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A Comprehensive Overview Of Host Defense Mechanisms In Microbial Infections: Significance Of Innate And Adaptive Immunity In Body For Human Health

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Abstract

The immune system is a complex and an extremely flexible line of defense that is simply critical in the protection of an organism against diseases. It is normally classified into two key categories namely innate and adaptive immunity. Innate immunity is the first line of defense comprising of timely actions against infections and non-specific responses with the aid of epithelial and mucosa barriers, inflammatory molecules, and cells, namely macrophages, neutrophils, and natural killer (NK) cells. The same cells perceive and destroy infectious agents and trigger the cascade of inflammation at the same time and other immune pathways. The difference in contrast is adaptive immune which is characterized by antigen-specificity and immunological memory. The T and B lymphocytes have specificity to antigens and the differentiation T cells into the helper or the T cytotoxic cells, and B cells produce the antibodies that neutralize pathogens and activate the complement response. Immunological memory allows the adaptive system to elicit a faster and better response on repeated exposure to the pathogen previously challenged. An integrated functional immune response is enabled by the synergistic fusing of both innate and adaptive immunity. Also, the microbiome present within individuals has a shaping effect on systemic and local immune activities. These immune components can only be completely understood to accurately improve therapeutic measures in vaccination, immunotherapy and in the treatment of autoimmune diseases. This review therefore outlines the principle functions of immunity and the key importance of the innate and adaptive systems in maintaining health and overcome infectious challenges.

Keywords Innate Immunity, Adaptive Immunity, Pathogen Recognition, Immunological Memory, Inflammatory Response, Microbiome.

Introduction

The immunity is an elaborate and highly adaptive biological process, which outfits organisms to struggle with infections and diseases by effectively identifying and then neutralizing and/or eradicating pathogenic microorganisms and their harmful products through recognition. The immune system lays

the elaborate game plan, differentiating the constituents of the body and comparing them to the alien causes and deciding what action to be taken against foreign antagonists (McComb et al., 2019). The network is highly elaborate in that it involves various interacting cells, tissues, and soluble mediators all of which collaborate to ensure homeostasis of the body despite challenging and ever-changing environment (Crisman, 2001). The capacity of the immune system to distinguish between self and non-self can be considered as the fundamental performant of the immune system and it should not attack its own system tissues at the same time it should be able to target and destroy foreign invaders. The discussion on the use of NPs in the United States is presented by (Catanzaro et al., 2018).

Infections caused by microbes especially pathogenic microbe including bacteria, viruses, fungi and parasites are a major health hazard to humans and may lead to a broad array of disease with mild, self-limiting illnesses at one end of the spectrum, to severe and life-threatening on the other. The focus of the youth on innovation is a topic of concern to the youth (D Accolti et al, 2023). To guard against the universe of pathogens it encounters, the human immune system places in motion a wide range of innate and adaptive responses with the object of defence (Chaplin, 2006). Because of the complex interactions between hosts and pathogens, research based on this topic is essential in the creation of new therapeutic plans and preventive methods to infectious diseases (Jo, 2019). This is conducted by assessing the facet of the microbiota and the immune system and this is based on the study of germ-free animals (Hooper et al., 2012). The presence of numerous changes possible in signal transduction during exposure to pathogenic and commensal bacteria is one of the reasons the host immune responses to bacteria differ (Perry & Arsenault, 2022). The immune responses of the host can be altered when non-specific host defenses, humoral antibody, or cell-mediated immune responses are modulated thus modifying the capabilities of the body to prevent or destroy agents that cause the diseases (Harun et al., 2019).

Innate Immunity in Microbial Infection

The innate immune system is the first line of protection against invading microorganisms and features a mixed set of mechanisms that will detect these microorganisms and disrupt their inception or growth (Merk, 2016). The first line of defense is physical, and it is presented by the skin and mucous membranes; the second line of defense is a combination of chemical barriers (antimicrobial peptides and enzymes) that prevents the growth of microbes directly (Kobayashi et al., 2018). These systems operate together as gatekeepers with a broad defense against a broad range of potential pathogens. The major method of preserving a host homeostatic relationship between microbiota is to prevent contact between microorganisms and epithelial surfaces and thus hamper tissue inflammation as well as microbial translocation (Belkaid & Hand, 2014). Therefore, the effectiveness of these first-line defenses is determinant of the general host susceptibility to infection (Okumura & Takeda, 2024).

The pattern recognition receptors are a key component of the innate immune system that acts as sentinel to identify pathogens based on their recognition of endogenous conserved microbial structures, or pathogen-associated molecular patterns (Hajishengallis & Russell, 2015). These receptors are expressed in macrophages, dendritic cells, neutrophils and other immune cells where they activate a cascade of signalling that lead to the activation of inflammatory and antimicrobial responses. An early host response to pathogens is the use of inflammatory reactions that are highly controlled by various molecular pathways (Chandra, 2019).

Cellular Components of the Innate Immune System: Macrophages, Neutrophils, and Natural Killer Cells

Macrophages are the key players in the innate immune response and adaptive immune response. They take up pathogens and break them down via phagocytosis, although at the same time producing cytokines and chemokines, which organize the inflow of other types of leukocytes to sites of infection (Atri et al. 2018; Campbell et al. 2023). It is interesting to note that the most abundant circulating leukocyte, neutrophils, confers a tissue-based immune effect within minutes through mobilisation to inflammatory foci and subsequent microbe engulfment and killing by their production of reactive oxygen species, as well as the extracellular release of antimicrobial enzymes (Merk 2016). Natural killer (NK) cells represent a subgroup of cytotoxic lymphocytes that can recognise and kill the infected or transformed cell, which are mediated by a cytotoxic granule, which contains a perforin and granzymes

(Li et al. 2022). They achieve this by controlling the action of these lymphocytes via activating and inhibitory receptors that differentiate between normal/pathologically deranged cells thus avoiding undesirable cytotoxicity. This immune reaction is vital in destruction of infected cells, and reducing viral diffusion. The most important defence mechanism involving phagocytic cells, such as macrophages and neutrophils, is the recognition of the components of microbial organisms, their attachment within phagosomes, and degradation (Kaufmann & Walker 2006; Witkowski 2022). The ability of these cells to destroy pathogens determines whether there would be suppression of infection or whether there would be spared tissue damages.

Table 1: Key components in Innate Immunity.

Component	Type	Function	References
Macrophages	Immune Cells	Phagocytosis of pathogens Release cytokines and chemokines to recruit other immune cells Antigen presentation to T cells	Atri et al., 2018; Campbell et al., 2023
Neutrophils	Immune Cells	Rapidly recruited to infection sites Engulf and kill pathogens through reactive oxygen species (ROS) and antimicrobial enzymes	Merk, 2016; Rosales, 2018
Natural Killer Cells (NK)	Immune Cells	Kill infected or tumor cells by releasing cytotoxic granules containing perforin and granzymes	Li et al., 2022
Dendritic Cells	Immune Cells	Antigen-presenting cells that bridge innate and adaptive immunity Capture and present antigens to T cells	Yang et al., 2025
Pattern Recognition Receptors (PRRs)	Receptors	Detect pathogens via pathogen-associated molecular patterns (PAMPs) Initiate immune signaling and inflammation	Hajishengallis & Russell, 2015; Chandra, 2019
Complement System	Proteins	Enhance phagocytosis (opsonization) Promote inflammation Lyse pathogens directly (membrane attack complex)	Dunkelberger & Song, 2009; Volanakis, 2002

The Inflammatory Response: A Double-Edged Sword

Inflammation is a highly complex biological response of organ damage or infection and is carried out by the combined efforts of various types of immune cells and mediators. It begins with secretion of inflammatory mediators: histamine, prostaglandins, and cytokines, which induce vasodilation, enhanced vascular permeability and recruitment of immune cells to damaged area. Inflammation is essential since it eliminates pathogens and assists during the healing process of a damaged tissue, even though prolonged or uncontrolled activation of inflammation lead to tissue breakdown and hasten the development of a long-term disease (Newton & Dixit, 2012).

When confined, small-scale tissue damage, sometimes sufficient neutrophil population of the body can be provided by the existing resident pool of the circulatory neutrophiles to support the appropriate

formation of the inflammatory response subsequently, creating the necessary and required processes of pathogen clearance and tissue repair (Nunes, 2020). With the help of phagocytosis and the deposition of neutrophil extracellular traps (neutrophil-derived DNA templates covered with proteases and antimicrobial peptides), neutrophils coordinate the lysis of pathogens very quickly (Yang et al., 2025). The decisive significance of their involvement in the initial stage of inflammation requires a strict control to regulate anti-pathogen defense coupled with minimum tissue damage. Neutrophils are the most important defense against many of the harmful microorganisms: they eliminate the attacking microbes by producing reactive oxygen species and gas-exhaling the microbicidal granule content to the environment (Aroca-Crevillenz et al., 2024). Hence, this fragile balance between tissue homeostasis and resolution of immune activity is central to prevent chronic inflammations. The powerful effectors released by neutrophils may however damage the host tissue accidentally. When the neutrophils are active too long or too much, they lead to chronic inflammatory pathologies (Yang et al., 2025).

Crosstalk Between Innate and Adaptive Immunity: Bridging the Gap

Empirical studies have shown that the innate and the adaptive immune systems are not mutually exclusive, but rather, they are continuously intertwined in a bidirectional process that is necessary in the coordination of the effective immune responses. Dendritic cells are a specialised group of antigen-presenting cells that play a strategic role in the liaison between the two systems, taking and presenting antigens that are pathogen-related to T lymphocytes in the lymph nodes hence triggering an adaptive immune response (Yang et al., 2025). T lymphocytes Differentiation Innate immune cells secrete various cytokines that regulate the differentiation of T lymphocytes into different effector subsets e.g. T helper 1 cells and T helper 2 cells which play a specific role in the anti-reaction against specific pathogens. Additionally, stimulation of the immune system also translates to neurohormonal releases that involve the neurohormone production of corticotropin, cortisol and catecholamines (Sikora et al., 2023). These hormones coordinate the pro and anti-inflammatory mediators and hence they affect the duration and strength of the resultant inflammatory process. The neutrophil recruitment is also closely regulated: these cells leave the bloodstream, bind vessel walls, and stick to the endothelium (Margraf et al., 2019). They will form trans endothelial migration to travel through the vessel and then enter tissues in response to the action of chemoattractant (Filep, 2022). Tissue-resident cells play a major role in it as they regulate the recruitment of neutrophils and start and end the inflammation process (Kim & Luster, 2015).

The new studies indicate that neutrophils also enter the secondary lymphoid organs, infiltrate them, and, thus, regulate the development processes of adaptive immunity (Odobasic et al., 2016). They also affect the T cell reaction towards pathogens and tumor antigens (Kumar & Sharma, 2010). Since neutrophils have a short life span, proper clearance of these cells is necessary in restoring tissue functionality and avoiding tissue damage after the neutrophils undergo apoptosis or necrosis (Bratton & Henson, 2011). Subtleties of the interaction of neutrophils and pathogens provide the understanding of the sophistication of neutrophil defensive host mechanisms (Merk, 2016). Neutrophil also NET release by a protective action against invading pathogens, with decondensed DNA along with histones and granule proteins spread.

B-cell Responses and Antibody Production

B cells make an important part of adaptive immunity, since they produce antibodies that can detect and destroy pathogens (Yang et al., 2025). They depend on the recognition of antigens and co-stimulatory signals, and interactions with lymphocytic T cells, which consequently enables the division and the transformation in plasma cells and memory B cells. The main antibodies secreted by plasma cells are the inactivation of viruses, activation of complement and stimulation of phagocytosis (Shameena et al., 2021). T helper cells of the CD4 active T cells additionally enhance the work of macrophages, and there is an emphasis on the collaborative nature of immune protection (Kavathas et al., 2019). B cells do not only express antigens but also release cytokines of pro- and anti-inflammatory effect thereby mediating immune regulation (Bluestone et al., 2010). T lymphocytes and natural killer cells have complementary functions in immune homeostasis (Yang et al., 2025).

Adaptive immunologic response also features production of antibodies and activation of B cells and lasts longer than other responses, offering pathogen protection. Primary aim of B cells, that of antibody production, is just that: coexisting with a number of minor roles, such as the presentation of antigens or the secretion of cytokines, both of which affect T-cell responses and which thus may contribute to pathology of autoimmunity (Marcus et al., 2011; Robinson et al., 2024). These complex functions make B cells interesting therapeutic options of autoimmune diseases (Robinson et al., 2024). At the same time, orchestrated actions of naive CD8+ T lymph cells are obligatory to fight against the infectious factor (Zhang & Bevan, 2011). Neutrophils play a primary role in innate immunity because they move to the area of infection and tissue damage quickly (Capucetti et al., 2020; Rosales, 2018). The formerly considered homogenous cells proved to possess heterogeneous phenotypes, especially in the cancer and inflammatory conditions, and it led to the emergence of new possibilities related to the treatment of the atherosclerosis disease (Mortaz et al., 2018; Wood, 2012). Neutrophils are one of the main defense mechanisms, and their large share of circulating white blood cells, as well as defense against pathogens via extracellular traps, make them one of the most important defenses (Kruk et al., 2021; Selders et al., 2017).

Table 2: Differences Between Innate and Adaptive Immunity.

Feature	Innate Immunity	Adaptive Immunity
Response Speed	- Immediate (hours) - First line of defense	- Delayed (days to weeks) - Requires activation of T and B cells
Specificity	- Non-specific - Broad recognition of pathogens via PAMPs	- Highly specific - Antigen-specific response targeting particular pathogens
Memory	- No memory formation - Immediate but short-lived response	- Strong memory - Long-lasting immunity through memory B and T cells
Types of Cells	- Macrophages - Neutrophils - Natural Killer (NK) cells - Dendritic cells - Epithelial cells	- T cells (helper, cytotoxic) - B cells (plasma cells, memory B cells)
Response Duration	- Short-lived, resolves quickly once pathogens are cleared	- Long-lasting and can be reactivated upon re-exposure to the same pathogen
Effector Mechanism	- Phagocytosis - Inflammation - Direct pathogen killing (e.g., NK cells, complement system)	- Antibody production (B cells) - Cytotoxic activity (T cells)
Immune Regulation	- Primarily regulated by cytokines and pattern recognition receptors	- Regulated by cytokines, T-cell help, and antigen presentation
Examples of Activation	- Detection of PAMPs via PRRs - Immediate inflammatory response	- Antigen presentation to T cells - Activation of helper and cytotoxic T cells

Memory Response and Vaccination

The name of the adaptive immunity, which is characterized by an opportunity to create immunological memory, is associated with the provision of long-lasting immunity against pathogens which were met

during the past infections (Pennock et al., 2013). This fact is used in vaccination that presents a person with attenuated or inactivated pathogens to induce an adaptive immune response that can help prevent disease, in addition to creating memory T and B cells that can mount a rapid and potent response to future exposure (Spiering, 2015). The size of immune response is determined by the amount of antigen. B cells cannot produce antibodies without T-cells, a process that is known as humoral immunity or another term, serological protection physiologically speaking (Boomer et al., 2013). Memory B cell swiftly change to antibody-secreting plasma cells after re-exposure to antigen causing chronically protection against recurrent infection (Chaplin, 2010). Dysregulated immune mechanisms are the foundation of a number of diseases, which makes a thorough knowledge of immunological systems of vital importance in the development of improved immunization techniques and immune-based immunotherapies (Marshall et al., 2024).

The adaptive immune system has all the amazing possibilities of being capable to recognize any antigen and this is also the difference which predisposes autoimmune disease (Turvey & Broide, 2009). Moieties that destroy autoreactive lymphocytes limit autoreactive lymphocytes, and defects in their action contribute to autoimmune disease as in rheumatoid arthritis and systemic lupus erythematosus. Currently, a debate on trained immunity has challenged a historical assumption that solely the adaptive immune system has the capacity to create immunological memory (Netea et al., 2016). Studies on immunological memory maintained that antigen-specific responses of the cell are controlled by innate-like mechanisms, wherein with the help of innate-based vaccination strategy, these controls get disrupted, whereas the acquisition of high-affinity B-cell memory is controlled in a direct manner (McHeyzer-Williams et al., 2011).

Practices of adaptive immunization take advantage of the speed and efficacy of antigen recognition and memory development in the system (Marshall et al., 2018). Vaccination regimen is designed to provoke the creation of immunological memory which is evidenced by the growth and subsequent maintenance of memory lymphocytes, namely memory T cells and memory B cells. They are ready to vigorously and quickly respond once they are re-exposed to them, thus providing long-lasting immunity to infection (Pennock et al., 2013). The use of the adaptive immune system as a result of vaccination and the associated prevention and control of infectious diseases has revolutionised the containment of infectious diseases to such an extent that in most cases these pathogens no longer pose a threat to life (Pashine et al., 2005). The adaptive immune system shares similar features with innate immunity and immunological tolerance during early life that transforms to memory formation as time increases (Pieren et al., 2022). Efficacy of vaccines against respiratory infections in infants to prevent infection may be affected by such developmental dynamics (Pieren et al., 2022).

Immune Evasion by Microbes

Pathogens use varied methods to avoid or evade the immune system of the host, therefore maintaining chronic infections. One of these strategies is the antigenic variation, the suppression of the major histocompatibility complex (MHC), and production of immunosuppressive molecules. The antigenic variation allows the alteration of the surface antigens of the pathogen to evade the antibody and T lymphocyte detection. The molecular basis of antigenic variation in the microbial systems is explained by a number of models (Deitsch et al., 2009). The antigen presentation can be weakened by downregulating MHC molecules and because of this, T-cells activations are subdued. There have also been ways through which parasites have exploited host immune mechanisms so as to gain attachment, although the mechanisms through which this happens are ill understood (Iwanowicz, 2011). The most common responses in hosts against parasites are the production of more mucus which counters damage of the parasite by immune system reaction (Iwanowicz, 2011). Immunosuppressant molecules block an immune cell activation and proliferation thus preventing humoral and cellular immune responses.

This co-evolution of pathogens and their hosts is dynamic as each day the pathogen develops evasive strategies, yet the host immune system is ever ready to develop a countering mechanism (Iwanowicz, 2011). As a part of the line of defense in pathogen attacks, the complement system stands as a key connection between the innate and adaptive immune systems (Merk, 2016). After compliment activation the system produces opsonins, chemoattractants, and membrane attack complex which lead

to phagocytosis, inflammatory recruitment, and direct microbial lysis, respectively. There are more than 30 plasma and cell-surface proteins which make the complement pathway and constitute about 15 % of the globulin fraction of plasma (Dunkelberger & Song, 2009). The complement system is the very old system and was found in blood and lymph of the vertebrates and certain invertebrates and provides an excellent first line of defense (Volanakis, 2002). Its cellular elements are inter-related to those of the adaptive immune system due to the reason that it interacts with B- and T-cell responses.

Microbiome and Immune Modulation

Trillions of microorganisms of the gut microbiome play a determinantal role in the development of the host immune system, and its effectiveness (Youssef et al., 2021). Epidemiologic studies show people, who live in rural or developing environments, have low risk of allergic diseases (Liu et al., 2018). Similarly, the respiratory microbiome plays a role in balancing infection by mediating the pathogen-suppressive to pro-infectious processes (Morens et al., 2023). The immune differentiation and functional development were necessary due to colonisation by microbial populations in early-life (Gensollen et al., 2016). Processes that are used to limit the growth of bacterial pathogens are also deployed in maintaining homeostatic relationships between the host and established commensals (Belkaid & Hand, 2014). Commensal bacteria aid in the formation of mucosal immune structures like the Peyer patches and isolated lymphoid follicles which are essential in the initiation of the mucosal immune responses. Microbial signals also promote normal immune cell development and servicing of immune tissue in the intestine, and adjust pro/anti-inflammatory axis to attain immune homeostasis (Round & Mazmanian, 2009; Lazar et al., 2018).

There is an increased association between dysbiosis, or changes in the makeup of microbial populations, with diseases such as inflammatory bowel disease, obesity, and autoimmune diseases. It has been revealed that 10 % of host gene expression is controlled by the microbiota, especially on the transcripts associated with metabolism, proliferation, and immunological activities (Mahdavi-Roshan et al., 2022). These discoveries highlight the role of microbe in huge physiological functions and immunity (Moens & Veldhoen, 2011). The primary mediators of host inflammation caused by the metabolites of gut microorganisms are carried out by working directly or indirectly on host immune cells (Ullah et al., 2024). In addition, commensal microbes may compete in the niche or varying patterns of immunological pathways, hence influencing their host response to pathogens (Vieira et al., 2013). Microbiota-immune-system interaction occurs at the level of immune cell acquisition and maturation all the way to immune tissue formation process that is dependent upon the interaction with both innate and adaptive immune compartments (Xiu et al., 2024). This balance is lost as a result of dysbiosis, and results in impaired epithelial barrier, pathological responses of the immune system and chronic inflammation, which make one more prone to disease (Sanders et al., 2021).

Immunopathology of Microbial Infections

An adaptive immune response is essential to the clearance of pathogens, but robust immunopathology and tissue damage are triggered by excessive or unregulated immune stimulation. This can either manifest as chronic inflammation, autoimmune disease, or immunidi-mediated organ damage. Recent infectious diseases are usually propelled by an alteration in human behavior, demographic trends, and environmental changes (Harun et al., 2019). Climate change is also postulated to contribute to the development of a number of infectious diseases (Harun et al., 2019). In regard to the gut-brain axis, disruptions in immune regulation, especially microbiome-driven immune regulation, have far-reaching effects in the neurological and psychological pathways (O Hardy it al., 2025; Zhang et al., 2025). The microbiome composition of the gut is linked to various psychiatric issues, highlighting the complex interrelationship between the gut microbiome, immune system, and mental state (Kelly et al., 2022).

The complex nature of the interaction between the immune system and the mycobiota the Rich and varied fungal population that inhabits the host is essential to physiological homeostasis (Sachdeva & Das, 2022). In the case of the immune system not being able to control a pathogenic fungus, then a chronic inflammation process occurs, which affects the tissue and renders the organs nonfunctional. The driving force behind a substantial proportion of pathogenic pathways in cancer, cardiovascular disease, neurodegenerative disorders, and other diseases is a chronic inflammation caused by chronic

infections. It has been shown that the intestinal microbiome regulates many of the signaling pathways, which led to the idea of microbiota-gut-brain axis: intestinal microbiomes control the activity of the central nervous system, whereas the state of the brain feedbacks to the development and the composition of microbiomes (Liu et al., 2022; Montiel-Castro et al., 2013).

Communication between the microbiome and brain exists in various pathways, encompassing the immune network, the vagal nerve, gut-connected nervous system, and microbilic metabolism like ordinary fatty acids and tryptophan utility (Lin et al., 2024). Alongside this paradigm, there exist strong effects of the microbiota of the gastrointestinal tract on innate and adaptive immune reactivity. The gut microbiota is crucial in the development of immune system during early development (Ullah et al., 2025). Moreover, the intestinal microbiome is known to regulate tolerance and inflammatory response balance and favors the ei-ther induction of immunological tolerance or inflammatory activation regarding pitfalls. Imbalance of the microbiome or dysbiosis can be attributed to inflammatory bowel disease, obesity, and autoimmune diseases (Min & Rhee, 2015). Intestinal epithelial cells are a significant part of the intestinal barrier, and they can display abnormal behavior, affect the integrity of the barrier and preserving inflammation (Yang et al., 2025). In circumstances of intestinal inflammation, epithelial impairment may permit infectious organism translocation, thus stimulating distal tissue belts immunity (Li et al., 2018). The gut microbiota has a strict control over immune modulation; however, in cases of dysbiosis, alterations to this balance disturb microbial-immune interface interactions and initiate inflammatory pathologies and disease related to the immune system (Jin et al., 2023).

Table 3: Examples of Immunomodulatory Natural Products and Their Mechanisms.

Natural Product	Active Components	Mechanism of Action	References
Centella Asiatica	Triterpene glycosides, asiaticoside, madecassoside	- Enhances immune cell function - Modulates inflammation - Increases the production of pro-inflammatory cytokines	Harun et al., 2019; Catanzaro et al., 2018
Neem (Azadirachta indica)	Azadirachtin, nimbidin, flavonoids	- Modulates immune response by enhancing both humoral and cell-mediated immunity - Exhibits anti-inflammatory properties	Raman, 2017; Harun et al., 2019
Garlic (Allium sativum)	Allicin, sulfur compounds, flavonoids	- Stimulates macrophages and enhances the activity of natural killer (NK) cells - Modulates cytokine production (e.g., TNF-α, IL-6)	Valenzuela-Gutiérrez et al., 2021; Raman, 2017
Echinacea purpurea	Alkylamides, caffeic acid derivatives	- Stimulates immune response by activating macrophages, natural killer cells, and T cells - Increases production of IL-1 and TNF-α	Catanzaro et al., 2018; Sotto et al., 2020

Turmeric (Curcuma longa)	Curcumin, demethoxycurcumin, bisdemethoxycurcumin	- Inhibits inflammatory cytokines such as TNF-α and IL-1β - Enhances macrophage function - Suppresses NF-κB signaling	Catanzaro et al., 2018; Jantan et al., 2015
Ginseng (Panax ginseng)	Ginsenosides (Rb1, Rg1, Rc)	- Enhances immune function through modulation of macrophage and NK cell activity - Improves antibody production	Zebeaman et al., 2023; Jantan et al., 2015
Black Seed (Nigella sativa)	Thymoquinone, nigellidine, nigellone	- Boosts immunity by enhancing T cell proliferation and NK cell activity - Anti-inflammatory properties, inhibits inflammatory cytokines	Harun et al., 2019; Raman, 2017

Interaction between intestinal microbial ecosystems and the immune system communication is two-way and is typified by several molecules and cellular interactions. The most important mediators of this reciprocal loop are TRs, cytokines and particular subsets of immune cells. The complement system, which is a major constituent of innate immunity, plays a key role in providing surveillance of pathogens, elimination of pathogens, as well as modulating inflammatory reactions. The multifaceted interactions between the gut microbiome and the immune system cannot be overestimated in terms of designing the prevention or treatment of immune-mediated diseases (Li et al., 2018).

Recent Advances in Immunotherapy and Vaccines

In a recent review of literature, it was possible to show that a strong association exists between the composition of a microbiome and infectious disease risk (Laz depressor et al., 2018). At the same time, advances in immunotherapy and vaccination make possible both preventive and treatment strategies (Harun et al., 2019). The effects of the microbiota on the performance of the immune system and the health of the central nervous system highlights the therapeutic potential of manipulation of the microbiome-gut-brain axis in a large collection of neurodevelopmental, stress-related neuropsychiatric, and neurological illnesses (O Riordan et al., 2025). The increased interest in using natural modalities, especially herbs and medicinal plants, can be explained by the presence of bioactive compounds, providing a therapeutic effect with a limited number of risks compared to several common synthetic drugs (Harun et al., 2019).

One of them is an example of Centella asiatica, which was suggested as an immunomodulatory agent with a potential to prevent pathogen-induced diseases (Harun et al., 2019). Some subclasses of bioactive compounds such as triterpene glycosides, vitamin C, and carotenoids have been reported to improve immune response based on their effects on numbers and activities of immune cells in a way that enables them to produce antibodies and cytokines (Harun et al., 2019). Saponins, glycyrrhizin, aloe, and azadirachtin excite the nonspecific immune system through non-specific interactivity in fish systems (Raman, 2017). Most of the herbal preparations have been found to have an immunomodulatory effect and can stimulate both non-specific and specific immunity (Raman, 2017). The immunostimulatory activity of Azadirachta indica (neem) is also recorded; the extracts show strong influence on the humoral and cell-mediated immune system (Raman, 2017). The use of herbal immunostimulants including tube neem (Emblica officinalis), Chenopodium dactylon, and adathoda vasica also demonstrates efficacy in

boosting immunity and reducing microbial infections in fish (Raman, 2017), therefore, falling under the holistic approaches to aquaculture. The various observations of the presence of immunomodulatory effects of plants have been attributed to the wide variety of polysaccharides, lactones, alkaloids, glycosides, and saponins, found in a variety of plants (Swaroop et al., 2021).

Research as to natural sources, viz., plants, fungi, marine organisms, and animals have discovered a wide range of immunomodulatory bioactive compounds deserving investigation in relation to development of vaccines (Woods et al., 2017). Although the biological natural products as immunomodulators have been found pharmacologically useful, their exploitation has been minimal in the management of immune disorders mainly due to institutional and regulatory barriers (Wen et al., 2012). Seen in light of this, the traditional medical practitioners and a larger scientific community at large have highlighted the importance of multivalent natural agents as opposed to the monovalent commercially produced pharmaceuticals (Zebeaman et al., 2023). Natural products have been reported to have bias-free response to immune effects (Alhazmi et al., 2021). Various medicinal herbs have been assessed and tested as potential in the treatment of fish and shellfish diseases and some of the polyherbal immunomodulatory preparations have been launched (Raman, 2017). Further studies are necessary, though, to see more powerful and specific immunomodulators in this area (Zebeaman et al., 2023). Volatile oils, saponins, phenolics, tannins, alkaloids, polysaccharides, and polypeptides are only some of the important types of plant extracts that remain of interest as immunostimulants due to their pleiotropic character (Raman, 2017).

Challenges and Future Perspectives

Recently, the rising application of immunostimulatory substances in aquaculture has been conditioned by their ability to boost innate immune responses (Raman 2017). In the body of empirical research, it has been identified that plant extract exhibits immunostimulatory and health-protective properties, thus, offering another possibility of having environmentally friendly substitutes in aquaculture (Valenzuela-GutiÃ©rz et al., 2021). Immunostimulation using immunostimulatory substances (such as those composed of bacterial cells walls, and glucans, among others), has expanded into the aquaculture context as part of a preventive approach towards reducing the extent and prevalence of diseases, aiming at creating more sustainable and durable aquaculture industries.

The immunostimulants have also been used as an adjuvant to fish immunization and an aquafeed component as an increasing understanding of disease control potential of immunostimulants (Barman & Nen 2013). Whereas the chemotherapeutic repertoire comprising mostly of antibiotics has been a long-established tool in the armory to control pathogens in aquatic animals, careless and overuse has led to the development of resistance. As a countermeasure, modern aquaculture is associated with the need to use sustainable technologies in which, bit by bit, antibiotics are already being replaced with probiotics, prebiotics, postbiotics, and immunostimulants (Valenzuela-Gutierrrez et al., 2021). Studies conducted on the immunostimulant property of herbal extracts in aquaculture have estimated its effectiveness due to ease of preparation, low cost, and diversified broad-spectrum antipathogen and antiparasitic activity (Raman 2017). Most of such extracts have traditionally been used and passed on intergenerationally without an explicit understanding of their biochemical composition (Jana et al., 2018).

The study of aquaculture is moving ahead in which current candidates of immunostimulants are combined with the next generation candidates like polysaccharides to improve the resistance to diseases and general health of aquatic life (Wang et al., 2016). Artificial chemicals and antibiotics have developed resistant strains although they have historically been used to treat fish and shrimp pathogens. Thus the addition of garlic into fish diets has provided promising results with increased survival in those people exposed to pathogens, boosting the immune system, altering gut microbiome, and an overall healthier animal performance, solidifying its future use as an additive to fish diets (Valenzuela-Gutierrrez et al., 2021). The plant compounds are also growing popular to increase immune reactivity and resistance to disease in fish that have been infected by pathogenic microbes in line with the burgeoning interest in natural and plant based products in this regard. Having the known benefits of immunostimulatory and health-enhancing properties, herbal extracts present an ecologically benign

alternative to synthetic drugs in the alleviation of infectious diseases (Valenzuela-Gutierrz et al., 2021). The preventative use of immunostimulants before circumstances, in which the likelihood of increasing the occurrence of a disorder is high, becomes the norm in the aquaculture industry (Barman & Nen 2013).

Conclusion

The immune system presents a very formidable and adaptive mechanism of defense to deal with microbial infections. Innate immune system produces immediate, non-specific reactions against pathogens, and adaptive immune system improves on those reactions by being specific and creating a long-term memory of how to attack some pathogen by developing immunological memory. The robust balance maintained between the two arms of immunity creates a very healthy and potent defense against a wide range of pathogens. In addition, more recent evidence shows that the makeup of the microbiome has a significant impact in immune response, hence the importance of a balanced microbe community in ensuring excellent immune health. The promising directions of therapeutic intervention, such as the development of vaccines and immunotherapy, contrast with the current achievements in the sphere of immunology especially in disease-modulating and immune-memory aspects. The holistic analysis of the mechanistic basis of innate and adaptive immunity is yet to become dispensable to the development of the targeted preventative measures establishing the possibility to combat infectious diseases and promote the overall health.

Conflict of Interest

The authors declare they don’t have any conflict of interest.

Author contributions

The original author and the supervisor of the cross-ponding author write the initial drafts of the work. Each author contributed to the manuscript's writing, gathered information, revised it, made tables, and received approval to submit it to a journal for publication.

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References

1. Alfaro, S., Acuña, V., Ceriani, R., Cavieres, M. F., Weinstein-Oppenheimer, C., & Campos-Estrada, C. (2022). Involvement of Inflammation and Its Resolution in Disease and Therapeutics [Review of Involvement of Inflammation and Its Resolution in Disease and Therapeutics]. International Journal of Molecular Sciences, 23(18), 10719. Multidisciplinary Digital Publishing Institute. https://doi.org/10.3390/ijms231810719

2. Alhazmi, H. A., Najmi, A., Javed, S. A., Sultana, S., Bratty, M. A., Makeen, H. A., Meraya, A. M., Ahsan, W., Mohan, S., Taha, M. M. E., & Khalid, A. (2021). Medicinal Plants and Isolated Molecules Demonstrating Immunomodulation Activity as Potential Alternative Therapies for Viral Diseases Including COVID-19 [Review of Medicinal Plants and Isolated Molecules Demonstrating Immunomodulation Activity as Potential Alternative Therapies for Viral Diseases Including COVID-19]. Frontiers in Immunology, 12. Frontiers Media. https://doi.org/10.3389/fimmu.2021.637553

3. Aroca-Crevillén, A., Vicanolo, T., Ovadia, S., & Hidalgo, A. (2024). Neutrophils in Physiology and Pathology. Annual Review of Pathology Mechanisms of Disease, 19(1), 227. https://doi.org/10.1146/annurev-pathmechdis-051222-015009

4. Atri, C., Guerfali, F. Z., & Laouini, D. (2018). Role of Human Macrophage Polarization in Inflammation during Infectious Diseases [Review of Role of Human Macrophage Polarization in Inflammation during Infectious Diseases]. International Journal of Molecular Sciences, 19(6), 1801. Multidisciplinary Digital Publishing Institute. https://doi.org/10.3390/ijms19061801

5. Barman, D., & Nen, P. (2013). Immunostimulants for Aquaculture Health Management. Journal of Marine Science Research & Development, 3(3). https://doi.org/10.4172/2155-9910.1000134

6. Belkaid, Y., & Hand, T. W. (2014). Role of the Microbiota in Immunity and Inflammation [Review of Role of the Microbiota in Immunity and Inflammation]. Cell, 157(1), 121. Cell Press. https://doi.org/10.1016/j.cell.2014.03.011

7. Bluestone, J. A., Herold, K. C., & Eisenbarth, G. S. (2010). Genetics, pathogenesis and clinical interventions in type 1 diabetes [Review of Genetics, pathogenesis and clinical interventions in type 1 diabetes]. Nature, 464(7293), 1293. Nature Portfolio. https://doi.org/10.1038/nature08933

8. Boomer, J., Green, J. M., & Hotchkiss, R. S. (2013). The changing immune system in sepsis [Review of The changing immune system in sepsis]. Virulence, 5(1), 45. Taylor & Francis. https://doi.org/10.4161/viru.26516

9. Bratton, D. L., & Henson, P. M. (2011). Neutrophil clearance: when the party is over, clean-up begins. Trends in Immunology, 32(8), 350. https://doi.org/10.1016/j.it.2011.04.009

10. Campbell, C., Kandalgaonkar, M. R., Golonka, R. M., Yeoh, B. S., Vijay-Kumar, M., & Saha, P. (2023). Crosstalk between Gut Microbiota and Host Immunity: Impact on Inflammation and Immunotherapy [Review of Crosstalk between Gut Microbiota and Host Immunity: Impact on Inflammation and Immunotherapy]. Biomedicines, 11(2), 294. Multidisciplinary Digital Publishing Institute. https://doi.org/10.3390/biomedicines11020294

11. Capucetti, A., Albano, F., & Bonecchi, R. (2020). Multiple Roles for Chemokines in Neutrophil Biology [Review of Multiple Roles for Chemokines in Neutrophil Biology]. Frontiers in Immunology, 11. Frontiers Media. https://doi.org/10.3389/fimmu.2020.01259

12. Catanzaro, M., Corsini, E., Rosini, M., Racchi, M., & Lanni, C. (2018). Immunomodulators Inspired by Nature: A Review on Curcumin and Echinacea [Review of Immunomodulators Inspired by Nature: A Review on Curcumin and Echinacea]. Molecules, 23(11), 2778. Multidisciplinary Digital Publishing Institute. https://doi.org/10.3390/molecules23112778

13. Chandra, R. (2019). Host inflammatory responses to intracellular invaders: Review study [Review of Host inflammatory responses to intracellular invaders: Review study]. Life Sciences, 240, 117084. Elsevier BV. https://doi.org/10.1016/j.lfs.2019.117084

14. Chaplin, D. (2006). 1. Overview of the human immune response [Review of 1. Overview of the human immune response]. Journal of Allergy and Clinical Immunology, 117(2). Elsevier BV. https://doi.org/10.1016/j.jaci.2005.09.034

15. Chaplin, D. (2010). Overview of the immune response [Review of Overview of the immune response]. Journal of Allergy and Clinical Immunology, 125(2). Elsevier BV. https://doi.org/10.1016/j.jaci.2009.12.980

16. Crisman, M. V. (2001). Integration of the immune system: a complex adaptive supersystem. Proceedings of SPIE, the International Society for Optical Engineering/Proceedings of SPIE, 4512, 144. https://doi.org/10.1117/12.446761

17. D'Accolti, M., Soffritti, I., Bini, F., Mazziga, E., Cason, C., Comar, M., Volta, A., Bisi, M., Fumagalli, D., Mazzacane, S., & Caselli, E. (2023). Shaping the subway microbiome through probiotic-based sanitation during the COVID-19 emergency: a pre–post case–control study. Microbiome, 11(1). https://doi.org/10.1186/s40168-023-01512-2

18. Deitsch, K., Lukehart, S. A., & Stringer, J. R. (2009). Common strategies for antigenic variation by bacterial, fungal and protozoan pathogens [Review of Common strategies for antigenic variation by bacterial, fungal and protozoan pathogens]. Nature Reviews Microbiology, 7(7), 493. Nature Portfolio. https://doi.org/10.1038/nrmicro2145

19. Dunkelberger, J., & Song, W. (2009). Complement and its role in innate and adaptive immune responses [Review of Complement and its role in innate and adaptive immune responses]. Cell Research, 20(1), 34. Springer Nature. https://doi.org/10.1038/cr.2009.139

20. Filep, J. G. (2022). Targeting Neutrophils for Promoting the Resolution of Inflammation [Review of Targeting Neutrophils for Promoting the Resolution of Inflammation]. Frontiers in Immunology, 13. Frontiers Media. https://doi.org/10.3389/fimmu.2022.866747

21. Gensollen, T., Iyer, S. S., Kasper, D. L., & Blumberg, R. S. (2016). How colonization by microbiota in early life shapes the immune system [Review of How colonization by microbiota in early life shapes the immune system]. Science, 352(6285), 539. American Association for the Advancement of Science. https://doi.org/10.1126/science.aad9378

22. Hajishengallis, G., & Russell, M. W. (2015). Innate Humoral Defense Factors. In Elsevier eBooks (p. 251). Elsevier BV. https://doi.org/10.1016/b978-0-12-415847-4.00015-x

23. Harun, N. H., Septama, A. W., Ahmad, W. A. N. W., & Suppıan, R. (2019). The Potential of Centella asiatica (Linn.) Urban as an Anti-Microbial and Immunomodulator Agent: A Review [Review of The Potential of Centella asiatica (Linn.) Urban as an Anti-Microbial and Immunomodulator Agent: A Review]. Natural Product Sciences, 25(2), 92. Korean Society of Pharmacognosy. https://doi.org/10.20307/nps.2019.25.2.92

24. Hooper, L. V., Littman, D. R., & Macpherson, A. J. (2012). Interactions Between the Microbiota and the Immune System [Review of Interactions Between the Microbiota and the Immune System]. Science, 336(6086), 1268. American Association for the Advancement of Science. https://doi.org/10.1126/science.1223490

25. Iwanowicz, D. D. (2011). Overview on the effects of parasites on fish health. 176. https://www.lsc.usgs.gov/files/D%20Iwanowicz%202011.pdf

26. Jana, P., Karmakar, S., Roy, U. K. G., Paul, M., Singh, A. K., & Bera, K. K. (2018). Phytobiotics in aquaculture health management: A review [Review of Phytobiotics in aquaculture health management: A review]. Journal of Entomology and Zoology Studies, 6(4), 1422. AkiNik Publications. https://www.entomoljournal.com/archives/2018/vol6issue4/PartX/6-3-358-992.pdf

27. Jantan, I., Ahmad, W., & Bukhari, S. N. A. (2015). Plant-derived immunomodulators: an insight on their preclinical evaluation and clinical trials [Review of Plant-derived immunomodulators: an insight on their preclinical evaluation and clinical trials]. Frontiers in Plant Science, 6. Frontiers Media. https://doi.org/10.3389/fpls.2015.00655

28. Jin, Y., Chi, J., LoMonaco, K., Boon, A., & Gu, H. (2023). Recent review on selected xenobiotics and their impacts on gut microbiome and metabolome. TrAC Trends in Analytical Chemistry, 166, 117155. https://doi.org/10.1016/j.trac.2023.117155

29. Jo, E. (2019). Interplay between host and pathogen: immune defense and beyond. In Experimental & Molecular Medicine (Vol. 51, Issue 12, p. 1). Springer Nature. https://doi.org/10.1038/s12276-019-0281-8

30. Kabat, A. M., Srinivasan, N., & Maloy, K. J. (2014). Modulation of immune development and function by intestinal microbiota [Review of Modulation of immune development and function by intestinal microbiota]. Trends in Immunology, 35(11), 507. Elsevier BV. https://doi.org/10.1016/j.it.2014.07.010

31. Kaufmann, S. H. E., & Walker, B. D. (2006). Host–pathogen interactions. In Current Opinion in Immunology (Vol. 18, Issue 4, p. 371). Elsevier BV. https://doi.org/10.1016/j.coi.2006.05.009

32. Kavathas, P., Krause, P. J., & Ruddle, N. H. (2019). Adaptive Immunity: Effector Functions, Regulation, and Vaccination. In Springer eBooks (p. 75). Springer Nature. https://doi.org/10.1007/978-3-030-25553-4_5

33. Kelly, J. R., Clarke, G., Harkin, A., Corr, S. C., Galvin, S., Pradeep, V., Cryan, J. F., O'Keane, V., & Dinan, T. G. (2022). Seeking the Psilocybiome: Psychedelics meet the microbiota-gut-brain axis. International Journal of Clinical and Health Psychology, 23(2), 100349. https://doi.org/10.1016/j.ijchp.2022.100349

34. Kim, N. D., & Luster, A. D. (2015). The role of tissue resident cells in neutrophil recruitment [Review of The role of tissue resident cells in neutrophil recruitment]. Trends in Immunology, 36(9), 547. Elsevier BV. https://doi.org/10.1016/j.it.2015.07.007

35. Kobayashi, S. D., Małachowa, N., & DeLeo, F. R. (2018). Neutrophils and Bacterial Immune Evasion [Review of Neutrophils and Bacterial Immune Evasion]. Journal of Innate Immunity, 10, 432. Karger Publishers. https://doi.org/10.1159/000487756

36. Kruk, A., Piwowarski, J. P., Pawłowska, K. A., Popowski, D., & Granica, S. (2021). High molecular pyrogens present in plant extracts interfere with examinations of their immunomodulatory properties in vitro. Scientific Reports, 11(1). https://doi.org/10.1038/s41598-020-79579-2

37. Kumar, V., & Sharma, A. (2010). Neutrophils: Cinderella of innate immune system [Review of Neutrophils: Cinderella of innate immune system]. International Immunopharmacology, 10(11), 1325. Elsevier BV. https://doi.org/10.1016/j.intimp.2010.08.012

38. Lazăr, V., Diţu, L.-M., Pîrcălăbioru, G. G., Gheorghe, I., Curuţiu, C., Holban, A. M., Picu, A., Petcu, L., & Chifiriuc, M. C. (2018). Aspects of Gut Microbiota and Immune System Interactions in Infectious Diseases, Immunopathology, and Cancer [Review of Aspects of Gut Microbiota and Immune System Interactions in Infectious Diseases, Immunopathology, and Cancer]. Frontiers in Immunology, 9. Frontiers Media. https://doi.org/10.3389/fimmu.2018.01830

39. Lehman, H. K., & Segal, B. H. (2020). The role of neutrophils in host defense and disease [Review of The role of neutrophils in host defense and disease]. Journal of Allergy and Clinical Immunology, 145(6), 1535. Elsevier BV. https://doi.org/10.1016/j.jaci.2020.02.038

40. Lei, Y. M., Nair, L., & Alegre, M. (2014). The interplay between the intestinal microbiota and the immune system [Review of The interplay between the intestinal microbiota and the immune system]. Clinics and Research in Hepatology and Gastroenterology, 39(1), 9. Elsevier BV. https://doi.org/10.1016/j.clinre.2014.10.008

41. Li, B., Selmi, C., Tang, R., Gershwin, M. E., & Ma, X. (2018). The microbiome and autoimmunity: a paradigm from the gut–liver axis [Review of The microbiome and autoimmunity: a paradigm from the gut–liver axis]. Cellular and Molecular Immunology, 15(6), 595. Springer Nature. https://doi.org/10.1038/cmi.2018.7

42. Li, Y., Ye, Z., Zhu, J., Fang, S., Meng, L., & Chen, Z. (2022). Effects of Gut Microbiota on Host Adaptive Immunity Under Immune Homeostasis and Tumor Pathology State [Review of Effects of Gut Microbiota on Host Adaptive Immunity Under Immune Homeostasis and Tumor Pathology State]. Frontiers in Immunology, 13. Frontiers Media. https://doi.org/10.3389/fimmu.2022.844335

43. Lin, Y., Xie, Z., Li, Z., Yuan, C., Zhang, C., Li, Y., Xie, K., & Wang, K. (2024). The microbiota-gut-brain axis: A crucial immunomodulatory pathway for Bifidobacterium animalis subsp. lactis' resilience against LPS treatment in neonatal rats. International Journal of Biological Macromolecules, 266, 131255. https://doi.org/10.1016/j.ijbiomac.2024.131255

44. Liu, L., Huh, J. R., & Shah, K. (2022). Microbiota and the gut-brain-axis: Implications for new therapeutic design in the CNS [Review of Microbiota and the gut-brain-axis: Implications for new therapeutic design in the CNS]. EBioMedicine, 77, 103908. Elsevier BV. https://doi.org/10.1016/j.ebiom.2022.103908

45. Liu, Y., Tran, D. Q., & Rhoads, J. M. (2018). Probiotics in Disease Prevention and Treatment. The Journal of Clinical Pharmacology, 58. https://doi.org/10.1002/jcph.1121

46. Mahdavi-Roshan, M., Salari, A., Kheirkhah, J., & Ghorbani, Z. (2022). The Effects of Probiotics on Inflammation, Endothelial Dysfunction, and Atherosclerosis Progression: A Mechanistic Overview [Review of The Effects of Probiotics on Inflammation, Endothelial Dysfunction, and Atherosclerosis Progression: A Mechanistic Overview]. Heart Lung and Circulation, 31(5). Elsevier BV. https://doi.org/10.1016/j.hlc.2021.09.006

47. Marcus, C. Z., Dhillon, G., & Anolik, J. H. (2011). B Cell Immunology for the Clinician [Review of B Cell Immunology for the Clinician]. The Pediatric Infectious Disease Journal, 30(2), 158. Lippincott Williams & Wilkins. https://doi.org/10.1097/inf.0b013e318207447f

48. Margraf, A., Ley, K., & Zarbock, A. (2019). Neutrophil Recruitment: From Model Systems to Tissue-Specific Patterns [Review of Neutrophil Recruitment: From Model Systems to Tissue-Specific Patterns]. Trends in Immunology, 40(7), 613. Elsevier BV. https://doi.org/10.1016/j.it.2019.04.010

49. Marshall, J. S., Upton, J., Vliagoftis, H., Hildebrand, K. J., Byrne, A. J., & Watson, W. (2024). Introduction to immunology and immune disorders [Review of Introduction to immunology and immune disorders]. Allergy Asthma and Clinical Immunology, 20. BioMed Central. https://doi.org/10.1186/s13223-024-00932-5

50. Marshall, J. S., Warrington, R., Watson, W., & Kim, H. L. (2018). An introduction to immunology and immunopathology [Review of An introduction to immunology and immunopathology]. Allergy Asthma and Clinical Immunology, 14. BioMed Central. https://doi.org/10.1186/s13223-018-0278-1

51. McComb, S., Thiriot, A., Akache, B., Krishnan, L., & Stark, F. C. (2019). Introduction to the Immune System. Methods in Molecular Biology, 1. https://doi.org/10.1007/978-1-4939-9597-4_1

52. McHeyzer-Williams, M. G., Okitsu, S. L., Wang, N., & McHeyzer-Williams, L. J. (2011). Molecular programming of B cell memory [Review of Molecular programming of B cell memory]. Nature Reviews. Immunology, 12(1), 24. Nature Portfolio. https://doi.org/10.1038/nri3128

53. Merk, T. M. (2016). Effects of antiparasitic treatment for argulosis on innate immune system of a cyprinid fish (Fathead Minnow; Pimephales promelas, Rafinesque 1820). https://edoc.ub.uni-muenchen.de/19236/1/Merk_Teresa.pdf

54. Min, Y. W., & Rhee, P. (2015). The Role of Microbiota on the Gut Immunology [Review of The Role of Microbiota on the Gut Immunology]. Clinical Therapeutics, 37(5), 968. Elsevier BV. https://doi.org/10.1016/j.clinthera.2015.03.009

55. Moens, E., & Veldhoen, M. (2011). Epithelial barrier biology: good fences make good neighbours [Review of Epithelial barrier biology: good fences make good neighbours]. Immunology, 135(1), 1. Wiley. https://doi.org/10.1111/j.1365-2567.2011.03506.x

56. Montiel-Castro, A. J., González-Cervantes, R. M., Bravo-Ruiseco, G., & Pacheco-López, G. (2013). The microbiota-gut-brain axis: neurobehavioral correlates, health and sociality [Review of The microbiota-gut-brain axis: neurobehavioral correlates, health and sociality]. Frontiers in Integrative Neuroscience, 7. Frontiers Media. https://doi.org/10.3389/fnint.2013.00070

57. Morens, D. M., Taubenberger, J. K., & Fauci, A. S. (2023). Rethinking next-generation vaccines for coronaviruses, influenzaviruses, and other respiratory viruses [Review of Rethinking next-generation vaccines for coronaviruses, influenzaviruses, and other respiratory viruses]. Cell Host & Microbe, 31(1), 146. Cell Press. https://doi.org/10.1016/j.chom.2022.11.016

58. Mortaz, E., Alipoor, S. D., Adcock, I. M., Mumby, S., & Koenderman, L. (2018). Update on Neutrophil Function in Severe Inflammation [Review of Update on Neutrophil Function in Severe

Inflammation]. Frontiers in Immunology, 9. Frontiers Media. https://doi.org/10.3389/fimmu.2018.02171

59. Netea, M. G., Joosten, L. A. B., Latz, E., Mills, K. H. G., Natoli, G., Stunnenberg, H. G., O'neill, L., & Xavier, R. J. (2016). Trained immunity: A program of innate immune memory in health and disease [Review of Trained immunity: A program of innate immune memory in health and disease]. Science, 352(6284). American Association for the Advancement of Science. https://doi.org/10.1126/science.aaf1098

60. Newton, K., & Dixit, V. M. (2012). Signaling in Innate Immunity and Inflammation [Review of Signaling in Innate Immunity and Inflammation]. Cold Spring Harbor Perspectives in Biology, 4(3). Cold Spring Harbor Laboratory Press. https://doi.org/10.1101/cshperspect.a006049

61. Nunes, A. C. F. (2020). Introductory Chapter: Overview of the Cellular and Molecular Basis of Inflammatory Process. In IntechOpen eBooks. IntechOpen. https://doi.org/10.5772/intechopen.88967

62. Odobasic, D., Kitching, A. R., & Holdsworth, S. R. (2016). Neutrophil-Mediated Regulation of Innate and Adaptive Immunity: The Role of Myeloperoxidase [Review of Neutrophil-Mediated Regulation of Innate and Adaptive Immunity: The Role of Myeloperoxidase]. Journal of Immunology Research, 2016, 1. Hindawi Publishing Corporation. https://doi.org/10.1155/2016/2349817

63. Okumura, R., & Takeda, K. (2024). The role of the mucosal barrier system in maintaining gut symbiosis to prevent intestinal inflammation [Review of The role of the mucosal barrier system in maintaining gut symbiosis to prevent intestinal inflammation]. Seminars in Immunopathology, 47(1). Springer Science+Business Media. https://doi.org/10.1007/s00281-024-01026-5

64. O'Riordan, K. J., Moloney, G. M., Keane, L., Clarke, G., & Cryan, J. F. (2025). The gut microbiota-immune-brain axis: Therapeutic implications [Review of The gut microbiota-immune-brain axis: Therapeutic implications]. Cell Reports Medicine, 101982. Elsevier BV. https://doi.org/10.1016/j.xcrm.2025.101982

65. Pashine, A., Valiante, N. M., & Ulmer, J. B. (2005). Targeting the innate immune response with improved vaccine adjuvants [Review of Targeting the innate immune response with improved vaccine adjuvants]. Nature Medicine, 11. Nature Portfolio. https://doi.org/10.1038/nm1210

66. Pennock, N. D., White, J. T., Cross, E., Cheney, E. E., Tamburini, B. A. J., & Kedl, R. M. (2013). T cell responses: naïve to memory and everything in between. AJP Advances in Physiology Education, 37(4), 273. https://doi.org/10.1152/advan.00066.2013

67. Perry, F., & Arsenault, R. J. (2022). The Study of Microbe–Host Two-Way Communication. Microorganisms, 10(2), 408. https://doi.org/10.3390/microorganisms10020408

68. Pieren, D. K. J., Boer, M. C., & Wit, J. de. (2022). The adaptive immune system in early life: The shift makes it count [Review of The adaptive immune system in early life: The shift makes it count]. Frontiers in Immunology, 13. Frontiers Media. https://doi.org/10.3389/fimmu.2022.1031924

69. Raman, R. P. (2017). Application of herbal-based immunostimulants in aquaculture: an overview.

70. Robinson, W. H., Fiorentino, D., Chung, L. W. K., Moreland, L. W., Deodhar, M., Harler, M., Saulsbery, C., & Kunder, R. (2024). Cutting-edge approaches to B-cell depletion in autoimmune diseases [Review of Cutting-edge approaches to B-cell depletion in autoimmune diseases]. Frontiers in Immunology, 15. Frontiers Media. https://doi.org/10.3389/fimmu.2024.1454747

71. Rosales, C. (2018). Neutrophil: A Cell with Many Roles in Inflammation or Several Cell Types? [Review of Neutrophil: A Cell with Many Roles in Inflammation or Several Cell Types?]. Frontiers in Physiology, 9. Frontiers Media. https://doi.org/10.3389/fphys.2018.00113

72. Round, J. L., & Mazmanian, S. K. (2009). The gut microbiota shapes intestinal immune responses during health and disease [Review of The gut microbiota shapes intestinal immune responses during health and disease]. Nature Reviews. Immunology, 9(5), 313. Nature Portfolio. https://doi.org/10.1038/nri2515

73. Sachdeva, G., & Das, A. (2022). Communication between immune system and mycobiota impacts health and disease. DELETED, 88(3), 250. https://doi.org/10.1007/s43538-022-00082-5

74. Sanders, D. J., Inniss, S., Sebepos-Rogers, G., Rahman, F., & Smith, A. (2021). The role of the microbiome in gastrointestinal inflammation. Bioscience Reports, 41(6). https://doi.org/10.1042/bsr20203850

75. Selders, G. S., Fetz, A. E., Radic, M., & Bowlin, G. L. (2017). An overview of the role of neutrophils in innate immunity, inflammation and host-biomaterial integration [Review of An overview of the role of neutrophils in innate immunity, inflammation and host-biomaterial integration]. Regenerative Biomaterials, 4(1), 55. University of Oxford. https://doi.org/10.1093/rb/rbw041

76. Shameena, S. S., Kumar, K., Kumar, S., Kumari, P., Krishnan, R., Karmakar, S., Kumar, H. S., Rajendran, K. V., & Raman, R. (2021). Dose-dependent co-infection of Argulus sp. and Aeromonas hydrophila in goldfish (Carassius auratus) modulates innate immune response and antioxidative stress enzymes. Fish & Shellfish Immunology, 114, 199. https://doi.org/10.1016/j.fsi.2021.04.026

77. Sikora, J. P., Karawani, J., & Sobczak, J. (2023). Neutrophils and the Systemic Inflammatory Response Syndrome (SIRS) [Review of Neutrophils and the Systemic Inflammatory Response Syndrome (SIRS)]. International Journal of Molecular Sciences, 24(17), 13469. Multidisciplinary Digital Publishing Institute. https://doi.org/10.3390/ijms241713469

78. Sotto, A. D., Vitalone, A., & Giacomo, S. D. (2020). Plant-Derived Nutraceuticals and Immune System Modulation: An Evidence-Based Overview [Review of Plant-Derived Nutraceuticals and Immune System Modulation: An Evidence-Based Overview]. Vaccines, 8(3), 468. Multidisciplinary Digital Publishing Institute. https://doi.org/10.3390/vaccines8030468

79. Spiering, M. J. (2015). Primer on the Immune System. PubMed, 37(2), 171. https://pubmed.ncbi.nlm.nih.gov/26695756

80. Swaroop, A. K., Chaitanya, M., Shanmugam, M., Subramanian, G., Natarajan, J., & Selvaraj, J. (2021). Plant Derived Immunomodulators; A Critical Review [Review of Plant Derived Immunomodulators; A Critical Review]. Advanced Pharmaceutical Bulletin. Tabriz University of Medical Sciences. https://doi.org/10.34172/apb.2022.074

81. Turvey, S. E., & Broide, D. H. (2009). Innate immunity [Review of Innate immunity]. Journal of Allergy and Clinical Immunology, 125(2). Elsevier BV. https://doi.org/10.1016/j.jaci.2009.07.016

82. Ullah, H., Arbab, S., Chang, C., Bibi, S., Muhammad, N., Rehman, S. U., Suleman, Ullah, I., Hassan, I. U., Tian, Y., & Li, K. (2025). Gut microbiota therapy in gastrointestinal diseases [Review of Gut microbiota therapy in gastrointestinal diseases]. Frontiers in Cell and Developmental Biology, 13. Frontiers Media. https://doi.org/10.3389/fcell.2025.1514636

83. Ullah, H., Arbab, S., Tian, Y., Chen, Y., Liu, C., Li, Q., & Li, K. (2024). Crosstalk between gut microbiota and host immune system and its response to traumatic injury [Review of Crosstalk between gut microbiota and host immune system and its response to traumatic injury]. Frontiers in Immunology, 15. Frontiers Media. https://doi.org/10.3389/fimmu.2024.1413485

84. Valenzuela-Gutiérrez, R., Lago-Lestón, A., Vargas-Albores, F., Cicala, F., & Martínez-Porchas, M. (2021). Exploring the garlic (Allium sativum) properties for fish aquaculture [Review of Exploring the garlic (Allium sativum) properties for fish aquaculture]. Fish Physiology and Biochemistry, 47(4), 1179. Springer Science+Business Media. https://doi.org/10.1007/s10695-021-00952-7

85. Vieira, A. T., Teixeira, M. M., & Martins, F. S. (2013). The Role of Probiotics and Prebiotics in Inducing Gut Immunity [Review of The Role of Probiotics and Prebiotics in Inducing Gut Immunity]. Frontiers in Immunology, 4. Frontiers Media. https://doi.org/10.3389/fimmu.2013.00445

86. Volanakis, J. E. (2002). The Role of Complement in Innate and Adaptive Immunity [Review of The Role of Complement in Innate and Adaptive Immunity]. Current Topics in Microbiology and Immunology, 41. Springer Science+Business Media. https://doi.org/10.1007/978-3-662-04700-2_4

87. Wang, W., Sun, J., Liu, C., & Xue, Z. (2016). Application of immunostimulants in aquaculture: current knowledge and future perspectives. Aquaculture Research, 48(1), 1. https://doi.org/10.1111/are.13161

88. Wen, C.-C., Chen, H.-M., & Yang, N. (2012). Developing Phytocompounds from Medicinal Plants as Immunomodulators. Advances in Botanical Research, 197. https://doi.org/10.1016/b978-0-12-394591-4.00004-0

89. Witkowski, J. M. (2022). Immune system aging and the aging-related diseases in the COVID-19 era [Review of Immune system aging and the aging-related diseases in the COVID-19 era]. Immunology Letters, 243, 19. Elsevier BV. https://doi.org/10.1016/j.imlet.2022.01.005

90. Wood, P. J. (2012). Immunological response to infection: inflammatory and adaptive immune responses. Anaesthesia & Intensive Care Medicine, 13(6), 269. https://doi.org/10.1016/j.mpaic.2012.03.005

91. Woods, N., Niwasabutra, K., Acevedo, R., Igoli, J. O., Altwaijry, N., Tusiimire, J., Gray, A. I., Watson, D. G., & Ferro, V. A. (2017). Natural Vaccine Adjuvants and Immunopotentiators Derived From Plants, Fungi, Marine Organisms, and Insects. In Elsevier eBooks (p. 211). Elsevier BV. https://doi.org/10.1016/b978-0-12-804019-5.00011-6

92. Xiu, W., Peng, J., Cai, P., Xia, Y., Yi, C., Shang, A., Akanyibah, F. A., & Mao, F. (2024). The emerging role of the gut microbiota and its application in inflammatory bowel disease [Review of The emerging role of the gut microbiota and its application in inflammatory bowel disease]. Biomedicine & Pharmacotherapy, 179, 117302. Elsevier BV. https://doi.org/10.1016/j.biopha.2024.117302

93. Yang, Y., Zhang, C., Li, H. C., He, Q., Xie, J., Liu, H., Cui, F., Lei, Z., Qin, X., Liu, Y., Xu, M., Huang, S., & Zhang, X. (2025). A review of molecular interplay between inflammation and cancer: The role of lncRNAs in pathogenesis and therapeutic potential [Review of A review of molecular interplay between inflammation and cancer: The role of lncRNAs in pathogenesis and therapeutic potential]. International Journal of Biological Macromolecules, 142824. Elsevier BV. https://doi.org/10.1016/j.ijbiomac.2025.142824

94. Youssef, M., Ahmed, H. Y., Zongo, A. W., Korin, A., Zhan, F., Hady, E., Umair, M., Rajoka, M. S. R., Xiong, Y., & Li, B. (2021). Probiotic Supplements: Their Strategies in the Therapeutic and Prophylactic of Human Life-Threatening Diseases [Review of Probiotic Supplements: Their Strategies in the Therapeutic and Prophylactic of Human Life-Threatening Diseases]. International Journal of Molecular Sciences, 22(20), 11290. Multidisciplinary Digital Publishing Institute. https://doi.org/10.3390/ijms222011290

95. Zebeaman, M., Tadesse, M. G., Bachheti, R. K., Bachheti, A., Gebeyhu, R., & Chaubey, K. K. (2023). Plants and Plant-Derived Molecules as Natural Immunomodulators [Review of Plants and Plant-Derived Molecules as Natural Immunomodulators]. BioMed Research International, 2023(1). Hindawi Publishing Corporation. https://doi.org/10.1155/2023/7711297

96. Zhang, N., & Bevan, M. J. (2011). CD8+ T Cells: Foot Soldiers of the Immune System [Review of CD8+ T Cells: Foot Soldiers of the Immune System]. Immunity, 35(2), 161. Cell Press. https://doi.org/10.1016/j.immuni.2011.07.010

97. Zhang, R., Ding, N., Feng, X., & Liao, W. (2025). The gut microbiome, immune modulation, and cognitive decline: insights on the gut-brain axis [Review of The gut microbiome, immune modulation, and cognitive decline: insights on the gut-brain axis]. Frontiers in Immunology, 16. Frontiers Media. https://doi.org/10.3389/fimmu.2025.1529958