Role of green nanocarriers in delivering microbiome-Balancing therapeutics against dysbiosis




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Abstract

The microbiome inhabiting the gastro-intestinal tract (GIT) known as the gut-microbiome, is crucial for sustaining metabolic, immunological and neurological balance. The microbiome cells exceed the human host cells by a factor of 10. Contemporary lifestyle, exposure to antibiotics, environmental toxins lead to disruption of a healthy balance of gut microbes resulting in dysbiosis related diseases like inflammatory bowel disease, colorectal cancer, atopy, obesity, type 2 diabetes, neuroinflammation and related disorders like anxiety, depression, Alzheimer's disease. Conventional approaches including antioxidant supplements, dietary probiotics, and prebiotics encounter inadequate intestinal transport, low bioavailability, and poor stability. Recent research has revealed that green nanocarriers are a viable and biocompatible choice for gut-targeted delivery. Originating from naturally occurring materials have enhanced gastrointestinal stability, exceptional biodegradability, and minimal toxicity. This review highlights the current progress and potential of green nanocarriers in delivering microbiome-balancing therapeutics. Emerging evidence supports their promise as eco-friendly, precision-targeted platforms capable of re-establishing eubiosis with minimal systemic toxicity.

Keywords: Gut-microbiome, dysbiosis, green nano carriers, eubiosis

1. Introduction

The microbial colonization of the human GIT commences immediately after birth. The neonatal intestine however considered sterile, harbours a minimal microbial GIT population during gestation. Rapid growth and development of microbiome instigate during and after parturition shaping the initial gut microbiota especially during vaginal delivery which facilitates the transfer of maternal vaginal species to the neonate which commences early stages of microbial succession. In contrast the caesarean section infants are reported to develop a delayed colonization of gut- microbial community. As the environmental and dietary factors influence the progression of gut microbe population, these differences tend to dimmish by the period of six months. (1) The gut microbiome encodes a collective gene pool which exceeds human genome. This enables them to perform numerous metabolic functions beyond the intrinsic capacity of human host cells. They provide critical enzymatic pathways for metabolism for complex carbohydrates, oligosaccharides, unabsorbed dietary sugars, alcohols and host-derived mucin compounds.

Table 1. Summarises important metabolites produced by gut microbiome and their key roles in maintaining physiological processes and promoting overall health in host human.

Sr. No.	Metabolite	Micro-organism	Function	Reference
1.	Deoxycholic acid and Lithocholic acid	*Clostridium scindens* and *Clostridium sordellii*	Modifies the bile acid pool by transforming primary bile acids (produced by the liver) into these secondary bile acids (DCA and LCA).	(6)
2.	SCFAs	*Bacteroides, Bifidobacterium Faecalibacterium,*	Energy source for colonocytes and hepatic epithelial cells, anti-carcinogenic. Gluconeogenesis, insulin secretion	(7)
3.	Branched chain fatty acids	*Bacteroides and Clostridium species*	Histone acetylation	(8)
4.	Indoxyl sulfates and Indole-3-propionic acid	*Lactobacillus and Bifidobacterium*	Neuroprotective, antioxidant, regulation of intestinal barrier function	(9)
5.	Lipopolysaccharides	*Proteobacteria Bacteroidetes*	Anti-inflammatory, epigenetic regulation of genes in colorectal cancer	(10)
6.	Vitamins B1, B2, B3, B5, B6, B7, B12, K2	*Bacteroidetes Bifidobacterium Escherichia coli Lactobacillus*	Erythropoiesis, DNA replication, enzymatic co-factors and immune functions	(11)

Through these metabolic processes, gut microbes play vital role in extraction of energy yielding molecules and production of absorbable metabolites for the host in a symbiotic connection while simultaneously supporting their own colonial proliferation. Bacterial species, mainly Proteobacteria, Bacteroidetes and Firmicutes phylum, play key role in carbohydrate digestion, immune regulation and protection against pathogenic colonization.(2) They are involved in fermentation and digestion of complex and indigestible carbohydrates to generate short chain fatty acids (SCFAs), lactates, ethanol, hydrogen and carbon dioxide which are either utilised by the host cell or excreted out in faeces. (3) These are also involved in production of several crucial compounds and their derivatives like lipopolysaccharides, indole derivatives, branched chain fatty acids, deoxycholic acids, peptidoglycans, phenolic derivatives, choline metabolites like trimethylamine -N-oxide and betaines which serve as fuel for regulating several physiological and cell-protective activities Studies reveal that gut microbiota is also involved in synthesis of variety of essential vitamins like biotin, folate and vitamin K which are mot independently produced by the human host, thereby contributing directly to nutritional status of host. (4) Beyond aiding digestion of individual compounds, gut microbiome metabolises carcinogenic substances and detoxify potentially harmful substrates such as pyrolysates formed primarily through thermal decomposition (pyrolysis) of organic matter, often from dietary sources. The host's systemic metabolism is strongly influenced by a wide array of microbial metabolites, many of which interact with specific host receptors, including cell surface and nuclear receptors, to regulate signalling pathways that impact physiology, immunity, and homeostasis. (5) The table below summarises the crucial role of microbial metabolites and their physiological effects in human host.

In recent times, with the intensified exploration of medical studies, individuals' comprehension of the connection between gut microbiota and human health has grown deeper. Gut microbiota dysbiosis is a commonly prevailing health issue which refers to disruption of healthy microbial population in the gut characterised by decline in the ratio of beneficial bacteria as compared to harmful or disease-causing bacteria. Dysbiosis leads not only to indigestion and nutritional imbalance in individuals but also becomes major cause for multiple chronic diseases. (12) The table below highlights several chronic illnesses caused by gut microbiome dysbiosis.

Table 2. List of dysbiosis causing organisms and associated diseases.

Sr. No.	Disease	Increased species	Decreased species	Reference
1.	Colorectal cancer	*Acidaminobacter*	*Prevotella, Ruminococcus*	(13)
2.	Gastric cancer	*Clostridium, Fusobacterium*	*Eubacterium rectalie*	(14)
3.	Diabetes	*Clostridium, Bacteroides*	*Lactobacillus*	(15)
4.	Autism	*Bacteroides vulgates, Desulfovibrio*	*Firmicutes* *Actinobacteria*	(16)
5.	Cardiovascular	*Enterobacteriaceae*	*Bifidobacterium*	(17)

Factors affecting gut microbiome balance and dysbiosis

1.1.1 Dietary factors

Diet plays a crucial role in maintaining gut metabolism and a healthy microbiome. Rapid lifestyle changes have increased the intake of high-fat, high-sugar, and high-salt foods while reducing dietary fiber consumption, disrupting microbial balance. Such dysbiosis impairs fat digestion and absorption. Normally, bile acids emulsify fats into absorbable forms, and most primary bile acids are reabsorbed through enterohepatic circulation. However, those that escape get converted by gut microbes into secondary bile acids (deoxycholic and lithocholic acids), which influence host metabolism and immune signalling. Under dysbiosis, excessive secondary bile acid production can damage intestinal cells, induce oxidative stress and inflammation, and contribute to colorectal cancer, liver disorders, and metabolic diseases. (18)

1.1.2 Physical activity

Varying level of physical fitness is directly correlated to difference in healthy gut condition of individuals. Studies reveal that physical activities and exercise positively alter the gut microbiota composition and structure. Peak oxygen uptake during physical activities is reported to enhance the ration of α- diversity of microbes. (19)

1.1.3 Antibiotic associated dysbiosis

Antibiotic-associated dysbiosis refers to the imbalance of gut microbiota caused by antibiotic use, particularly broad-spectrum antibiotics that eliminate both harmful and beneficial bacteria. This disruption reduces microbial diversity, alters gut metabolism and immune regulation, and compromises gut homeostasis. The loss of beneficial microbes promotes the overgrowth of opportunistic pathogens and contributes to antibiotic resistance. Clinically, it manifests as digestive disturbances, increased infection susceptibility, immune dysregulation, and a higher risk of allergies, atopic disorders, and chronic metabolic diseases. (20) Several other factors contribute to microbial dysbiosis which include psychological stress through gut-brain axis (alters gut motility and microbial balance), exposure to environmental pollutants and toxins (damages healthy microbiome), aging factors (naturally shifts microbial composition) and infections. Additionally, factors such as hygiene practices, sleep practices and patterns and medication use like proton pump inhibitors and NSAIDs significantly impact gut microbial stability.

2. Limitations of Conventional Microbiome-Modulating Therapies

Several traditional approaches and food supplements such as dietary interventions, probiotics, prebiotics, synbiotics and faecal microbiota transplantation have been extensively employed to restore gut microbial balance. Although these strategies have shown a beneficial outcome in specific context but their efficacy and long-term consistency still stand as a challenge due to multiple reasons. Many studies have revealed that most probiotics strains fail to survive the acidic gastric environment or becomes inactive upon bile exposure resulting in low viability upon reaching intestine. They often show slow onset and require long-term administration to achieve measurable results. It makes them less effective in case of severe dysbiosis. The other possible cause is exogenous probiotics exhibit transient colonization and suffer being outcompeted by native microbiota. (21) Host genetics, age, diet pattern, medication type and term and existing gut microbiome composition significantly influence the therapeutic outcome and reproducibility of these exogenous supplements.(22) Conventional formulations and supplements lack site-specific delivery leading to premature release and degradation of active components which in turn reduce their therapeutic potential and bioavailability. (23) Therapies like faecal microbiota transplantation (FMT) limit widespread adoption due to major safety concerns like potential transmission of pathogens, antibiotic resistant genes or unwanted microbial community and lack of global standardization of donor screening. (24) Most of the conventional methods exhibit non-specificity as they broadly alter the gut microbial composition rather than specifically targeting metabolic pathways responsible for disease-related dysbiosis. This gap highlights the need for next generation delivery platforms like green nanocarrier-based approaches to counter the limitations and enable a safe and stable site-targeted delivery of eubiotic agents.

3. Green Nano-carriers as next generation platforms for eubiotic agents

Synthetic nanocarriers such as polymeric nano-particles (NPs), metallic nano-particles (MNPs) and liposomes for gut targeted delivery have demonstrated excellent drug loading efficiency and impressive controlled release properties yet their fabrication involves utilization of toxic solvents, high energy processes and non-biodegradable components. In contrast to these concerns, green nano-carriers have emerged as a sustainable and biocompatible alternative which not only demonstrates long-term efficacy but also proves environmental sustainability. (25) Green nano-carriers are synthesised from naturally-derived materials like polysaccharides, lipids, proteins, chitosan, plant extracts which endow them with properties like increased biocompatibility, biodegradability and minimal toxicity, enhanced gut stability and improved tolerance. (26)

3.1 Green Nano-delivery: Mechanistic approach

By various connected mechanistic routes, green nanocarriers can rebalance gut ecology and host-microbiome dialog, with repercussions upon microbial metabolite profiles, oxidative stress and inflammation, barrier integrity to the epithelium, and signals to the immune system.

3.1.1 Modulation of Microbial Metabolites

One of the core axes through which nanocarrier-based therapeutics act on gut homeostasis is through the modulation of microbial metabolism. Through the targeted release of prebiotic molecules, substrates, or microbial modulators (e.g. oligosaccharides, polyphenols, or probiotic strains), green nanocarriers can non-selectively expand the quantity or activity of SCFA producing communities. Raising important SCFA (particularly butyrate, propionate, acetate) aids in the energy metabolism of colonocytes, dampened the fluctuations of luminal pH, and inhibit opportunistic pathogens. In one study, engineered postbiotic nanoparticles that release butyrate locally in the colon were found to restructure the dysbiotic microbiota in Dextran Sulphate Sodium (DSS) induced colitis, amplify the gut levels of butyrate, as well as restructure microbiota diversity to resemble that of healthy controls. The outcome was the concurrent decrease in the levels of systemic inflammatory cytokines TNF-α and IL-6 (27).

Besides that, green nanocarriers can also have an impact on enterohepatic bile acid metabolism. (28) Through microbiota taxa modulation (e.g. Clostridium clusters, Bacteroides), that produce bile salt hydrolases (BSH) or 7α-dehydroxylases, they change the ratios between primary to secondary bile acids. This change in bile acid pools acts as feedback into host receptors (TGR5, FXR), to control intestinal motility, barrier integrity, and regional self-immune tone. As limited direct proofs of changed bile acid pools by green nanocarriers are smaller in number, the overarching generalization of nanocarrier-controlled microbiome alteration can be extrapolated to additional metabolite axes beyond SCFAs (e.g. indoles, bile acids). Metabolite modulation as a focal point in microbiome therapies has recently featured in some reviews of oral functional nanomaterials. (29,30)

3.1.2 Reduction of ROS and Inflammatory Cytokines

Excessive reactive oxygen species (ROS) and inflammation are features of dysbiosis and gut barrier breakdown. Green nanocarriers typically integrate antioxidant functionalities (e.g. phenolic molecules, flavonoids, metal oxides prepared through green reduction) or co-deliver antioxidant enzymes or molecules, scavenging ROS and abolishing oxidative stress in the process. By decreasing ROS levels, they inhibit oxidative damage to the epithelium and to the immune cells, decrease lipid peroxidation, and suppress redox-sensitive inflammatory pathways like NF-κB and MAPK. In one study, biogenic selenium nanoparticles (SeNPs) enhanced intestinal oxidative damage in models suppressing epithelial–immune crosstalk with consequent barrier integrity preservation. Notably, through the dampening of local inflammation, green nanocarriers can disrupt the vicious cycle wherein microbial dysbiosis spawns ROS and overproduction of cytokines, subsequently disrupting microbiota as well as barrier function. (31–33)

3.1.3 Influence on Epithelial Barrier and Immune Signalling

A third mechanistic area involves direct modulation of epithelial barrier integrity and signalling networks of the immune system. The gut epithelial barrier, with tight junction proteins such as occludin, claudins, ZO-1 (Zonula Occludens-1), the mucus barrier, along with intercellular communication with the immune compartment, plays a crucial role in the gut barrier function. Green nanocarriers can promote barrier integrity in multiple ways.

First mechanistic area is the local production of protective metabolites like butyrate induces regulation of barrier tight junction proteins along with Mucin gene expression. Butyrate mediated activation of signalling pathway *viz.* stabilization of HIF-1, inhibition of histone deacetylases in epithelial cells, helps to strengthen barrier stability and reduces para-cellular permeability. Secondly, significant response can be observed due to the possible interaction of green nanocarriers with goblet cells by adjusting cell signalling pathway. Recent reviews on interaction of nanoparticle and intestinal cell, explained that nanocarriers can move through mucus, be internalized by M cells or enterocytes, or even temporarily open tight junctions to enable localized delivery without causing any prolonged change in barrier function. Lastly, at the level of immune signalling, by controlling antigen exposure and cytokine environments, green nanocarriers influence how key immune cells such as dendritic cells, macrophages, and innate lymphoid cells respond. In this way, green nanocarriers help maintain a stronger link between epithelial health and immune regulation. (34,35)

4. Green-nano delivery approaches for restoring eubiosis

4.1 Antioxidants and polyphenols

Several recent green nano-formulations demonstrate potentially enhanced antioxidant gut-target delivery to restore microbial balance. Polyphenol based “nano-armor” coatings combine nano-enzymes with potent antioxidants to reduce oxidative stress and promote SCFA-producing bacteria. The polyphenol-nanoenzyme-armoured *E.coli* strategy has resulted to scavenge reactive oxygen species and ameliorate intestinal inflammation and dysbiosis in murine inflammatory bowel disease (IBD) models. (36) Another study reveals curcumin loaded selenium-decorated biodegradable NPs potentially increased curcumin bioavailability, reduced gut inflammation and favoured modulation of gut microbiome in preclinical models. (37) Quercetin, a potent bioflavonoid when delivered via pH-sensitive NPs, targeted to colon attenuates DSS-induced colitis, repaired endothelial barrier function and shifted gut microbe population towards healthy profile. (38) Similar such studies are also reported for microbe-modulating effect for tea polyphenols encapsulated in green NPs system which were reported to successfully protect labile antioxidants from gastric degradation and reduced intestinal oxidative stress. (39)

4.2 Probiotic encapsulation

Multiple formulation studies indicate enhanced efficacy of green NPs improving in-vivo probiotic survival, delivery and clinical efficacy. Naturally derived encapsulation matrices such as alginate, chitosan and protein-based hydrogels protect probiotic strains from gastric and bile acid degradation which significantly increase gut viability. Meta-analytical evidences show that encapsulated probiotics are associated with improved colonization of microbes, reduced antibiotic associated diarrhoea and enhanced metabolic markers suggesting improved functional delivery to the gut and downstream systemic effects. Collective researches also indicate that advanced coatings such as dual-layer alginate-chitosan and pH-sensitive Eudragit enable target release of probiotics in colon and enhanced gut population of beneficial microbial taxa. (40)

4.3 Enzymatic delivery

Enzyme therapy targeted to gut is oriented to deliver detoxifying and metabolism restoring enzymes such as superoxide dismutase (SOD), catalase, lactase and hydrolases. Oral administration of enzymes is restricted due to proteolytic degradation, poor gut stability and limited intestinal residence time. Green nano-carriers address these challenges by protecting enzyme structure through pH or enzyme responsive colon-targeted delivery. (41) Numerous findings illustrate functional benefits of SOD loaded oral NPs which significantly attenuated experimental colitis and oxidative markers while improving gut mucosal healing. The table below summarises few highlighted green nanocarrier-based formulations antioxidants, prebiotics/probiotics and enzymes.

5. Conclusion and future prospect

The human gut microbiome plays crucial role in maintaining immunity, metabolism and neurological functions. Dysbiosis of healthy gut microbe population is root cause for major metabolic syndromes and gastro-intestinal disorders. Conventional methods of delivering gut health restoring food, diets, supplements like probiotics and prebiotics are frequently constrained by their lower bioavailability, slow onset, biocompatibility and insufficient site targeting. By facilitating their delivery into the gut by green nano and micro carriers offer better strategies for restoring eubiosis with lower risk of systemic effects. Future researches ought to concentrate on standardizing fabrication procedures for improving target specificity to particular strains and substrates or metabolites and assessing long term safety and bridge the gap between improved drug delivery for clinical translation and natural treatment by offering customised nanotherapeutics.

Table No. 3 Summarises various green nanocarrier systems carrying microbiome balancing therapeutic agents for restoring gut eubiosis.

Sr. No.	Therapeutic agent	Nano-carrier type	Delivery strategy	Model system	Key outcome	Reference
1.	Curcumin	Chitosan NPs	Colon targeted/ pH-responsive release	DSS induced colitis mice	Reduced gut inflammation, enhanced SCFAs levels	(42)
2.	Quercetin	Alginate-chitosan NPs	Colon targeted	DSS colitis rats	Reduced oxidative stress and inflammation, improved barrier function.	(43)
3.	Probiotics (*Bifidobacterium*, *Lactobacillus*)	Alignate/ chitosan-coated nano-capsules	Colon targeted	Simulated GI model	Improved viability, enhanced colonization	(44)
4.	Lactase enzyme	Alginate-chitosan NPs	Colon targeted/pH-responsive release	Preclinical mice	Enzyme protection in GIT, enhanced stability, reduced inflammation	(45)
5.	Resveratrol	Zein NPs	Controlled intestinal release	Rodent model	Reduced oxidative stress	(46)
6.	Polyphenol-loaded nano bubbles	Bio-degradable lipid carriers	Colon targeted antioxidant delivery	Murine colitis	Enhanced antioxidant activity, improved microbiome balance	(47)

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