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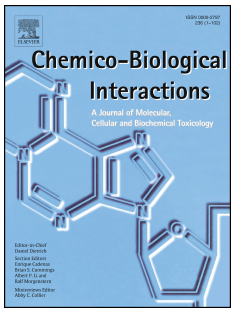

Revolutionising Lung Health: Exploring the Latest Breakthroughs and Future Prospects of Synbiotic Nanostructures in Lung Diseases

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Revolutionising Lung Health: Exploring the Latest Breakthroughs and Future Prospects of Synbiotic Nanostructures in Lung Diseases

Ayeh Bani Saeid [a,b], Gabriele De Rubis [a,b], Kylie A Williams [a], Stewart Yeung [a,b], Dinesh Kumar Chellappan [c], Sachin Kumar Singh [b, d], Gaurav Gupta [e,f,g], Philip M. Hansbro [h], Mohammad-Ali Shahbazi [i], Monica Gulati [b,j], Indu Pal Kaur [k], Hélder A. Santos [i,l], Keshav Raj Paudel [h, **], Kamal Dua [a,b,*]

[a] Discipline of Pharmacy, Graduate School of Health, University of Technology Sydney, Ultimo, NSW, 2007, Australia

[b] Faculty of Health, Australian Research Centre in Complementary and Integrative Medicine, University of Technology Sydney, Ultimo, NSW, 2007, Australia

[c] Department of Life Sciences, School of Pharmacy, International Medical University, Bukit Jalil, 57000, Kuala Lumpur, Malaysia

[d] School of Pharmaceutical Sciences, Lovely Professional University, Jalandhar-Delhi G.T Road, Phagwara, 144411, India

[e] Centre for Global Health Research, Saveetha Medical College, Saveetha Institute of Medical and Technical Sciences, Saveetha University, India

[f] School of Pharmacy, Graphic Era Hill University, Dehradun 248007, India

[g] School of Pharmacy, Suresh Gyan Vihar University, Jagatpura, 302017, Jaipur, India

[h] Centre for Inflammation, Faculty of Science, School of Life Sciences, Centenary Institute and University of Technology Sydney, Sydney, NSW, 2007, Australia

[i] Department of Biomaterials and Biomedical Technology, University Medical Center Groningen, University of Groningen, Groningen, 9713 AV, The Netherlands

[j] School of Pharmaceutical Sciences, Lovely Professional University, Phagwara, Punjab, India

[k]University Institute of Pharmaceutical Sciences, Punjab University Chandigarh, India

[l] Drug Research Program Division of Pharmaceutical Chemistry and Technology, Faculty of Pharmacy, University of Helsinki, Helsinki, FI-00014, Finland

Corresponding Authors: Kamal.dua@uts.edu.au & KeshavRaj.Paudel@uts.edu.au

Abstract

The escalating prevalence of lung diseases underscores the need for innovative therapies. Dysbiosis in human body microbiome has emerged as a significant factor in these diseases, indicating a potential role for synbiotics in restoring microbial equilibrium. However, effective delivery of synbiotics to the target site remains challenging. Here, we aim to explore suitable nanoparticles for encapsulating synbiotics tailored for applications in lung diseases. Nanoencapsulation has emerged as a prominent strategy to address the delivery challenges of synbiotics in this context. Through a comprehensive review, we assess the potential of nanoparticles in facilitating synbiotic delivery and their structural adaptability for this purpose. Our review reveals that nanoparticles such as nanocellulose, starch, and chitosan exhibit high potential for synbiotic encapsulation. These offer flexibility in structure design and synthesis, making them promising candidates for addressing delivery challenges in lung diseases. Furthermore, our analysis highlights that synbiotics, when compared to probiotics alone, demonstrate superior anti-inflammatory, antioxidant, antibacterial and anticancer activities. This review underscores the promising role of nanoparticle-encapsulated synbiotics as a targeted and effective therapeutic approach for lung diseases, contributing valuable insights

into the potential of nanomedicine in revolutionizing treatment strategies for respiratory conditions, ultimately paving the way for future advancements in this field.

Keywords: Synbiotic; nanoencapsulation; nutraceuticals; lung disease; prebiotic; probiotic

1. Introduction

The human microbiome, a complex and diverse community of microorganisms inhabiting various parts of the body, plays a pivotal role in maintaining overall health (Alam et al., 2022; Gilbert et al., 2018). Comprising trillions of bacteria, viruses, fungi, and other microorganisms, the human microbiome actively contributes to essential physiological functions (Gilbert et al., 2018; Swanson et al., 2020). Disturbances in this delicate microbial balance, known as dysbiosis, have been linked to various health conditions, with lung diseases emerging prominently on the list of potential consequences (McAleer & Kolls, 2018).

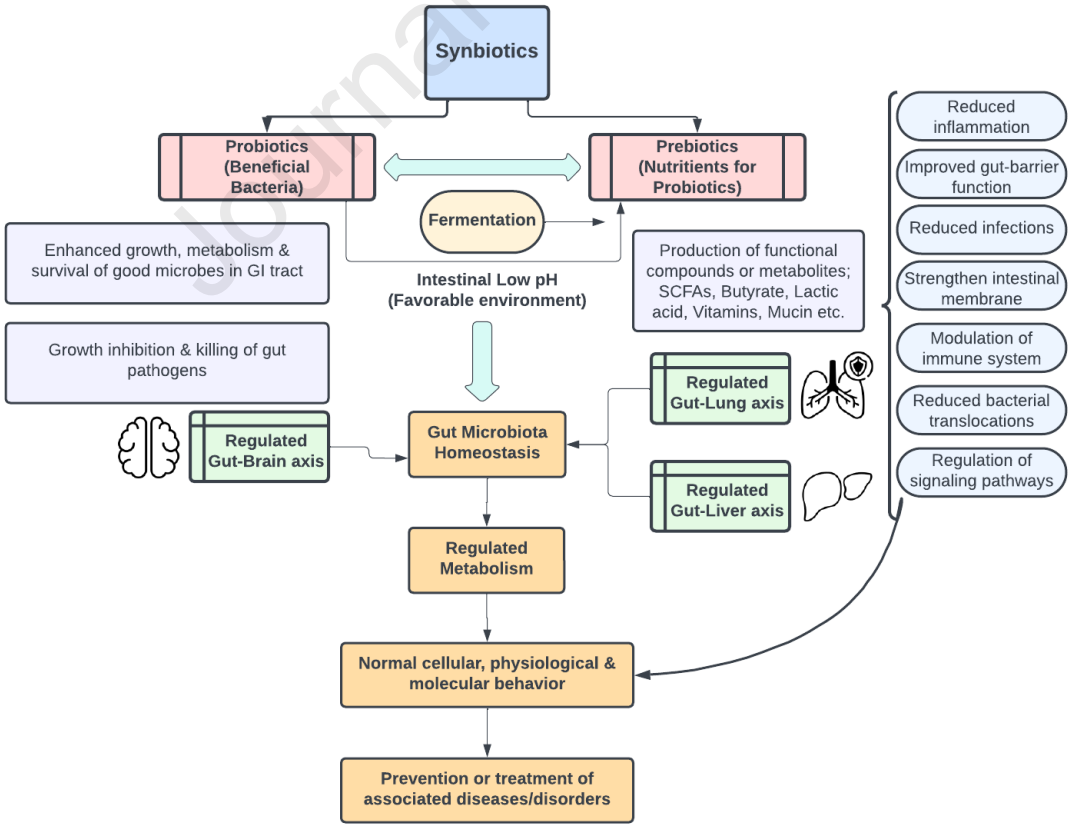

Figure 1. Major roles of probiotics, prebiotics and synbiotics on human health. This figure illustrates the diverse mechanisms through which probiotics, prebiotics, and synbiotics exert their positive effects on human health, including modulation of gut microbiota composition, enhancement of gut barrier function, immune system modulation, production of bioactive compounds, and potential therapeutic applications in various diseases. Figure were designed on Lucidcharts: https://www.lucidchart.com/pages/

As per the World Health Organisation (WHO), respiratory-related conditions account for three out of the top six global causes of death. Chronic Obstructive Pulmonary Disease (COPD), lower respiratory tract infections (LRTI), and lung cancers hold the third, fourth, and sixth positions, respectively, underscoring the crucial need for comprehensive research into these health issues (Saeid et al., 2023). Central to the pathophysiology of these conditions are intricate interplays of inflammation, oxidative stress, and the impact of lung infections. Inflammation, often triggered by various environmental factors such as pollution or smoking, plays a pivotal role in the initiation and progression of chronic respiratory diseases, including asthma, COPD, and interstitial lung diseases (Hikichi et al., 2019). Concurrently, oxidative stress, arising from an imbalance between reactive oxygen species (ROS) generation and antioxidant defences, exacerbates tissue damage and perpetuates inflammatory responses within the respiratory system (Boukhenouna et al., 2018). Moreover, lung infections, whether viral, bacterial, or fungal in origin, further exacerbate inflammation and oxidative stress, heightening the risk and severity of chronic respiratory disorders. Importantly, these pathophysiological mechanisms are intricately linked to the development and progression of lung cancer, wherein chronic inflammation and oxidative stress create a conducive microenvironment for oncogenesis and tumour progression (Kim et al., 2023). While conventional therapies for lung diseases, including bronchodilators and corticosteroids, often

focus on symptom management (Kerstjens et al., 2019; Mkorombindo & Dransfield, 2020), a growing body of research underscores the significance of addressing dysbiosis at its root (McAleer & Kolls, 2018). Among the emerging strategies to restore microbial equilibrium, the use of prebiotics and probiotics has gained substantial attention (Gollwitzer & Marsland, 2014). Probiotics, which are live microorganisms primarily consisting of bacteria and sometimes yeasts, have shown immunomodulatory effects when administered in adequate quantities. They influence the balance of Th1/Th2 cells and promote anti-inflammatory responses (Gollwitzer & Marsland, 2014; McAleer & Kolls, 2018). On the other hand, prebiotics, selective substrates for beneficial microorganisms, contribute to the overall health of the host (Gollwitzer & Marsland, 2014). Synbiotics, a combination of live microorganisms and their selectively utilised substrates, bring together the synergistic effects of probiotics and prebiotics to confer health benefits on the host (Swanson et al., 2020). It is important to note that the role of synbiotics is not limited to respiratory health and has been extensively studied in other branches of medicine (Alam et al., 2022; Ale & Binetti, 2021; Markowiak & Śliżewska, 2018; Patel et al., 2014), as shown in Figure 1.

However, synbiotic structures involve carefully chosen prebiotic types, such as fibres or oligosaccharides and specific probiotic strains with proven health benefits (Ladaycia et al., 2021). To enhance viability and stability, protective mechanisms like microencapsulation or nanoparticles may be employed, allowing targeted delivery to the gastrointestinal tract (Gilbert et al., 2018). Achieving optimal ratios and balancing the synergistic effects of prebiotics and probiotics is crucial, with considerations for controlled release mechanisms and bioavailability (Liang Hong et al., 2021). With recent advancements in nanotechnology, the design of many medicinal compounds is trending towards nanoencapsulation for more efficient patient responses (Gilbert et al., 2018). For instance, in plant-derived bioactives known as phytoceuticals, nanotechnology has been estimated to dominate the design of 75% of such

compounds in the next 10 years (Joseph et al., 2023). Nutraceuticals, such as synbiotics, are also not exceptions. The integration of nanotechnology into synbiotics involves encapsulating probiotics and prebiotics within nanostructures, such as nanoparticles or liposomes, to optimise their delivery to the lungs (Liang Hong et al., 2021; Pandey et al., 2015). However, the selection of the right nanostructures for the encapsulation of synbiotics is much more challenging than those in phytoceuticals (Khursheed et al., 2022), mostly due to the potential of some nanoformulations (*e.g.*, TiO_2 NPs) to react with the human microbiome (Zhao et al., 2020). Hence, the effects of selected nanostructures on both the synbiotic components and human microbiota should be take into account simultaneously.

The purpose of this review article is to delve into recent trends, applications, and prospects surrounding synbiotic nanostructures in the context of lung diseases. By examining the current state of research and developments, we review the common nanoformulation techniques available for the delivery of synbiotics to the desired location for better respiratory-related outcomes.

2. Synbiotic Nanostructures: Concept and Composition

Synbiotic nanostructures represent an innovative approach that synergises the benefits of probiotics and prebiotics with the advancements in nanotechnology for targeted drug delivery (Liang Hong et al., 2021; Khursheed et al., 2022). The exact mechanism of action of synbiotics is not fully understood, but their effects on various health pathways have been studied, as shown in Figure 2. In the gut, they contribute to microbiota modulation, fostering a balance of beneficial bacteria and producing short-chain fatty acids through fermentation, which not only nourishes colonocytes but also reinforces the intestinal barrier, preventing the translocation of harmful substances into the bloodstream (Marco et al., 2017). The immune system benefits from synbiotics through the regulation of immune responses (Marco et al., 2017; Markowiak

& Śliżewska, 2017). They influence cytokine production and enhance the activity of immune cells, contributing to a balanced immune system. Additionally, the antimicrobial activity of probiotics within synbiotics helps inhibit the growth of pathogenic bacteria, maintaining a healthy microbial balance (Gunaswetha et al., 2023). In the cardiovascular system, synbiotics may contribute to the reduction of serum cholesterol levels and modestly impact blood pressure regulation (Theofilis et al., 2024). Metabolically, they play a role in regulating blood glucose levels and may aid in weight management through their influence on energy metabolism (Theofilis et al., 2024). Furthermore, as shown in Figure 1, the gut-brain axis serves as a crucial link between synbiotics and the central nervous system. By influencing bidirectional communication between the gut and the brain, synbiotics may impact mood and cognitive function (Mayer et al., 2015). Probiotics, found in synbiotics, may contribute to neurotransmitter production, further influencing mental well-being (Mayer et al., 2015). Synbiotics extend their benefits to skin health, potentially alleviating conditions such as acne or eczema through their anti-inflammatory effects (Gurry, 2017). In the respiratory system, they may enhance immune support, reducing the frequency and severity of respiratory infections (Gurry, 2017).

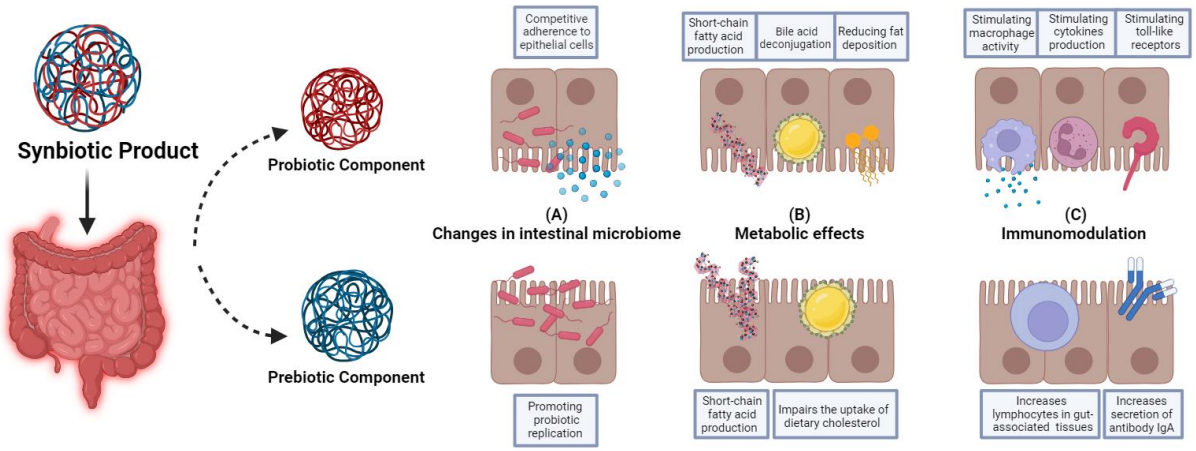

Figure 2. Multi-faceted impact of synbiotics on human health. The tripartite representation highlights the interconnected dynamics of the intestinal microbiome, metabolic processes, and

immunomodulatory responses influenced by synbiotic interventions. Figure 2 were designed on Biorender: https://www.biorender.com/

Nanotechnology confers several advantages in delivering synbiotics to the lungs. The small size of nanocarriers allows for increased stability and protection of probiotics during transit through the harsh gastrointestinal environment. This, in turn, enhances their survival and viability in the lungs upon delivery (Liang Hong et al., 2021). Nanoparticle-based delivery systems, either through inhalation or orally, can target specific lung tissues, ensuring localised treatment and minimising off-target effects (Chen et al., 2022). By fine-tuning the physicochemical properties of the nanostructures, researchers can achieve tailored release kinetics and optimise the therapeutic impact of synbiotic agents in the lung microenvironment (Chen et al., 2022). This section provides a detailed review of the nanoparticles (NPs) with the most potential for being used in the encapsulation and delivery of synbiotics.

2.1. Organic NPs

2.1.1 Starch NPs

Starch, the most abundant carbohydrate polymer, comprises linear amylose and highly branched amylopectin molecules. Amylose consists of glucosyl moieties linked by α-1,4 glycosidic bonds, while amylopectin is a highly branched polymer with α-1,6 glycosidic bonds per 30 glucosyl molecules linked through α-1,4 glycosidic linkage (Prasher et al., 2021; Razavi et al., 2021). Starch nanoparticles (SNPs) and starch nanocrystals (SNCs), derived from purified starch granules, find widespread use in drug delivery (Dufresne et al., 1996). SNCs result from enzymatic or acid hydrolysis, yielding crystalline structures, while SNPs are amorphous and synthesised from congealed starch (Dufresne et al., 1996). Understanding the exact structure of starch would help to only use it to encapsulate those structurally compatible

synbiotics. Hydrochloric acid (HCl) or sulfuric acid (H_2SO_4) is typically used for SNC synthesis, involving suspension of starch in acid, washing, and sonication (Ahmad et al., 2019). In contrast, SNPs are obtained by disrupting the non-crystalline domain of semi-crystalline starch granules (Ahmad et al., 2019; Dangi et al., 2023). While according to Angelllier et al. SNPs were found unsuitable for probiotic encapsulation due to decreased survival, efforts to enhance SNP properties using chemical reactions were explored (Angellier et al., 2004). Capsules made from SNCs-alginate starch gel exhibited a higher survival rate for *Lactobacillus brevis* under simulated gastrointestinal conditions, highlighting their potential in probiotic and synbiotic delivery (Kumari et al., 2020; Thangrongthong et al., 2020).

In another study conducted by Hong et al., the application of SNPs in treating probiotics yielded remarkable results. The probiotics, when treated with starch NPs, exhibited exceptionally potent antimicrobial activity against both gram-positive and gram-negative pathogens (L Hong et al., 2021). Moreover, when examining the antimicrobial efficacy of *Lactobacillus spp.* (LL) treated with PSNs (Presumably Polysaccharide Nanoparticles), it was found to surpass that of both the untreated group and the group treated with starch alone. This enhanced effectiveness was particularly notable against gram-negative *Escherichia coli k88*, *Salmonella gallinarum*, and gram-positive *Listeria monocytogenes* (L Hong et al., 2021). This team also conducted another study on the genetic response of the treated groups, revealing a significant increase in the expression levels of stress response genes, including dnaK, dnaJ, and groES, in the PSNs-treated groups compared to the groups treated with starch alone or the untreated LL group (Liang Hong et al., 2021). This observation suggests a potential link between the application of PSNs and the upregulation of stress response genes, which may contribute to the enhanced antimicrobial effects observed in the treated probiotics and synbiotics.

It is notable that the effects of starch in lung diseases related treatments have been shown for a while. In one of the recent studies in this area, starch served as a nanocarrier for the cytotoxic

drug "gefitinib," yielding promising outcomes (Amin et al., 2023). This resulted in reduced side effects, improved solubility and bioavailability, better therapeutic control, higher cellular uptake into A549 cells, and greater cytotoxicity, represented by a significantly higher apoptotic effect and cell growth inhibition (Amin et al., 2023). In the context of synbiotics, the enhanced bioavailability after encapsulation with starch has been linked to efficient absorption of prebiotics and better adherence of probiotics to the intestinal lining (Kvakova et al., 2021). Therefore, despite the difficulties in the synthesis of starch for synbiotic encapsulation, it's essential to further study its advantages, especially in improving the pharmacokinetic profile for treating lung diseases.

2.1.2. Chitosan NPs

Chitin (poly-(1 → 4)-β-linked N-acetyl-D-glucosamine) is a natural macromolecule found in the cell wall of zygomycetes fungi and arthropod exoskeletons (Gharieb et al., 2015). Through alkaline deacetylation chitosan is derived, representing a 70% deacetylated food-grade polycationic polymer of chitin (Köhler et al., 2009). Unlike chitin, chitosan has a degree of deacetylation exceeding 50%, contributing to its solubility in weak acids and enhancing its applicability in biomedical fields such as pharmaceuticals and food industries (Mohammed et al., 2017; Shajahan et al., 2017; Solanki et al., 2020). Notably, chitosan's positive charge allows it to form strong electrostatic interactions with the negatively charged mucin in the intestinal mucus, facilitating robust binding for synbiotics (Dangi et al., 2023).

Chitosan NPs have been widely proposed for micro and nanoencapsulation of bacterial cells and probiotics, exhibiting higher muco-adhesive strength than chitosan alone (Liang et al., 2017; Shajahan et al., 2017). For instance, microencapsulation of the probiotic *Escherichia coli* Nissle (EcN) in a mixture of alginate and chitosan-NPs demonstrated increased resistance to high temperature, low pH, and high bile salt concentrations (Mawad et al., 2018). Recent

studies further revealed enhanced adhesion of chitosan-loaded EcN to intestinal cells, providing greater absorption and bioavailability (Chen et al., 2013). Say et al. also showed that combining chitosan and probiotic *Acinetobacter* can enhance the immune-related genes and serum immune parameters comparing to the groups treated with probiotic only (Say et al., 2023), even more highlighting the compatibility of chitosan as a nanocarrier with probiotics/synbiotics. According to the findings of Ivanovska and colleagues, the anti-inflammatory potential of *Lactobacillus casei* 01 (L. casei 01) is notably higher when encapsulated in synbiotic chitosan-Ca-alginate nanoparticles compared to the effects observed with the non-encapsulated probiotic L. casei 01 and prebiotic oligofructose-enriched inulin (Ivanovska et al., 2017; Kouhkan et al., 2020). This research supports the utilisation of encapsulated probiotic and/or synbiotic-based treatments as a promising step forward in conceptualising successful therapeutic perspectives for inflammatory diseases.

In addition to chitosan being a proper candidate for the delivery of synbiotics, it has also been shown that chitosan-loaded nanomedicines present a promising avenue for treating respiratory diseases, utilising the natural biopolymer's diverse pharmacological benefits (Gulati et al., 2021). According to Gulati et al., the proven actions ranging from antioxidant and anti-inflammatory to antimicrobial and regenerative, chitosan's unique characteristics, including excellent mucoadhesion and gel-forming properties, ensure prolonged drug retention in the respiratory tract, enhancing therapeutic outcomes of nutraceuticals including synbiotics (Chan et al., 2023; Gulati et al., 2021). Additionally, a significant obstacle encountered in the oral delivery of probiotic bacteria is their swift passage through the intestine and excretion in feces (Razavi et al., 2021). This challenge can be mitigated through the utilisation of certain nanomaterials like chitosan nanoparticles or nanocoatings, which have demonstrated the ability to improve mucoadhesion to the gastrointestinal wall (Chen et al., 2013; Razavi et al., 2021). Therefore, chitosan can be considered a suitable nanocarrier for active moiety, synbiotics or

248 probiotics in the treatment of lung diseases due to its simpler synthesis method compared to
249 starch and various biological effects.

250 *2.1.3. Nanocellulose*

251 Cellulose, a crucial carbon source, consists of (1 → 4)-linked β-D-glucose units forming
252 anhydroglucose units (Shi et al., 2019). Strong inter- and intramolecular hydrogen bonds result
253 in its semi-crystalline nature (Pinkert et al., 2010). Due to its amphiphilic nature,
254 biocompatibility, tunable surface properties, and low toxicity, cellulose is favoured as an
255 encapsulation material (Kian et al., 2019; Liu et al., 2017; Salimi et al., 2019). Nanocellulose
256 types, cellulose nanofibers (CNF) and cellulose nanocrystals (CNCs), are developed through
257 mechanical treatment and acidic dissolution, respectively (Kian et al., 2019; Kupnik et al.,
258 2020). Microgels from high cellulose nanofiber levels exhibit enhanced cell survival and
259 sustained probiotic release of a synbiotic containing *Lactobacillus plantarum* (Luan et al.,
260 2018). *Lactoplantibacillus plantarum* probiotic strain has the anti-influenza virus potential that
261 can protect against lung infection (Majumder et al., 2022). Nanocellulose can also form viscous
262 gels upon hydration, acting as a cryoprotectant for probiotics. Many studies have been trying
263 to modify and improve the synthesis of nanocellulose as a drug carrier. For instance, hydrogen
264 bond formation between sodium alginate and nanocellulose was found to offer an efficient
265 controlled release system (Zhang et al., 2018). Gel microspheres encapsulating *L. plantarum*
266 demonstrated better protection under harsh conditions comparing to non-capsulated probiotics
267 (Klemm et al., 2018).

268 Moreover, bacterial cellulose from *Komagataeibacter xylinus*, a non-toxic and pure alternative,
269 offers superior mechanical properties and versatile production modifications (Bottan et al.,
270 2015; Zaborowska et al., 2010). Other studies also showed that bio-nanocomposites comprising
271 bacterial nanocellulose, pectin, and Schizophyllum commune extract improved probiotic

survival rates under various conditions, suggesting nanocellulose's potential for prolonged probiotic/synbiotic storage and high survivability in harsh environments (Khorasani & Shojaosadati, 2016; Maleki et al., 2020). Encapsulation in a bio-composite of whey protein isolate, inulin, and crystalline nanocellulose further enhanced *L. rhamnosus* survivability in simulated gastrointestinal conditions (Maleki et al., 2020). Among different types of nanocellulose, CNC can reduce gastric fluid absorption, significantly enhancing the survival of probiotic bacteria throughout the gastrointestinal tract (Huq et al., 2017; Razavi et al., 2021). Additionally, CNCs find applications in the development of pharmaceutical products with extended shelf life, particularly those not requiring refrigeration. Its incorporation enhances the mechanical strength of carriers, as evidenced by improved compression strength in freeze-dried microbeads (Huq et al., 2017; Nahr et al., 2015). These findings highlight nanocellulose's utility in improving probiotic storage and viability under diverse conditions. Hence, compared to the last two discussed NPs, nanocellulose has proven to be more accessible, structurally adjustable, and well-tested in various fields, especially drug delivery, exhibiting great potential for further testing in the synbiotic field.

2.1.4. Phthalyl pullulan NPs

Pullulan is a neutral water-soluble polymer derived from starch *via* fermentation (Rekha & Sharma, 2007). Due to its unique structure, pullulan can be modified into hydrophobic derivatives such as cholesteryl-pullulan, forming self-assembling nanoparticles (NPs) (Rekha & Sharma, 2007). These NPs exhibit versatility by forming stable complexes with both hydrophobic and hydrophilic active ingredients, including probiotics (Hong et al., 2019; Rekha & Sharma, 2007). In a study by Hong et al., it was demonstrated that these NPs can create stable complexes with various medicines, enhancing flexibility (L Hong et al., 2021; Hong et al., 2019). The integration of *L. plantarum* with Phthalyl pullulan NP (PPN) resulted in the development of a novel prebiotic form. Probiotics, including *L. plantarum*, produce

297 bacteriocins as a primary defence mechanism (Castro et al., 2015; L Hong et al., 2021). Factors
298 such as culture pH, temperature, and pressure influence bacteriocin expression, affecting genes
299 associated with heat shock proteins (HSPs) and the stress response (Bove et al., 2013). The
300 study revealed that the encapsulation of synbiotic containing *L. plantarum* into PPNs induced
301 a modest intracellular stress response, stimulating antimicrobial activity without causing host
302 cell death. Consequently, the expression level of the plantaricin gene increased, activating the
303 host's defence system. Further research is needed to understand the precise process, but what
304 is obvious from the limited data on hand is that these probiotic/synbiotic pullulan-based NPs
305 have the capability to generate antimicrobial peptides effective against both Gram-positive and
306 Gram-negative bacteria. Furthermore, a study on phthalyl dextran nanoparticles, similar to
307 pullulan containing more novel forms of prebiotics, showed the capability to control the
308 metabolism of probiotic bacteria (Bove et al., 2013). This implies a promising approach for
309 modulating probiotics and utilising them to tackle the issue of bacterial resistance (Bove et al.,
310 2013).

311 ***2.2. Inorganic NPs***

312 Metal-based nanoparticles play a crucial role in synbiotic encapsulation, with magnesium oxide
313 nanoparticles (MgO NPs) gaining popularity due to their large surface area, cost-effectiveness,
314 and non-toxic characteristics (García-Rodríguez et al., 2022; D. Singh et al., 2023). In a study
315 by Yao et al., alginate-gelatin microbeads were used to encapsulate the probiotic *Pediococcus*
316 *pentosaceus* in the presence of MgO NPs (Yao et al., 2018). The MgO-loaded probiotic showed
317 enhanced viability in gastric fluids compared to non-encapsulated cells, suggesting that MgO
318 NPs may fill void spaces in microgels, reducing oxygen availability and protecting probiotics
319 from aerobic conditions (Nguyen et al., 2018). MgO NPs also demonstrated the ability to
320 neutralise hydrogen ions in the gastric environment, offering additional protection to probiotics
321 (García-Rodríguez et al., 2022; Nguyen et al., 2018).

Furthermore, investigations into commonly used probiotic bacteria are essential to fully comprehend the role of magnesium oxide in enhancing cell survival rates. Other metal-based nanoparticles, such as Silver (Ag) and titanium dioxide (TiO2), have been studied for their antimicrobial activity. Silver oxide NPs, in the presence of prebiotics, significantly decreased the populations of *L. casei*, *L. plantarum*, and *L. fermentum* (Rezaee et al., 2014). Similarly, TiO2 NPs exhibited potential antimicrobial effects, emphasising the need for further research to explore the applications and impacts of these nanoparticles on different probiotic strains in various conditions (Zhao et al., 2020). The antimicrobial properties of Silver Nanoparticles (Ag NPs) make them attractive for synbiotic encapsulation, enhancing protection against harmful microorganisms (Cattò et al., 2019; Rezaee et al., 2014). Additionally, Ag NPs have been explored for drug delivery systems, improving targeted delivery in the gastrointestinal tract (Cattò et al., 2019). Gold Nanoparticles (Au NPs) are known for biocompatibility and can be easily modified for better interaction with probiotics and prebiotics, offering a versatile platform for synbiotic delivery systems (Datkhile et al., 2023; Rezaee et al., 2014).

Titanium Dioxide Nanoparticles (TiO2 NPs) exhibit photocatalytic properties, suggesting advantages in controlled release triggered by external stimuli such as light (Zhao et al., 2020). The stability of titanium dioxide contributes to maintaining the integrity of synbiotics during storage and transit through the digestive system. Finally, Copper Oxide Nanoparticles (CuO NPs) with antimicrobial properties could enhance the overall antimicrobial Effect against pathogens in the gut when incorporated into synbiotic formulations (D. Singh et al., 2023). In summary, the diverse properties of metal-based nanoparticles present exciting possibilities for advancing synbiotic encapsulation and addressing various challenges in pro-/synbiotic modulation.

Table 1. Summary of the well-proven nanosynbiotics, nanoprobiotics and nanoprebiotics with potential respiratory-related effects.

Nutraceuticals	Nanoparticles Used	Key Findings	References
Lactobacillus caseissp. Casei	CuO NPs	Antimicrobial and anticancer effects	(Kouhkan et al., 2020)
Lactobacillus plantarum	Phthalyl pullulan	Significant anti-microbial activity against gram +/- bacteria	(Hong et al., 2019)
Lactobacillus casei	Se NPs	Probiotic bacteria and selenium nanoparticles both reduced inflammation and restore antioxidant enzymes	(Laslo et al., 2022)
Phthalyl pullulan nanoparticle (PPN)- treated *Lactobacillus plantarum*	Nanoemulsion	Increase in level of antibacterial peptides and reduce in infection rate/severity	(Hong et al., 2019)
Selenium (prebiotic) and L. *Rhamosus* (probiotic)	Se NPs	Moderate free radical scavenging capability leading to antioxidant activity	(Kaur & Rath, 2019)
Lactobacillus brevis	Ag NPs	Acceptable antibacterial activity against gram +/-	(Rajoka et al., 2020)

		bacteria and outstanding antioxidant activity through reduction in reaction oxygen species level	
Bifidobacteriumanimalisssp. lactis	Au NPs	Inhibition of autophagy leading to apoptosis and anticancer activity	(Wang et al., 2021)
***Lactobacillus rhamnosus* GG**	Ag NPs	Decrease in the number of HT-29 viable cells leading to anticancer properties.	(Dangi et al., 2023)

3. Synbiotic Nanostructures: Applications in Lung Diseases

As mentioned previously, the application of synbiotic nanostructures in lung diseases holds great promise. Asthma and COPD, two prevalent inflammatory lung conditions, could significantly benefit from this approach. Probiotics have been shown to improve lung function and alleviate inflammation in asthma patients (Hufnagl et al., 2020). In COPD, synbiotics can potentially ameliorate dysbiosis and restore gut-lung axis homeostasis, leading to better disease outcomes (Qu et al., 2022). Therefore, it is worthy to investigate the effect of synbiotics on common respiratory pathophysiological pathways, including inflammation, oxidative stress, infection, and cancer which will be reviewed in this section.

3.1. Anti-inflammatory Effect

As mentioned earlier, dysbiosis may lead to elevated production of pro-inflammatory cytokines in the intestine, and an imbalanced gut microbiome has the potential to trigger a pro-inflammatory reaction in the respiratory system contributing to the development of asthma or COPD (Hikichi et al., 2019). The utilisation of probiotics can boost mucus secretion, and prevent the degradation of tight junction proteins by reducing the presence of lipopolysaccharides (LPSs) (Cristofori et al., 2021). The binding of LPS to toll-like receptors (TLR 2, 4) on endothelial cells triggers the activation of dendritic cells and macrophage cells, leading to an increase in inflammatory markers (Sichetti et al., 2018). Additionally, probiotic therapy has been observed to reduce gut dysbiosis and intestinal permeability, thereby minimising the release of inflammatory biomarkers and attenuating unnecessary activation of the immune system (Martin et al., 2010). Consequently, probiotics contribute to the differentiation of T-cells toward Th2 and the production of Th2 cytokines such as IL-4 and IL-10 (Kwon et al., 2010). Probiotics typically function as ligands, engaging receptors of the innate immune system like TLRs expressed on intestinal epithelial cells and mucosal immune cells (Gunaswetha et al., 2023). This engagement also modulates various signalling pathways, including mitogen-activated protein kinases (MAPK), nuclear factor kappa B (NF-κB), phosphoinositide-3-kinase (PI3K), and peroxisome proliferator-activated receptor gamma (PPAR-γ), leading to the production of diverse cytokines and chemokines (Chan et al., 2021; Liu et al., 2016; Liu et al., 2018; Maldonado Galdeano et al., 2019). Furthermore, immune cells like dendritic cells uptake probiotics, facilitating dendritic cell maturation and stimulation of regulatory T cells (Treg), crucial for immune homeostasis and maintaining gut immune tolerance (Mohammed et al., 2019). Ultimately, this process leads to the generation of tolerogenic T-cell responses against food antigens and the commensal microbiota, preventing undesirable hypersensitivity and inflammation (Chan et al., 2023; Liu et al., 2018; Maldonado Galdeano et al., 2019).

Carvalho et al. conducted a study using a cigarette smoke-induced COPD mice model. They found that oral administration of *Lactobacillus rhamnosus*, a probiotic, suppressed lung inflammation, hindered tissue remodelling, and modulated key immune response factors (Carvalho et al., 2020). These included a reduction in TLR2, TLR4, TLR9, pro-inflammatory transcription factors, and an increase in anti-inflammatory proteins such as IL-10, thereby mitigating cytokine storm associated with COPD pathogenesis (Carvalho et al., 2020). Similar anti-inflammatory effects were observed in a study by Mortaz et al., where *Lactobacillus rhamnosus* and *Bifidobacterium* breve strains efficiently counteracted pro-inflammatory mediators induced by cigarette smoke in a human macrophage cell line model of COPD (Mortaz et al., 2015). Furthermore, in a study conducted by Wong et al., prebiotics, probiotics, and synbiotics demonstrated positive and anti-inflammatory outcomes, likely by influencing the gut microbiota, reinforcing the integrity of the intestinal barrier, and inhibiting IL-6/STAT3 signalling (Wong et al., 2022). In an umbrella review conducted by Mahapatro et al., probiotics and synbiotics demonstrated promising effects on inflammatory markers, especially TNF-α and C-reactive protein (CRP), important inflammatory markers in the pathogenesis of COPD and asthma (Mahapatro et al., 2023). In addition, the intake of synbiotic supplements can result in an increase in beneficial bacteria, including *Clostridium*, *Lactobacillus*, *Bifidobacterium,* and *Collinsella* and various functional pathways associated with the synthesis of amino acids and short-chain fatty acids (SCFA) (Tan et al., 2014). This was accompanied by a decrease in potentially pro-inflammatory *Parabacteroides* compared to the initial levels (Kim et al., 2013). Notably, changes in anti-inflammatory markers (IL-10 and sIgA) showed significant correlations with the alterations in the microbiota induced by synbiotic supplementation (Li et al., 2023). The systemic impacts of the gut microbiota are, in part, ascribed to the production of metabolites, such as SCFAs, known to mitigate lung inflammation by activating G protein-coupled receptors (Ivanovska et al., 2017). Analysing the interplays between microbiota and

immune cells holds promise for pinpointing therapeutic targets in the context of chronic lower respiratory diseases. For example, a rise in the *Bacteroidetes* to *Firmicutes* species ratio triggered by high-fibre diets can enhance SCFA production, thereby dampening inflammation through the activation of GPR40-43 (McAleer & Kolls, 2018). Ivanovska et al. also proved the presence of another specie , *L. casei 01*, as a safe probiotic strain for administration in conditions of chronic lower respiratory diseases (Ivanovska et al., 2017).

These findings collectively suggest that probiotics may serve as beneficial nutraceuticals, offering lung-protective effects while mitigating inflammation and immune response exacerbation in inflammatory respiratory diseases (Chan et al., 2023; Mortaz et al., 2015). Nonetheless, the optimal dosages and treatment durations remain undefined, and the molecular mechanisms of action for the majority of these agents are yet to be established.

3.2. Antioxidant Effect

Oxidative stress is characterised by an imbalance favouring oxidants over antioxidants (Nucera et al., 2022; Panth et al., 2016; Paudel et al., 2020). This disrupts cellular redox signalling and control, leading to molecular damage (Sies, 2015). The imbalance occurs when overall oxidant levels exceed the total antioxidant capacity within cells. Consequences include DNA hydroxylation, protein denaturation, lipid peroxidation, and apoptosis (Chan & Liu, 2022). In respiratory diseases, oxidative stress contributes to conditions like asthma and COPD (Qu et al., 2022). Synbiotics, as mentioned earlier, may counteract oxidative stress by enhancing antioxidant defences, offering potential therapeutic benefits for respiratory health (Qu et al., 2022). The antioxidant capabilities of synbiotics are associated with their capacity to activate and relocate nuclear factors (Cukkemane et al., 2020). These factors trigger the antioxidant defence enzymatic system, generate essential antioxidant molecules, and neutralise the generation of singlet oxygen and free radicals (Mohammed et al., 2019; Zheng et al., 2019).

Among probiotics, *Lactobacillus* and *Bifidobacterium* strains, especially *L. casei*, and the inclusion of inulin in synbiotics have demonstrated efficacy in protecting against free radical-induced damage (Kleniewska et al., 2016; Kleniewska & Pawliczak, 2017). Studies involving multistrain probiotics, such as VSL#3, combined with prebiotics like FOS and inulin, show significant *in-vitro* and *in-vivo* radical-scavenging abilities, leading to decreased respiratory oxidative stress indicators and increased catalase activity (Cruz et al., 2021). Recent meta-analyses indicate that synbiotic supplementation enhances antioxidant resistance and enzyme activity, with higher levels of TAC, GSH, SOD, and NO, and lower MDA levels compared to controls (Heshmati et al., 2018; Roshan et al., 2019).

Extensive research has been conducted on the prebiotic properties of NPs such as silver, gold, and metallic oxides including CuO and TiO2, particularly due to their antimicrobial and antioxidant capabilities (Mughal et al., 2021). The antibacterial effectiveness of these NPs is size-dependent, with smaller particles exhibiting greater efficacy against various pathogens. For instance, gold NPs incorporating *Lactobacillus kimchicus* demonstrated notable free radical scavenging against 2,2-diphenyl-1-picrylhydrazyl (DPPH) and displayed antimicrobial properties, contrasting with their corresponding gold salt (Markus et al., 2016). Similarly, a nanoformulation of the commercial probiotic Protexin® using selenium NPs, when administered to Wistar rats exposed to cadmium-induced oxidative stress, exhibited significant hepatoprotective effects (Al-Enazi et al., 2020; Laslo et al., 2022). The presence of nanoprobiotics effectively reversed the undesirable alterations induced by cadmium toxicity, showcasing their potential as a safe and effective nutritional intervention against heavy metal-induced oxidative stress (Al-Enazi et al., 2020; Kaur & Rath, 2019).

Collectively, these findings underscore the shared mechanism among probiotics and synbiotics which involves the neutralisation of oxidative agents, mitigating oxidative stress and its associated diseases linked to accelerated aging. Probiotics employ both enzymatic and non-

457 enzymatic antioxidant mechanisms, yielding metabolites with radical-scavenging abilities
458 (Mounir et al., 2022; Rajoka et al., 2020). Synbiotics, whether combined with antioxidant
459 prebiotics or not, demonstrate the capacity to generate superior antioxidant compounds. This
460 exploration of synbiotic-based approaches unveils a promising avenue for addressing health
461 issues in both animals and humans through the enhancement of natural antioxidants
462 (Kleniewska & Pawliczak, 2017). To fully optimize antioxidant production, a thorough
463 understanding of interactions within synbiotics and their impact on the host is imperative
464 (Kleniewska et al., 2016; Mounir et al., 2022). The effectiveness of synbiotics, such as those
465 containing L. casei and inulin, in protecting against oxidative stress damage further underscores
466 the potential therapeutic benefits of these compounds in positively influencing oxidative stress
467 parameters (Kleniewska & Pawliczak, 2017).

468 ***3.3. Antimicrobial Effect***

469 As per the WHO, respiratory tract infections (RTIs) manifest through various clinical
470 symptoms, encompassing typical flu, rhinitis, bronchitis, pneumonia, upper and lower RTIs.
471 Beyond their synergistic immune system effects, synbiotics play a crucial role in nutritional
472 strategies for addressing global challenges associated with respiratory infections and the
473 overuse of antibiotics in treating RTIs, as indicated by Markowiak in 2017 (Markowiak &
474 Śliżewska, 2017). Notably, the synbiotic intervention has demonstrated a 16% reduction in the
475 occurrence and prevalence of RTI cases, as reported by Chan et al. in 2020 (Chan & Liu, 2022).
476 Hence, their potential positive impact on eradication of respiratory pathogens should be
477 reviewed.

478 As mentioned previously, recent studies have explored the use of inulin, dextran, starch, and
479 pullulan as prebiotics in combination with nanotechnology, revealing that the resulting
480 nanoprebiotics significantly boost the antimicrobial capabilities of probiotics *in-vitro* (L Hong

et al., 2021; Hong et al., 2019; Liang Hong et al., 2021; Kim et al., 2013). These nanoprebiotics enhance the expression of Bacteriocin biosynthetic genes and stimulate the defence mechanisms of probiotics, leading to the production of antimicrobial peptides (Liang Hong et al., 2021). When exposed to nanoprebiotics, probiotics demonstrate broad-spectrum antimicrobial activity against both gram-positive and gram-negative pathogenic bacteria (Kim et al., 2019). In an *in-vivo* feeding experiment with normal mice, the inclusion of dextran as a nanoprebiotic improved gut microbiota in synbiotic association with probiotics (Kim et al., 2019). Phthalylpullulan NPs, when added to *Lactobacillus Plantarum*, resulted in a synbiotic combination that exhibited potent antimicrobial action against *Escherichia coli K99* and *Listeria monocytogenes* through the secretion of the naturally antimicrobial peptide Plantaricin (Kim et al., 2019). This aligns with the study conducted by Hong et al. where a mouse model with dysbiosis was subjected to treatment with a combination of *Lactobacillus plantarum*, pullulan, and PPNs. The group of mice receiving synbiotics containing PPNs effectively suppressed the infection induced by *Escherichia coli K99* and contributed to the recovery of the gut barrier (Cukkemane et al., 2020). Moreover, the findings suggest that nanoprebiotics have the potential to serve as synbiotic partners in probiotic foods, improving sensitivity to pathogens and contributing to respiratory infection treatment (Hong et al., 2019).

A different synbiotic strategy, combining Immunofortis® (90% short-chain galacto-oligosaccharides + 10% long-chain fructooligosaccharides) with live B. breve M-16V, resulted in reduced symptoms and allergic inflammation in individuals with asthma (Van De Pol et al., 2011). A recent investigation has unveiled that this synbiotic blend operates by increasing serum galectin-9 levels, reducing mast cell degranulation and consequent alleviating allergic symptoms, as reported by de Kivit et al. in 2012 (de Kivit et al., 2017). Therefore, synbiotic approaches may prove more effective in preventing allergic diseases compared to the use of

probiotics or prebiotics alone, making them a potentially more promising option for both preventive and therapeutic interventions (Gollwitzer & Marsland, 2014)

In summary, although most present studies focus on the effects of synbiotic nanostructures on gastrointestinal infections, the similarity between lung pathogens and gastrointestinal pathogens can be a bridge to conclude that probiotics and synbiotics can exhibit a broad-spectrum antimicrobial effect. However, further investigation is still needed to explore the effects of synbiotics on more respiratory-specific pathogens.

3.4 Anticancer Effect

Synbiotics influence the composition of the gut microbiota, enhancing the abundance of beneficial bacteria such as *Lactobacillus* and *Bifidobacterium* while reducing harmful microbes (Kim et al., 2013; Wang et al., 2021). This modulation promotes systemic immune activation through the gut-lung axis, leading to improved antitumor immune responses (Cristofori et al., 2021). Prebiotics in synbiotics serve as substrates for beneficial bacteria, facilitating their growth and activity, which in turn enhances the production of SCFAs, as previously discussed (Williams et al., 2022). SCFAs exert anti-inflammatory effects and promote immune cell activation, including cytotoxic T cells and natural killer cells, which play crucial roles in tumour surveillance and elimination (Tan et al., 2014; Williams et al., 2022).

Synbiotics also mitigate chronic inflammation, a hallmark of cancer progression, by modulating pro-inflammatory cytokines such as IL-6, TNF-α, and IL-1β (Sadrekarimi et al., 2022). By dampening inflammatory signalling pathways, synbiotics help create an unfavourable microenvironment for tumour growth and metastasis (Armstrong et al., 2018; Mishra et al., 2023; Sadrekarimi et al., 2022). Studies also showed that synbiotics augment the efficacy of immune checkpoint inhibitors (ICIs) by enhancing the infiltration and activation of effector immune cells within the tumour microenvironment (Li et al., 2022). Furthermore,

probiotics within synbiotics produce metabolites such as butyrate, which exert anti-inflammatory effects by inhibiting NF-κB signalling, thereby reducing the expression of pro-inflammatory mediators within lung tumours (Armstrong et al., 2018; Cristofori et al., 2021). Probiotics also stimulate the maturation and activation of dendritic cells, promoting antigen presentation and priming of cytotoxic T cells against tumour-associated antigens (Aindelis & Chlichlia, 2020). Many studies have also concluded that prebiotics can stimulate the production of mucosal-associated invariant T (MAIT) cells, a subset of innate-like T cells with potent antitumor activity (Aindelis & Chlichlia, 2020; Yoo & Oh, 2023). MAIT cells exhibit cytotoxicity against tumour cells and enhance the recruitment and activation of conventional T cells within lung tumours (Amini et al., 2020). In a study conducted by Aspriţoiu et al. synbiotics showed to inhibit tumour angiogenesis, a critical process for tumour growth and metastasis, by downregulating vascular endothelial growth factor (VEGF) and matrix metalloproteinases (MMPs) (Aspriţoiu et al., 2021). Prebiotics attenuate angiogenesis by reducing the expression of pro-angiogenic factors and promoting the secretion of angiogenesis inhibitors within the tumour microenvironment (Aspriţoiu et al., 2021; Farshi Radvar et al., 2020). Probiotics exert antimetastatic effects by modulating the expression of epithelial-to-mesenchymal transition (EMT)-related genes and inhibiting the invasiveness of lung cancer cells (Aspriţoiu et al., 2021; Farshi Radvar et al., 2020). By preventing the dissemination of tumour cells to distant sites, synbiotics help constrain tumour progression and improve overall survival in lung cancer patients.

Additionally, lung cancer patients undergoing antibiotic-related chemotherapy including penicillin, cephalosporin, and quinolones often experience severe diarrhea due to the degradation of their gut microbial flora and intestinal walls (Polanski et al., 2016). Supplementing these patients with a probiotic strain of *Clostridium butyricum* reduces the severity of diarrhea and other inflammatory bowel diseases (Liu et al., 2021; N. K. Singh et al.,

554 2023). This reduction in side effects leads to improved patient adherence to treatment,
555 ultimately enhancing their quality of life and prognosis (N. K. Singh et al., 2023). Moreover,
556 non-Small Cell Lung Cancer (NSCLC) patients exhibit dysbiosis of butyrate-producing
557 microorganisms, crucial for synthesizing mucin and inducing apoptosis in tumour cells (Zhou
558 et al., 2021). Synbiotic administration of these depleted microbes with a suitable substrate can
559 lower the risk of lung cancer (Prakash et al., 2023). In addition to the roles of synbiotics in
560 directly treating cancer-related factors and alleviating chemotherapy side effects, its role has
561 also been studied as a diagnostic tool in cancer diagnosis. In today's medical landscape, chest
562 X-ray and CT scans remain the primary diagnostic tools for identifying lung cancer, yet the
563 widespread use of low-dose spiral CT is hindered by its high cost and inconvenience (van Beek
564 et al., 2015). With advancements in deep sequencing, researchers and clinicians have
565 increasingly focused on understanding the links between microbiota in various body sites and
566 cancer development, including lung cancer, melanoma, and pancreatic ductal adenocarcinoma
567 (Hosgood III et al., 2014; Liu et al., 2020). Numerous studies have demonstrated significant
568 correlations between microbiota composition and lung cancer, offering promise for non-
569 invasive detection methods and the identification of predictive microbial markers (van Beek et
570 al., 2015; Yan et al., 2015). Zheng et al. discovered specific gut microbial patterns that could
571 predict early-stage lung cancer, while Yan et al. found higher levels of certain bacteria (e.g.,
572 *Neisseria, Steptococcus, and Porphyromonas)* in the saliva of lung cancer patients, suggesting
573 their potential as biomarkers for disease detection or classification (Yan et al., 2015; Zheng et
574 al., 2020). Additionally, a preliminary study utilising 16S rRNA sequencing revealed that
575 increased levels of certain bacterial families in lung tissue were associated with improved
576 recurrence-free and disease-free survival rates (Liu et al., 2020; Peters et al., 2019). Further
577 research is necessary to explore whether manipulating the gut microbiota could emerge as a

viable clinical strategy to aid in the treatment of lung cancer using chemotherapy, diagnosis of early-stage lung cancer and to mitigate chemotherapy-induced toxicity.

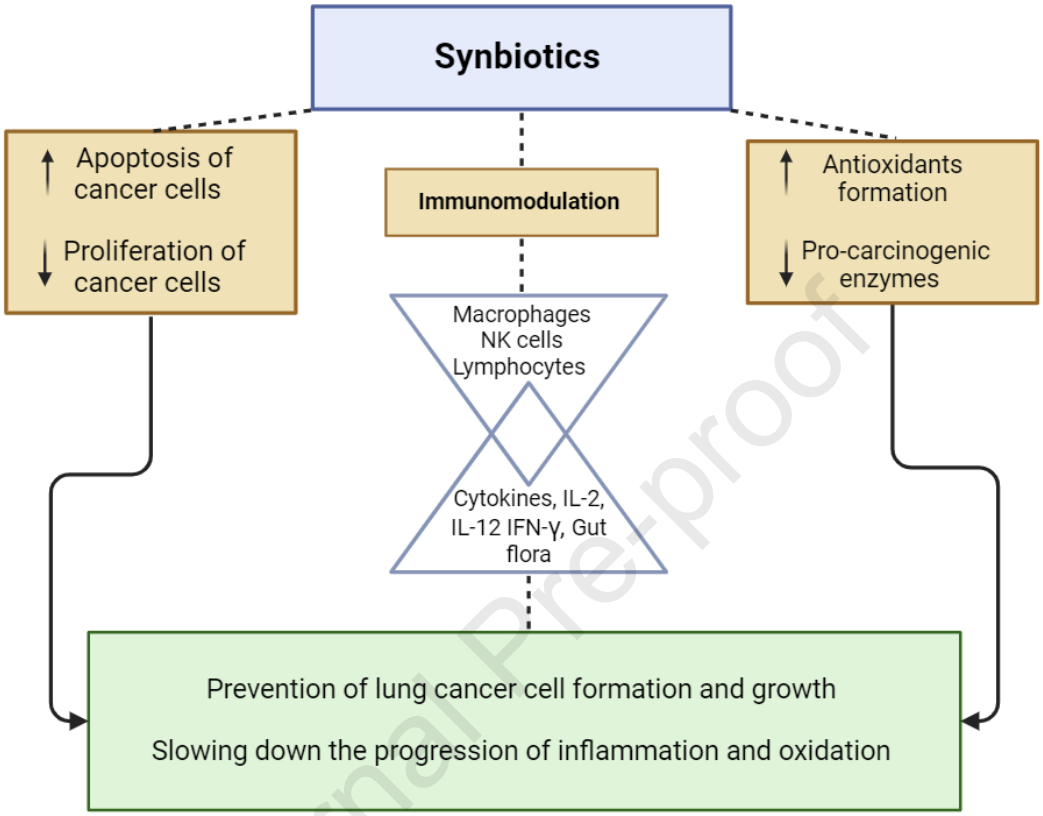

Figure 3. Summary of major synbiotic effects on lung diseases pathophysiology of lung diseases. Synbiotics exhibit diverse effects on lung diseases, including increased apoptosis and reduced proliferation of cancer cells, modulation of immune responses involving macrophages, natural killer cells, and lymphocytes, elevation of cytokine levels such as IL-2, IL-12, and IFN-gamma, promotion of a healthy gut flora, facilitation of antioxidant formation, and reduction of pro-carcinogenic enzyme levels. These multifaceted actions highlight the potential therapeutic role of synbiotics in lung disease prevention and management. Figure were designed on Biorender: https://www.biorender.com/

4. Clinical Trials Investigating the Effectiveness of Synbiotics in Lung Diseases

Despite the promising potential of synbiotics for the treatment of respiratory disorders, a limited number of clinical trials evaluated their safety and/or efficacy in humans. Furthermore, no clinical trial investigating the efficacy of nanosynbiotics has been conducted to date.

Early clinical trials involving synbiotics focused on their effect on the prevention of respiratory tract infections. These have been reviewed by a number of systematic reviews and meta-analyses. In one meta-analysis involving more than 10,000 patients across 16 clinical studies, the administration of synbiotics of different types was found to reduce the incidence rate of respiratory tract infections, as well as the proportion of participants experiencing respiratory tract infections, by 16% (Chan et al., 2020). In another meta-analysis of 15 randomized controlled clinical trials involving 3805 participants, Rashidi *et al.* found that the supplementation of infant formula with prebiotics, probiotics, and synbiotics exerted a significant protective impact against the incidence of respiratory tract infections in infants (Rashidi et al., 2021). More recently, a systematic review by Williams et al. analyzed 58 studies, demonstrating that dietary supplementation with probiotics and synbiotics significantly reduced the incidence of respiratory tract infections, especially in infants and children (Williams et al., 2022). Overall, the three meta-analyses discussed consistently highlight a potential protective role of dietary supplementation with synbiotics against the development of respiratory tract infections.

A number of clinical trials have investigated or aim at investigating the therapeutic potential of synbiotics as a treatment for asthma. In a clinical trial from Iran, Hassanzad and colleagues have investigated the efficacy and safety of Kilidact®, a synbiotic product containing *Lactobacillus casei*, *L. acidophilus*, *L. rhamnosus*, *L. bulgaris*, *Bifidobacterium infantis*, *B. breve*, *Streptococcus thermophiles*, and the prebiotic fructooligosaccharide, on asthmatic children aged 12 years or younger (Hassanzad et al., 2019). The study found that Kilidact® significantly alleviated asthma symptoms, resulting in fewer asthma-related outpatient visits to

616 the hospital (Hassanzad et al., 2019). In a more recent study (NCT03341403), Moermans et al.
617 investigated the efficacy of Probiotical®/Bactecal®, a synbiotic preparation containing
618 different strains of Lactobacillus, Bifidobacterium and Streptococcus and
619 fructooligosaccharides, on refractory asthma (Moermans et al., 2022). The results of this study
620 showed that, compared to placebo, the administration of Probiotical®/Bactecal® for up to three
621 months significantly improved the asthma control questionnaire (ACQ) score and the asthma
622 quality of life questionnaire (AQLQ) score, simultaneously the FEV1/FVC post
623 bronchodilation and decreasing fibrinogen, IgE, and neutrophils blood levels (Moermans et al.,
624 2022). Furthermore, a large, multicenter study involving patients with severe chronic
625 conditions including asthma (sPATIALS3, NCT04581018), is currently investigating the
626 therapeutic effect of a synbiotic preparation containing *Lactobacillus plantarum, L.*
627 *acidophilus*, and the slow-fermenting prebiotic fiber Fibergum®. Among the secondary
628 outcome measures, the study will include FEV1/FCV and asthma control survey test scores.

629 In a recent proof-of-concept study (NCT04581018), Zhang and colleagues tested the efficacy
630 of SIM01, a synbiotic formula containing several *Bifidobacterium* strains, resistant dextrin,
631 galactooligosaccharides, and xylooligosaccharide, as adjuvant therapy for COVID-19 patients
632 (Zhang et al., 2022). The results of the study showed that administration of SIM01 for 28 days
633 significantly improved the production of anti-SARS-CoV-2 IgG antibodies compared to
634 placebo control, reducing the viral load, and simultaneously reducing the plasma levels of
635 proinflammatory cytokines such as IL-6, M-CSF, and TNF-α (Zhang et al., 2022). Finally, Pei
636 et al. recently published a protocol for a systematic review and meta-analysis aimed at
637 investigating the effect of synbiotics, as well as both pre- and probiotics, on the management
638 of COPD (Pei et al., 2020).

639 In conclusion, while numerous clinical trials have investigated the effectiveness of synbiotics
640 in managing lung diseases, it is important to note that as of today, no synbiotic nanostructure

641 has received approval from major regulatory bodies such as the FDA and EMA. Despite
642 promising findings from research endeavours, the journey from experimental trials to
643 regulatory approval remains a significant hurdle in the path towards implementing synbiotic
644 therapies for lung diseases on a widespread scale. Continued research efforts and regulatory
645 scrutiny are essential to ensure the safety and efficacy of such treatments before they can be
646 made available to patients.

647 **5. Safety Aspects of Synbiotic Nanostructures**

648 In formulating synbiotics with proven safe prebiotics and probiotics, it is essential to ensure
649 the safety of new compositions through proper assessments. Unfortunately, historical
650 intervention trials often overlooked reporting adverse events (AEs) or serious AEs, possibly
651 due to assumptions about inherent product safety (Ioannidis et al., 2004). CONSORT
652 guidelines provide clear standards for AE reporting that should be followed to address these
653 shortcomings (de Jonge et al., 2021). A systematic review identified a significant lack of safety-
654 related data in trials involving prebiotics, probiotics, and synbiotics, highlighting the need for
655 improved reporting practices (Bafeta et al., 2018). Reviews of probiotic and synbiotic
656 interventions revealed lower AE incidence in control groups, emphasising the importance of
657 rigorous safety assessments for synergistic synbiotics (Bafeta et al., 2018). Such assessments
658 must consider the enhanced functionality of added microorganisms in the presence of a targeted
659 substrate, recognising that safety evaluations on isolated microorganisms may be insufficient
660 when paired with substrates, altering physiology or delivery dose *in-vivo* (Van den Nieuwboer
661 et al., 2015). In general, a probiotic's safety encompasses factors such as its origin, absence of
662 association with pathogenic cultures, and resistance to antimicrobials (Chan et al., 2023).
663 Functionality pertains to its survival in the gut and its immunomodulatory capacities, while

technological feasibility involves its ability to endure and retain properties during storage and distribution processes (Chan et al., 2023).

Concerns about nanomaterials in formulations arise from their potential adverse effects on human health, necessitating adherence to criteria like non-toxicity, biodegradability, biocompatibility, and Generally Recognised as Safe (GRAS) status (Dangi et al., 2023). Safety concerns persist due to a limited understanding of the mechanisms and health impacts of NPs (Loira et al., 2020). The diverse physicochemical characteristics and thermal stability of structured molecules at nanoscale and macroscale contribute to these concerns (McClements & Xiao, 2017). Prolonged exposure to specific NPs, such as silica and silver, may lead to cytotoxicity, oxidative stress, cell damage, and inflammation (McClements & Xiao, 2017) and (Poh et al., 2018). While animal models suggest most NPs pose no harm, advanced human research is crucial for conclusive assessments (Poh et al., 2018). This information is vital for regulatory decisions, ensuring product quality, efficacy, and safety, and supporting the commercialisation of nanoproducts.

6. Conclusions and Future Perspectives

In the present review, we have provided a depiction of the major roles of probiotics, prebiotics, and synbiotic preparations, consisting in the combination of probiotics with prebiotics, on human health. We have also introduced the concept of synbiotic nanostructures, consisting in an innovative approach applying the technological advancements of nanoparticle-based drug delivery systems to the targeted delivery of synbiotics. Furthermore, we provided a thorough overview of the therapeutic potential of synbiotic nanostructures against diseases affecting the respiratory system. Among the several classes of advanced drug delivery systems existing nowadays, subtypes of nanoparticles resulting particularly suitable for the lung-directed application of synbiotics included organic nanoparticles such as those composed of starch,

chitosan, nanocellulose, and phthalyl pullulan, as well as inorganic nanoparticles composed of MgO, Ag, and TiO_2. The therapeutic activity of these synbiotic nanostructures was mainly exerted through anti-inflammatory, antioxidant, and antimicrobial effects, whose synergism ensures a multifaceted therapeutic potential, and the current data available in literature confirm that synbiotics offer an enhanced health benefit compared to probiotics alone.

Despite the extremely promising potential of synbiotics, and particularly synbiotic nanostructures, as components of novel treatment strategies for respiratory disorders, several challenges must be addressed in order to ensure the clinical translation of these products. First of all, as mentioned in a previous section, a thorough and reliable reporting of the adverse events observed during the clinical trials should be implemented (Bafeta et al., 2018). Secondly, particular attention should be focused on the choice of the right materials used to encapsulate synbiotics, with the aim of prioritizing the use of materials which do not interact with the human microbiome. In this context, current research opens new avenues on emerging topics that are set to radically improve the way we design synbiotics nanostructures. An example of this is provided by the rational formulation and design of synbiotic formulations which maximize the extent of synergism between the probiotic and prebiotic components of the synbiotic mixture (Gomez Quintero et al., 2022). In terms of nanostructure and nanoformulation development, the application of nanostructured platforms allowing stimuli-responsive release of the synbiotic load would also improve the therapeutic activity of synbiotic nanostructures, potentially minimizing the occurrence of adverse effects, by allowing site-specific release of the payload with increased residence time at the site of action and reduced off-target release (Garcia-Brand et al., 2022).

Finally, a thorough clinical investigation of the therapeutic potential of synbiotic nanostructures is currently lacking, as highlighted by the relative low number of clinical trials conducted to investigate the safety and efficacy of synbiotics on lung diseases, as well as by the current

absence of existing clinical trials assessing nanostructure-based synbiotics formulations. These clinical trials would be fundamental to ensure the widespread implementation of synbiotics within existing therapeutic regimens for respiratory disorders.

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Disclosure Statement

The authors report there are no competing interests to declare.

Data Availability Statement

The present study used no data, being a literature review.

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References

Ahmad, M., Gani, A., Hamed, F., & Maqsood, S. (2019). Comparative study on utilization of micro and nano sized starch particles for encapsulation of camel milk derived probiotics (Pediococcus acidolactici). *Lwt*, *110*, 231-238.

Aindelis, G., & Chlichlia, K. (2020). Modulation of anti-tumour immune responses by probiotic bacteria. *Vaccines*, *8*(2), 329.

Al-Enazi, A. M. M., Virk, P., Hindi, A., Awad, M. A., Elobeid, M., & Qindeel, R. (2020). Protective effect of probiotic bacteria and its nanoformulation against cadmium-induced oxidative stress in male Wistar rat. *Journal of King Saud University-Science*, *32*(7), 3045-3051.

Alam, Z., Shang, X., Effat, K., Kanwal, F., He, X., Li, Y., Xu, C., Niu, W., War, A. R., & Zhang, Y. (2022). The potential role of prebiotics, probiotics, and synbiotics in adjuvant cancer therapy especially colorectal cancer. *Journal of Food Biochemistry*, *46*(10), e14302.

Ale, E. C., & Binetti, A. G. (2021). Role of probiotics, prebiotics, and synbiotics in the elderly: insights into their applications. *Frontiers in Microbiology*, *12*, 631254.

Amin, H., Osman, S. K., Mohammed, A. M., & Zayed, G. (2023). Gefitinib-loaded starch nanoparticles for battling lung cancer: Optimization by full factorial design and in vitro cytotoxicity evaluation. *Saudi Pharmaceutical Journal*, *31*(1), 29-54.

Amini, A., Pang, D., Hackstein, C.-P., & Klenerman, P. (2020). MAIT cells in barrier tissues: lessons from immediate neighbors. *Frontiers in immunology*, *11*, 584521.

Angellier, H., Choisnard, L., Molina-Boisseau, S., Ozil, P., & Dufresne, A. (2004). Optimization of the preparation of aqueous suspensions of waxy maize starch nanocrystals using a response surface methodology. *Biomacromolecules*, *5*(4), 1545-1551.

Armstrong, H., Bording-Jorgensen, M., Dijk, S., & Wine, E. (2018). The complex interplay between chronic inflammation, the microbiome, and cancer: understanding disease progression and what we can do to prevent it. *Cancers*, *10*(3), 83.

Aspriţoiu, V. M., Stoica, I., Bleotu, C., & Diaconu, C. C. (2021). Epigenetic regulation of angiogenesis in development and tumors progression: Potential implications for cancer treatment. *Frontiers in Cell and Developmental Biology*, *9*, 689962.

Bafeta, A., Koh, M., Riveros, C., & Ravaud, P. (2018). Harms reporting in randomized controlled trials of interventions aimed at modifying microbiota: a systematic review. *Annals of internal medicine*, *169*(4), 240-247.

Bottan, S., Robotti, F., Jayathissa, P., Hegglin, A., Bahamonde, N., Heredia-Guerrero, J. A., Bayer, I. S., Scarpellini, A., Merker, H., & Lindenblatt, N. (2015). Surface-structured bacterial cellulose with guided assembly-based biolithography (GAB). *Acs Nano*, *9*(1), 206-219.

Boukhenouna, S., Wilson, M. A., Bahmed, K., & Kosmider, B. (2018). Reactive oxygen species in chronic obstructive pulmonary disease. *Oxidative medicine and cellular longevity*, *2018*.

Bove, P., Russo, P., Capozzi, V., Gallone, A., Spano, G., & Fiocco, D. (2013). Lactobacillus plantarum passage through an oro-gastro-intestinal tract simulator: Carrier matrix effect and transcriptional analysis of genes associated to stress and probiosis. *Microbiological research*, *168*(6), 351-359.

Carvalho, J., Miranda, M., Fialho, A., Castro-Faria-Neto, H., Anatriello, E., Keller, A., & Aimbire, F. (2020). Oral feeding with probiotic Lactobacillus rhamnosus attenuates cigarette smoke-induced COPD in C57Bl/6 mice: Relevance to inflammatory markers in human bronchial epithelial cells. *PLoS one*, *15*(4), e0225560.

Castro, S., Kolomeytseva, M., Casquete, R., Silva, J., Saraiva, J., & Teixeira, P. (2015). Effect of high pressure on growth and bacteriocin production of Pediococcus acidilactici HA-6111-2. *High Pressure Research*, *35*(4), 405-418.

Cattò, C., Garuglieri, E., Borruso, L., Erba, D., Casiraghi, M. C., Cappitelli, F., Villa, F., Zecchin, S., & Zanchi, R. (2019). Impacts of dietary silver nanoparticles and probiotic administration on the microbiota of an in-vitro gut model. *Environmental Pollution*, *245*, 754-763.

Chan, C. K., Tao, J., Chan, O. S., Li, H.-B., & Pang, H. (2020). Preventing respiratory tract infections by synbiotic interventions: a systematic review and meta-analysis of randomized controlled trials. *Advances in Nutrition*, *11*(4), 979-988.

Chan, M. Z. A., & Liu, S.-Q. (2022). Fortifying foods with synbiotic and postbiotic preparations of the probiotic yeast, Saccharomyces boulardii. *Current Opinion in Food Science*, *43*, 216-224.

Chan, Y., Ng, S. W., Dua, K., & Chellappan, D. K. (2021). Plant-based chemical moieties for targeting chronic respiratory diseases. *Targeting cellular signalling pathways in lung diseases*, 741-781.

Chan, Y., Raju Allam, V. S. R., Paudel, K. R., Singh, S. K., Gulati, M., Dhanasekaran, M., Gupta, P. K., Jha, N. K., Devkota, H. P., & Gupta, G. (2023). Nutraceuticals: Unlocking newer paradigms in the mitigation of inflammatory lung diseases. *Critical reviews in food science and nutrition*, *63*(19), 3302-3332.

Chen, M., Shou, Z., Jin, X., & Chen, Y. (2022). Emerging strategies in nanotechnology to treat respiratory tract infections: realizing current trends for future clinical perspectives. *Drug Delivery*, *29*(1), 2442-2458.

Chen, S., Cao, Y., Ferguson, L. R., Shu, Q., & Garg, S. (2013). Evaluation of mucoadhesive coatings of chitosan and thiolated chitosan for the colonic delivery of microencapsulated probiotic bacteria. *Journal of microencapsulation*, *30*(2), 103-115.

Cristofori, F., Dargenio, V. N., Dargenio, C., Miniello, V. L., Barone, M., & Francavilla, R. (2021). Anti-inflammatory and immunomodulatory effects of probiotics in gut inflammation: a door to the body. *Frontiers in immunology*, *12*, 578386.

Cruz, B. C. d. S., de Sousa Moraes, L. F., De Nadai Marcon, L., Dias, K. A., Murad, L. B., Sarandy, M. M., Conceição, L. L. d., Gonçalves, R. V., Ferreira, C. L. d. L. F., & Peluzio, M. d. C. G. (2021). Evaluation of the efficacy of probiotic VSL# 3 and synbiotic VSL# 3 and yacon-based product in reducing oxidative stress and intestinal permeability in mice induced to colorectal carcinogenesis. *Journal of Food Science*, *86*(4), 1448-1462.

Cukkemane, A., Kumar, P., & Sathyamoorthy, B. (2020). A metabolomics footprint approach to understanding the benefits of synbiotics in functional foods and dietary therapeutics for health, communicable and non-communicable diseases. *Food Research International*, *128*, 108679.

Dangi, P., Chaudhary, N., Chaudhary, V., Virdi, A. S., Kajla, P., Khanna, P., Jha, S. K., Jha, N. K., Alkhanani, M. F., & Singh, V. (2023). Nanotechnology impacting probiotics and prebiotics: A paradigm shift in nutraceuticals technology. *International Journal of Food Microbiology*, 110083.

Datkhile, K. D., Durgawale, P. P., Chakraborty, S., Jagdale, N. J., More, A. L., & Patil, S. R. (2023). Biogenic Nanoparticles: Synthesis, Characterization, and Biological Potential of Gold Nanoparticles Synthesized using Lasiosiphon eriocephalus Decne Plant Extract. *Pharmaceutical Nanotechnology*, *11*(3), 303-314.

de Jonge, S., Wolfhagen, N., Zwinderman, A., Hollmann, M., & Boermeester, M. (2021). UPDATE Open Access.

de Kivit, S., Kostadinova, A. I., Kerperien, J., Morgan, M. E., Muruzabal, V. A., Hofman, G. A., Knippels, L. M., Kraneveld, A. D., Garssen, J., & Willemsen, L. E. (2017). Dietary, nondigestible oligosaccharides and Bifidobacterium breve M-16V suppress allergic inflammation in intestine via targeting dendritic cell maturation. *Journal of Leukocyte Biology*, *102*(1), 105-115.

Dufresne, A., Cavaille, J.-Y., & Helbert, W. (1996). New nanocomposite materials: microcrystalline starch reinforced thermoplastic. *Macromolecules*, *29*(23), 7624-7626.

Farshi Radvar, F., Mohammad-Zadeh, M., Mahdavi, R., Andersen, V., Nasirimotlagh, B., Faramarzi, E., & Lotfi Yagin, N. (2020). Effect of synbiotic supplementation on matrix metalloproteinase enzymes, quality of life and dietary intake and weight changes in rectal cancer patients undergoing neoadjuvant chemoradiotherapy. *Mediterranean Journal of Nutrition and Metabolism*, *13*(3), 225-235.

Garcia-Brand, A. J., Quezada, V., Gonzalez-Melo, C., Bolaños-Barbosa, A. D., Cruz, J. C., & Reyes, L. H. (2022). Novel developments on stimuli-responsive probiotic encapsulates: from smart hydrogels to nanostructured platforms. *Fermentation*, *8*(3), 117.

García-Rodríguez, A., Stillwell, A. A., Tochilovsky, B. V., Tanzman, J. V., Limage, R., Kolba, N., Tako, E., Marques, C. N., & Mahler, G. J. (2022). The mechanistic effects of human digestion on magnesium oxide nanoparticles: implications for probiotics Lacticaseibacillus rhamnosus GG and Bifidobacterium bifidum VPI 1124. *Environmental Science: Nano*, *9*(12), 4540-4557.

Gharieb, M. M., El-Sabbagh, S. M., Shalaby, M. A., & Darwesh, O. M. (2015). Production of chitosan from different species of zygomycetes and its antimicrobial activity. *Int. J. Sci. Eng. Res*, *6*, 123-130.

Gilbert, J. A., Blaser, M. J., Caporaso, J. G., Jansson, J. K., Lynch, S. V., & Knight, R. (2018). Current understanding of the human microbiome. *Nature medicine*, *24*(4), 392-400.

Gollwitzer, E. S., & Marsland, B. J. (2014). Microbiota abnormalities in inflammatory airway diseases—Potential for therapy. *Pharmacology & therapeutics*, *141*(1), 32-39.

Gomez Quintero, D. F., Kok, C. R., & Hutkins, R. (2022). The future of synbiotics: Rational formulation and design. *Frontiers in Microbiology*, *13*, 919725.

Gulati, N., Dua, K., & Dureja, H. (2021). Role of chitosan based nanomedicines in the treatment of chronic respiratory diseases. *International Journal of Biological Macromolecules*, *185*, 20-30.

Gunaswetha, K., Sujatha, E., Anusha, K., Prathyusha, A., Chandra, M. S., Berde, C. V., Reddy, N. N. R., & Bramhachari, P. V. (2023). Understanding the Probiotics and Mechanism of Immunomodulation Interactions with the Gut-Related Immune System. In *Human Microbiome in Health, Disease, and Therapy* (pp. 67-79). Springer.

Gurry, T. (2017). Synbiotic approaches to human health and well-being. *Microbial Biotechnology*, *10*(5), 1070-1073.

Hassanzad, M., Mostashari, K. M., Ghaffaripour, H., Emami, H., Limouei, S. R., & Velayati, A. A. (2019). Synbiotics and treatment of asthma: A Double-blinded, randomized, placebo-controlled clinical trial. *Galen Medical Journal*, *8*, e1350.

Heshmati, J., Farsi, F., Shokri, F., Rezaeinejad, M., Almasi-Hashiani, A., Vesali, S., & Sepidarkish, M. (2018). A systematic review and meta-analysis of the probiotics and synbiotics effects on oxidative stress. *Journal of functional foods*, *46*, 66-84.

Hikichi, M., Mizumura, K., Maruoka, S., & Gon, Y. (2019). Pathogenesis of chronic obstructive pulmonary disease (COPD) induced by cigarette smoke. *Journal of thoracic disease*, *11*(Suppl 17), S2129.

Hong, L., Cho, C. S., Kim, W. S., Choi, Y. J., & Kang, S. K. (2021). Phthalyl starch nanoparticles as prebiotics enhanced nisin production in Lactococcus lactis through the induction of mild stress in probiotics. *Journal of Applied Microbiology*, *130*(2), 439-449.

Hong, L., Kim, W.-S., Lee, S.-M., Kang, S.-K., Choi, Y.-J., & Cho, C.-S. (2019). Pullulan nanoparticles as prebiotics enhance the antibacterial properties of Lactobacillus plantarum through the induction of mild stress in probiotics. *Frontiers in Microbiology*, *10*, 142.

Hong, L., Lee, S.-M., Kim, W.-S., Choi, Y.-J., Oh, S.-H., Li, Y.-L., Choi, S.-H., Chung, D. H., Jung, E., & Kang, S.-K. (2021). Synbiotics containing nanoprebiotics: a novel therapeutic strategy to restore gut dysbiosis. *Frontiers in Microbiology*, *12*, 715241.

Hosgood III, H. D., Sapkota, A. R., Rothman, N., Rohan, T., Hu, W., Xu, J., Vermeulen, R., He, X., White, J. R., & Wu, G. (2014). The potential role of lung microbiota in lung cancer attributed to household coal burning exposures. *Environmental and molecular mutagenesis*, *55*(8), 643-651.

Hufnagl, K., Pali-Schöll, I., Roth-Walter, F., & Jensen-Jarolim, E. (2020). Dysbiosis of the gut and lung microbiome has a role in asthma. Seminars in immunopathology,

Huq, T., Fraschini, C., Khan, A., Riedl, B., Bouchard, J., & Lacroix, M. (2017). Alginate based nanocomposite for microencapsulation of probiotic: Effect of cellulose nanocrystal (CNC) and lecithin. *Carbohydrate polymers*, *168*, 61-69.

Ioannidis, J. P., Evans, S. J., Gøtzsche, P. C., O'neill, R. T., Altman, D. G., Schulz, K., Moher, D., & Group*, C. (2004). Better reporting of harms in randomized trials: an extension of the CONSORT statement. *Annals of internal medicine*, *141*(10), 781-788.

Ivanovska, T. P., Mladenovska, K., Zhivikj, Z., Pavlova, M. J., Gjurovski, I., Ristoski, T., & Petrushevska-Tozi, L. (2017). Synbiotic loaded chitosan-Ca-alginate microparticles reduces inflammation in the TNBS model of rat colitis. *International journal of pharmaceutics*, *527*(1-2), 126-134.

Joseph, T. M., Kar Mahapatra, D., Esmaeili, A., Piszczyk, Ł., Hasanin, M. S., Kattali, M., Haponiuk, J., & Thomas, S. (2023). Nanoparticles: Taking a unique position in medicine. *Nanomaterials*, *13*(3), 574.

Kaur, K., & Rath, G. (2019). Formulation and evaluation of UV protective synbiotic skin care topical formulation. *Journal of Cosmetic and Laser Therapy*, *21*(6), 332-342.

Kerstjens, H. A., Upham, J. W., & Yang, I. A. (2019). Airway pharmacology: treatment options and algorithms to treat patients with chronic obstructive pulmonary disease. *Journal of thoracic disease*, *11*(Suppl 17), S2200.

Khorasani, A. C., & Shojaosadati, S. A. (2016). Bacterial nanocellulose-pectin bionanocomposites as prebiotics against drying and gastrointestinal condition. *International Journal of Biological Macromolecules*, *83*, 9-18.

Khursheed, R., Gulati, M., Wadhwa, S., Vishwas, S., Sharma, D. S., Corrie, L., Alam, A., Alnasser, S. M., Alkhayl, F. F. A., & Parveen, Z. (2022). Multifaceted role of synbiotics as nutraceuticals, therapeutics and carrier for drug delivery. *Chemico-biological interactions*, 110223.

Kian, L., Saba, N., Jawaid, M., & Sultan, M. (2019). A review on processing techniques of bast fibers nanocellulose and its polylactic acid (PLA) nanocomposites. *International Journal of Biological Macromolecules*, *121*, 1314-1328.

Kim, M., Park, S. J., Choi, S., Jeong, S., Chang, J., Park, Y. J., Son, J. S., Kim, J. S., Cho, Y., & Oh, Y. H. (2023). Association of antibiotic use with risk of lung cancer: A nationwide cohort study. *Journal of Infection and Public Health*, *16*(7), 1123-1130.

Kim, M. H., Kang, S. G., Park, J. H., Yanagisawa, M., & Kim, C. H. (2013). Short-chain fatty acids activate GPR41 and GPR43 on intestinal epithelial cells to promote inflammatory responses in mice. *Gastroenterology*, *145*(2), 396-406. e310.

Kim, W.-S., Han, G. G., Hong, L., Kang, S.-K., Shokouhimehr, M., Choi, Y.-J., & Cho, C.-S. (2019). Novel production of natural bacteriocin via internalization of dextran nanoparticles into probiotics. *Biomaterials*, *218*, 119360.

Klemm, D., Cranston, E. D., Fischer, D., Gama, M., Kedzior, S. A., Kralisch, D., Kramer, F., Kondo, T., Lindström, T., & Nietzsche, S. (2018). Nanocellulose as a natural source for groundbreaking applications in materials science: Today's state. *Materials Today*, *21*(7), 720-748.

Kleniewska, P., Hoffmann, A., Pniewska, E., & Pawliczak, R. (2016). The influence of probiotic Lactobacillus casei in combination with prebiotic inulin on the antioxidant capacity of human plasma. *Oxidative medicine and cellular longevity*, *2016*.

Kleniewska, P., & Pawliczak, R. (2017). Influence of synbiotics on selected oxidative stress parameters. *Oxidative medicine and cellular longevity*, *2017*.

Köhler, S., Liebert, T., & Heinze, T. (2009). Ammonium-Based Cellulose Solvents Suitable for Homogeneous Etherification. *Macromolecular bioscience*, *9*(9), 836-841.

Kouhkan, M., Ahangar, P., Babaganjeh, L. A., & Allahyari-Devin, M. (2020). Biosynthesis of copper oxide nanoparticles using Lactobacillus casei subsp. casei and its anticancer and antibacterial activities. *Current Nanoscience*, *16*(1), 101-111.

Kumari, S., Yadav, B. S., & Yadav, R. B. (2020). Synthesis and modification approaches for starch nanoparticles for their emerging food industrial applications: A review. *Food Research International*, *128*, 108765.

Kupnik, K., Primožič, M., Kokol, V., & Leitgeb, M. (2020). Nanocellulose in drug delivery and antimicrobially active materials. *Polymers*, *12*(12), 2825.

Kvakova, M., Bertkova, I., Stofilova, J., & Savidge, T. C. (2021). Co-encapsulated synbiotics and immobilized probiotics in human health and gut Microbiota modulation. *Foods*, *10*(6), 1297.

Kwon, H.-K., Lee, C.-G., So, J.-S., Chae, C.-S., Hwang, J.-S., Sahoo, A., Nam, J. H., Rhee, J. H., Hwang, K.-C., & Im, S.-H. (2010). Generation of regulatory dendritic cells and CD4+ Foxp3+ T cells by probiotics administration suppresses immune disorders. *Proceedings of the National Academy of Sciences*, *107*(5), 2159-2164.

Ladaycia, A., Passirani, C., & Lepeltier, E. (2021). Microbiota and nanoparticles: Description and interactions. *European Journal of Pharmaceutics and Biopharmaceutics*, *169*, 220-240.

Laslo, V., Pinzaru, S. C., Zaguła, G., Kluz, M., Vicas, S. I., & Cavalu, S. (2022). Synergic effect of selenium nanoparticles and lactic acid bacteria in reduction cadmium toxicity. *Journal of Molecular Structure*, *1247*, 131325.

Li, X., Hu, S., Yin, J., Peng, X., King, L., Li, L., Xu, Z., Zhou, L., Peng, Z., & Ze, X. (2023). Effect of synbiotic supplementation on immune parameters and gut microbiota in healthy adults: a double-blind randomized controlled trial. *Gut Microbes*, *15*(2), 2247025.

Li, X., Zhang, S., Guo, G., Han, J., & Yu, J. (2022). Gut microbiome in modulating immune checkpoint inhibitors. *EBioMedicine*, *82*.

Liang, J., Yan, H., Puligundla, P., Gao, X., Zhou, Y., & Wan, X. (2017). Applications of chitosan nanoparticles to enhance absorption and bioavailability of tea polyphenols: A review. *Food Hydrocolloids*, *69*, 286-292.

Liu, F., Xuan, N.-X., Ying, S.-M., Li, W., Chen, Z.-H., & Shen, H.-H. (2016). Herbal medicines for asthmatic inflammation: from basic researches to clinical applications. *Mediators of Inflammation*, *2016*.

Liu, H., Geng, B., Chen, Y., & Wang, H. (2017). Review on the aerogel-type oil sorbents derived from nanocellulose. *ACS sustainable chemistry & engineering*, *5*(1), 49-66.

Liu, N.-N., Ma, Q., Ge, Y., Yi, C.-X., Wei, L.-Q., Tan, J.-C., Chu, Q., Li, J.-Q., Zhang, P., & Wang, H. (2020). Microbiome dysbiosis in lung cancer: from composition to therapy. *NPJ precision oncology*, *4*(1), 33.

Liu, X., Cheng, Y., Zang, D., Zhang, M., Li, X., Liu, D., Gao, B., Zhou, H., Sun, J., & Han, X. (2021). The role of gut microbiota in lung cancer: from carcinogenesis to immunotherapy. *Frontiers in Oncology*, *11*, 720842.

Liu, Y., Tran, D. Q., & Rhoads, J. M. (2018). Probiotics in disease prevention and treatment. *The Journal of Clinical Pharmacology*, *58*, S164-S179.

Loira, I., Morata, A., Escott, C., Del Fresno, J. M., Tesfaye, W., Palomero, F., & Suárez-Lepe, J. A. (2020). Applications of nanotechnology in the winemaking process. *European Food Research and Technology*, *246*, 1533-1541.

Luan, Q., Zhou, W., Zhang, H., Bao, Y., Zheng, M., Shi, J., Tang, H., & Huang, F. (2018). Cellulose-based composite macrogels from cellulose fiber and cellulose nanofiber as intestine delivery vehicles for probiotics. *Journal of agricultural and food chemistry*, *66*(1), 339-345.

Mahapatro, A., Bawna, F., Kumar, V., Daryagasht, A. A., Gupta, S., Raghuma, N., Moghdam, S. S., Kolla, A., Mahapatra, S. S., & Sattari, N. (2023). Anti-inflammatory effects of probiotics and synbiotics on patients with non-alcoholic fatty liver disease; an umbrella study on meta-analyses. *Clinical nutrition ESPEN*.

Majumder, R., Alam, M. B., Paudel, K. R., Ahmed, K. A., Devkota, H. P., Lee, S.-H., Hansbro, P. M., & Park, Y.-H. (2022). Anti-Influenza Virus Potential of Probiotic Strain Lactoplantibacillus plantarum YML015 Isolated from Korean Fermented Vegetable. *Fermentation*, *8*(11), 572.

Maldonado Galdeano, C., Cazorla, S. I., Lemme Dumit, J. M., Vélez, E., & Perdigón, G. (2019). Beneficial effects of probiotic consumption on the immune system. *Annals of Nutrition and Metabolism*, *74*(2), 115-124.

Maleki, O., Khaledabad, M. A., Amiri, S., Asl, A. K., & Makouie, S. (2020). Microencapsulation of Lactobacillus rhamnosus ATCC 7469 in whey protein isolate-crystalline nanocellulose-inulin composite enhanced gastrointestinal survivability. *Lwt*, *126*, 109224.

Marco, M. L., Heeney, D., Binda, S., Cifelli, C. J., Cotter, P. D., Foligné, B., Gänzle, M., Kort, R., Pasin, G., & Pihlanto, A. (2017). Health benefits of fermented foods: microbiota and beyond. *Current opinion in biotechnology*, *44*, 94-102.

Markowiak, P., & Śliżewska, K. (2017). Effects of probiotics, prebiotics, and synbiotics on human health. *Nutrients*, *9*(9), 1021.

Markowiak, P., & Śliżewska, K. (2018). The role of probiotics, prebiotics and synbiotics in animal nutrition. *Gut pathogens*, *10*(1), 1-20.

Markus, J., Mathiyalagan, R., Kim, Y.-J., Abbai, R., Singh, P., Ahn, S., Perez, Z. E. J., Hurh, J., & Yang, D. C. (2016). Intracellular synthesis of gold nanoparticles with antioxidant activity by probiotic Lactobacillus kimchicus DCY51T isolated from Korean kimchi. *Enzyme and microbial technology*, *95*, 85-93.

Martin, R., Nauta, A., Ben Amor, K., Knippels, L., Knol, J., & Garssen, J. (2010). Early life: gut microbiota and immune development in infancy. *Beneficial microbes*, *1*(4), 367-382.

Mawad, A., Helmy, Y. A., Shalkami, A.-G., Kathayat, D., & Rajashekara, G. (2018). E. coli Nissle microencapsulation in alginate-chitosan nanoparticles and its effect on Campylobacter jejuni in vitro. *Applied microbiology and biotechnology*, *102*, 10675-10690.

Mayer, E. A., Tillisch, K., & Gupta, A. (2015). Gut/brain axis and the microbiota. *The Journal of clinical investigation*, *125*(3), 926-938.

McAleer, J. P., & Kolls, J. K. (2018). Contributions of the intestinal microbiome in lung immunity. *European journal of immunology*, *48*(1), 39-49.

McClements, D. J., & Xiao, H. (2017). Is nano safe in foods? Establishing the factors impacting the gastrointestinal fate and toxicity of organic and inorganic food-grade nanoparticles. *npj Science of Food*, *1*(1), 6.

Mishra, N., Bhatt, S., Paudel, K. R., Hansbro, P. M., & Dua, K. (2023). *Synbiotics for the Management of Cancer*. Springer Nature.

Mkorombindo, T., & Dransfield, M. T. (2020). Inhaled corticosteroids in chronic obstructive pulmonary disease: benefits and risks. *Clinics in Chest Medicine*, *41*(3), 475-484.

Moermans, C., Graff, S., Laurie, M., Florence, S., Paulus, V., Guissard, F., Henket, M., & Louis, R. (2022). Effects of probiotics in uncontrolled asthma. In: Eur Respiratory Soc.

Mohammed, A., Jiang, S., Jacobs, J., & Cheng, H. (2019). Effect of a synbiotic supplement on cecal microbial ecology, antioxidant status, and immune response of broiler chickens reared under heat stress. *Poultry science*, *98*(10), 4408-4415.

Mohammed, M. A., Syeda, J. T., Wasan, K. M., & Wasan, E. K. (2017). An overview of chitosan nanoparticles and its application in non-parenteral drug delivery. *Pharmaceutics*, *9*(4), 53.

Mortaz, E., Adcock, I. M., Ricciardolo, F. L., Varahram, M., Jamaati, H., Velayati, A. A., Folkerts, G., & Garssen, J. (2015). Anti-inflammatory effects of lactobacillus rahmnosus and bifidobacterium breve on cigarette smoke activated human macrophages. *PLoS one*, *10*(8), e0136455.

Mounir, M., Ibijbijen, A., Farih, K., Rabetafika, H. N., & Razafindralambo, H. L. (2022). Synbiotics and their antioxidant properties, mechanisms, and benefits on human and animal health: a narrative review. *Biomolecules*, *12*(10), 1443.

Mughal, B., Zaidi, S. Z. J., Zhang, X., & Hassan, S. U. (2021). Biogenic nanoparticles: Synthesis, characterisation and applications. *Applied Sciences*, *11*(6), 2598.

Nahr, F. K., Mokarram, R. R., Hejazi, M. A., Ghanbarzadeh, B., Khiyabani, M. S., & Benis, K. Z. (2015). Optimization of the nanocellulose based cryoprotective medium to enhance the viability of freeze dried Lactobacillus plantarum using response surface methodology. *LWT-food Science and Technology*, *64*(1), 326-332.

Nguyen, N.-Y. T., Grelling, N., Wetteland, C. L., Rosario, R., & Liu, H. (2018). Antimicrobial activities and mechanisms of magnesium oxide nanoparticles (nMgO) against pathogenic bacteria, yeasts, and biofilms. *Scientific Reports*, *8*(1), 16260.

Nucera, F., Mumby, S., Paudel, K. R., Dharwal, V., A, D. I. S., Casolaro, V., Hansbro, P. M., Adcock, I. M., & Caramori, G. (2022). Role of oxidative stress in the pathogenesis of COPD. *Minerva Med*, *113*(3), 370-404. https://doi.org/10.23736/s0026-4806.22.07972-1

Pandey, K. R., Naik, S. R., & Vakil, B. V. (2015). Probiotics, prebiotics and synbiotics-a review. *Journal of food science and technology*, *52*, 7577-7587.

Panth, N., Paudel, K. R., & Parajuli, K. (2016). Reactive Oxygen Species: A Key Hallmark of Cardiovascular Disease. *Adv Med*, *2016*, 9152732. https://doi.org/10.1155/2016/9152732

Patel, P. J., Singh, S. K., Panaich, S., & Cardozo, L. (2014). The aging gut and the role of prebiotics, probiotics, and synbiotics: A review. *Journal of Clinical Gerontology and Geriatrics*, *5*(1), 3-6.

Paudel, K. R., Wadhwa, R., Mehta, M., Chellappan, D. K., Hansbro, P. M., & Dua, K. (2020). Rutin loaded liquid crystalline nanoparticles inhibit lipopolysaccharide induced oxidative stress and apoptosis in bronchial epithelial cells in vitro. *Toxicol In Vitro*, *68*, 104961. https://doi.org/10.1016/j.tiv.2020.104961

Pei, C., Wu, Y., Wang, X., Wang, F., & Liu, L. (2020). Effect of probiotics, prebiotics and synbiotics for chronic bronchitis or chronic obstructive pulmonary disease: A protocol for systematic review and meta-analysis. *Medicine*, *99*(45).

Peters, B. A., Hayes, R. B., Goparaju, C., Reid, C., Pass, H. I., & Ahn, J. (2019). The microbiome in lung cancer tissue and recurrence-free survival. *Cancer Epidemiology, Biomarkers & Prevention*, *28*(4), 731-740.

Pinkert, A., Marsh, K. N., & Pang, S. (2010). Reflections on the solubility of cellulose. *Industrial & Engineering Chemistry Research*, *49*(22), 11121-11130.

Poh, T. Y., Ali, N. A. t. B. M., Mac Aogáin, M., Kathawala, M. H., Setyawati, M. I., Ng, K. W., & Chotirmall, S. H. (2018). Inhaled nanomaterials and the respiratory microbiome: clinical, immunological and toxicological perspectives. *Particle and fibre toxicology*, *15*, 1-16.

Polanski, J., Jankowska-Polanska, B., Rosinczuk, J., Chabowski, M., & Szymanska-Chabowska, A. (2016). Quality of life of patients with lung cancer. *OncoTargets and therapy*, 1023-1028.

Prakash, D., Venkataramanan, S. K., Gopal, G., Muralidar, S., & Ambi, S. V. (2023). Synbiotics in Lung Cancer. In *Synbiotics for the Management of Cancer* (pp. 191-204). Springer.

Prasher, P., Sharma, M., Mehta, M., Satija, S., Aljabali, A. A., Tambuwala, M. M., Anand, K., Sharma, N., Dureja, H., & Jha, N. K. (2021). Current-status and applications of polysaccharides in drug delivery systems. *Colloid and Interface Science Communications*, *42*, 100418.

Qu, L., Cheng, Q., Wang, Y., Mu, H., & Zhang, Y. (2022). COPD and gut–lung axis: how microbiota and host inflammasome influence COPD and related therapeutics. *Frontiers in Microbiology*, *13*, 868086.

Rajoka, M. S. R., Mehwish, H. M., Zhang, H., Ashraf, M., Fang, H., Zeng, X., Wu, Y., Khurshid, M., Zhao, L., & He, Z. (2020). Antibacterial and antioxidant activity of exopolysaccharide mediated silver nanoparticle synthesized by Lactobacillus brevis isolated from Chinese koumiss. *Colloids and Surfaces B: Biointerfaces*, *186*, 110734.

Rashidi, K., Darand, M., Garousi, N., Dehghani, A., & Alizadeh, S. (2021). Effect of infant formula supplemented with prebiotics and probiotics on incidence of respiratory tract infections: A systematic review and meta-analysis of randomized clinical trials. *Complementary Therapies in Medicine*, *63*, 102795.

Razavi, S., Janfaza, S., Tasnim, N., Gibson, D. L., & Hoorfar, M. (2021). Nanomaterial-based encapsulation for controlled gastrointestinal delivery of viable probiotic bacteria. *Nanoscale Advances*, *3*(10), 2699-2709.

Rekha, M., & Sharma, C. P. (2007). Pullulan as a promising biomaterial for biomedical applications: a perspective. *Trends Biomater Artif Organs*, *20*(2), 116-121.

Rezaee, P., Kermanshahi, R., & Katouli, M. (2014). Prebiotics decrease the antibacterial effect of nano silver and nano TiO 2 particles against probiotic bacteria of food. *Current Nutrition & Food Science*, *10*(2), 88-93.

Roshan, H., Ghaedi, E., Rahmani, J., Barati, M., Najafi, M., Karimzedeh, M., & Nikpayam, O. (2019). Effects of probiotics and synbiotic supplementation on antioxidant status: A meta-analysis of randomized clinical trials. *Clinical nutrition ESPEN*, *30*, 81-88.

Sadrekarimi, H., Gardanova, Z. R., Bakhshesh, M., Ebrahimzadeh, F., Yaseri, A. F., Thangavelu, L., Hasanpoor, Z., Zadeh, F. A., & Kahrizi, M. S. (2022). Emerging role of human microbiome in cancer development and response to therapy: special focus on intestinal microflora. *Journal of Translational Medicine*, *20*(1), 1-20.

Saeid, A. B., Patel, V. K., Mehndiratta, S., Rajput, R., Kundu, R. K., Singh, S. K., Chellappan, D. K., Kokkinis, S., De Rubis, G., & Collet, T. (2023). Dissecting the in vitro fate of plant-derived bioactive encapsulated nanoparticles in lung diseases. *Food Bioscience*, 103205.

Salimi, S., Sotudeh-Gharebagh, R., Zarghami, R., Chan, S. Y., & Yuen, K. H. (2019). Production of nanocellulose and its applications in drug delivery: A critical review. *ACS sustainable chemistry & engineering*, *7*(19), 15800-15827.

Say, P., Nimikul, S., Bunnoy, A., Na-Nakorn, U., & Srisapoome, P. (2023). Long-Term Application of a Synbiotic Chitosan and Acinetobacter KU011TH Mixture on the Growth Performance, Health Status, and Disease Resistance of Hybrid Catfish (Clarias gariepinus× C. macrocephalus) during Winter. *Microorganisms*, *11*(7), 1807.

Shajahan, A., Shankar, S., Sathiyaseelan, A., Narayan, K. S., Narayanan, V., Kaviyarasan, V., & Ignacimuthu, S. (2017). Comparative studies of chitosan and its nanoparticles for the adsorption efficiency of various dyes. *International Journal of Biological Macromolecules*, *104*, 1449-1458.

Shi, Q., Liu, D., Wang, Y., Zhao, Y., Yang, X., & Huang, J. (2019). High-performance sodium-ion battery anode via rapid microwave carbonization of natural cellulose nanofibers with graphene initiator. *Small*, *15*(41), 1901724.

Sichetti, M., De Marco, S., Pagiotti, R., Traina, G., & Pietrella, D. (2018). Anti-inflammatory effect of multistrain probiotic formulation (L. rhamnosus, B. lactis, and B. longum). *Nutrition*, *53*, 95-102.

Sies, H. (2015). Oxidative stress: a concept in redox biology and medicine. *Redox biology*, *4*, 180-183.

Singh, D., Jain, D., Rajpurohit, D., Jat, G., Kushwaha, H. S., Singh, A., Mohanty, S. R., Al-Sadoon, M. K., Zaman, W., & Upadhyay, S. K. (2023). Bacteria assisted green synthesis of copper oxide nanoparticles and their potential applications as antimicrobial agents and plant growth stimulants. *Frontiers in Chemistry*, *11*, 1154128.

Singh, N. K., Beckett, J. M., Kalpurath, K., Ishaq, M., Ahmad, T., & Eri, R. D. (2023). Synbiotics as Supplemental Therapy for the Alleviation of Chemotherapy-Associated Symptoms in Patients with Solid Tumours. *Nutrients*, *15*(7), 1759.

Solanki, N., Mehta, M., Chellappan, D. K., Gupta, G., Hansbro, N. G., Tambuwala, M. M., Aa Aljabali, A., Paudel, K. R., Liu, G., Satija, S., Hansbro, P. M., Dua, K., & Dureja, H. (2020). Antiproliferative effects of boswellic acid-loaded chitosan nanoparticles on human lung cancer cell line A549. *Future Med Chem*, *12*(22), 2019-2034. https://doi.org/10.4155/fmc-2020-0083

Swanson, K. S., Gibson, G. R., Hutkins, R., Reimer, R. A., Reid, G., Verbeke, K., Scott, K. P., Holscher, H. D., Azad, M. B., & Delzenne, N. M. (2020). The International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of synbiotics. *Nature Reviews Gastroenterology & Hepatology*, *17*(11), 687-701.

Tan, J., McKenzie, C., Potamitis, M., Thorburn, A. N., Mackay, C. R., & Macia, L. (2014). The role of short-chain fatty acids in health and disease. *Advances in immunology*, *121*, 91-119.

Thangrongthong, S., Puttarat, N., Ladda, B., Itthisoponkul, T., Pinket, W., Kasemwong, K., & Taweechotipatr, M. (2020). Microencapsulation of probiotic Lactobacillus brevis ST-69 producing GABA using alginate supplemented with nanocrystalline starch. *Food Science and Biotechnology*, *29*, 1475-1482.

Theofilis, P., Vlachakis, P. K., Oikonomou, E., Tsioufis, K., & Tousoulis, D. (2024). Targeting the Gut Microbiome to Treat Cardiometabolic Disease. *Current Atherosclerosis Reports*, 1-10.

van Beek, E. J., Mirsadraee, S., & Murchison, J. T. (2015). Lung cancer screening: Computed tomography or chest radiographs? *World journal of radiology*, *7*(8), 189.

Van De Pol, M. A., Lutter, R., Smids, B. S., Weersink, E. J., & Van Der Zee, J. (2011). Synbiotics reduce allergen-induced T-helper 2 response and improve peak expiratory flow in allergic asthmatics. *Allergy*, *66*(1), 39-47.

Van den Nieuwboer, M., Brummer, R. J., Guarner, F., Morelli, L., Cabana, M., & Claassen, E. (2015). The administration of probiotics and synbiotics in immune compromised adults: is it safe? *Beneficial microbes*, *6*(1), 3-17.

Wang, R., Xu, X., Puja, A. M., Perumalsamy, H., Balusamy, S. R., Kim, H., & Kim, Y.-J. (2021). Gold nanoparticles prepared with Phyllanthus emblica fruit extract and Bifidobacterium animalis subsp. lactis can induce apoptosis via mitochondrial impairment with inhibition of autophagy in the human gastric carcinoma cell line AGS. *Nanomaterials*, *11*(5), 1260.

Williams, L. M., Stoodley, I. L., Berthon, B. S., & Wood, L. G. (2022). The effects of prebiotics, synbiotics, and short-chain fatty acids on respiratory tract infections and immune function: a systematic review and meta-analysis. *Advances in Nutrition*, *13*(1), 167-192.

Wong, W.-Y., Chan, B. D., Leung, T.-W., Chen, M., & Tai, W. C.-S. (2022). Beneficial and anti-inflammatory effects of formulated prebiotics, probiotics, and synbiotics in normal and acute colitis mice. *Journal of functional foods*, *88*, 104871.

Yan, X., Yang, M., Liu, J., Gao, R., Hu, J., Li, J., Zhang, L., Shi, Y., Guo, H., & Cheng, J. (2015). Discovery and validation of potential bacterial biomarkers for lung cancer. *American journal of cancer research*, *5*(10), 3111.

Yao, M., Li, B., Ye, H., Huang, W., Luo, Q., Xiao, H., McClements, D. J., & Li, L. (2018). Enhanced viability of probiotics (Pediococcus pentosaceus Li05) by encapsulation in microgels doped with inorganic nanoparticles. *Food Hydrocolloids*, *83*, 246-252.

Yoo, J.-S., & Oh, S. F. (2023). Unconventional immune cells in the gut mucosal barrier: Regulation by symbiotic microbiota. *Experimental & Molecular Medicine*, *55*(9), 1905-1912.

Zaborowska, M., Bodin, A., Bäckdahl, H., Popp, J., Goldstein, A., & Gatenholm, P. (2010). Microporous bacterial cellulose as a potential scaffold for bone regeneration. *Acta biomaterialia*, *6*(7), 2540-2547.

Zhang, H., Yang, C., Zhou, W., Luan, Q., Li, W., Deng, Q., Dong, X., Tang, H., & Huang, F. (2018). A pH-responsive gel macrosphere based on sodium alginate and cellulose nanofiber for potential intestinal delivery of probiotics. *ACS sustainable chemistry & engineering*, *6*(11), 13924-13931.

Zhang, L., Xu, Z., Mak, J. W., Chow, K. M., Lui, G., Li, T. C., Wong, C. K., Chan, P. K., Ching, J. Y., & Fujiwara, Y. (2022). Gut microbiota-derived synbiotic formula (SIM01) as a novel adjuvant therapy for COVID-19: An open-label pilot study. *Journal of Gastroenterology and Hepatology*, *37*(5), 823-831.

Zhao, Y., Tang, Y., Chen, L., Lv, S., Liu, S., Nie, P., Aguilar, Z. P., & Xu, H. (2020). Restraining the TiO2 nanoparticles-induced intestinal inflammation mediated by gut microbiota in juvenile rats via ingestion of Lactobacillus rhamnosus GG. *Ecotoxicology and Environmental Safety*, *206*, 111393.

Zheng, H. J., Guo, J., Jia, Q., Huang, Y. S., Huang, W.-J., Zhang, W., Zhang, F., Liu, W. J., & Wang, Y. (2019). The effect of probiotic and synbiotic supplementation on biomarkers of inflammation and oxidative stress in diabetic patients: a systematic review and meta-analysis of randomized controlled trials. *Pharmacological research*, *142*, 303-313.

Zheng, Y., Fang, Z., Xue, Y., Zhang, J., Zhu, J., Gao, R., Yao, S., Ye, Y., Wang, S., & Lin, C. (2020). Specific gut microbiome signature predicts the early-stage lung cancer. *Gut Microbes*, *11*(4), 1030-1042.

Zhou, A., Lei, Y., Tang, L., Hu, S., Yang, M., Wu, L., Yang, S., & Tang, B. (2021). Gut microbiota: the emerging link to lung homeostasis and disease. *Journal of Bacteriology*, *203*(4), 10.1128/jb.00454-00420.

- Dysbiosis in human microbiome has a role in the development of lung diseases
- Synbiotics consist in the association of probiotic and prebiotic supplements
- Synbiotics have potential to treat lung diseases but are limited by poor delivery
- Nanoencapsulation is a promising strategy to enhance the delivery of synbiotics
- Nanocellulose, starch and chitosan have great potential for synbiotic encapsulation

The authors of the submitted manuscript have no conflict of interest to declare.