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Review Article

The Role of Dietary Peptides and the Gut Bacteria in Maintaining Intestinal and Homeostatic Balance

Asif Iqbal Khan[1,2]*, Yi Xin[1]

[1]Department of Biotechnology, College of Basic Medical Science, Dalian Medical University, Dalian 116044, China.
[2]Institute of Medical Technology, Dow University of Health Sciences, Karachi, Pakistan.
*Correspondence: asif.iqbal@duhs.edu.pk

Abstract

The gut bacteria and the host have a mutually beneficial relationship. This complex interdependence plays a critical role in resource collection via prebiotic carbohydrate breakdown in the intestinal tract, the supply of important nutrients, vitamin synthesis, metabolic operations, and maintenance, as well as sheltering against colonization of pathogens, and opportunistic fungal infections. This leads to 'gut microbiota homeostasis' or 'gut microbial equilibrium', i.e., a stable and healthy gastrointestinal tract's microbial community. In this review, we discuss the gut micro biome's role in the development of the immune system, including oral tolerance and immunity. The therapeutic approach must begin with the interaction of functional foods and enterocytes. Furthermore, we discuss current knowledge and the promising application of functional foods that may stimulate the immune system to perform a further pro- or anti-inflammatory activity in the gastrointestinal system. When evaluating the immune system function of nutraceuticals, designs that modulate the membrane must be used whenever possible. Moreover, nutraceutical products' claim to be immunity boosters should have valid and accurate data to back it up. While assessing the stimulation of blood cell immunity through functional foods is more useful, it does not accurately reflect physical reality, and an investigation into the colonic immune response is a better way to understand it.

Keywords: Functional peptide, intestine, intestinal microbiota, protein hydrolysate, bioactive peptide, immunomodulation

1. Gut Microbiota

Microbiota refers to the hundreds of billions of microbes that live inside and outside the human body, fungi, viruses, protozoa, and archaea. Bacterial ecology encompasses a wide range of ecosystems(Costello et al. 2012).However, With over 100 trillion bacteria, the human intestinal microbiota has the most diverse microbial population (Khudojberdievich 2022). The gut bacteria and the host have a mutually beneficial relationship. (Dinan and Cryan 2012, Sommer and Bäckhed 2015). Immunological, mechanical, biological, and chemical barriers are the four layers of the intestinal barrier system that work together to keep the gastrointestinal tract in a state of homeostasis (Viggiano et al. 2015, Zhang et al. 2020). The intestinal barrier integrity is critical for a normal healthy body, which is typically retained by the immune system and intestinal bacteria working together (Wells et al. 2011).

The intestinal bacteria population has an impact on inflammation and immunological interactions. The importance of gut bacteria for the growth and development of host defense by influencing its immune function has been further elaborated in experimental models (Chen et al. 2022).

The host's pattern of genetic inheritance, method of gene transfer, eating habits, lifestyle, immune response, exposure to chemicals, drugs, and severity of symptoms are all the factors that impact the intestinal bacterial patterns (Dominguez-Bello et al. 2010, Maurice, Haiser, and Turnbaugh 2013, David, Maurice, et al. 2014, Tulstrup et al. 2015). The proportion of the intestinal microbiota varies throughout an individual's life (Bäckhed et al. 2015). Although the characterization of the gut flora population is usually steady during whole of the adulthood, yet numerous intrinsic and extrinsic variables, such as host nature and nurture, could also have an impact on it (Faith et al. 2013, David, Materna, et al. 2014, David, Maurice, et al. 2014, Goodrich et al. 2014). Similarly, numerous links have been found between intestinal flora and innate immune system's nutrition, metabolism, and immune function (Lee and Mazmanian 2010, Abreu 2010, Frank et al. 2007). Immune response diseases, coronary artery disease, ulcerative colitis, colorectal cancer, prediabetes, renal failure, and psychological disorders have all been linked to microbial demographic shifts (Nishida et al. 2018, Perez-Lopez et al. 2016, Lane, Zisman, and Suskind 2017, Zhu et al. 2011, Wang et al. 2011, Vaziri, Yuan, and Norris 2013, Cenit, Sanz, and Codoñer-Franch 2017, Dwivedy and Aich 2011). Understanding the importance of gut flora in connection to human health has deepened significantly. Most studies determine the relative abundance profiles for estimating microbial diversity in the human intestine with the use of longitudinal analysis and comparisons of fecal 16S ribosomal RNA (rRNA) (Talapko et al. 2022). The causes behind varying prevalence of particular microorganisms and their capacity to cohabit with or reject others are unknown. It has been estimated that about 30,000 microbial interactions take place at the same time(Goyal et al. 2021, Donaldson, Lee, and Mazmanian 2016). Furthermore, microorganisms have preferences for certain sites in the gut, which influences their population density and degrees of activity in different regions, adding to the complexity. The microbiota's makeup is highly impacted by complicated microbial interactions, yet our understanding of this process is still limited(Faust and Raes 2012, Abu-Ali et al. 2018). A comparative study between the microbiomes of healthier people with the sick ones could reveal new information about its contribution to a disease pathology and prognosis. However, the underlying mechanisms, and connection of gut bacteria with the pathological changes have yet to be determined.

2. The Microbiota Composition

The microorganism can be found all over the body, but the intestinal mucosa has the highest number of microorganisms. The gut mucosa provides a warm, moist, and nutrient-rich environment for microbial growth and survival. It secretes mucus, which serves as a barrier and a source of nourishment for microorganisms (Gustafsson and Johansson 2022). The intestine has a distinct immune system that encourages the growth of helpful bacteria while suppressing the growth of harmful microbes (Linares, Ross, and Stanton 2016). In various areas of the body, the gut bacteria component differs (Ravel et al. 2011). Microbial clades in a given body part are

comparable across individuals, such as oral micro flora, which is similar to other body regions, and there is a significant variation in the bacteriological communities among humans (Robinson, Bohannan, and Young 2010). The worldwide population shares roughly 1150 microorganism species, (Tilg and Kaser 2011, Nam et al. 2011). Firmicutes and Bacteroidetes are perhaps the greatest mutual intestinal flora on the phylum basis, responsible for nearly 90% of all genetically diverse types (Thangaleela et al. 2022, Cheng, Xu, and Shao 2022). Verrucobacteria, Actinobacteria, Proteobacteria, and Fusobacteria constitute a substantially lower percentage of the microbial composition (Scanlan and Marchesi 2008, Thangaleela et al. 2022, Cheng, Xu, and Shao 2022). Bacteroidetes (genus *Prevotella, Porphyromonas,* and *Bacteroides*) are gram-negative bacteria, while Firmicutes, which comprise *Enterococcus, Lachnospireceae, Clostridiales, Streptococcaceae, Helicobacterium,* and *Lactobacillus*, contains roughly 50–60 percent of the bacteria (Ghoshal et al. 2018, Vickers 2017).

Fusobacteria,and Proteobacteria, are among the other phyla, Actinobacteria (genus *Collinsella, Bifidobacterium*) are gram-positive bacteria (Qin et al. 2010, Eckburg et al. 2005, Ghoshal et al. 2018). These main phyla contribute to the structural system of the intestinal population, which aids in protection of the host's health. The characterization of microbes throughout most people depends on the most prevailing and diverse species of the genra such as Prevotella, Bacteroides, or Ruminococcus, according to previous findings (Arumugam et al. 2011). Additionally, microbial diversity and proportions vary across different parts of the body (Goodman et al. 2011, Frank et al. 2007). The large intestine has an enormous microbial diversity; on the other hand, the small intestine has less microbial distribution and abundance. Predominantly nutritional status affects enteral microbial bio-density (Frank et al. 2007, Wu et al. 2011).

3. Population of the Intestinal Tract

The intestine is a large digestive, absorbing, and immune organ in which gut microbiota and immunity are continually interacting to achieve immune intestinal integrity and hemostasis (Ying et al. 2020, Shi et al. 2017). The gastrointestinal tract has an acidic environment that is rich in a variety of bacterial communities (Elinav et al. 2011, Vivijs, Aertsen, and Michiels 2016, Hillman et al. 2017). *Bacteroidetes, Proteobacteria, Firmicutes, Fusobacetria and Actinobacteria* are the most abundant taxa in the intestinal community, while Deferribacteres, TM7, and other taxa account for a smaller proportion (Zwielehner et al. 2011, Xu and Zhang 2015, Bik et al. 2006, Andersson et al. 2008). The bacterial composition of the esophageal and oral regions is very similar, with *Gemella, Prevotella, Actinomyces*, and *Streptococcus* (Andersson et al. 2008). The microbial variation occurs from the small intestine towards the colon, with indispensable anaerobic bacteria being the prominent taxa (Hayashi et al. 2005, Wang et al. 2003). The microbial density is greater in the gut, comprised of approximately 5000 microbiological taxa. Despite such diversity, only a few taxa are studied, with Firmicutes and Bacteroidetes among the most common phyla (Ley, Peterson, and Gordon 2006, Eckburg et al. 2005, Dethlefsen et al. 2008). In its first two years of age, the layout of pediatric gut bacteria differs from that of an adult's. *Enterococci, Staphylococci, Escherichia coli, Clostridia, Streptococci, Bacteroides, Enterobacteria,* and *Bifidobacteria* are by far the most prevalent taxa during infant stages

(Favier et al. 2002, Palmer et al. 2007, Mackie, Sghir, and Gaskins 1999). The mode of transmission, feeding, and environmental factors all have an impact on the microbial population of infants (Mackie, Sghir, and Gaskins 1999). Throughout adulthood, there is less variation, but minor interferences do take place in some groups, such as *Bifidobacteria*, and *Lactobacillus* groups (Scanlan et al. 2006, Rajilić-Stojanović et al. 2009).

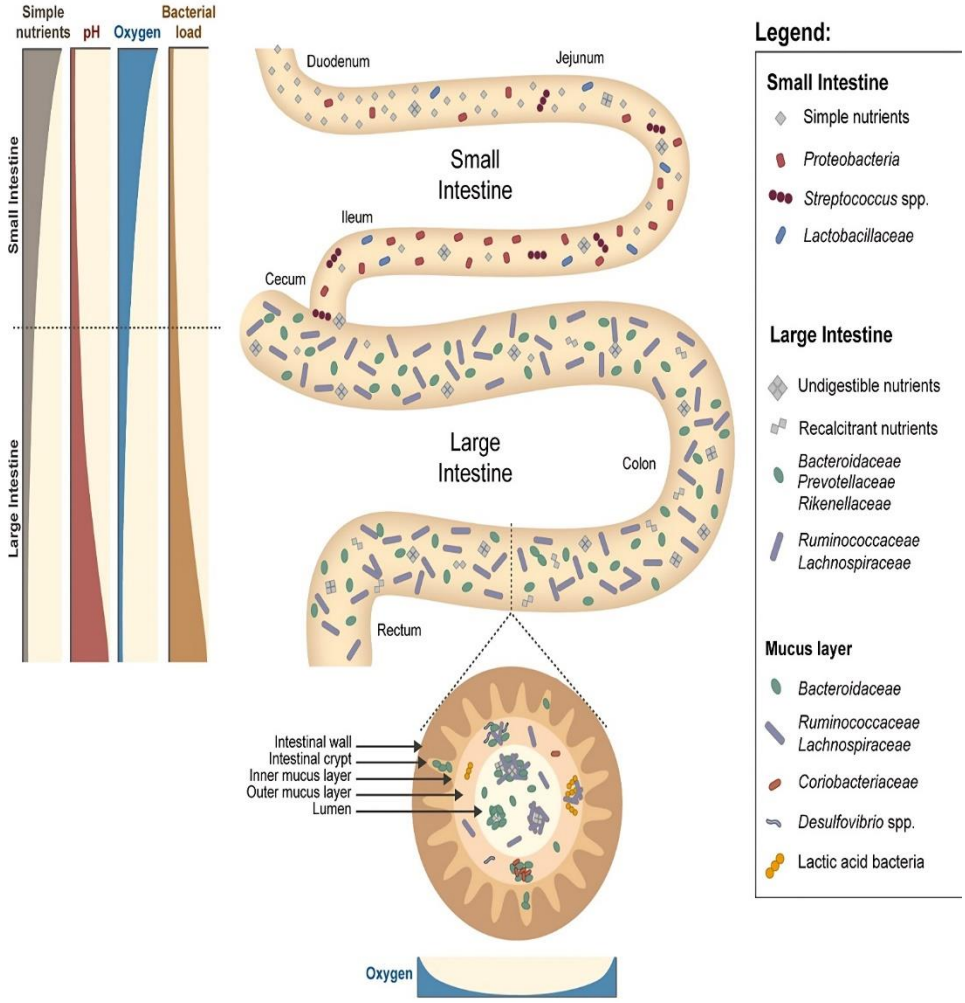

Figure 1. The gut microbiota's compositional diversity throughout the intestinal system. The proximal parts of the small intestine have low bacterial loads due to pH and oxygen gradients along the longitudinal axis, whereas the large intestine has high number of bacterial loads (Pereira and Berry 2017).

4. Dysbiosis of the Gut Intestinal Microbiota

The intestinal microbes promote healthy intestinal function and regulate cellular metabolism (Jandhyala et al. 2015). The 'intestinal barrier system' consists of four layers that work together to keep the gastrointestinal tract in a state of homeostasis: immunological, mechanical, biological, and chemical barriers (Viggiano et al. 2015, Zhang et al. 2020). Dysbiosis contributes to the growth of the gut microenvironment as well as in many external systemic diseases and metabolic syndromes (De Santis et al. 2015, Hansson 2012, Sommer and Bäckhed 2013).

The composition of the gut microbiota changes dynamically throughout infancy and stabilizes during adulthood. However, compositional changes can occur as a result of extrinsic and intrinsic factors. "Dysregulation" or "Dysbacteriosis" refers to the microbial change or alteration in the intestinal bacteria proportions. The characterization of the gut microbial group is influenced by a variety of elements. These include diet, host genetics, age, antibiotic use, geographic location, environment, disease and health status, medications and supplements usage (Greenhalgh et al. 2016, Santoro et al. 2018). Microbiological dysbiosis has been associated with multiple factors such as inflammatory conditions (CD & UC), metabolic and immune disorders (diabetes, obesity-related diseases), among others. If the hemostatic imbalance occurs, dysbiosis of gut microbial communities will trigger a variety of diseases and abnormal immune responses (Berg, Clemente, and Colombel 2015).

Table 1. Microbial metabolites or components that are implicated in disease (Rooks and Garrett 2016).

Human diseases and preclinical models	Microbial metabolites and components	Refs
Allergic and Immune Disorders		
Asthma	SCFAs	40,45
Inflammatory Bowel Disease	SCFAs	42-44, 53
	B Vitamins	53
Cancer		
Colorectal cancer	SCFAs	53,118,119
	B Vitamins	53
	N^1, N^{12} -diacetlyspermine	80
Gynaecological and Reproductive Disorders		
Bacterial vaginosis and other sexually transmitted infections	Polyamine	120
	HBP	100
Preterm labour	SCFAs	50
Metabolic Disorders		
Cardiovascular disease	TMAO	121
Kidney disease	SCFAs	122
	p-Cresol	123
Obesity and metabolic syndrome	TMAO	121
Type 2 diabetes	TMAO	121
Neurological Disorders		
Autism spectrum disorder	4-EPS	124
Central nervous system dysfunction	SCFAs	52,125
Other Gastrointestinal Disorders		
Infectious colitis (*Clostridium difficile*)	Bile acids	126

4-EPS, 4-ethyl phenol sulfate; HBP, D-glycero-β-D-manno-heptose-1,7-biphosphate; SCFAs, short-chain fatty acids; TMAO, trimethylamine N-oxide.

5. Immune System

The immune system is the body's capacity to mount rapid, precise, and protective responses against a diverse range of potentially harmful microorganisms, including viruses, parasites, bacteria, and fungi that are prevalent in our surroundings (Paul 2013, Williams 2011a). The immune system is divided into two components that work together effectively despite their differences. The host immune system comes first, followed by the adaptive immune system. When confronted with a pathogen, the innate immune system responds quickly, whereas adaptive immunity is highly specialized and capable of recognizing a pathogenic organisms. However, adaptive immunity develops slower than innate immunity and occurs in specified organs within the lymph glands (Aderem and Ulevitch 2000, Lamb 2012).The Immune System, both Innate and Adaptive is made up of Secondary lymphatic tissues, main lymphoid organs, and several immune cells. The body's innate immune response consists of chemical barriers (reactive oxygen and antimicrobial peptides), soluble mediators (complement system), innate immune cells, innate antibodies, physical barriers (skin and mucous membranes), and associated cytokines (Koenderman, Buurman, and Daha 2014, Williams 2011b). Adaptive immunity is more extensive, and highly attuned to variety of self, non-self-antigen recognition, T-cell receptors, and clone-specific antibodies, modulated in reconfiguring Ig gene superfamily genes, direct the immune system (Bonilla and Oettgen 2010, Medzhitov and Janeway Jr 1997). Chemical and physical barriers prevent pathogen entry. Complement system and other humoral factors inhibit infection through phagocytosis, removal by cytotoxicity mechanism, activate antigen-presenting cells for T and B lymphocytes, and cytokine synthesis of adaptive immune response (Williams 2011b, Beutler 2004, Tosi 2005). This results in immunological effector pathways unique to pathogens, immunologic memory formation, and immune homeostasis modulation in the host (Bonilla and Oettgen 2010).

6. The microbiome of gut and mucosal immune system

The mucous membrane plays a crucial function in the immune system because it contains specialized chemical and mechanical boundaries that keeps foreign contaminants from entering by disintegrating them through a wide variety of chemical processes, the majority of which are yet to be understood (Ogra et al. 2012). The mucosal immune system is unique because it contains cells that aren't even present in the circulation and have a distinct immunological response, as well as the secretory antibody IgA (Dwivedy and Aich 2011, Phalipon et al. 2002). Most infections aim to enter host body through the digestive system. Fortunately, it has the biggest mucosal barrier of almost any molecular mechanisms involved. The most important portion of intestinal epithelium, intestinal epithelial cells, regulates variety of gastrointestinal activities including metabolism, secretions, absorption, and protection (Phalipon et al. 2002, Strober, Fuss, and Blumberg 2002).

Moreover, it plays a prominent part in antigen presentation, with the opportunity to demonstrate two very different Class I and Class II antigens along with releasing immunologically active substances in responses to pro-inflammatory mediators, protecting the gastrointestinal mucosa and lumen from injury (Bland 1998). T helper (Th) cells are critical in autoimmunity even though they eliminate infections even during the host defense system and cause inflammatory

responses, ultimately contributing to internal necrosis. T regulatory cell plays an important role in immunological tolerance and inflammatory regulation. As just a result, gastrointestinal autoimmunity is linked to the imbalance of T regulatory as well as pro-inflammatory T helper lymphocytes inside the intestine (Colombo et al. 2015, Shi et al. 2017, Johansson, DeNardo, and Coussens 2008). When the equilibrium is disrupted, the gastrointestinal immune response malfunctions, resulting in disorders including inflammatory bowel disease (IBD). IBD is a complicated disorder caused by inherited, ecological, and microbiological reasons which leads to inflammatory response by activating an abnormal immune response. IBDs such as ulcerative colitis (UC) and Crohn's disease (CD) are common (Berg, Clemente, and Colombel 2015).

7. Immunoregulatory Pathways

The gut microbiota has a strong influence on the health of the intestines and their host. Intestinal epithelial cells (IECs) create a physiological and immunologic shield to prevent the intestinal flora from pattern recognition receptor-mediated degradation (Carvalho et al. 2012). Innate immune processes, such as microbial substance ligation of targets dedicated to the identification of microbe-associated pattern recognition receptors, is most likely used to regulate colonic microorganisms in the intestinal epithelium, macrophages of spleen, lymph nodes, and bone marrow (Daddaoua et al. 2013). It included Toll-like receptors (TLRs), which may help with maintaining intestinal homeostasis by improving the epithelial intestinal barrier and innate immune expression of genes (Daddaoua et al. 2013, Zhao et al. 2020). Toll-like receptor 4 (TLR4) is a transmembrane protein, member of the toll-like receptor family, which belongs to the pattern recognition receptor (PRR) family. It plays a significant role in boosting our natural immune responses and triggering the production of certain proteins called cytokines. This process occurs when a molecule called MyD88 binds to TLR4 inside the cell, which then sets off a series of chemical reactions and signals within the cell. These signals help activate various important substances and pathways within the cell. (Li et al. 2020, Liu et al. 2021, Xiang et al. 2021). MyD88 activates the IKK complex, which releases substances like IL-1β and TNF-α. These substances activate the immune system through the NF-κB pathway. In short, MyD88 triggers a process that boosts immune response. (Chen, Chen, et al. 2019, Mitchell, Vargas, and Hoffmann 2016).

NF-κB (nuclear factor-κB) is a critical transcriptional factor that is composed of Rel family heterodimer proteins p65 and p50, NF-κB is a transcription factor that affects the expression of several genes as well as immunological activities. It also is implicated in immunological and inflammatory functions (Gilmore, Siggers, and Gerondakis 2015, Liang, Zhou, and Shen 2004). The IκB kinase (IKK) protein kinase is a key part of the NF-κB signaling pathway and is crucial for modulating NF-κB stimulation and gene regulation. It stimulates the phosphorylated and ubiquitination breakdown mechanism of the IκB protein, resulting in the release of the NF-κB dimer (Li et al. 2019, Zhang et al. 2019). Even amongst the IκB family proteins, IκB-α is primarily responsible for the baseline suppression of NF-κB activity. In resting cells, the inhibitory protein IκB adheres to the NF-κB dimer and adsorb it in the cytoplasm in an inactive form. When cells are stimulated by numerous stimulating substances activated IκB kinase (IKK). The active NF-κB dimer

enters the nucleus and attaches to genes include TNF-α, IL-8, ICAM-1, COX-2, and IL-1β, (Laveti et al. 2013, Lee and Yang 2012, Agarwal and Shanmugam 2022) that provide an NF-κB-binding receptor, causing the transcription and production of inflammatory and pro-inflammatory mediators to activate. The nuclear transcription factor NF-κB is required for the control of oxidative stress, pro-inflammatory, and immunological responses (Li et al. 2019, DiDonato, Mercurio, and Karin 2012, Zhang et al. 2019).which determines immunological and inflammation processes regulates the genes involved to modulate innate and acquired immunity, B cell development, inflammatory processes, lymphoid organ synthesis, and stress reaction, among other cellular mechanisms (Hayden and Ghosh 2004, Zhao et al. 2020, Wang et al. 2019).

Furthermore, IL-6-induced intracellular signaling increases the production of associated genes like iNOS. Nitric oxide is a free nitrogen oxide radical that is a crucial constituent of a cell for stimulating macrophages and plays a vital role in the non-specific immune response. It not only protects against extracellular microbes and cancer cells but that also responsible for regulating immunity-related biological functions (Guzik, Korbut, and Adamek-Guzik 2003, Li et al. 2019, Zhang et al. 2019). NO synthase (NOS) in mammals is divided into three categories: endothelial (eNOS), neuronal (nNOS), and inducible (iNOS). The most essential enzyme in NO synthesis, iNOS, is quickly stimulated and demonstrated in activated macrophages (Li et al. 2019, Vannini, Kashfi, and Nath 2015, Sessa 1994). The isoenzyme iNOS is responsible for the majority of NO synthesis. In macrophages, cytokines such as TNF-α, interferon-ϒ (IFN-ϒ), and lipopolysaccharide stimulate the interpretation of iNOS mRNA and protein. Through NADPH and oxygen-dependent mechanism, iNOS catalyzes the synthesis of NO and L-citrulline from L-arginine (Hu et al. , Zhang et al. 2019). The NF-κ B is one of the most essential signaling pathways for generating iNOS expression in cells, which eventually leads to an increased in NO production, and NO plays a key role in macrophage activation (Tao et al. 2018, Vannini, Kashfi, and Nath 2015).

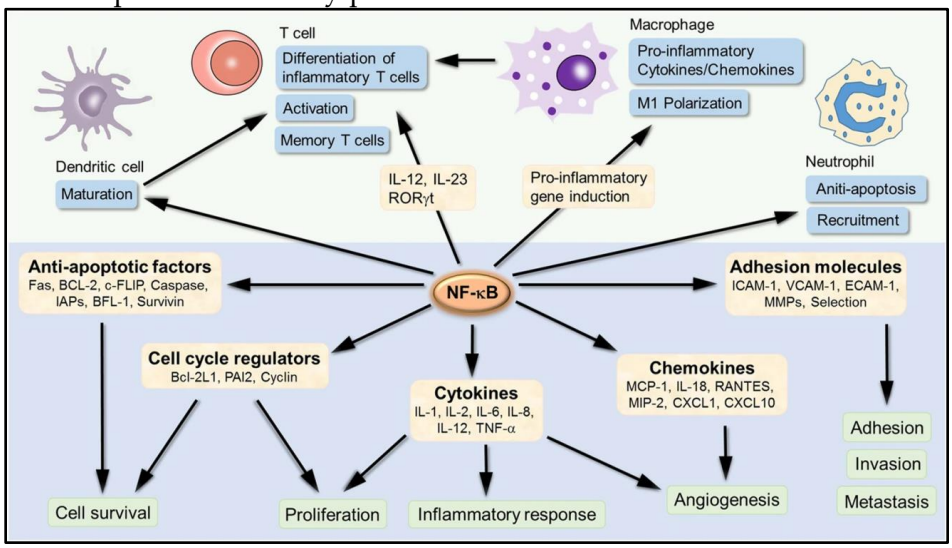

Figure 2. NFκB has an important role in the generation of inflammatory markers, chemokines, and cell adhesion, as well as in the cell cycle regulation, apoptosis, morphogenesis, and differentiation. (Liu et al. 2017).

8. Dietary Modification of Gut Microbiota

There has been implementation and evaluation of the gut microbiota in recent years, with the logical use of probiotics as a functional food being particularly well established (Shi et al. 2017, Delcenserie et al. 2008, Gamallat et al. 2019). Pathogens cause infections and are closely associated with illness onset or progression. While commensal gut microbiota influences both genetic and epigenetic factors that directly or indirectly modulates host health (Kurashima, Goto, and Kiyono 2013, Gamallat et al. 2019). Functional foods are non-digestible dietary products/natural ingredients that foster healthy microorganisms in the large gastrointestinal system (Roberfroid 2007). Protective benefits have been discovered in a portion from casein hydrolysate for about the first time in 1984 (Kiewiet, Faas, and De Vos 2018).

9. Protein Hydrolysates

Protein hydrolysates are commonly used in commercial applications as an important food supplement and are comprised of two different proteins and peptides that are formed when complete proteins hydrolysis occurs (Kiewiet, Faas, and De Vos 2018). Several studies on functional foods, marine protein hydrolysate, and bioactive peptides for immune system enhancement have been published in recent years (Ambigaipalan and Shahidi 2017). A bioactive peptide is a polypeptide group that has been degraded by enzymatic digestion of natural and marine dietary protein. The most frequent method is the enzymatic hydrolysis of the whole protein to create bioactive peptides using enzymes such as chymotrypsin, trypsin, pepsin, alcalses, thermolysin, and pancreatin (Bhat et al. 2015, Chen, Su, et al. 2019). These peptides are made up of amino acids that are arranged in different ways. It contains more than 2 -20 amino acid residues structurally because of its hydrophobic characteristics and small dimensions. Bioactive chemicals are much easier to absorb (Hartmann and Meisel 2007). Peptide 6 kDa has a high molecular weight, good absorption, and various health benefits, including antimicrobial, antihypertensive, antimicrobial, antioxidative, antithrombotic, anticancer efficacies, and immunomodulatory effects on the adaptive and innate immune response. Bioactive peptides in the form of short peptides, dipeptides, and tripeptides are absorbed faster than the same composition of the free amino acid (Chen, Su, et al. 2019).

10. The Impact of Protein Hydrolysates on Gastric Barrier and Immunity

In the intestinal lumen, epithelial cells serve as the first line of defense against dangerous bacteria and chemicals. A coating of mucus protects these cells, so the luminal composition and the rest of the body are separated by this physical barrier (Farhadi et al. 2003). Protein hydrolysates and bioactive peptides fortify the epithelial barrier and increase mucus production to defend against harmful microorganisms (De Santis et al. 2015). Peptides may play a significant role in the intestine by regulating digestive enzymes, stabilizing the intestinal epithelial tight junctions, and modulating dietary absorption (Shimizu 2004, Korhonen and Pihlanto 2006). They also increase mucus production and the number of goblet and Paneth cells, which regulate mucus and anti-bacterial peptide production (Elshaer and Begun 2017). Dairy-derived peptides, such as those found in yoghurt, can boost the production of mucus-related genes and anti-bacterial factors (Plaisancié et al. 2013). Epithelial cells regulate immune cell differentiation by secreting cytokines. Consumption of egg yolk peptide,

for example, enhanced IL-6 production in epithelial cells, can influence innate and adaptive immunological responses in mice (Nelson et al. 2007). However, the overall consequence of elevated IL-6 is complex and context-dependent. The concentration of IgA in the colon following hydrolysate delivery in the animal study is among the most researched immunological responses, As proven in the case of a common carp egg hydrolysate, hydrolysate consumption might produce an increase in IgA level (Chalamaiah et al. 2015).

Changes in gene expression in target cells consist of the cellular responses to most cytokines, numerous cytokine-induced changes in gene expression result in T and B lymphocyte differentiation and effector cells activation such as macrophages. IL-2 becomes cytokine-producing by T-helper cells and is a key component of immune response to trigger T cell proliferation and promote B cell growth, acting on the natural killer, glioma, and Th1 cell. IL-4 is a cytokine that can be produced by activated Th2 cells, stimulate B cells growth, differentiation of B cells, and effects on T, B cells, endothelial cells, fibroblasts and mast cells, and macrophages (Hou et al. 2016, Abraha 2020). IL-10 is an inflammatory cytokine that inhibits the host immune system and regulates immune-mediated inflammation. It particularly inhibits the responses involving activated macrophages and dendritic cells. Protein hydrolysates, particularly those generated from cow's milk, offer anti-inflammatory properties that prevent intestinal damage and weight loss in colitis and ileitis models. Furthermore, they increase IL-10 and other regulatory cytokines while decreasing pro-inflammatory cytokines (Fernandez-Tome et al. 2019, Khan, Rehman, Farooqui, Siddiqui, Ayub, Ramzan, Zexu, et al. 2022). IFN-γ is an important cytokine and is critical for its immune-stimulatory and immunomodulatory effects, which activate the macrophages, regulate the cells of Th1, Th2 and induce the generation of T cells (Hou et al. 2016, Abraha 2020). Protein hydrolysates have been demonstrated to upregulate genes involved in innate immunity and host defense in gut-associated lymphoid tissue, specifically the Peyer's patches. In another investigation on adaptive responses, sensitization with partially hydrolyzed whey protein inhibited the growth of specific T cell types in the Peyer's patches following a challenge with intact whey (Kiewiet et al. 2015, Adolfsson, Meydani, and Russell 2004). These findings suggest that protein hydrolysates can modulate various aspects of the immune system in the intestine, impacting IgA levels, cytokine production, inflammation, and adaptive immune responses.

The mesenteric lymph nodes (MLN) are responsible for tolerance induction and antigen presentation processes (Rescigno 2011). Dendritic cells carrying antigens from the Peyer's patches and lamina propria migrate to the MLN, where they activate T and B cells, leading to immune response or tolerance induction (Pabst and Mowat 2012). Studies using bovine milk hydrolysates or peptides in murine sensitization models have examined the cell types present in the MLN after hydrolysate consumption (Kiewiet, Faas, and De Vos 2018). Milk peptides alone or in combination with indigestible oligosaccharides fed to mice prior to sensitization with intact whey enhanced Treg population in the MLN (Meulenbroek et al. 2013). Consumption of casein-derived glycomacropeptide enhanced tolerogenic IL-10 production in MLN cells of a mouse model with colitis, indicating a potential increase in Treg (Lozano-Ojalvo and López-Fandiño 2018).

In addition to T cell responses, B cells can be activated in the MLN, leading to follicle expansion. Sensitization with partially hydrolyzed whey protein increased the number of IgA+ B cells (Kiewiet et al. 2017). Protein hydrolysates affect the immune system both locally and systemically. Peptides produced from hydrolysates have been found in the blood after consuming dairy and soy products (Chalamaiah et al. 2014). Different protein hydrolysates, such as those from milk, oyster, salmon, and fish, enhance macrophage phagocytosis in the peritoneal cavity and increase NK cell activity in the spleen (Martínez-Medina et al. 2022). Administration of specific hydrolysates, including oyster, tuna cooking drip, salmon, and common carp eggs, promotes splenocyte proliferation in mice (Chalamaiah et al. 2014). These hydrolysates can modulate the populations of CD4+ and CD8+ cells, induce a mixed Th1/Th2 response, and impact the production of cytokines (Martínez-Medina et al. 2022). Whey hydrolysate increases Treg and regulatory B cells (Breg) in the spleen, while casein hydrolysate induces IL-10-producing Breg. Protein hydrolysate consumption also leads to increased antibody levels, such as IgG and IgA (Khan, Rehman, Farooqui, Siddiqui, Ayub, Ramzan, Wang, et al. 2022). Studies on humans show similar immunomodulatory effects, including altered leukocyte numbers, increased CD11b+ and CD56+ cells, and enhanced NK cell activity (Bernardini et al. 2016, Yimit et al. 2012). However, further well-designed studies are necessary to comprehensively understand the effects of protein hydrolysates on human immune responses.

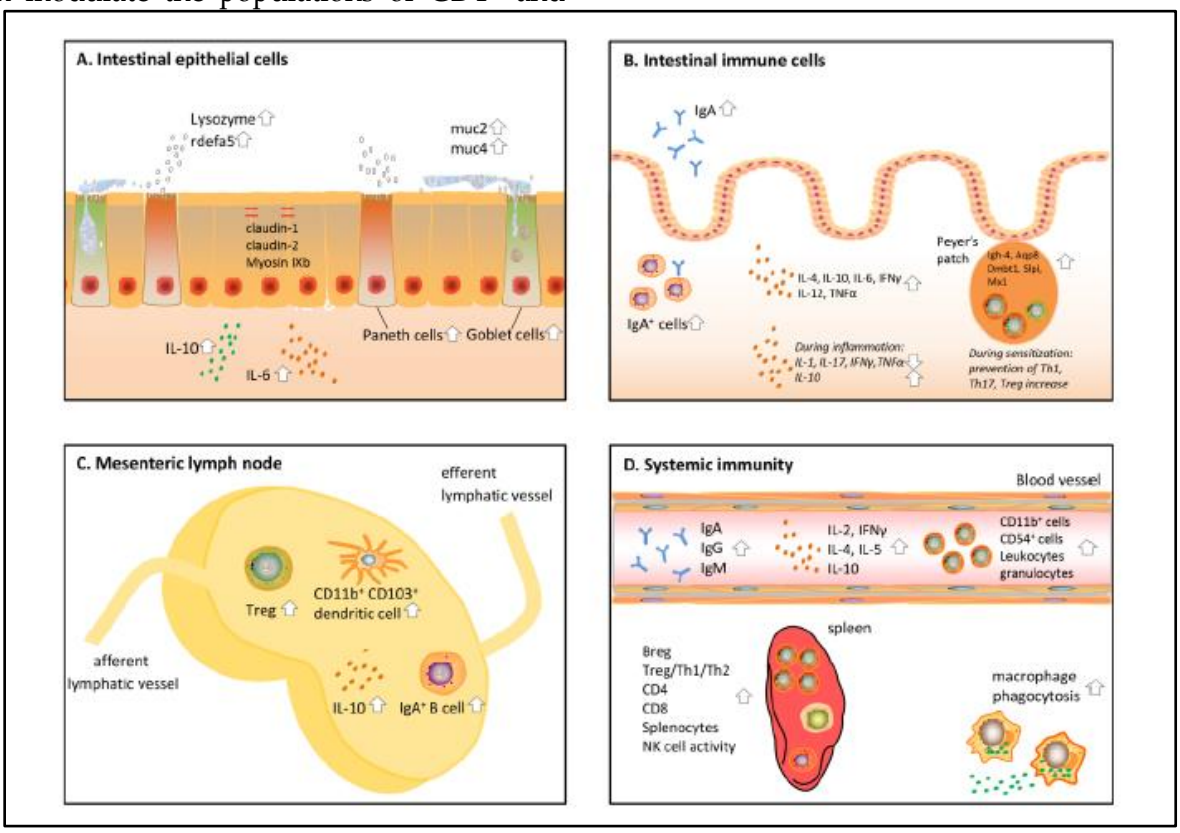

Figure 3. A summary of the immunological activities of protein hydrolysates (Kiewiet, Faas, and De Vos 2018).

11. Conclusions

The gut microbiota, consisting of diverse microorganisms, plays a vital role in maintaining intestinal function, and protecting against pathogens. The immune system, including innate and adaptive components, defends the body against harmful microorganisms. The gut microbiota and immune system have a complex relationship, and dysbiosis of the gut microbiota can lead to various diseases and abnormal immune responses. The mucosal immune system, present in the gastrointestinal tract, plays a crucial role in preventing the entry of pathogens. Functional foods, such as protein hydrolysates and bioactive peptides, have been found to modulate the immune system and offer potential benefits for intestinal health. Further research is needed to fully understand the effects of protein hydrolysates on human immune responses.

Conflict of Interest

All contributing authors declare no conflicts of interest.

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Ethics Approval

NA

Consent Forms

NA

Data Availability

NA

Authors Contribution

AIK conceptualized the study and wrote the final manuscript, AIK and YX did the literature analysis, AIK and YX contributed to manuscript writing and AIK supervised the whole project and wrote the final manuscript.

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