Original Article

A REVIEW ON NATURAL PRODUCTS AS IMMUNE SYSTEM MODULATORS AGAINST INFECTIONS

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Abstract

The immune system is the most complex biological system in the body that recognizes and attacks viruses, bacteria, fungi, and parasitic infections by creating an immediate reaction through the stimulation of the cells, cytokines, chemokines, and inflammatory mediator components of the immune system. Currently, regulating the immune system with various natural products has become a focus of scientific study worldwide. Natural immunomodulators are compounds that activate or inhibit the components of the immune system, whether innate or adaptive immune responses. Different natural products, such as medicinal plants (the whole plants, their extracts, and phytochemicals), probiotics, prebiotics, micro-nutrients, bees, and marine products, are used to modulate the immune system. Because they regulate immune system responses, natural products play a significant role in sustaining wellbeing and retaining organic resistance to infection. The present review tracks some of the natural immunomodulators and the functional diversity of their bioactive compounds from various sources in the immune system during infection. Conclusion: It has been documented that several natural products have immunomodulatory functions. Different natural products provide great protection against various pathogens through the modulation of innate and adaptive immune responses. Therefore, because of their large safety margin, high effectiveness, and low cost, natural products are recommended for use as positive immunomodulatory agents, for prophylactic and therapeutic applications.

Keywords: Natural Immunomodulators; Phytochemicals; Probiotics; Prebiotics; Marine products.

Introduction

Immunity is a homeostasis procedure composed of a series of multi-cellular and physiological mechanisms by which an individual distinguishes “self” and “non-self” matter to neutralize and/or eliminate it (Singh et al. 2016). The immune system consists of innate and adaptive immune responses. The innate immune response, which is the first line of defense, represents the natural barriers that prevent the pathogens from entering the body. It includes intact skin, epithelial linings, peptides against microorganisms, the complement system, various phagocytic cells, and other cells such as neutrophils, macrophages, natural killer cells (NK). These cells distinguish “self” and “non-self” matter. Quickly the innate system recognizes the foreign antigen, destroys or neutralizes it then, resolves inflammation, and starts the healing process (Murphy and Weaver 2017). The second line of defense is adaptive immunity that is a much slower and more specific response. It produces immunological memory that generates rapid antigen-specific reactions on the same pathogen repeated infection. Adaptive immunity is composed of a set of specialized cells such as T lymphocytes subsets and B lymphocytes (Calder et al. 2020). T cells coordinate the whole adaptive immune response by the aiding of cytokines secreted by T helper cells while B cells secrete specific antibodies against infecting antigen and produce immunological memory cells (Di Sotto et al. 2020). Cytotoxic T cells, helper T (Th) cells, and regulatory T (suppressor T) cells are the three

subtypes of T lymphocytes. A surface receptor, of differentiation cluster $CD8^+$, which identifies endogenous antigens associated with important histocompatibility complex class I and destroys infected cells is expressed by cytotoxic T cells. The surface receptor $CD4^+$ is expressed by Th cells and recognizes exogenous antigens complexed with class II main histocompatibility complex (Kang et al. 2019). The cytokines are substantial mediators of the immune system that excreted extra cellularly. Cytokines are formed of proteins or glycoprotein such as interleukins, interferon's, chemokines, etc. It regulates the immune response either by stimulation or suppression (Sharma et al. 2017).

Recently immunotherapy is used for the treatment of either infectious or non-infectious diseases. The technique of the therapy depends on stimulation or inhibition of the immune system by using synthetic or natural medication or antibodies to combat pathogens (Bascones-Martinez et al. 2014). The use of immunomodulators that affect immune responses to control immunity status is the leading basis of immunotherapy (Di Sotto et al. 2020). Many natural products are used as immunomodulators to cure vast amounts of diseases by modulating the immune system or its functions since ancient times (Nagoba and Davane 2018; Singh et al. 2016). Natural products are chemicals or organic compounds generated from living organisms in nature. Its production is by the primary and secondary pathways of metabolism (Woldeyes et al. 2012). The primary metabolites are essential substances for the organism's survival, including respiratory and photosynthetic enzymes. The secondary metabolites primarily affect other organisms but offer assistance to make strides in the competitiveness of the living organism being in its environment (Chintoju et al. 2015).

The American Society of Pharmacognosy defines pharmacognosy as: "It is the study of natural product molecules (typically secondary metabolites) that are useful for other functional properties". The species that are the source of the compounds under study span all biological kingdoms, most notably marine invertebrates, plants, fungi, and bacteria (Krause and Tobi 2013). Also, Chintoju et al. (2015) define the natural product as "The natural product is an organic substance which is produced by the living organisms found in nature that is produced by the pathways of primary and secondary metabolism".

This review will address the study of immunity-related medicinal properties of natural products within the different assortments and exciting capabilities within the arena of natural immunomodulators.

Classifications of immunomodulators (Figure 1)

Classification according to immunological effect

Immunosuppressant

These types of immunomodulators are inhibitors of the immune response or reduce the activity of the components of the immune system (Di Sotto et al. 2020). The usage of immunosuppressors is to inhibit the rejection of transplanted organs or grafts and the treatment of autoimmune diseases such as myasthenia gravis and rheumatoid arthritis (Singh et al. 2016).

Immunostimulants

Immunostimulators are substances that activate or potentiate the induction of immune system mediators. They are none specifically potentiating the immunity against infection, activating both innate and adaptive immunity (Nagoba and Davane 2018). It is possible to use immunostimulators as prophylactic or therapeutic agents (Singh et al. 2016) due to their raising effect of the individual immunity against infection (viral, bacterial, or fungal), toxic chemicals, and tumors (Nagoba and Davane 2018). It is feasible to subdivide immunostimulants into two types: The first is specific immunostimulants that actuate antigenic specificity of immune reaction e.g., antigen, while the second is non-specific immunostimulants which invigorate immune responses without antigenic specificity e.g., female sex hormones (Kumar and Kumar 2011).

Immunoadjuvants

Immunoadjuvants induce a defensive immune response used in conjugation with vaccines. It is a sub-type of non-specific immunostimulants enhancing vaccine efficacy without the production of specific antigenic effects e.g. propolis and ginseng extract (Di Sotto et al. 2020).

According to their nature

Synthetic immunomodulators

Synthetic immunomodulators are extremely efficient chemotherapeutic agents that mostly have immunosuppressive action (Nagoba and Davane 2018). Synthetic immunomodulators possess many adverse effects such as fatigue, hair loss, Hepatic fibrosis, blood diseases (leucopenia, thrombocytopenia, serum sickness), hypertension, constipation, neurotoxicity (tremor, headache, and motor disturbances), nephrotoxicity, growth retardation, hyperglycemia, hyperlipidemia, hyperkalemia, etc (Singh et al. 2016). Most synthesized immunomodulatory drugs show harmfulness and side impacts, restricting their utilization (Bascones-Martinez et al. 2014).

Natural immunomodulators

Since ancient times, many natural products derived from different natural sources have been used as immunomodulators. The use of natural products has historically been studied for a long time for the prevention of a significant variety of diseases via modulating the immune system (Nagoba and Davane 2018; Singh et al. 2016). Many kinds of substances are included in natural immunomodulatory products such as phytochemicals (flavonoids, phloroglucinols, quinones, glycosides, polysaccharides, terpenoids, essential oils, alkaloids, biopolymers, glycolipids, phenolics, macrocyclic lactones, saponins, polyacetylene, coumarins, gallic acid, lignans, artemesin, alpha-amyrin, hexacosanol, and kaempferol) (Nagoba and Davane 2018), vitamins (A, B6, B12, C, D, E, and folate), trace elements (zinc, iron, selenium, magnesium, and copper) (Calder et al. 2020), etc.

According to their molecular size and skeletal structure

All natural products may be classified according to their molecular size into:

Macronutrients

This type includes nutrients that contain carbohydrates, proteins and lipids which may be of plant origin, bees products, probiotics, prebiotics, and marine product origin

Micronutrients

Micronutrients include minerals such as zinc, selenium, magnesium and vitamins such as vitamin D, A, E, C, B complex.

Macronutrients immunomodulators

Immunomodulators of plant origin

Numerous medicinal plants in nature are used as agents for immune modulation. It is assumed that certain medicinal plants encourage positive wellbeing and preserve organic tolerance to infection by re-establishing immunity and conditioning the tissues of the body.

The whole or part of the plant

Curcumin as immunomodulator

The spice herb *Curcuma longa L*. is a member of the Zingiberaceae family (commonly known as the ginger family), with more than 1300 species in 52 genera (Tamokou et al. 2017). The grinding of the curcumin root includes volatile and non-volatile oils, lipids, proteins, carbohydrates, trace elements, and curcuminoids (Catanzaro et al. 2018). The ability of curcumin to potentiate cellular immunity and to reduce inflammation, as shown by clinical argument, stated that it is functioning as an immunostimulant (Di Sotto et al. 2020). Curcumin immunomodulatory characters derived from its involvement with different components of the immune system, including not just cellular components as dendritic cells (DC), macrophages, and both B and T lymphocytes, but also molecular contents active in inflammatory processes such as cytokines and different transcription factors with their downstream signaling pathways (Momtazi-Borojeni et al. 2018).

Curcumin impairs DCs activity and interferes with the maturation of myeloid DC. Also, curcumin suppresses the expression of CD80 and CD86, which are co-working membrane proteins supplying the stimulatory signal needed for T cell activation. Besides, it reduces pro-inflammatory cytokine production (IL-12) (Catanzaro et al. 2018).

The effect of curcumin has been studied in vitro using a human macrophage model against infection by *Mycobacterium tuberculosis.* The anti-inflammatory effect of curcumin was mediated by activation of caspase 3 and inhibition of the nuclear factor-κB (NF-κB) (Bai et al. 2016) which is a powerful apoptosis inducer and this the mechanism used to kill intracellular MTB by the macrophage (Ailioaie and Litscher 2020). Also, curcumin showed to preserve BALB/c mice from *Klebsiella pneumonia*-induced inflammation of the lungs (Bansal and Chhibber 2010) by impressive reduction in the migration of neutrophils into the lungs and a significant decrease in the levels of NO, MPO, and TNF-α. Dietary supplementation of curcumin increased coccidiosis resistance in the broiler chickens through the rise of serum levels of *Eimeria* microneme protein antibodies (humeral immune response) and increased the proliferation of spleen cells by concanavalin A (cellular immune response) (Catanzaro et al. 2018). Also, curcumin regulates numerous transcription factors, cytokines, adhesion molecules, and enzymes related to inflammation. The same responses happened in infected mice with acute murine *schistosomiasis mansoni* resulting in a substantial reduction of the parasite burden and liver pathology (Singh et al. 2016).

In the case of experimental colitis, mastitis induced by LPS (Fu et al. 2014), and gastritis caused by H. pylori, curcumin modulation effect on the signaling pathway of TLR4/MyD88/NF-?B affect the development of various diseases (Catanzaro et al. 2018). The intranasal inoculation of pathogens (bacteria or viruses) into a mouse to deliver pneumonia revealed that curcumin increased mouse survival although there is still debate about the inhibitory role of pathogen replication. This result may be due to the fact that curcumin is a potent anti-inflammatory agent through reducing the penetration of neutrophils and the exaggerated inflammatory response. Also, the inhibition of pneumonic inflammation might be mediated by the inhibition of the three inflammation-related pathways, TGFβ, P38, and NF-κB signaling pathways, which modulate other downstream inflammation mediators (Alikiaii et al.2020).

Ginseng as immunomodulator

Ginseng is a multi-action immunomodulator act as immunostimulant and immunoadjuvant. As immune adjuvant, it was found that it provides pigeons with the double of immune protection (cellular and humeral) when used as adjuvant for *Salmonella typhi* vaccine by increasing both cellular and humeral immunity. Also, it was found that ginseng has Erns glycoprotein which have the antigenic specificity of bovine viral diarrhea so may be used as an antigen source for possible vaccine against it (Riaz et al. 2019). In the case of FMD infection it stimulates the Th1/Th2 so act as very effective vaccine adjuvant (Zhang et al. 2014). Ginseng enhances viral specific immunity by increasing B and T lymphocytes when used as adjuvant with inactivated influenza virus vaccine by increasing Th1, Th2 and IgA (Riaz et al. 2019).

As immunostimulant, it combats respiratory syncytial virus that cause severe lung inflammation. It inhibits viral replication, save epithelial cells; stimulate INF-γ production, $CD8^+$, and CD11. In case of septicemia, its polysaccharide increase NO production which stimulate phagocytosis and cytokine production (Mohebbi et al. 2018). While in *Candida albicans* infection it reduces the inflammatory cytokines (Ratan et al. 2020). In mice, it was found that its usage as dietary supplement increases the production of interferon α and γ resulting in protection

against H5N1 influenza virus. When chronically infected rat with *Pseudomonas aeruginosa* administrated ginseng extract, the phagocytosis and the survival time increased (Park et al. 2020).

Plant extract

Coconut oil

In ancient literature, the authors suggested that coconut oil and mother's milk had the same health benefits, and in modern science, a shared relation between them has now been discovered (Lima and Block 2019). Monoglycerides and medium-chain fatty acids mostly present in coconut oil have marvelous curing capacity that serves as a natural anti-microbial and helps to modulate immunity. Various coconut oil formulations induce hair production and prevent skin infection with bacterial, protozoal, and viral infections (Shashank et al. 2020). Coconut oil is the only oil that contains 48% lauric acid of its fatty acid composition. The benefits of Coconut Oil is due to the presence of Lauric Acid and secondary metabolite monolaurin (Thaweboon et al. 2011). Breast milk contains 50% saturated fat, out of it is 20% lauric acid, where 60% of coconut oil medium-chain length fatty acids existing in breast milk. Medium-chain length fatty acids and coconut oil metabolites have immunomodulatory effects. Both improve gastrointestinal epithelium and modulate cytokine production to prevent infections. So it is a safe and effective immunomodulator (Zil et al. 2012).

Coconut oil affects the immune system in many ways that are by modulating epithelial cytokine production, decreases IL-8 production in intestinal cells of rats, and promotes neutrophils aggregation (Shashank et al. 2020). On feeding chicken with coconut fresh wet endosperm extraction for four weeks, there was an increase in lymphocytes number and Th-$CD4^+$. Also, administration of 45mL daily for AIDs patients for six months showed a higher number of $CD4^+$ and $CD8^+$, while for six weeks, there was an increased $CD4^+$ count (Tobias et al. 2018).

Phytochemicals as immunomodulators

Phytochemicals are groups of chemicals of plant origin having bioactive properties referred to as naturally secondary metabolites including alkaloids, flavonoids, coumarins, glycosides, gums, polysaccharides, phenols, tannins, terpenes, and terpenoids (Bhavna et al. 2020). Phytochemicals serve as natural protection of plants and have useful therapeutic effects such as antioxidant, anti-diabetic, hypocholesterolemic, anticancer, and immunomodulatory functions. They are classified into high-molecular immunomodulatory compounds such as polysaccharides and low-molecular immunomodulatory compounds such as terpenoids, phenolic compounds, and alkaloids (Venkatalakshmi et al. 2016).

Alkaloids: are the largest single class of phytochemicals of 5500 known members, contains nitrogen atoms (one or more) combined to a cyclic structure including cocaine, morphine and, quinine, etc. Alkaloids have immunostimulant, antimicrobial, and analgesic effects (Zhao et al. 2015).

Polysaccharides: are high-molecular immunomodulatory compounds that have immunostimulant properties on the innate immune system mainly via affecting macrophages. So, used as an adjuvant immunomodulator (Zhong et al. 2010).

Phenolic compounds: are water-soluble compounds mostly conjugated to sugar to form glucosides and present in cell vacuoles. Its phenol content is a pathogen toxic that prevents its growth. Phenolic compounds include flavonoids, tannins, and others (Yatoo et al. 2018).

Flavonoids immunomodulators: are the most widely distributed phytochemicals present in glucoside form or free form. These are water-soluble antioxidant free radical scavengers, preventing cellular oxidative damage and have an anti-cancer effect (Nenaah 2013).

Terpenoids immunomodulators: These are a group of compounds include saponins, steroids, and cardiac glycosides, present in the waxy coat of leaves or fruits as a protective way against microbial and insect attack. Their immunological effect is performed through stimulating antibodies production and suppression of T-cell response (Venkatalakshmi et al. 2016).

Sterols immunomodulators: These are a mixture of sterols and sterolins both compounds have a cytotoxic effect on NK cells. Sterols can modulate the Th1-Th2 cells' balance determining immune outcome response while β-Sitosterol, and its glycoside stimulate the in vitro T-cell (Park et al. 2020).

Glucosides: These are a group of chemicals that contain sugar (glycan) and not sugar (aglycan) including saponins and anthracin derivatives. Glycosides possess cardiac and central nervous system stimulating effect, antimicrobial action besides immunostimulation [Table 1] (Nenaah 2013).

Bees products immunomodulators

Bees supply us with pollen, propolis, royal jelly, and wax alongside honey, which is undoubtedly the most widespread bee food. Another substance from which individuals will benefit is bee venom. In fact, Propolis is the rarest treasure of the beehive, since it is a natural antibiotic and immunomodulator.

Propolis

Propolis has been shown to have antimicrobial, antiviral, anti-inflammatory, anticancer, antioxidant, immunomodulatory and adjuvant treatment because of its cheap, availability, and not cause undesirable effects. There are more than 600 compounds of propolis as flavonoids, phenolic compounds, steroids, amino and waxy acids (Santos et al. 2019). The immunomodulatory effects of propolis are by increase $CD4^+/CD8^+$ T cell production, activation of macrophage through increasing the production of NO that is essential for the killing of microbes by inhibition of mitochondrial respiration, DNA synthesis, and membrane-active transport of bacteria and fungus (Mohammed 2020). Propolis increases macrophage phagocytic activity, INF-γ, IL-6, and IL-1 release production. Also, trigger higher levels of several forms of immune cells and different immunomodulatory cytokines that are essential for homeostasis maintenance (Tao et al. 2014). Short-term ethanol extract administration in immunized mice (with red blood cells of sheep) showed higher levels of antibodies due to the activation of macrophages, which participate in the release of cytokines, hence modulate the functions of B and T cells (Mohammed 2020). Three days' intake of propolis (200 mg/kg) in mice inhibited the development of INF-γ in splenocyte cultures (Orsatti et al. 2010). While, mice treated with the same dose of propolis for 14 days displayed suppression of IL-1, IL-6, INF-γ, IL-2, and IL-10 production demonstrating their anti-inflammatory function by modulation of cytokines (Missima et al. 2010).

In the case of leishmaniasis, caused by the mandatory intracellular *Leishmania* parasite, treatment of infected macrophage with propolis increase NO production by 175-230% more than infected non treated macrophages. The production of nitric oxide is a powerful cytotoxin involved in the inhibition of intracellular pathogens, including *Leishmania* (Ayari et al. 2020).

In the case of cystic echinococcosis, a major zoonotic infection, caused by *Echinococcus granulosus*, a high inhibitory effect on hydatid cyst growth was induced by the administration of propolis at 100 mg/kg for three months due to decreases the immune-activity of NF-κB of the spleen, systemic NO, and TNF-α (Nahla et al. 2019).

On using propolis as a vaccine adjuvant, it increases phagocytic activity, producing higher antibody titers, and increases mucosal immunity, enhancing cellular response. Besides, encouraging peripheral lymphocyte proliferation, increasing leukocyte reaction, decreasing optimum dose concentration, expanding vaccine safety, promoting early protection, and improving nonspecific immunity (Yuan et al. 2012). When immunizing mice with inactivated Suid herpes virus type 1, the findings showed that propolis improved the cellular immune response, demonstrated by the rise in mRNA expression to INF-α, the proportion of saved mice against the challenge of a lethal dose of Suid herpesvirus type 1 increased. These results suggest the potency of using propolis as a possible vaccine adjuvant (Mohammed 2020). Propolis had a positive adjuvant effect on the canine corona virus vaccines. Flavonoids of propolis can improve serum IgG, IL-4, and INF-γ as adjuvant. INF-γ is essential to assess a vaccine's mediated cellular response (Tao et al. 2014).

Probiotics as immunomodulators

Probiotics are certain types of healthy living microorganisms (bacteria and/or yeasts) which on administrating in sufficient quantity provide the host with health benefits.

Proboiotics of bacterial origin

The most widely used genera in probiotic preparations are *Lacticaseibacillus spp., Lactiplantibacillus spp., Levilactobacillus spp., Ligilactobacillus spp., Limosilactibacillus spp., Bifidobacterium spp.,* and *Bifidobacterium spp* (Zheng et al. 2020). Probiotic bacteria have two ways to affect immunity, direct and indirect pathways. The direct pathway is through the reaction of the bacteria itself or its metabolites with immune and epithelial cell receptors as toll-like receptors (TLRs). The indirect pathway is through its effects on the microbiota of the host by changing its composition and activities (van Baarlen et al. 2013). In the case of respiratory system infection, the effect of probiotics is via gut-lung axis, where probiotics adhere to chemokine receptor 1 (CX3CR1) of macrophages in the gut epithelium then transported to DCs changing its polarization and effect. DCs activate T and B lymphocytes that are transferred into the respiratory system.

Probiotic bacteria stimulate TLRs which cause stimulation and increase production of NF-κB, INF-γ pathways and IL-10 of immune cells responsible for antiviral resistance (Enaud et al. 2020). *Lactobacillus gasseri* upregulate INF-γ and myxovirus resistance mRNA expression in macrophage-derived RAW264 cells. Also, *Lactobacillus gasseri* activates type I INFγ-dependent gene in monocyte-derived macrophages. INF-γ genes regulation includes IL-6, 12, 1 and 8. Besides, upregulation of gene expression TLR3, TLR7 viral recognition receptors (Nakayama et al. 2014).

In the case of experimental infection of mice with the influenza virus, it was found that the levels of antibodies specific to influenza virus and IL-4 expression were increased by *Bifidobacterium bifidum* therapy, which succeeded in increasing INF-γ and lymphocyte proliferation following challenge infection. The IL-12 level increased, which is the stimulatory for agent of the natural killer, which are necessary for activating the immune response and managing influenza infection (Ohs et al. 2016). Thus, *Bifidobacterium bifidum* improved the Th1/Th2 balance as shown by an increased level of IgG1-IgG2a isotype antibody titers, up-regulation of INF-γ, IL-12, and IL-4 secreting splenocytes (Mahooti et al. 2019).

Probiotics of fungal origin

The usage of yeast as probiotics based on the yeast species, the isolation source, and the dosage used. The immunostimulatory impacts of yeast are due to its structural content and secretory bioactive compounds. It contains β-glucan and chitin in its wall and secretes various compounds such as mannoproteins and nucleic acids (Hai 2015). These compounds are contributing to gut microvillus morphology, cellular maturation, differentiation, and alleviated animal stress (Ran et al. 2015). Several yeast species are used as probiotics such as *Saccharomyces cerevisiae, Candida haemulonii,* and *Debaryomyces hansenii*. The ability of yeast to increase survival, cell differentiation and proliferation, digestive function stimulation, antioxidant status enhancement, and immune system stimulation has been documented (Vohra et al. 2016).

Saccharomyces spp. is efficient in *Candida* infection. In case of infection of mice with *C. albicans, S. boulardii* prevented the spreading of *Candida* into internal organs and reducing inflammation in vivo models. Also, *S. boulardii* increased IgA production in *Clostridium diffcile* infection of the colon in mice model. While *S. boulardii* produces some bioactive molecules *Saccharomyces* anti-inflammatory factor, causes a decrease in inflammatory cytokines production (TNF-α and INF-γ) from colon epithelium, *S. cerevisiae* reduces the production of TNF-α and stimulates the expression of IL-10 (Kunyeit and Rao 2020). Pattern recognition receptors (PRRs) recognize many probiotics components inducing signaling pathways, trigger innate immunity, and adaptive immune responses. Also, probiotics regulate the gut microbiota by decreasing opportunistic pathogen count and increasing beneficial bacteria counting. These probiotic properties have preserved animals from pathogens such as *E. coli, Salmonella spp.,* and *H. pylori* from infections (Ma and Suzuki 2018).

In the case of the ruminant animals, the selection of probiotic yeast in ruminant depending on its tolerance of pH of the rumen, development, being digested, fermentation of rumen, the blood profile of metabolite, the content of fecal flora, and parameters of immunity. On assessing the immunomodulatory impact of *D. hansenii* yeast as a probiotic in goats, the components of the cell wall, such as β-glucan, were the prime effectors (Ekwemalor et al. 2017).

D. hansenii cell wall were able to stimulate intracellular regulators (Syk/TRAF6 and MyD88), transcription factors (NF-κB and AP1), and proinflammatory cytokines (IL-1β and TNF-α) and decrease *Escherichia coli*'s cytotoxic effects and lived *D. hansenii* remain active and attached itself to the goat intestinal wall (Angulo et al. 2019). Other studies have shown that *D. hansenii* in the bowel helps to sustain the natural environment of microbiomes, outgrowth lactase-producing bacteria, and eliminate opportunistic pathogens and regaining the intestinal microbiota on clinical symptoms of diarrhea and providing new curative treatment techniques (Angulo et al. 2020). Yeasts yield short-chain fatty acids and β-glucan, both considered as prebiotics immunomodulator effect (Kunyeit and Rao 2020).

Prebiotics as immunomodulators

Gibson and Roberfroid described the term "prebiotics" as a non-digestible food ingredient that beneficially affects the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria and thus improving host health (Ohshima et al. 2016).

β-Glucan preboitics

β-glucans are well-established natural immunomodulators with sixty years of recorded research experience (Vetvicka and Vetvickova 2020). It is a characteristic polysaccharide widely distributed within the cell dividers of bacteria, fungi, cereals, algae, oat, and mushrooms (Sun et al. 2020). β-glucan has several biological activities, including hypoglycemic, antitumor, anticoagulant, anti-inflammatory, anti-viral, anti-bacterial, and anti-fungal (Basso et al. 2019; Sun et al. 2020). Other than, have different organic activities, such as controlling the immune reaction, diminishing liver damage, and controlling cecum microflora composition (Basso et al. 2019). Throughout the animal world, no species is β-glucan resistant so far. β-glucan effects are expressed by binding to many particular receptors such as CR3 and dectin-1, then signaling pathway NF-κB receptor tyrosine kinase axis. Furthermore, dectin-1 engagement leads to nitrosative/oxidative blasts and phagocytosis (Basso et al. 2019). So, β-glucan is considered to be a nonspecific stimulator of cellular resistance. The impacts of β-glucans on phagocytosis is due to interaction with β-glucan receptors (Vetvicka and Vetvickova 2020). The yeast extracted β-glucan has been reported to improve the ability to combat the infection of *Porphyromonas gingivalis* in mice. In infected sites, β-glucan can facilitate bacterial phagocytosis, killing, and boost the development of white blood cells (Sun et al. 2020).

On infecting the urinary tract of mice with *E. coli* and treating them with β-glucan, the results showed a decrease in colony forming unit of *E. coli* in the bladder. Also, the count of bacterial *E. coli* cells in kidneys significantly decreased after three days of treatment. In another experiment, mice infecting with *P. aeruginosa* to cause pneumonia, consumption of β-glucan leads to decrease neutrophil and bacterial count too (Vetvicka and Vetvickova 2020). From these two studies, β-glucan greatly improved the secretion of IL-2 by spleen cells. However, splenocytes do not secrete IL-2 without any stimulus. Besides, there is an immunomodulatory activity of β-glucan, which enhances the host immune response against infection. When bone marrow-derived dendritic cells and macrophages were treated with β-glucan, producing considerable amount of TNF-α and IL-10 (Basso et al. 2019). In a case of vaginal infection with *C. albicans* treated with β-glucan, the results revealed that β-glucan removed the fungal burden, relieved the invalid immune reaction, and changed vaginal microorganism structure, suggesting that β-glucan was a possible therapeutic agent for *C. albicans* vaginitis (Peters et al. 2014; Sun et al. 2020). β-glucan vaginal administration increased the amount of *Enterococcus* and reduced *Proteus* levels. *Enterococcus* is known as a lactic acid bacterium that produces lactic acid that can suppress the growth of fungi and preserve vaginal health. β-glucan may reduce the burden of infection, so decreasing dectin1 mRNA expression and consequently alleviating the harmful inflammatory response (Peters et al. 2014).

Dietary fibers prebiotics

Dietary fiber is defined as primary polysaccharides that cannot be digested nor absorbed by the gastrointestinal tract, obtained from cereals, fruit, vegetables, as well as algae, that facilitated bowel movement; regulate body weight by influencing appetite, energy intake and thereby safeguarding human health. However, dietary fiber has some effects on gut microbes as well and lowers the prevalence of *Clostridium* (Shanahan et al. 2017). Dietary fibers cause increasing thickness of intestinal mucosa and lowering mucosal permeability by stimulating prostaglandin secretion, so increasing epithelial mucin. In contrast, insufficient intake of dietary fiber results in disturbed gut balance, damage of the membrane barrier by gut microbes (Schroeder et al. 2018). Also, it leads to a reduction of microbial variety and less production of SCFAs. Besides, increase the utilization of endogenous protein and mucin of the host by microbes that increase the incidence of infectious diseases (Slavin 2013). Dietary fibers contain many active components such as:

Inulin is one of the dietary fiber content present in Chicory root, onion, and cereals. It causes mucilage degradation of bacteria and repair of intestinal epithelium by the effect of SCFAs against *Salmonella, E.coli*, *Campylobacter jejuni*, and *Citrobacter rodentium* (Kathene et al. 2014).

Fructo-oligosaccharides are polymers derived from polysaccharides by hydrolysis. It has an effect against *Salmonella typhi* through its effect on mucosal immunity (Eva et al. 2013).

Galacto-oligosaccharide which present in garlic, barley, onion, has an effect against *Listeria monocytogens* by Intestinal colonization and translocation of a pathogenic bacteria (Yang et al. 2019).

Short-chain fatty acids as immunomodulators

SCFAs produced by gut microbes as a result of microbial fermentation of dietary fibers. It supplies the host with energy and play a role in immunomodulation (Shanahan et al. 2017). SCFs have seemed as histone deacetylase inhibitors (HDAC) which regulate the immune system through inhibiting pro-inflammatory macrophage response and DC differentiation, as well as controlling cytokine production in T cells. Inhibition of HDAC by butyrate enhances the secretion of IL-10 by T cells and IL-18 in intestinal epithelial cells (John and Fergus 2019). SCFAs decrease toxic gene expression of some pathogens, e.g., *Salmonella, E. coli, Campylobacter jejuni* (Sun and Riordan 2013). Receptors of SCFA are present in different cells of the immune system. So it may have a role in the differentiation of T cells to the effectors, and regulatory T cells (Park et al. 2015; Yang et al. 2019).

Marine products as immunomodulators

Marine-Derived Proteins and Peptides

Marine life forms give a source of potential medications. Numerous of the marine-derived bio-active materials have been appeared to act as natural immunomodulators creating successful immune responses. The aquatic ecosystem is abundant in bioactive materials, but few studies have explored their capacity to modulate the immune response. It is assumed that there are approximately 2,210,000 species in the sea, but only about 190,000 species have been recorded (Ruiz-Ruiz et al. 2017). Proteins, enzymes, oligosaccharides, biopolymers, fatty acids, pigments, minerals, etc. form natural aquatic immunomodulators. Peptides, proteins, and protein hydrolysates extracted from aquatic algae and fish are considered as immunostimulants. Numerous of these peptides destroy bacteria directly and display immunomodulatory actions that stimulate the innate immune response and eradicate infection effectively (Kang et al. 2019). The mechanisms of action are by activation of macrophages, NK cell, phagocytosis, NF-κB, MAPK-dependent, $CD4^+$, $CD8^+$ T cells, and $CD45R/B220^+$B cells (Ahn et al. 2008). Also, it increases the production of NO, immunoglobulins, and cytokines. By studying marine products, it was found that many compounds, such as metalloproteins, glycoprotein, amino sulphonic acid, antimicrobial peptides (AMPs), protease inhibitors, and coagulation factors, several proteins in hemolymphs and hemocytes are playing essential roles in the innate immune system (Kang et al. 2019).

Marine products include huge numbers of bioactive substances such as:

Taurine

The amino acid taurine (2-amino ethane sulfonic acid) is broadly dispersed in animal tissues, including marine clams. Taurine is enriched in immune cells, including lymphocytes, monocytes, and neutrophils. It has cytoprotective and immunomodulatory impacts (Marcinkiewicz and Kontny 2014) indicating that its elevated levels in the inflammatory lesion are mediating phagocytes and have a role in innate immunity (Schuller-Levis and Park 2004). Taurine accumulates in phagocytes, develops toxic oxidants and several antibacterial compounds via the peroxidase mechanism after encountering a pathogen, and serves to destroy pathogens at inflammatory sites. Toxic oxidants are part of the innate immune system that destroying bacteria, shield the host from infections. By stimulating NF-κB, an efficient signal transducer of inflammatory cytokines, taurine adjusts the immune system (Marcinkiewicz and Kontny 2014).

Antimicrobial peptides immunomodulators

Although peptides has immunomodulator effects, such as lymphocyte stimulation to propagate, natural killer cell activation, and regulation of cytokine, are known to promote immune responses, the mechanisms of these actions remain unclear (Singh et al. 2014). AMPs (Marine-derived) are molecules of defense with the capacity to stimulate innate immunity by attacking particular cells that confirmed their immunomodulatory ability (Kang et al. 2015).

Piscidin 3 (TP3) and Piscidin 4 (TP4) of Tilapia

Tilapia piscidins are AMPs, a category of antimicrobial, wound-healing, and antitumor peptides capacities extracted from *Oreochromis niloticus*. TP3 and TP4 essentially stimulated the expression of numerous muscular genes of immune-related IL-1β, IL-6, IL-8, TGF-β, IκB and diminished the expression of TLR5 after infection with *Vibrio vulnificus*. Because of *Streptococcus agalactiae* infection of fish reduced IL-1β, IL-8, TLR5, TGF-β and IκB, TP3 and TP4 indicate promise for development to treat fish bacterial infections in aquaculture (Lin et al. 2016).

Fish oil

Poly unsaturated fatty acids (PUFA) are energy provider macronutrients and their metabolites regulating functions of the cell. It is composed of eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) which affect the functions of immune cells (Calder 2017). The PUFAs have anti-inflammatory effects due to the reduction of the cytokines of pro-inflammation (IL-1b, TNF-α, IL-6), chemokines (IL-8, MCP-1), molecules of adhesion (ICAM-1, VCAM-1, selectins), eicosanoid inflammatory mediators, and ROS. Also, its anti-inflammatory effect is due to the activation of pro-inflammatory mediator genes through the control of B (NF-κB) (Wu et al. 2019).

In the case of *Streptococcus pneumoniae* infection, which causes severe morbidity and mortality, due to severe lung inflammation and respiratory failure, PUAFs is helpful as exert potent anti-inflammatory responses, and reduce lung infiltration by immune cells, lung consolidation, and reduce IL-6 (Hinojosa et al. 2020). Recently, researchers discovered that PUFAs are precursors for a pre-resolving mediator, protectins, and maresins (Serhan 2014). Where are resolvins and protectins decrease neutrophilic infiltration, cytokine-chemokine axis, and ROS. Besides, PUFAs reduce lymphocyte activation by the proliferation of $CD4^+$ T cells, and IL-2. It also suppresses Th2 and Th17 cell differentiation and increases Th2 and T reg cells. So PUFAs are useful as immunomodulators in bacterial infection (Wu et al. 2019).

Micronutrients immunomodulators

The stability of immune functions may be affected by dietary deficiencies or inadequacy. The host immunity depends on the availability of the group of micronutrients, like vitamins A, C, D, E, B6, B12, folate, Fe, Zn, Cu, Se, and Mg. The micronutrients are associated with the maintenance or enhancement of immune functions,

including suppression of pro-inflammatory mediators, advancement of anti-inflammatory impacts, regulation of cell-mediated immunity, modification of cellular antigen-presenting tasks, and cooperation between innate and adaptive immune systems (Wu et al. 2019).

Vitamins

Vitamin D

Vitamin D sources are sunlight-induced and/or diet-derived. For a long time, the classical value of vitamin D was assumed to be the management of calcium homeostasis and bone defense. Vitamin D extra-skeletal properties are well represented in the immune system (Baeke et al. 2010). However, it plays an essential role in the immune system. Most immune cells produce VDR, and some of them are capable of generating 1-a-hydroxylase, which hydroxylates vit. D to the active form; both systemic and locally produced vitamin D can thus function on VDR released by immune cells in its active state (Kongsbak et al. 2013). Vitamin D has been shown to have a large effect on immune cell functions of both the innate and adaptive immune systems, as well as the antigen-presenting cells (APC) that bind the two immune arms. So it helps maintain and reinforce the protection of the body against infection by fostering innate immunity through affecting both monocytes and macrophages (Baeke et al. 2010), and stimulating monocyte's proliferation and invigorates monocytes, neutrophils, and epithelium producing endogenous antimicrobial peptides (cathelicidin and defensins) (Liu et al. 2006). Also, inducing macrophages chemotaxis and phagocytosis. Vitamin D is included within the expression control of particular endogenous antimicrobial peptides in immune cells. So the stimulation of all these antimicrobial immune responses acts to eliminate invading of bacterial, viral and fungal pathogens (Wu et al. 2019). Vitamin D regulates adaptive immunity inhibiting both T and B lymphocytes. Vitamin D reduces T cell proliferation, effectors capacities of $CD4^+$ and $CD8^+$ (Kongsbak et al. 2013), and suppresses the production of IL-2 and INF-γ. It affects the subsets and differentiation of $CD4^+$. Where Naïve $CD4^+$ T cells can be divided into various subsets of effectors, such as Th1, Th17 which are involved in combating intracellular pathogens. While Th2 is responsible for humeral immune response and fighting extracellular pathogens. T-reg help to prevent sever and miss directed actions (Wei and Christakos 2015).

Regarding to the effect of vitamin D against autoimmune and infectious diseases it inhibit differentiation of APC functions especially DCs from bone marrow, monocytic precursors cell and their maturation so it help DCs tolerance. DC has a role in controlling adaptive immunity by transporting Ag signal to T cells. Vitamin D can regulate cytokines production by indirect regulation of NF-κB activity or modulate VDR- dependant gene (Wei and Christakos 2015; Wu et al. 2019). The regulation of pro-inflammatory cytokines secretion in the presence of vitamin D, monocyte-derived macrophages is essential to avoid adhesion of dengue virus (DENV) to cells and progression of illness. In the presence of vitamin D, the secretion of TNF-α, IL-1, and IL-10 in DENV infection was substantially lower than in the absence of vitamin D. Thus by indirect regulation of NF-κB activity or modulation of the VDR-dependent gene, vitamin D can regulate cytokine production (Licata et al. 2019).

25-OH vitamin D has two essential effects in the case of HCV infection as an antiviral by stimulating innate immunity and avoiding fibrosis, besides as an immunomodulator reducing inflammatory reactions. The anti-fibrotic activity of vitamin D is due to its reaction with fibroblast receptors that prevent fibroblast oxidative damage, regulating its proliferation and decreases the inflammatory activity of the liver stellate cells (Mohamed et al. 2019). Vitamin D preserves epithelial lining integrity. It induces antimicrobial peptides production in epithelium such as respiratory tract lining, so decrease the incidence of infection (Gombart 2009). Also, by promoting nitric-oxide synthase, calcitriol can preserve endothelial stabilization by up-regulating cytokines, cathelicidin (LL-37), and secretion of β-defensin. LL-37, the antimicrobial peptide which is created by neutrophils and expressed in macrophages (predilection site of *M.tb.*), inhibiting bacilli development within the lungs (Brighenti et al. 2018). The conversion of proteins involved in the development of autophagy membranes (LC3 protein precursors) will be enhanced by vitamin D3 (prohormone) and thus have a beneficial impact on bacterial load reduction, resulting in both innate and adaptive immunity mechanisms.

Vitamin D supplementation has immunomodulatory effect against DENV, HCV, IBD, systemic lupus, several infectious diseases such as TB upper respiratory infection and HIV (Wu et al. 2019).

Vitamin C

The importance of vitamin c is due to its role in many processes. It is responsible for epithelium integrity as participating in several biological processes such as synthesis of collagen, the differentiation of keratinocytes, migration of fibroblast, and replication (Carr and Maggini 2017). For innate immunity, it preserves actions, movements, replication, and differentiation of innate immune cells (Maggini et al. 2018; Wu et al. 2019). Also, boost antimicrobial activities, enhance complement protein of serum, and induce INF-γ. Besides, it serves in maintaining reductive-oxidative balance within the immune cells during immune functions. Vitamin C stimulates antibodies production by plasma cells and differentiation and multiplication of T-cells (mainly cytotoxic cells) (Carr and Maggini 2017; Gasmi et al. 2020). Thus vitamin C insufficiency increases the opportunity for respiratory infections such as pneumonia (Carr and Maggini 2017; Prentice 2017).

Vitamin A

Vitamin A is an essential factor in the maintenance of epithelium barrier integrity, so helps in immune responses of mucosa and suppressing inflammation (Wu et al. 2019). During the immune reaction, it controls NK cells' number and function, regulates macrophage phagocytic, and oxidative activities (Maggini et al. 2018), help in the regulation of Th1/Th2, and T-cells development (Gasmi et al. 2020). Besides, down-regulation of INF-γ, IL 2, and TNF-α secretions by Th1 so regulate antibodies mediation by Th2 reactions (Carr and Maggini 2017), and help in B cells antibodies production. The susceptibility to viral respiratory tract infections and diarrhea increased by vitamin A deficiency (Prentice 2017). In the case of vitamin A-deficient cow, there is a failure in the immunologic response to BRSV-NP vaccine. So vitamin A supplement helps in stimulating antibodies production to the vaccine, decrease the occurrence of *Mycoplasma pneumoniae* infection, and increase the immunity against young age infectious diseases (Gasmi et al. 2020).

Vitamin E

Vitamin E is one of the lipid-soluble vitamins as it is a powerful antioxidant responsible for the preservation of healthy cell membranes against oxidative damage. It supports respiratory epithelium integrity. Vitamin E has several immunological functions include stimulation of NK cell cytotoxicity, decreases macrophage production of prostaglandin E2, (Maggini et al. 2018; Wu et al., 2019) adjusting INF-γ and IL 2 production, stimulate lymphocyte multiplication, stimulate Th1, and suppresses Th2 response (Maggini et al. 2018). Besides, it augments the antigen-experienced memory T-cells proportion. So, vitamin E supplementation ameliorates the immune responses, decrease the occurrence of respiratory tract infection, augment antibody titer, and decrease the viral effect on lung tissues (Gasmi et al. 2020; Prentice 2017).

Minerals

Zinc

Zinc is one of the essential trace elements that adjust the functions of almost 2,000 enzymes, and 750 transcription factors of biological processes include development and preservation of innate and adaptive immune cell. Zinc, by its cofactor role in metalloenzymes, preserves the integrity of immune barriers (Calder et al. 2020). It stimulates activities of complement protein, T cell, NK- cells cytotoxicity, synthesis of INF-γ, the formation of cytokines by Th1, and evolution of T reg cells besides, stimulates the differentiation and growth of cytotoxic T cell. Also, Zinc is essential for the formation of antibodies especially IgG. Its anti-inflammatory properties are done via cytokine release regulation and production of Th17 and Th9 (Wu et al. 2019). Zinc deficiency results in a defect of lymphocyte development, activation, and maturation affecting cytokine intercellular connectivity and weakens the innate immunity which evidenced by increased diarrhea and viral respiratory infection due to weakness of innate immunity (Calder et al. 2020).

Selenium

Selenium is one of the required trace nutrients, essential in maintaining immunity and reductive -oxidative balance. Selenium regulates the activities of both innate and adaptive immunity to reduces viral pathogenicity such as avian influenza virus through the regulation of many processes, including the differentiation of NK cells and T cells, production of INF-α, INF-γ, and INF-β, and antibodies (Carr and Maggini 2017; Gasmi et al. 2020).

Conclusion

The main conclusions of this study including the ability of natural products to act as immunomodulators and functional ingredients for the immune system against various infectious diseases, especially via immune modulation, has been studied by many researchers. Some of the new results stated that natural products as immunomodulators against several pathogens are compiled in the present review. The immune functions of infected organisms are primarily modulated by natural products at both cellular and humeral levels. This study recorded that natural products can be use as prophylactic, preventive, and vaccine adjuvant against multiple pathogens to encourage a higher degree of the immune response to different infectious diseases without side effects., natural products play a promising role in actively or passively improving host immunity. Natural product as immunomodulators have a strong safety profile and thus the safety/risk balance is more inclined toward safety. So, for the development of novel and low-cost therapeutics targeting remedies, many exciting pathways can be investigated.

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Table (1): Examples of the most important phytochemicals immunomodulators

Plant source	**Phytochemicals**	**Mechanism of action**
Alkaloids		
Coptis chinensis Hydrasti canadensis	Berberine	Down-regulate T-helper cells cytokines [Th1 (TNF-α, IL-2, and Th2(IL-4)] production (**Venkatalakshmi et al., 2016**). Significant reduction of TNF-α, INF-γ and NO level (**Zhao et al., 2015)**.
Piper longum	Piperine	Reduce level of pro-inflammatory cytokines IL-1β, IL-6 and TNF-α. Down-regulate expression of COX-2, NOS-2, and NF-κB (**Venkatalakshmi et al., 2016**). Increases total WBCs

		count. Bone marrow cellularity, and total antibody production (**Zhao et al., 2015)**.
Phenolic compounds		
Terminalia chebula	Chebulagic acid (Tannis)	Down-regulation of TNF-α and IL-6, free radical scavenging and immunosuppressive (**Yatoo et al., 2018)**.
	Punicalagin	
Plantago major	Chlorogenic, Ferulic, and Vanilic acid	Enhances lymphocyte proliferation and secretion of INF (**Zhao et al., 2015)**.
Flavonoids		
Bidens pilosa	Centaurein	Augmentation of INF-γ promoter activity (**Venkatalakshmi et al., 2016**).

Figure (1): Classifications of immunomodulators