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Microbiome as therapeutics in vesicular delivery

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ABSTRACT

Microbiome refers to an ecological community of various symbiotic and pathogenic microorganisms, which plays a crucial role in human health and disease. The concept of novel drug delivery systems particularly the vesicular drug delivery systems is gaining massive attention. This emerging technology has started expanding its horizons in the area of microbiome delivery. This mini-review highlights the role of vesicular systems such as nanoparticles, liposomes *etc.* as a host/carrier for the microbiome in targeting various diseases. This review will be of interest for both the biological and formulation scientists to understand and explore the new vistas in the area of vesicular delivery system as carrier for microbiome delivery.

1. Introduction

Microbiome consists of all the symbiotic, commensals and pathogenic community of micro-organisms that are found nearly in all the body parts including skin, mucous membranes, reproductive and respiratory tract, *etc.* Nowadays, many of the nonspecific diseases are believed to be due to an imbalance in the microbe-host interactions, and/or dysbiosis. These microbial communities can be bacterial, viral and eukaryotic in nature both beneficial and harmful to the humans [1]. Such organisms majorly affect the metabolism, immunity and the gut-brain axis. The recent advancements in the synthetic biology technology have provided a new platform where the microbiome can be used as a potential drug delivery system due to its inherent ability of *in situ* production and delivery of biotherapeutic compounds, which are either naturally produced by this microbiota or otherwise can be made to release specific agents when modified by applying various bio-engineering tools and approaches [1,2].

Microbiome therapy bear high robustness towards interpersonal variability, have the ability to remain stable and dominant in the body environment, maintain their function in presence of native enzymes and have the potential to be used for screening of the patients based on the severity of the disease. The advantages of producing such therapeutics *in situ* include tragetted drug delivery, low dose administration of the therapeutic consequently reducing the side effects, non-invasive administration, production of multiple therapeutics by the same cell upon modification of the carrier system. Moreover, the *in situ* production is cost-effective [2]. Extensive research on the microbiome has established its application in variety of diseases and has been proved to be a predictive tool for the disease outcome including cardiovascular disease, *Clostridium difficile* infection, metabolic disorders and colorectal cancer [3,4].

Gut microbiota may serve many functions such as affecting the metabolism of the host by 1) modulating the conversion of dietary fibres and mucosal glycan into short chain fatty acids which further can act as energy source for the colonic epithelial cells and increasing the gut integrity, 2) synthesis of various vitamins including B12, 3) metabolism of bile salts and when conjugated with hepatic enzymes can cause accumulation of metabolites responsible for various disorders. It has also been proposed to interact with foreign living organisms 'xenobiotics' thereby regulating gene expression. Some microbes are found to possess a mucosal IgA antibody, secrete different antimicrobial peptides and thick mucous membrane making them an integral part in the regulation of host immunity. Their effects on the neuroendocrine function of the body is also prominent and believed to modulate the gut-brain axis, thus causing variability in the levels of various hormones [2]. It is also postulated that the presence of such microbial

Abbreviations: CRC, colorectal cancer; DHA, docosahexaenoic acid; GI, gastrointestinal; GRAS, generally regarded as safe; HAHp, half-fin anchovy hydrolysates; HPMC, hydroxy propyl methyl cellulose; NLCs, nanostructured lipid carriers; SCFA, small chain fatty acid; SHIV, simian-human immunodeficiency virus

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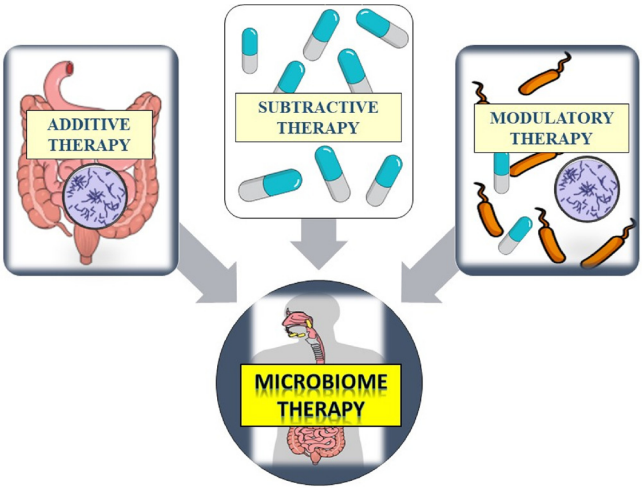

Fig. 1. Various areas of the microbiota therapy. In additive therapy, there is an addition of microbiota when natural microbiota is deficient in order to maintain the bodily functions. In the subtractive therapy, deleterious microbes are deleted using some bacteriophages. In the modulatory therapy, the working of the already present microbes is modified using some external agents.

communities in the body at the time of infancy, may contribute to increased or decreased chances of disorders like asthma, food sensitization, and irritable bowel disease *etc.* Therefore, bringing down the levels of toxic metabolites, production of therapeutic molecules and delivering them to specific sites, conditional demand-based release of specific therapeutic to the environment and controlling own population are the characteristics forming an ideal microbiota carrier/vector. It has also been investigated that gut microbiota influences drug pharmacokinetics and correspondingly bioavailability, efficacy or adverse effects of a various class of drugs. It is also proposed that engineered gut microbiome can contribute to the development of efficacious and tolerable new chemical entity and pharmacokinetic determination to improve healthcare outcomes and advance personalized medicine [5].

2. Engineering the microbiota

Engineering the microbiota forms three major areas of therapy (Fig. 1). *Additive Therapy* includes the addition of certain strains of microbes to overcome the deficiency disorders. In the *Subtractive Therapy*, some lethal members are eliminated using specific vectors or phages. Lastly, *Modulatory Therapy* is the one where some non-living agents are administered to modify the composition/activity of the natural microbiome [2,6]. Probiotics, prebiotics, and synbiotics are termed as first generation microbiome therapeutics. The new generation microbiome therapeutics include the modified or recombinant probiotics, some designed microbial consortia and some selective antimicrobials. Different approaches to microbiome therapy are presented in Fig. 2. These are also termed as ‘smart cell-based therapeutics”, “autonomous microbial physicians” or “therapeutic organisms”. To increase the bioavailability of the drug and decrease the instances of drug interaction, these recombinant probiotics produce the biomolecule continuously *in situ*. Generally regarded as safe (GRAS), engineered *Escherichia coli, Lactobacillus jensenii, L. lactis* has been used widely for the treatment of various infections including cholera, preventing transmission of chimeric simian-human immunodeficiency virus (SHIV), production of anti-inflammatory peptides and anti-antigen proinsulin in irritable bowel disease. Other modifications of the same microbiome have also proved efficacious in many metabolic disorders. Sometimes, there may be a need to substitute whole microbial community which can be achieved by engineered consortia. The major challenge in using this technology lies with the difficulty in identifying and modifying them to address the complexities of human diseases. In the subtractive therapy, use of broad-spectrum antibiotic agents leads to the damage of both the pathogenic cells as well as the normal cells with high possibilities of inducing antimicrobial resistance [4–6].

So, the development of targeted antibiotics like bacteriocins and bacteriophages is the need of the hour. Bacteriocins are ribosomally synthesized antimicrobial peptides while the bacteriophage are the natural or synthetic viral parasites. Studies investigating the effect of diet, diseases, and medication on the natural role of these phages in shaping the host-associated bacterial population is lacking. Engineering these phages with some immunoglobulin domains or altering the host adsorption factor or encoding a dispersal enzyme can help in increasing the residence time [2].

3. Vesicular drug delivery and microbiome

In one of the studies conducted to check the effect of fullerenol nanoparticles on the gut microbiota homeostasis, an increased number of short chain fatty acid producing bacteria was found which exhibited anti-hyperlipidemic effect [7]. Similar observations were demonstrated when nanocomposites of half-fin anchovy hydrolysates (HAHp) and zinc oxide nanoparticles were given at a dose of 1 g/kg body weight of mice [8]. Results from such studies help us to demonstrate the potential role of microbiota in treating various diseases.

Results from the Phase I and II clinical trials have emphasised on the potential use of microbiota in the disease management. But, considering the formulation aspect and the stability issues associated with these formulations, a lot more needs to be done. Therefore, to increase the shelf-life and storage of phages to produce reproducible dosages, encapsulation has been tried. Some other problems like high phage to bacteria ratio dose for sustained and prolonged release, their susceptibility to chemical and physical stress *in vivo* offer many challenges [9]. Encapsulation of these microbes with a suitable semi-permeable membrane can be done to protect them from host immune system and the harsh environment. Microencapsulation for various ligands including antibiotics, metabolites, hormones and food additives has been reported [10]. *L. plantarum* was microencapsulated and given orally to high-fat diet induced hyperlipidemic rats. An increased colonization of the bacteria was observed in the colon compared with the free cells in addition to the increased lipid-lowering action, thus indicating the protective action of microencapsulation on the viability of the carrier system. This was accompanied by a lesser amount of lipopolysaccharide producing and mucosa damaging bacteria in the feaces and an increased SCFA-producing bacteria showing its increased efficacy after coating [11].

As an attempt to increase the shelf-life and stability of the probiotics in functional foods, *L. lactis* was entrapped in calcium alginate beads. A significant increase in viability of encapsulated bacteria was observed compared with the non-encapsulated bacteria upon an aerobic storage for up to 7 days (1.5 log and 5.8 log reduction in cell count for encapsulated and free cells respectively) [12].

Using capsules of Hydroxy Propyl Methyl Cellulose (HPMC) based enteric coated polymers for the delivery of *E. coli* has been demonstrated to be more effective in preventing its inactivation in the rats [13]. In two different studies, Colom and his co-workers encapsulated a cocktail of three *Salmonella* phages in cationic liposomes and alginate microparticles respectively and tested in boilers. In both the cases, the number of phages was found to be more as compared with the control that were administered with free phage cocktail [14,15].

Apart from the gastro-intestinal-related disorders, tumor targeting has also been successfully experimented using microbiota in various animal models. An exhaustive review has been discussed elsewhere [16]. Immune system-microbiota interactions is being investigated as one of the reason contributing to the Colorectal cancer (CRC) pathology. Clodronate encapsulated liposomes were studied for their potential effect in altering the macrophage level in mouse models of CRC. A 36% decrease in the tumor number with a significant decrease in the

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