes of administration. Besides, postbiotics usually maintain original structures (possess high stability) in the host’ systemic circulation, and are therefore amenable for a scalable regulation of their concentration (Mohanta et al. 2020; Wong and Levy 2019). Presently scientific literature confirms that the postbiotic components could be employed as potential tools aimed at both prevention and treatment in intra- and extra-gastrointestinal disorders. However, it is sensible to presume that intaking such microbial metabolites may not always be satisfactory in treating microbiome-related infections, with several challenges deserving consideration. In this regard, some of the fundamental challenges include: (a) the microbiome may not be ineffective to the supplemented postbiotics, (b) unanticipated interactions of these biomolecules with members of the gut microbiome may induce dysbiosis or the biochemical alteration of the biomolecules via the commensal to an inactive or even poisonous form, (c) modifying the quantity of a biomolecule in the gut may also alter the equilibrium of a feedback loop, thereby disrupting the adjusted generation of the biomolecules, (d) and chronic exposure to a given biomolecule may improve resistance programs of the microbiome/host to change the therapeutic target to these biomolecules (Moradi, Mardani, and Tajik 2019; Rad, Aghebati-Maleki, et al. 2020; Russo et al. 2019; Zakuhan, Ling, and Yazan 2019). Despite the considerable progress in the field, additional researches should be conducted for the full comprehension of how postbiotics could be employed as

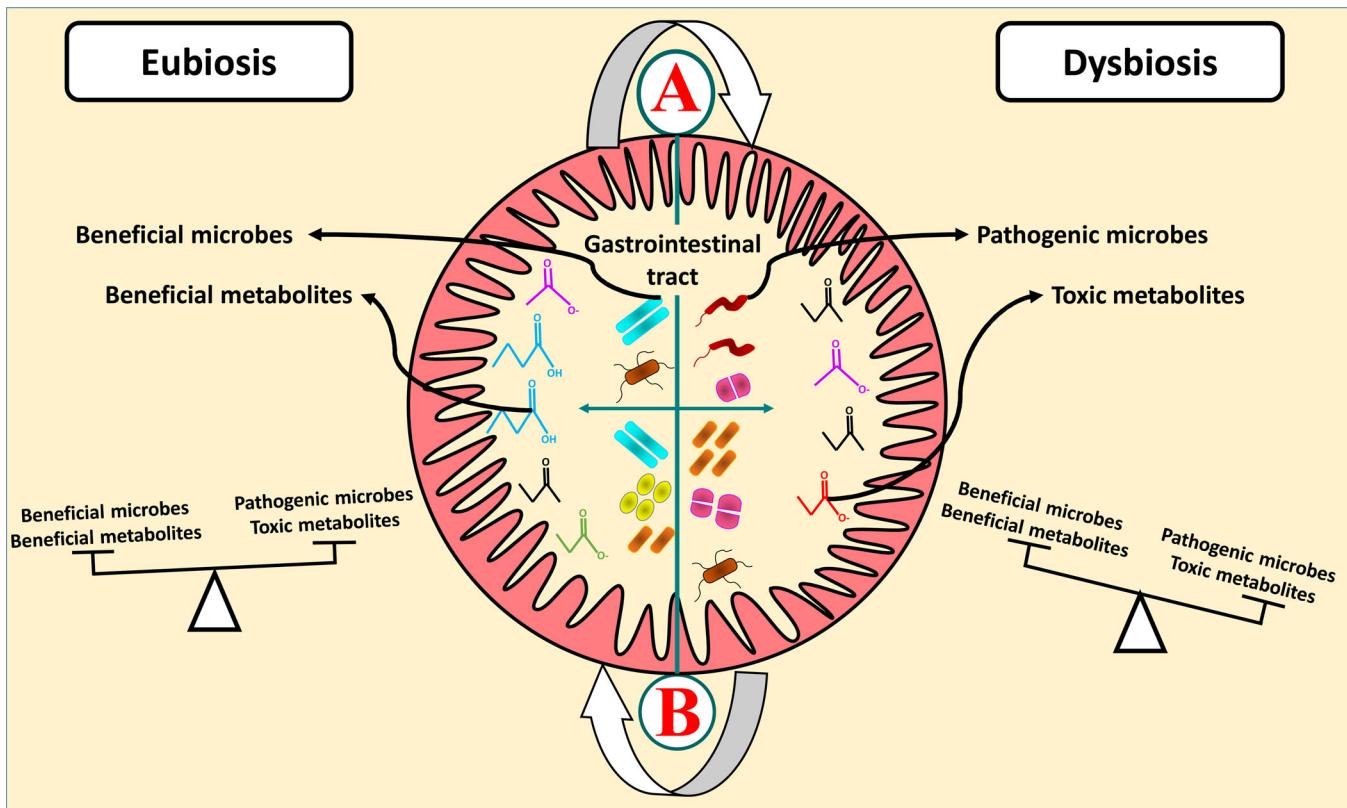


Figure 2. Postbiotic-based therapeutics. Under homeostatic conditions, the intestinal microbiota secrete small molecular weight metabolites that play a vital role in promoting growth, development, and reproduction of self/other gut beneficial organisms, and serve as an effective means of communication in host-microbe interactions as well as hugely affecting the host's health status. (A) Some issues such as the mother's gut microbiota composition, the type of birth, nurturing manner during infancy, under-treatment with various antibiotics, low-fiber diet, chronic disorders, and anxiety are important factors that can influence the balance of microbiota in the gut. In dysbiosis conditions, the presence of pathogenic microbes and their toxic metabolites reduces the population of beneficial microbes and decreases the immune function, making the host susceptible to a variety of infectious and noninfectious diseases. (B) Postbiotic-based therapeutics, is one of the main approaches which target downstream signaling pathways and operation of the gut microbiome via alleviating the undesirable effects of the surplus, paucity, or imbalance of metabolites contributed to these pathways. As well, the exogenous intake of postbiotics has the potential to be an effective therapy in the treatment of gut dysbiosis and the establishment of eubiosis conditions, as well as in the activation of relevant signaling pathways which are directly associated with the establishment of gastrointestinal homeostasis.

adjunct therapies for either preventing or treating various diseases in humans, as well as understanding potential side-effects of postbiotics (Aguilar-Toalá et al. 2018; Homayouni Rad, Aghebati Maleki, Samadi Kafil, and Abbasi 2020).

On the other hand, detecting low quantities of a given biomolecule in a fecal sample exhibits few of its physiological levels at an upstream biogeographical region in which it shows its vital role. Hence, it is vital to confirm that a biomolecule supplemented orally can transfer to its site of action while not being affected in more proximal regions of the gastrointestinal tract by digestive processes (especially in cases in which biomolecules are systemically bioactive) (Ahmadian et al. 2020; Kumar Giri et al. 2016; Thaiss, Levy, et al. 2016). A body of evidence corroborates that the targeted delivery systems significantly participate in the high therapeutic performance of bioactive biomolecules (Dima et al. 2020b; Lalzawmliana et al. 2020).

In vivo delivery of postbiotics

Although microbial-derived biomolecules are famous for their remedial characteristics, it is indispensable to design and develop effectual *in vivo* approaches that facilitate the delivery of biomolecules for reaching their specified tissue

and accomplishing their beneficial action in the host's body (Braga, Dourado, and Araújo 2016). The *in vivo* delivery of biomolecules principally pertains to their specific molecular mechanism in addition to their target site within the body of the host. For example, in diabetes patients, delivering the conventional anti-diabetic medications could be performed intravenously or/and straightly to the target site (pancreatic tissue) for realizing high performance inside the body. Two parameters that fundamentally characterize the bioavailability and the bio-accessibility of a bioactive molecule include its aqueous solubility and membrane permeability within the host. In this regard, a Biopharmaceutics Classification System (BCS) has been created by the United States Pharmacopeia (USP), according to which there exist four groups of therapeutics categorized based on membrane permeability and aqueous solubility (Cardot et al. 2016). Among the principal targets of BCS exists the anticipation of the *in vivo* efficiency of a therapeutic compound through the *in vitro* investigation of aqueous solubility and membrane permeability (Mehta et al. 2017; Mohanta et al. 2020).

The ideal performance of a therapeutic compound could be obtained by impressively delivering it into the host. On the other hand, the bioavailability of such therapeutics could be improved through selecting the targeted delivery systems.

Table 1. Postbiotic metabolites isolated from probiotics and their bioactivity and/or health benefits.

Probiotic strain	Inactivation method	Derived postbiotic	Bioactivity/health benefits	References
<i>L. rhamnosus</i> HN001	UV ^a	Indeterminate	Significant reduction in symptoms of the necrotizing enterocolitis in premature piglets and newborn mice Immunomodulatory activity	Good et al. (2014) Sokol et al. (2008)
<i>L. paracasei</i> , <i>L. reuteri</i> , <i>L. casei</i> , <i>L. plantarum</i>	Indeterminate	Inactivated cell		
<i>L. rhamnosus</i> GG	Indeterminate	Cell-free supernatant	Anti-inflammatory	Cicenia et al. (2016)
<i>L. bulgaricus</i> , <i>S. thermophilus</i> , <i>L. acidophilus</i>	TT ^b 65 °C for 60 min	Indeterminate	Protective role in proinflammatory cytokine-induced intestinal epithelial barrier dysfunction	Zeng et al. (2016)
<i>L. rhamnosus</i> MD	Indeterminate	Cell-free supernatant	↓ Cell proliferation	Sharma, Chandel, and Shukla (2019)
<i>L. amylovorus</i> CP1563 <i>Faecalibacterium prausnitzii</i> A2–165	Indeterminate Indeterminate	Fragmented cells Cell-free supernatant, Extracellular vesicles	Antibesogenic Up-regulate anti-inflammatory cytokines (IL-10, TGF-β2, and IL-1Ra) and down-regulate some of the important pro-inflammatory cytokines such as IL-6, TNF-α and TNF-β	Nakamura et al. (2016) Jafari et al. (2019)
<i>B. pumilus</i> SES	Indeterminate	Indeterminate	Inhibition the colonization of pathogenic bacteria	Wang et al. (2020)
<i>B. amyloliquefaciens</i> FPTB16 and <i>B. subtilis</i> FPTB13	TT ^b 60 °C for 2 h	Indeterminate	Stimulation of cellular immune responses	Kamilya et al. (2015)
<i>L. plantarum</i> sp <i>Penicillium</i> sp. <i>Garcinia nobilis</i>	Indeterminate Indeterminate	Cell-free supernatant Penialidin A-C, citromycetin, P-	↑ Apoptosis rate	Chuah et al. (2019)
hydroxyphenylglyoxalaldoxime and brefeldin A	Anticancerous activity against HeLa cells	Jouda et al. (2016)		
<i>Lactobacillus rhamnosus</i> MD	Indeterminate	Cell-free supernatant	↓ Cell proliferation	Sharma, Chandel, and Shukla (2020)
<i>B. pumilus</i> SES	TT ^b 95 °C for 60 min	Inactivated cells	Suppression of pathogenic bacterial species in fish intestinal microbiota	Yang et al. (2014)
<i>Clostridium butyricum</i> sp	Indeterminate	Short-chain fatty acid	Suppresses the Wnt/β-catenin signaling pathway and modulate the gut microbiota composition	Chen et al. (2020)
<i>L. fermentum</i> BGHV110 <i>Lactobacillus johnsonii</i>	Indeterminate Indeterminate	Cell-lysate suspension Inactivated cell	Hepatoprotective Inhibition of the colonization of <i>Helicobacter pylori</i>	Dinić et al. (2017) Aiba et al. (2017)
<i>Aaptos</i> sp	Indeterminate	Aaptamine	Trigger apoptosis in a monocytic leukemia cell line (THP-1)	Dyshlovoy et al. (2014)
<i>L. fermentum</i> VET9A, <i>L. plantarum</i> VET14A, and <i>L. rhamnosus</i> VET16A	TT ^b 80 °C for 30 min	Inactivated cells	Exclusion of enteropathogens (<i>E. canis</i> , <i>Salmonella enterica</i> serovar <i>Typhimurium</i> and <i>Clostridium perfringens</i>) in dogs' intestinal mucus	Grześkowiak et al. (2014)
<i>Lactobacillus rhamnosus</i> SHA111, SHA12, and SHA13	Indeterminate	Cell-free supernatant	Induction of apoptosis by up-regulation of BAD, BAX, Caspase-3, Caspase-8, Caspase-9, and down-regulation of BCL-2 genes	Riaz Rajoka et al. (2019)

↓ Decrease; ↑ Increase. ^a Ultraviolet rays; ^b Thermal treatments.

Based on the fact that most of the therapeutic biomolecules are more unstable chemical components in comparison with synthetic chemicals, it is vital to carry the therapeutic biomolecules to the treatment site until it is broken down throughout the pharmacokinetics' pathways (Cai et al. 2013; Yoshioka and Ochiya 2019). In recent years, researchers have utilized various drug delivery systems (e.g., nanoparticle encapsulation) for improving the effectiveness of these

therapeutic biomolecules. High performance and safety (lower potential cellular toxicity) are important factors, which must be considered in selecting the best delivery systems for therapeutic biomolecules. In this regard, lipid-based nanoparticles are efficaciously applied for delivering biomolecules *in vivo*, since they possess an appropriate safety profile in comparison with other categories of carbon nanotubes and metallic nanoparticles (Chuang et al. 2018;

Khan, Saeed, and Khan 2019). The three most frequently applied *in vivo* delivery approaches for biomolecules include: oral, intradermal, and intravenous.

Oral delivery

Between the different ways of administration that have been performed with a differing level of success is the buccal (Sayani and Chien 1996), ocular (Lee and Yalkowsky 1999), intranasal (Maggio 2006), inhalational (O'Hagan and Illum 1990), oral, vaginal (Hussain and Ahsan 2005), rectal (Mackay, Phillips, and Hastewell 1997), and transcutaneous (Banga and Chien 1993). Amid all these ways, the oral way is the most appropriate option for the administration of therapeutic agents (Shaji and Patole 2008). The oral way has some well-known superiority include: (a) improved patient acquiescence, (b) appropriateness for frequentative administration of the therapeutic agent, (c) low cost of treatment, (d) and potential to stimulate a mucosal antibody reaction (Table 2). The low bioavailability of several therapeutic biomolecules is a significant impediment for expanding the oral dosage of biomolecules (Lin et al. 2017). Besides, the poor chemical stability properties of biomolecules under digestive system circumstances prevent the general performances of the biomolecules and reduce their bioavailability in host plasma concentrations. On the subject of therapeutic biomolecules (such as postbiotic compounds), the main issue for expanding the oral dosage is maintaining their activity during storage, transport, and upon administration as well as assuring the fact that they must be sufficient to circumvent the intestinal first-pass metabolism and achieve their site of action (Dai et al. 2019). On the other hand, the systemic expansion of some biomolecules, however, may be correlated with toxicity and some unfavorable effects, including hypersensitivity responses and immunogenic reactions like antibodies against the biomolecules resulting in augmented clearance and the loss of performance (Maurer et al. 2016). A large part of the unfavorable effects linked to systemic expansion may be overcome through targeted biomolecules delivery to their active sites. Main advantages associated with local biomolecules delivery, by oral treatment, include: (a) reducing the incidence of unwanted systemic effects, (b) delivering the biomolecules directly to the site where it is needed, (c) requiring smaller doses, (d) high local concentration of the biomolecules in their active sites, (e) preventing the degradation by chemical and enzymatic agents in the stomach and small intestine, (f) enhancing the intestinal permeation, (g) and reducing the formation of complexes with other metabolites in the gut, which significantly intervenes

with their beneficial functions (Lautenschläger et al. 2014; Pattni and Torchilin 2015). Among various delivery systems, nanocarriers possess a noteworthy capability in preserving the therapeutic biomolecules to outstrip different metabolic degradation pathways, which in turn leads to enhancing the bioavailability of the therapeutic biomolecules (Dima et al. 2020a). The two vital parameters that significantly regulate the bioavailability of a therapeutic biomolecule are aqueous solubility and membrane permeability. Therefore, these parameters possess a substantial part in the development of oral therapeutic biomolecule's formulations.

As stated earlier, the therapeutic compounds/biomolecules are categorized under various classes by the BCS classification, where the admixture of aqueous solubility and membrane permeability parameters of the therapeutic compounds is actually considered. Various classes of pharmaceutical compounds/biomolecules in BCS classification are revealed in Figure 3 (Baki et al. 2015). In the BCS classification, the class I category encompasses therapeutics that are described by great aqueous solubility and membrane permeability. Also, the therapeutics in this category not only possess a higher bioavailability but also fundamentally a carrier system is not necessitated by them. Nevertheless, challenges such as poor chemical stability or/and undesirable solubility, especially in food systems, highlight the importance of using encapsulation for achieving the high performance of these compounds. The therapeutic compounds of the class II category possess low aqueous solubility while having high membrane permeability. Such therapeutics naturally possess lipophilic behavior, therefore, among various delivery systems, lipid-based nanocarriers (due to their inherent characteristics in increasing the solubility and safety profile) are

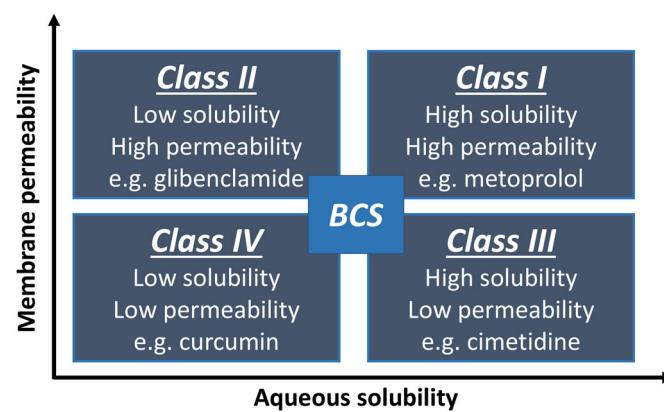


Figure 3. Biopharmaceutics classification system (BCS). This system differentiates therapeutic compounds on the basis of their aqueous solubility and membrane permeability.

Table 2. Some benefits associated with oral over intravenous delivery of therapeutic agents (postbiotics).

Factor	Oral delivery	Intravenous delivery
Patient acquiescence	High	Low
Safe profile	Safe most of the time	Probability of infection (for instance hepatitis B, and HIV, due to the contaminated needles)
Characteristics of administration	Self-administration, noninvasive	Medical support is indispensable, invasive
lymphatic absorption mechanism	Intestinal lymphatic uptake provides a systemic circulation with bypass the hepatic first-pass metabolism for lipid-based postbiotics	Not possible
Site of action	Local and systemic	Systemic

the most appropriate delivery systems that can be applied to promote the total bio-accessibility and bioavailability of the therapeutic compounds (Dolatabadi and Omidi 2016). The therapeutic compounds of the class III category have adequate aqueous solubility in the digestive system circumstances, despite having moderately lower membrane permeability. Under such circumstances, the ingredients of nanocarriers with mucoadhesive attributes may assist in enhancing the bioavailability via augmenting the time of the communication of the therapeutic and the gut epithelial cells. The inauguration of the intestinal tight junctions helps to disseminate the therapeutics, which will simplify increasing the effectiveness of the therapeutic compound. Amid BCS classes, the therapeutics of the class IV category is the most challenging, since they suffer low aqueous solubility and membrane permeability (e.g., aluminum hydroxide or/and curcumin). This category of therapeutic compounds necessitates an appropriate carrier (for example carriers that are in lipid phase or/and rich in surfactants) as well as a mucoadhesive compound (e.g., chitosan), which could significantly promote the aqueous solubility properties and the

communication time with the gut epithelial cells, respectively. In this regard, the capability to deliver a therapeutic agent (e.g., postbiotics) to the gut pertains to the communications between the mechanism of the delivery technology and pH, transit time, and gut microbiome as almost all the delivery systems depend to some extent on one or more of these parameters to drive release locally. In some gastrointestinal disorders (e.g., IBD), these characteristics are often modified and thus it is challenging to develop delivery tools that guarantee precise delivery to the colon. In this section, the most potent strategies for colonic delivery of postbiotics will be discussed (Figure 4 and Table 3).

pH-dependent delivery strategy

In a healthy person, the pH of the stomach is between 1 and 4, which increases to 6 and 7.4 in the proximal small intestine and the distal small intestine, respectively. Between the ileum and the colon, the pH decreases and then rises regularly throughout the colon (Evans et al. 1988). The mentioned polymers are typically insoluble at low pH values

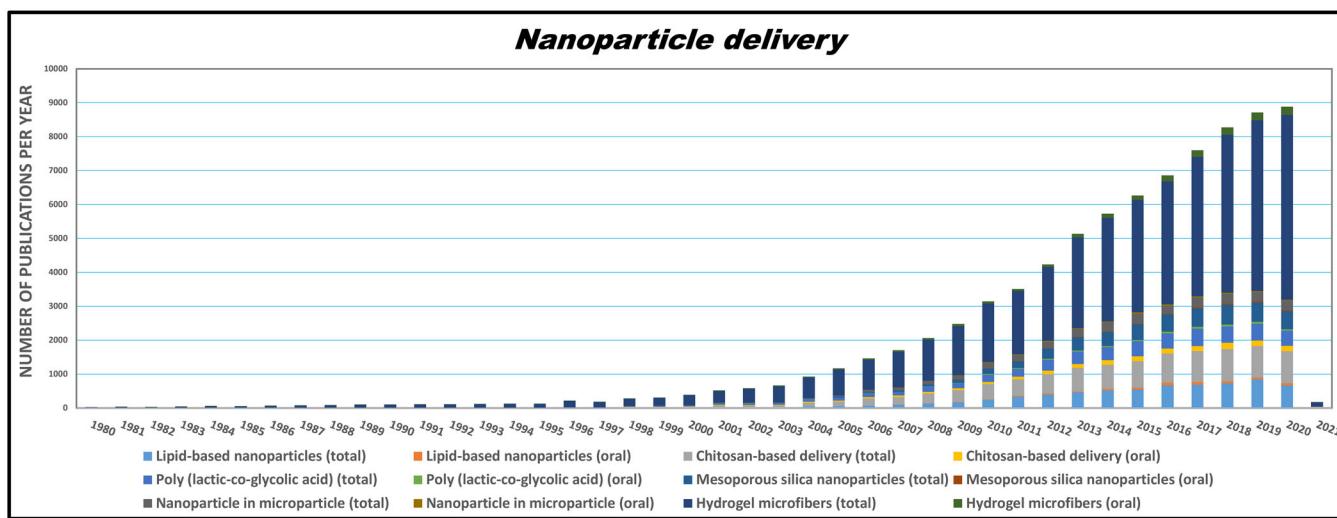
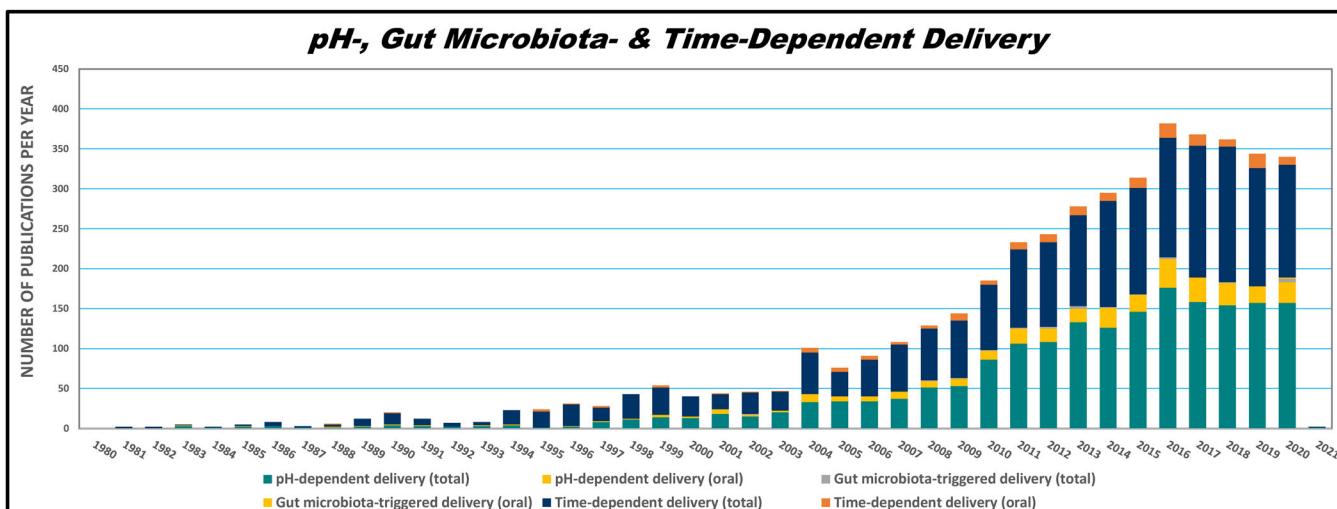


Figure 4. Illustrates the increase in the number of papers reporting the efficacy of pH-, gut-microbiota triggered-, and time-dependent delivery as well as various nanoparticle-based delivery systems. Comparison between the number of publications with a focus on the pH-, gut-microbiota triggered-, and time-dependent delivery as well as various nanoparticle-based delivery systems in PubMed December 2020.

Table 3. Potential strategies for colonic delivery of postbiotics.

Category	Delivery system/technology	Typical type	Characteristic(s)/mechanism(s)	References
pH-dependent delivery	Methacrylic-acid based polymers (Eudragit)	Eudragit L, Eudragit S, and Eudragit FS	Eudragit-polymers are the most frequently utilized pH-sensitive polymers; Eudragit L (soluble at pH $\geq 5.5-6$) and Eudragit S (soluble at pH ≥ 7) and Eudragit FS (soluble at pH ≥ 7) have been commonly used alone or in combination for an optimized dissolution rate coating	Balogh et al. (2017); Khan, Prebeg, and Kurjaković (1999); Thakral, Thakral, and Majumdar (2013)
	Hydroxypropyl methylcellulose acetate succinate (HPMC-AS)	L HPMC-AS, H HPMC-AS, and M HPMC-AS	An enteric coating substance designed for both the conventional enteric coating and continued release formulations; type L HPMC-AS describes polymer with a high ratio of succinoyl substitution to acetyl substitution (S/A ratio), while type H with a low S/A ratio and type M with a medium S/A ratio. With a high S/A ratio, type L HPMC-AS dissolves at a lower pH (≥ 5.5), compared with pH ≥ 6.0 for type M and pH ≥ 6.8 for type H	Pugliese et al. (2020)
	Cellulose acetate phthalate (CAP)		CAP, also known as cellulose acetate phthalate, is a generally utilized polymer phthalate in the formulation of therapeutic agents, such as the enteric coating of tablets or capsules, and for regulated release formulations	Indumathi, Sarojini, and Rajarajeswari (2019)
	ColoPulse		ColoPulse technology is a typical instance of a pH-dependent system, but it comprises of additional swelling disintegrant (croscarmellose sodium) in the coating or in the matrix resulting in faster and more pulsatile release process than other pH-dependent systems	Schellekens et al. (2012)
	Vcaps Enteric, enTRinsic capsules		Vcaps Enteric and enTRinsic capsules by Capsugel are intrinsically enteric capsules that offer enteric protection and delayed-release in the gastrointestinal tract without using a functional coating; the capsules consist of a blend of pH-sensitive polymers, like HPMC and HPMC-AS	Sager et al. (2019)
Gut microbiota-triggered delivery	COLAL		COLAL coating system composes of ethylcellulose and a particular form of amylose (derived from starch) called "glassy amylose"; glassy amylose is not digested by human amylase enzyme in the gastrointestinal tract but is digested by gut microbial enzymes; the inclusion of ethylcellulose is essential to control swelling in order to inhibit early release process	Lancuški et al. (2017)

(continued)

Table 3. Continued.

Category	Delivery system/technology	Typical type	Characteristic(s)/mechanism(s)	References
	Phloral		Phloral technology offers a hybrid pH and gut microbiota-triggered delivery method; the dosage form is coated with a mixture of Eudragit S, amylose, and ethylcellulose	Basit and Ibekwe (2019); Kotla et al. (2019)
	COlon-targeted Delivery System (CODES)		CODES employs a mixture of pH-sensitive and microbiota-triggered mechanisms; the core contains the therapeutic agent together with the disaccharide lactulose and is coated with a layer of acid-soluble Eudragit E (soluble at pH ≤ 5), which is overcoated with a layer of enteric Eudragit L; the outer layer dissolves in the small intestine exposing the inner acid-soluble coating; gut microbiota in the colon digest the lactulose generating organic acids causing pH decrease surrounding the tablet, which leads to the dissolution of Eudragit E leading to the release of the therapeutic agent	Katsuma et al. (2002); Singh et al. (2018)
TARGIT			An enteric-coated injection-molded starch capsule system developed for aiming at specific positions within the colonic area through a mixture of sequential pH and gut microbiota-dependent release; the coating contains a combination of pH-sensitive polymers, selected to offer a coating that starts dissolving in the small intestine; the choice and thickness of the coating polymers determine the position of release within the gastrointestinal system; degradation of starch capsule body is by the colonic microbiota; the utilize of a coated capsule as the targeting mechanism is extremely attractive as the therapeutic agent formulation does not affect the dissolution of the TARGIT coating and then its Vivo function should remain unaffected	Desai et al. (2018); Watts and Smith (2005)
Time-dependent delivery	ChronoCap		A time-dependent delivery method in which a therapeutic agent comprising of solid dosage core that coated with a hydrophobic surfactant inner layer and a water-soluble adhesion coat; the inner layer begins to decay after the water-soluble coating dissolved; the timing of the release process can be affected by	Briatico-Vangosa et al. (2019); Zema et al. (2013)

(continued)

**Table 3.** Continued.

Category	Delivery system/technology	Typical type	Characteristic(s)/mechanism(s)	References
	Pulsincap		the thickness of the hydrophobic layer Pulsincap comprises a non-decomposing capsule body including the therapeutic agent, a hydrogel plug that seals the opened end of this capsule body, and an enteric-coated cap that covers the hydrogel plug; the hydrogel plug starts swelling when the enteric-coated cap dissolves in the small intestine; the swelling is accountable for the lag time before the active ingredient gets released, and it is dependent on the length of the hydrogel plug	Jain et al. (2011); Sekhar (2019)
	Multimatrix (MMX)		MMX technology affords a regulated and uniform release process between the entire gut; the outer layer of the dosage form comprises of a pH-dependent layer that preserves the core until it arrives in the intestines, wherever the planned dissolution starts; the core comprises a hydrophilic and an inert polymer matrix; the inert matrix catches the therapeutic agent and the excipients in a web of an amphiphilic polymeric material; the amphiphilic element enhances the solubility of the therapeutic agent and the relaxation of the hydrophilic material resulting in swelling, which decreases the release of the therapeutic agent; this mechanism occurs in a homogenous and extended exposure of the whole gut mucosa to the enclosed therapeutic agent	Bezzio et al. (2018); Fiorino et al. (2010); Nardelli et al. (2017)
Nanoparticle delivery	Lipid-based nanoparticles	Solid lipid nanoparticle, liposomes, and bilosomes	Lipid-based nanoparticles possess attractive features for gut delivery such as general biocompatibility, biodegradability, and the ability to carry both hydrophobic and hydrophilic therapeutic agents	Fonseca-Gomes et al. (2020)
	Chitosan		A typical linear polycationic polysaccharide is achieving with incomplete deacetylation of chitin. Chitosan exhibits attractive characteristics such as biodegradability, biocompatibility, and mucoadhesion, and it has been used to develop several colon-targeting delivery systems for some gastrointestinal disorders such as colon cancer and inflammatory bowel disease	Dar et al. (2017); Kumar and Newton (2017)

(continued)

Table 3. Continued.

Category	Delivery system/technology	Typical type	Characteristic(s)/mechanism(s)	References
	Poly (lactic-co-glycolic acid) (PLGA)		A biodegradable and FDA accepted polymer that has been designed as nanoparticles toward gastrointestinal disorder (inflammatory bowel disease) treatment; although the outcomes of animal and human investigations did not entirely overlap, it has been made clear that nanoparticle size can alone be utilized to selectively target the inflamed mucosa; moreover particle size, the surface charge is another key factor in the communication with the mucus layer and epithelial cells: inflamed tissues comprise of high concentrations of positively charged proteins which can attract anionic PLGA	Ali et al. (2016); Naeem et al. (2018)
	Mesoporous silica nanoparticles (MSNs)	MCM-41 and SBA-15	MSNs are valuable methods for the targeted release process given their biocompatibility, motionless, chemical consistency, and the opportunity of developing gated systems capable to release the incorporated therapeutic agent only upon the presence of a specific irritant (e.g., the presence of redox molecules, antigens, anions, enzymes, and oligonucleotides)	Giménez et al. (2015); González-Alvarez et al. (2017)
	Nanoparticle-in-microparticle oral delivery system (NiMOS)		NiMOS is a novel colon-targeting delivery method and developed for the oral intake of siRNAs, plasmids, or proteins via incorporating them into type B gelatin nanoparticles, which are further encapsulated in poly (ϵ -caprolactone) (PCL) microspheres (PCL is an artificial hydrophobic polyester that preserves nanoparticles throughout transit through the stomach due to being resistant to acidic circumstances; the coated microparticles can hinder protein/enzyme adsorption, whereby bypassing the harsh circumstances of the gastrointestinal tract; the release of the nanoparticles occurs over time at inflamed situations in the intestine; this process happens by the regulated degradation of the outer PCL layer via lipases plentifully present in this area)	Kriegel and Amiji (2011); Ling et al. (2019)
	Hydrogel microfibers		Inflammation-targeting hydrogel microfibers can encapsulate hydrophobic therapeutic agents, and due to their negative surface charge, selectively adhere to the inflamed site/mucosa	Agüero et al. (2017); Gao et al. (2019)

but are soluble at neutral or slightly alkaline pH, which due to this feature, protects the postbiotics against unfavorable conditions (acidic pH) of the stomach and provides their targeted delivery to the colon. Nevertheless, intestinal pH values are not consistently stable at a specified range, and some factors such as diet, various diseases, etc., can cause significant changes, as well as it can have a remarkable difference between individuals (Van den Mooter 2006). This issue can lead to premature dissolution of the formulation containing postbiotics in the small intestine and thus irreproducible colon delivery. In addition to affecting the premature dissolution of the pH-dependent coating, diminished colonic pH recognized in some gastrointestinal disorders can also influence the solubility of the postbiotics in the colonic fluid, which in turn leads to reduced permeation. In this regard, the outcomes of a study evaluating the enTRinsic capsules (intrinsically enteric capsules) demonstrated that the capsules improved therapeutic agent bioavailability in humans as they guaranteed no release in the stomach and fast release in the small intestine (Sager et al. 2019). Targeted-release development of oral SCFA-based postbiotic, employing pH-dependent release strategy, is an alternative approach to colonic enema that had benefits in subjects with diverticulosis and Crohn's disease in pilot studies (Krokowicz et al. 2014; Sabatino et al. 2005). The Methacrylic-acid based-also known as Eudragit-polymers, ColoPulse technology, and Vcaps Enteric and enTRinsic capsules are the most commonly used pH-sensitive polymers/systems for oral pH-dependent delivery (Table 3). Puccetti et al. (2018) developed a novel indole-3-aldehyde-loaded gastro-resistant spray-dried microparticle for postbiotic small intestine local delivery. In this study, Eudragit S100 and L100 and ethyl cellulose were employed as wall materials and NaOH and ethanol solutions as solvent systems. The study outcomes support the use of spray-drying as a method for manufacturing gastro-resistant microparticle. The authors concluded that the obtained gastro-resistant formulation of the 3-aldehyde-loaded microparticle, which can permit targeted delivery to the small intestine, will be valuable to address novel applications for the postbiotics in various therapeutic areas (Puccetti et al. 2018).

Gut microbiota-triggered release/delivery strategy

The gut is a complex environment comprising of a large abundance of the commensal microbiota. The fundamental source of energy for this microbiota is from the fermentation of the numerous kinds of compounds that reach the colon unabsorbed (prebiotics). For this goal, the gut microbiota generates several enzymes such as different polysaccharidases (Cummings and Macfarlane 1991). This unique feature can be used to develop colon-targeted delivery of postbiotics by using polysaccharides in the coating. A large number of polysaccharides have already been employed for their unique characteristics as colon-targeted delivery systems, such as guar gum, xanthan gum, pectin, amylose, dextran, galactomannan, and chitosan (Hovgaard and Brondsted 1996). Besides polysaccharides, the potential of numerous azo functional polymers has been investigated for colon-targeted

coating. Azo functional polymers are cleaved by the gut microbiota-generated azoreductase enzymes (Hita, Singh, and Jain 1997). The COLAL coating system, COlon-targeted DElivery System (CODES), and TARGIT (an enteric-coated injection-molded starch capsule system) are examples of marketed gut microbiota-triggered release/delivery systems (Table 3). Lately, a double layer-coated colon-targeted delivery system was designed, which contains chitosan-based polymeric sub-coating of the core tablet comprising of citric acid for microclimate acidification, followed by an enteric coating. The manner presents a regulated delivery through hindering release process in the stomach and the small intestine but slowly releasing the therapeutic agent in the colon with the assistance of chitosanase generated by the gut microbiota (Kim et al. 2017). In the case of some gastrointestinal disorders, recurrent diarrhea can lead to the loss of gut microbiota, which can prevent the targeted release of this kind of delivery system. To cross this obstacle, in a recent investigation, probiotic cells were co-administered with tablets comprising of a guar gum core and an enteric outer layer (Eudragit S100) (S. Mohanta et al. 2019).

Time-dependent release/delivery strategy

Time-dependent release methods utilize gastrointestinal passage times as a pattern to the timing of the release process. The application of this system might be restricted by the evidence that there is a major variation in gastric evacuating times between various people, which makes the entry time of the therapeutic agent to the colon rather unforeseeable. Raised small intestinal passage times and diarrhea are common indications in patients with a gastrointestinal disorder, which can lead to the untimely release process and rapid clearance of the therapeutic agent from the colon. The ChronoCap, Pulsincap (Figure 5), and Multimatrix (MMX) (Figure 6) are examples of marketed time-dependent delivery systems/technology (Table 3). A study performed by Yu et al. (2017) investigated the direct measurement of therapeutic agent dissolution in the gastrointestinal tract as well as compared three different modified-release mesalamine formulations (locally acting gastrointestinal therapeutic agent) in terms of their release profiles in the gastrointestinal tract. The MMX-based formulation had insignificant therapeutic agent levels in the stomach and small intestine and high therapeutic agent levels in the colon region (Yu et al. 2017).

Osmotic pressure-controlled delivery strategy

An instance of an osmotic pressure-controlled delivery method is the OROS-CT technology (Figure 7). In this method, the outer layer consists of a hard gelatin capsule that easily dissolves in the small intestine. Each capsule can contain 4-6 push-pull osmotic units, which are usually covered by an enteric coating. At the interior side of the enteric coating, there is a semipermeable membrane that surrounds an osmotic push compartment and a therapeutic agent compartment. As soon as the enteric coating dissolves, the push compartment swells following the entry of water to the unit,

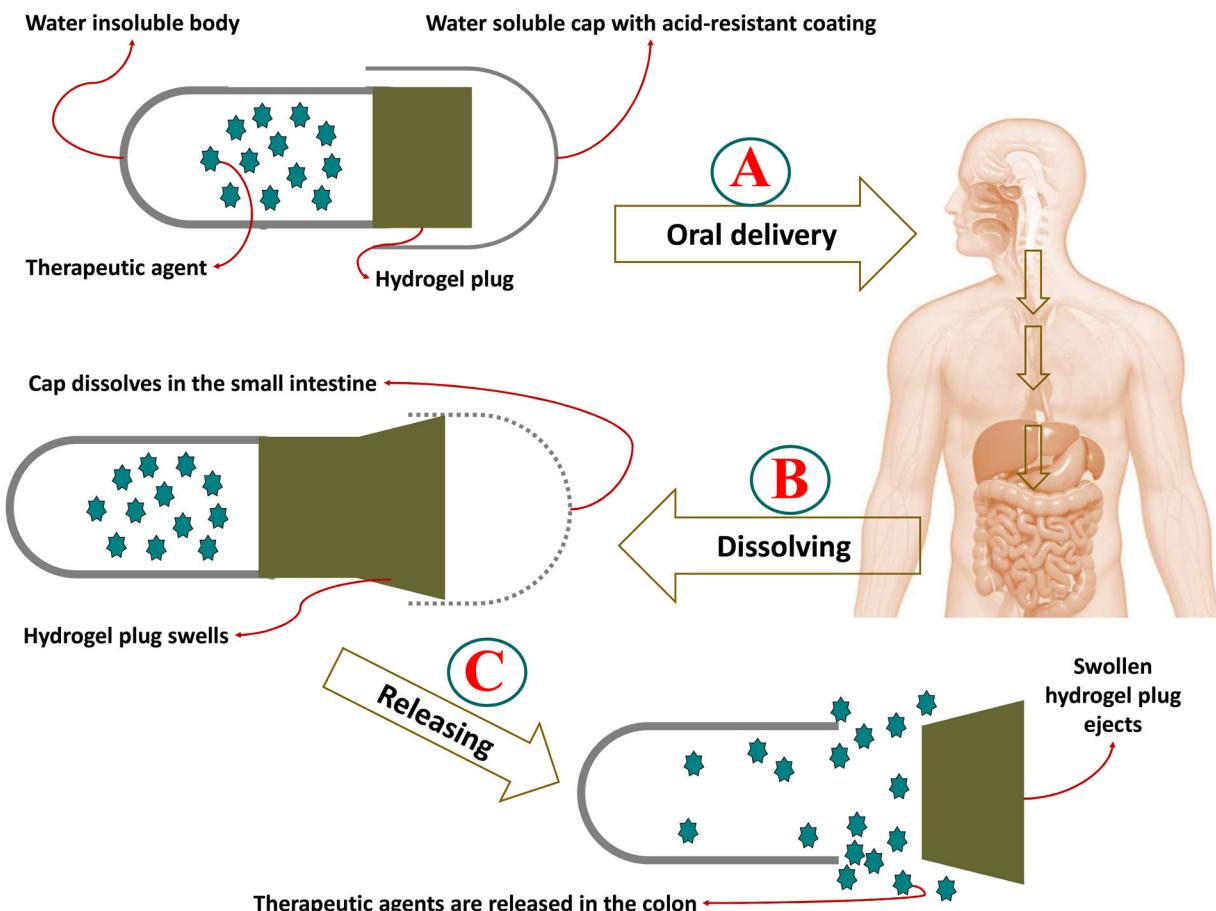


Figure 5. The Pulsincap system for time-dependent delivery/release.

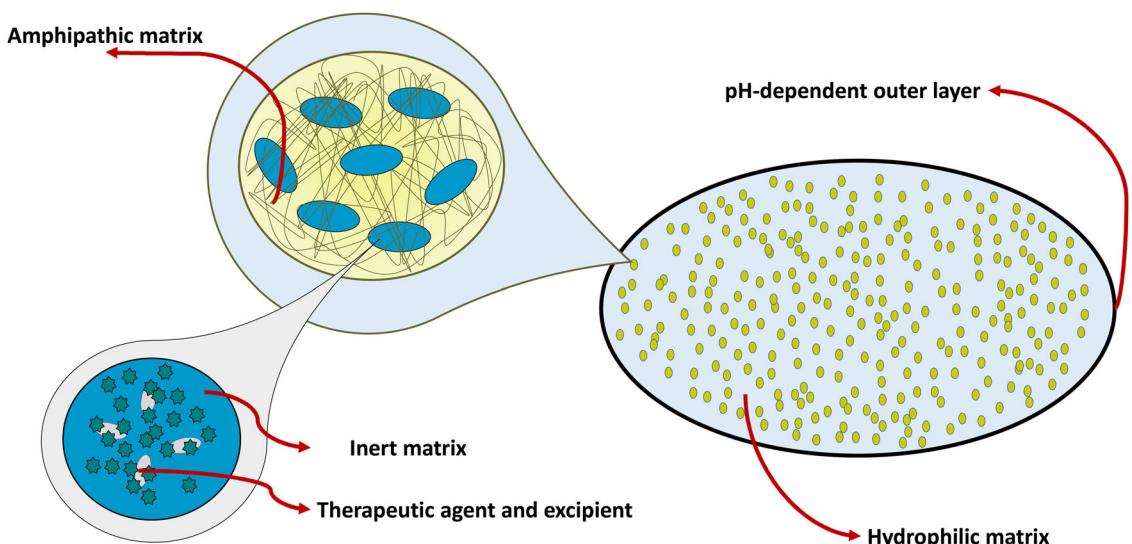


Figure 6. The Multimatrix (MMX) technology for targeted delivery/release.

which leads to pushing the therapeutic agent out through the orifice that is excavated into the coating membrane. OROS-CT units can also perform the release process for up to 24 hours.

Nanoparticle delivery strategy

A relatively novel approach for colon-targeted release is the application of nanotechnology-based delivery methods as

vehicles for therapeutic agents such as postbiotics. The main debility of the earlier described delivery practices is their deep dependence on the host's physiological and gut conditions (e.g., population and variety of gut microbiota), which can significantly be altered in some gastrointestinal disorders. Nanoparticle-based delivery methods aiming at the intestines can utilize the variations between cancerous cells or normal and inflamed mucosa resulting in tumor- or

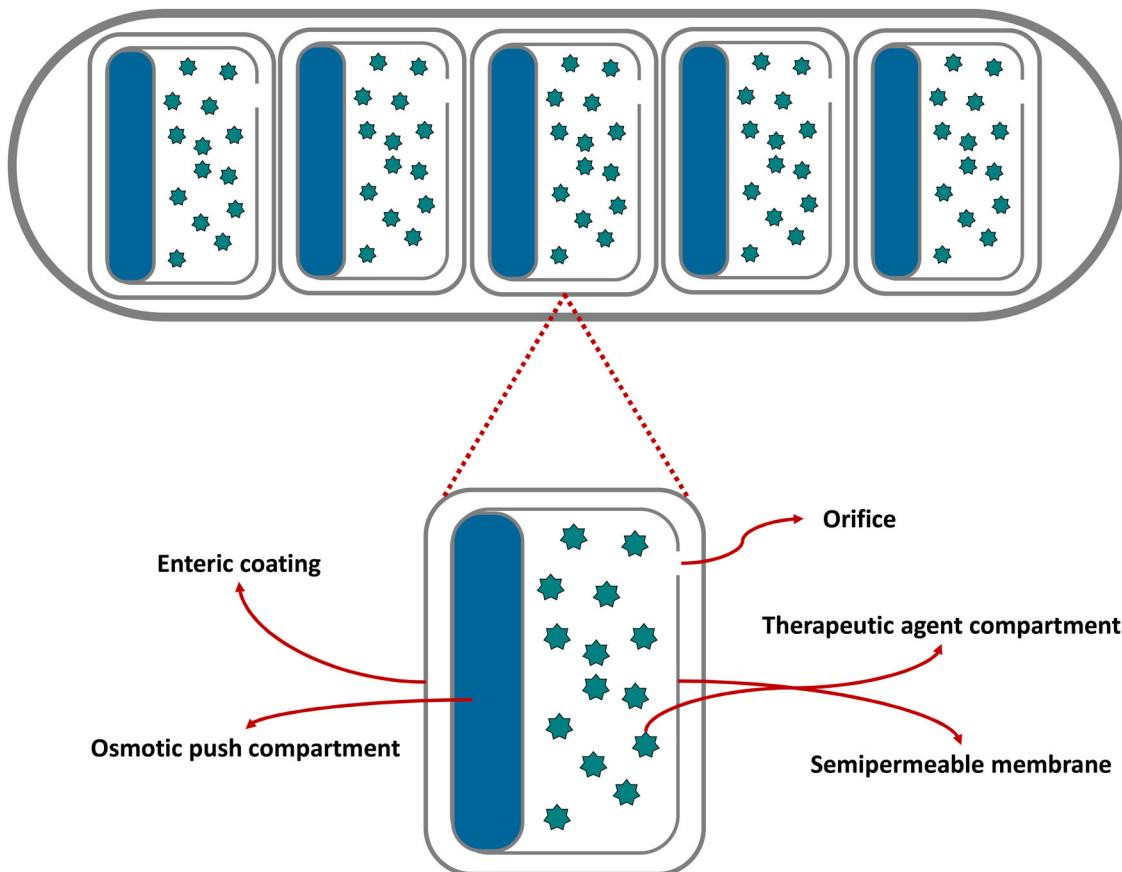


Figure 7. The OROS-CT system for osmotic pressure-controlled delivery.

inflammation-specific targeting, respectively. Figure 8 illustrates the various kinds of nanoparticle methods that can be applied for colon-targeted oral delivery. Lipid-based nanoparticles (NPs) own appealing natural characteristics for colon delivery, including general biodegradability, biocompatibility, and the capability to carry both hydrophobic and hydrophilic therapeutic agents (Cavalli et al. 2002; Shen et al. 2019). The characteristics of lipid-based NPs can be comfortably modified by the addition of various elements to the outer periphery of the membrane or via the alteration of the surface chemistry. Due to this adjustability, different lipid-based NPs have been developed for oral colon-targeting, such as solid lipid NPs and liposomes (Amekyeh et al. 2015; De Leo et al. 2018; Hua 2014; Kosaraju 2005; Zare et al. 2020). Anionic nano-delivery methods have been demonstrating to selectively attach to inflamed sites, wherever positively charged proteins are plentiful. Hence, the development of an anionic nanostructured lipid carrier loaded with postbiotics (with a significant anti-inflammatory activity), can be used as a novel targeted-delivery/release strategy in future *in vivo* studies.

In this regard, carrier compounds based on lipids or polysaccharides are the most frequently applied systems for the encapsulation of the therapeutic compounds (Table 3). Liposomes are among the nanocarriers that have a polysaccharide coating which impressively participates in encapsulating proteins or/and the peptides inside the lipid core (Ting et al. 2014). Castoldi et al. (2017) investigated the therapeutic activity of vitamin-loaded liposomes for local

treatment of pulmonary bacterial (*Pseudomonas aeruginosa*) infections. In this study, the designed vitamin-loaded liposomes were nanosized and monodisperse, with a negative surface charge and entrapment efficiency of approximately 23%. Noteworthy progress in antibacterial properties was detected as a result of the incorporation of investigated vitamin into liposomes as compared with administration in ethanolic solution. Besides, vitamin-loaded liposomes had no effect on the release of the proinflammatory cytokines, therefore seem like a promising anti-microbial therapy for lung chronic infections (Castoldi et al. 2017). Some vitamins also are formed as postbiotic compounds during the complex metabolism of gut microbiota. These types of postbiotics are poorly soluble in water and require dissolution in organic solvents such as ethanol, which in turn limits its *in vivo* administration. On the other hand, the results of studies demonstrated that a liposomal formulation of vitamin-based postbiotics with desirable and potent physicochemical features for *in vivo* delivery could be successfully developed (Łukawski et al. 2020; Merz and Sternberg 1994; Zucker et al. 2009). Bacteriocin is another functional type of postbiotics, which scientific literature has confirmed their vital role in promoting food safety and consequently in promoting host health status. Liposome nanoparticles have been employed to encapsulate natural and synthetic bacteriocins. The liposomal formulation of bacteriocins represents an alternative strategy to overcome the obstacles associated with the direct utilization of bacteriocins to food products, such as interactions with food components or/and

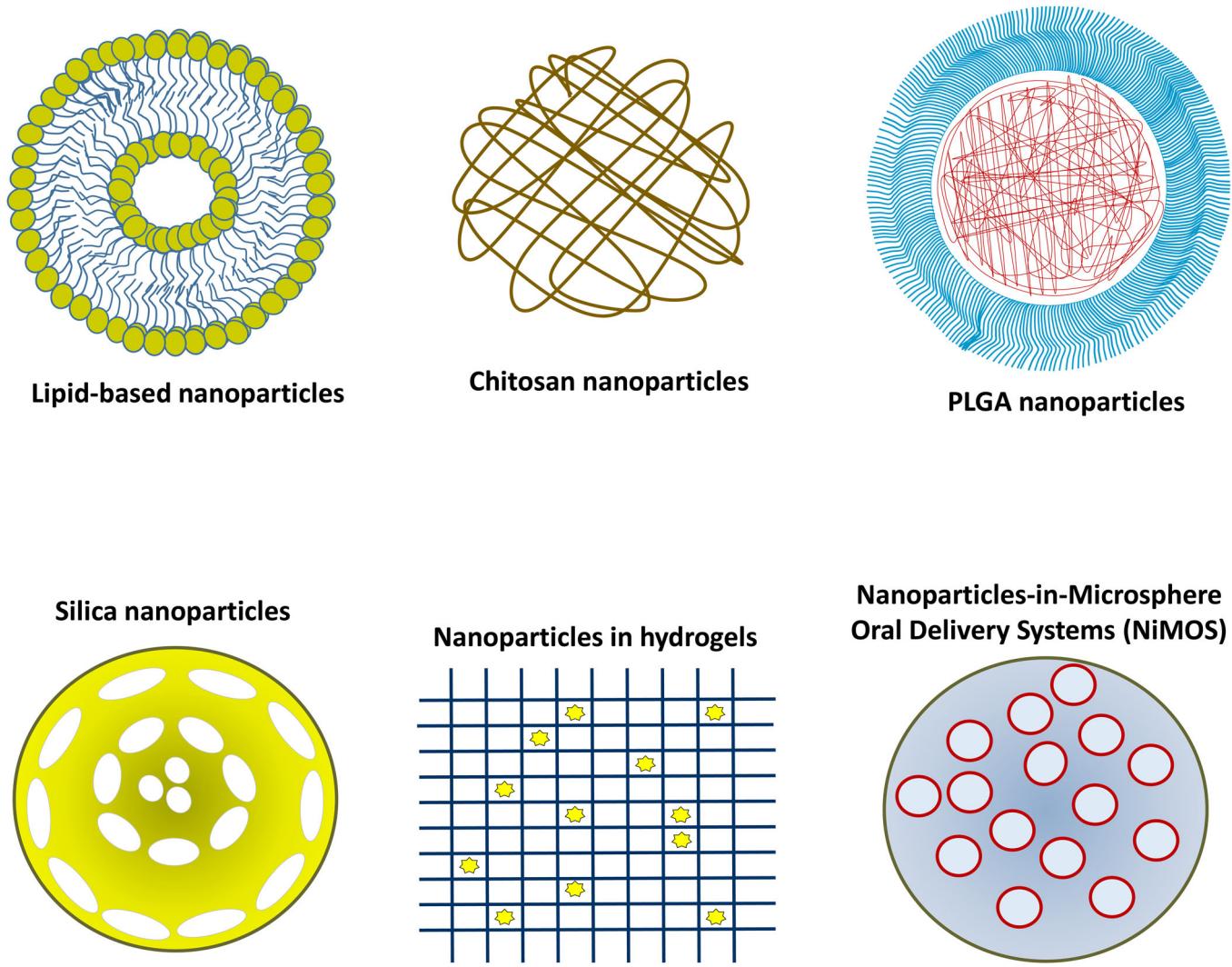


Figure 8. Main nanoparticle systems employed for colon-targeted delivery.

proteolytic degradation (Shukla et al. 2017). Benech et al. (2003) reported that the direct incorporation of nisin generating strain into the cheese starter culture remarkably modified lipolysis and proteolytic features of cheese, while the nisin, when encapsulated in the liposome, had no adversary effect on proteolytic, rheological, and sensory properties of cheese (Benech et al. 2003). Moreover, da Silva Malheiros, Daroit, and Brandelli (2010) encapsulated nisin A into liposome nanoparticles formed of partially filtered phosphatidyl-cholines of soybean as a low-cost and promptly accessible commodity. The designed nisin-loaded liposomes exhibited high encapsulation performance and demonstrated enhanced antimicrobial properties (da Silva Malheiros, Daroit, and Brandelli 2010). Therefore, these studies on liposome encapsulating bacteriocin-based postbiotics are favorable in terms of analyzing the effectiveness of liposome-entrapped molecule and free bacteriocin compound. These promising research results have encouraged high demand for the liposome-based investigation to improve food utilization, shelf-life, and safety of food.

Bilosomes are other novel colloidal carrier systems that are developed, by Scotland researchers for the first time, with the inclusion of bile salts within the vesicular lipid

bilayer membrane (El-Nabarawi et al. 2020). Bilosomes are the bilayer membrane vesicles incorporated with bile salts like deoxycholate (Conacher, Alexander, and Brewer 2001). The stability of bilosomes is deeply dependent on the concentration of bile salts. Such a way that the concentration of 5 and 15–20 mM of bile salt is directly associated with their resistant and sensitive condition, respectively (Senior 2001). The outcomes of investigations demonstrated that bilosomes possess hopeful potential in comparison to other vesicular carriers for oral delivery and can trigger meaningful systemic influence than through parenteral ways (Mann et al. 2006; Shukla et al. 2008; Singh et al. 2004). Additionally, incorporation of bile salts into the lipid bilayers of bilosomes can support the vesicles versus more instability by physiological bile salts in the gastrointestinal tract (Conacher, Alexander, and Brewer 2001; Joseph Naguib et al. 2020; Schubert et al. 1983). Nano-delivery methods are a very hopeful and deeply investigated area, but for these approaches to utilize in the clinic, the large-scale production opportunities, improved residence time in the colon, and safety assessment of the methods need to be investigated further (Vass et al. 2019).

Besides, some bioactive ingredients of functional foods can be effective in the delivery of therapeutic compounds. In this regard, prebiotics is one of the main food bioactive ingredients that have been applied for the encapsulation of therapeutic compounds because of the intrinsic capability they possess to preserve the embedded biomolecules within the upper gastrointestinal tract (Mohanta et al. 2020). Importantly, they are characterized as non-digestible ingredients of functional foods (inulin, fructose, galactose, oligofructose, stachyose, lactulose, oligosaccharides, and raffinose) that are not influenced via the host's digestive enzymes. However, they are utilized via gut colonized probiotics in the large colon and selectively stimulate the growth and development of beneficial microbes and subsequently improve the health status of the host (Rad, Maleki, et al. 2020; Tomaszik and Tomaszik 2020). Nevertheless, these approaches have not been further developed and require testing in larger placebo-controlled randomized clinical trials.

Intradermal delivery

The intradermal delivery method is one of the favorites *in vivo* delivery routes for postbiotics, which confers some impressive benefits for the individual as not only is it an appropriate technique, but it also enjoys a noninvasive nature. The intradermal delivery method, due to its unique characteristics such as the capability to pass the first-pass metabolism and escape the enzymatic degradation under digestive system conditions, is the most creditable path with regards to the diseases of the skin- or/and tissues (e.g., bacterial or/and fungal infection) (Hutin et al. 2003; Sadik and Zillikens 2013; Yellepeddi, Donnelly, and Singh 2015). Majeed, Majeed, Nagabhushanam, Lawrence, et al. (2020) investigated the skin protective properties of the postbiotic metabolite (LactoSporin) of a spore-forming probiotic *Bacillus coagulans* MTCC 5856 *in vitro*. In this study, LactoSporin was assessed for: (a) potential antioxidant properties by free radical scavenging activity and reactive oxygen quenching activity in human dermal fibroblast cells, (b) protection of fibroblasts from UV-induced apoptosis and cell death by flow cytometry and neutral red uptake assays, (c) enzyme inhibition for collagenase, elastase, and hyaluronidase, (d) gene expression by using polymerase chain reaction. The results demonstrated that the investigated postbiotic, LactoSporin, exhibited significant antioxidant properties, protecting skin cells from UV-induced apoptosis and cell death, and inhibiting collagenase, elastase, and hyaluronidase activity, as well as up-regulating the expression of hyaluronan synthase, transforming growth factor and epidermal growth factor (Majeed, Majeed, Nagabhushanam, Lawrence, et al. 2020). Hence, the positive outcomes from various investigations confirm the skin-protective effects of postbiotics and their potential for wide application in cosmetic formulations (Majeed, Majeed, Nagabhushanam, Lawrence, et al. 2020; Majeed, Majeed, Nagabhushanam, Mundkur, et al. 2020). However, the development of a carrier system containing postbiotic compounds can reduce the

impact of environmental factors on the active substance, and increase its performance, as well as provide a platform for their industrial-scale production.

It is well-known that microneedle (MN) arrays are capable of rising the number of biomolecules amenable to intradermal delivery via infiltrating the defensive tissue barrier of the skin, the stratum corneum (as the principal barrier to topically-applied), and developing a path for therapeutic compounds' infiltration to the subcutaneous layers of the skin (Courtenay et al. 2020). MN arrays are insignificant-invasive apparatuses with the ability to bypassing the skin's tissue defensive barrier, therefore achieving the microcirculation of the skin and accessing systemic delivery via the intradermal route. MNs have recently been studied broadly for biomolecule delivery and as insignificantly-invasive patient diagnostic apparatuses. MNs are employed to the skin surface and, with micro-scale sharp protrusions (25–2000 µm in height), pierce (painless) the stratum corneum and form tiny aqueous pores through which biomolecules disseminate to the skin microcirculation (Donnelly et al. 2014). The materials applied to fabricate MNs are mainly silicon, glass, metals, ceramics, carbohydrates, and polymers (Xie et al. 2020). Consequently, MNs can be used as a novel type of point-of-care tool, permitting painless intradermal sampling, sensing, and biomolecule delivery without the necessity for well-skilled personnel (Blicharz et al. 2018).

Intravenous delivery

Intravenous delivery of therapeutic compounds is frequently employed for the prompt dissemination of injected biomolecules from the veins to the tissues and organs. The main advantage in intravenous biomolecule delivery is the swift biotransformation of the biomolecule and probable short-timed excretion from the body. There exist several modern techniques, which are potentially valuable in augmenting the effectiveness of therapeutic compounds via persistent release within the body. In this regard, among other materials, nanoparticles are appropriate for transferring biomolecules *in vivo*. The utilization of nanoparticles as biomolecules' carriers via the intravenous path for *in vivo* delivery largely develops the effectiveness of therapies with current molecules (de la Torre et al. 2020). Their application in the delivery systems has made conceivable developing novel treatment techniques by utilizing new micro- and macro-biomolecules with the gut-microbial origin (postbiotics) that demonstrate a great therapeutic activity, for instance, proteins, peptides, carbohydrates, organic acids, and nucleic acids (Rad, Abbasi, Kafil, et al. 2020). Veloso et al. (2018) developed a novel formulation for the antifungal Voriconazole entrapped into liposomes for intravenous delivery. Their results showed that the capability of Voriconazole to exert fungicidal properties might be improved by its entrapment within liposomes. The authors concluded that liposomal encapsulation presented a specific level of protection from premature metabolism, providing more effective antimicrobial blood concentrations,

permitting for deeper and more selective infiltration and agglomeration into the tissues more critically influenced by the pathogen (Veloso et al. 2018). The optimal performance of biomolecule delivery techniques using nanoparticles is significantly affected by the capability of the biomolecules' carrier to bypass physiological barriers as well as the proprietary of its bio-circulation. The pulsed or/and pulsatile delivery systems are vital for the effectiveness of the intravenous delivery path. Pulsatile delivery systems are gaining a lot of attention as they deliver the therapeutic compounds to their precise site of action at the appropriate time and in an adequate amount, therefore offering spatial and temporal delivery and promoting patient compliance (El-Hady et al. 2020). Under the physiological conditions of the body (37°C , pH 7.0), many vital biological processes are controlled via the pulsed release of biomolecules at a particular time and site of action (Madhavi et al. 2020; Reddy Dumpa, Bandari, and Michael 2020). From a therapeutic landscape, in case we succeed to emulate the biological processes living systems possess, it would be essential to design and fabricate novel delivery tools that will support to accomplish the controlled delivery of a specified volume of a therapeutic at programmed intervals of time. The capability of delivering therapeutics to an individual in a pulsatile release profile is the main target in biomolecule delivery investigations. The plasma peak is gained at an ideal period through scheduling the administration of the therapeutic. Also, daily dose numbers could be diminished. According to the remedial capacity, a diversity of design/fabrication approaches has been developed in pulsatile release achievement. Generally, such systems of delivery could be classified under reservoir, capsular, and osmotic delivery device categories (Amani et al. 2020). The delivery systems based on the pulsatile release can be controlled via various parameters including pH, osmotic pressure, and controlled temperature. As an important class of polymeric compounds, hydrogels are most frequently applied as significant carriers in the pulsatile delivery systems (Dreiss 2020). Three-dimensional hydrophilic polymer networks of the hydrogels provide numerous unique properties such as swelling, hydrophilicity, and softness. Hydrogels possess interior micro-/nano-sized pores that authorize the dissemination of biomolecules to their environments (Chai, Jiao, and Yu 2017; Fu and In Het Panhuis 2019; Martín et al. 2019). Besides, hydrogels are mechanically soft and flexible, and these properties can to some extent follow the characteristics of the soft living tissues of the body (Xue et al. 2019). Therefore, these unique features make hydrogels invaluable tools for several biomedical applications, including the delivery of therapeutic compounds, tissue engineering scaffolds, and tissue reinforcement (Yi et al. 2020). Thermo-sensitive or thermo-responsive gels (gels that reversibly change their size in response to temperature alterations) are capable of shrinking at transitory temperatures that are straightly associated with the lower critical solution temperature behavior of the linear polymer (Lee and Bae 2020). The size alteration properties of hydrogels in response to alterations in temperature can be applied to attain a pressed hydrogel tool via locating

hydrogel inside an inflexible capsule. Such flexible size alteration enables an on-off switchable therapeutic release (Qu et al. 2019), which is regulated via swelling/deswelling phases, in a manner that the swelling and shrinking occur below and above 32°C temperature, respectively (James et al. 2014). Besides, hydrogels with pH-sensitivity could be applied for delivering therapeutic compounds to various tissues/organs. Postbiotics with significant anticancer activity could be embedded within pH-sensitive nanoparticles, by which they could be carried through a targeted strategy to different acidic tumor tissues. Depending upon the chemical properties as well as the potential therapeutic role of postbiotics, the hydrogels could be designed and applied for delivering biological postbiotic metabolites to particular target tissues/organs.

Conclusion

The delivery of therapeutically-valuable bioactive micro- and macro-molecules (postbiotics) derived from gut beneficial microbes is the main challenge and opportunity for the biomedical staff. In general, the effectiveness of postbiotics pertains basically to the formulation and the type of *in vivo* delivery routes. As described by the classification of BCS, the formulation of therapeutic compounds pertains to the aqueous solubility and membrane permeability. Due to the fact that the therapeutic compounds are mostly formulated for oral administration, considering their aqueous solubility and membrane permeability under digestive system circumstances is of paramount importance. Hence, various systems for effective delivery have been expanded in this regard, such as polysaccharide-, prebiotic-, and liposome-based formulations. Besides, scientists have offered targeted delivery systems based on nanoparticles for realizing the great therapeutic efficiency of bioactive molecules. MNs provide an almost painless and easy intradermal delivery path for therapeutic compounds. The "poke with patch" strategy of MNs assists in surmounting the first-pass metabolism, bringing about improved efficacy for delivering therapeutic formulations. The intravenous path aimed at therapeutic compound delivery is regarded as the main challenge due to rapid excretion from the circulation. In this respect, and to overcome such challenges, hydrogels (as a substantial carrier in the pulsatile delivery systems) provide controlled release as well as significantly improved effectiveness of intravenous delivery path. The *in vivo* delivery of bioactive micro- and macro-molecules derived from gut beneficial microbes are in their emerging phase and require massive investigation and randomized double-blind clinical trials if they are to be applied extensively as treatment strategies. Furthermore, the delivery routes of postbiotics possess a substantial part in attaining the high performance of these powerful drugs. Although currently few of the postbiotic products are in the market, long-term clinical trials that possess a substantial number of samples are ought to be implemented for the prescription of postbiotic metabolites intended for the treatment of diseases.

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Declaration of interest

The authors declare that they have no conflicts of interest.

Abbreviations

BCS	Biopharmaceutics Classification System
COVID-19	coronavirus disease 2019
FDA	Food and Drug Administration
FMT	fecal microbiota transplantation
HTS	high-throughput screening
IBD	inflammatory bowel disease
LTA	lipotichoic acid
MN	microneedle
NP	nanoparticle
SCFA	short-chain fatty acid
USP	United States Pharmacopeia

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