

Regulation of innate and adaptive immunity using herbal medicine: benefits for the COVID-19 vaccination

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Abstract

Vaccination is a major achievement that has become an effective prevention strategy against infectious diseases and active control of emerging pathogens worldwide. In response to the coronavirus disease 2019 (COVID-19) pandemic, several diverse vaccines against severe acute respiratory syndrome coronavirus 2 have been developed and deployed for use in a large number of individuals, and have been reported to protect against symptomatic COVID-19 cases and deaths. However, the application of vaccines has a series of limitations, including protective failure for variants of concern, unavailability of individuals due to immune deficiency, and the disappearance of immune protection for increasing infections in vaccinated individuals. These aspects raise the question of how to modulate the immune system that contributes to the COVID-19 vaccine protective effects. Herbal medicines are widely used for their immune regulatory abilities in clinics. More attractively, herbal medicines have been well accepted for their positive role in the COVID-19 prevention and suppression through regulation of the immune system. This review presents a brief overview of the strategy of COVID-19 vaccination and the response of the immune system to vaccines, the regulatory effects and mechanisms of herbal medicine in immune-related macrophages, natural killer cells, dendritic cells, and lymphocytes T and B cells, and how they help vaccines work. Later in the article, the potential role and application of herbal medicines in the most recent COVID-19 vaccination are discussed. This article provides new insights into herbal medicines as promising alternative supplements that may benefit from COVID-19 vaccination.

Keywords: COVID-19, Herbal medicines, Immunity, Dendritic cells, Macrophage, Vaccine protection

Graphical abstract: <http://links.lww.com/AHM/A31>.

Introduction

Despite rapid progress in understanding the pathogenesis of coronavirus disease 2019 (COVID-19), treatment options for this disease remain limited. As vaccination is one of the most successful and effective medical interventions for preventing infectious diseases, much effort has been made to develop COVID-19 vaccines. A series of vaccines are being well deployed and have consequently

reduced mortality, prolonged life expectancy, and improved quality of life, as expected^[1-3]. However, in addition to the safety of vaccination in immune-deficient patients^[4-5], the emergence of viral mutants with decreased sensitivity to vaccines^[6-7] and the unclear magnitude and duration of vaccine-induced immune responses and memory with different vaccine platforms require distinct demands and supplemental therapies^[8] in combination with vaccination for COVID-19 control and prevention. The novel, safe, and accessible strategies to enhance the immune effects of a vaccine, thus promoting body-specific and non-specific immunity, are therefore necessary and highly desirable^[9].

Herbal medicines have been widely used to treat various diseases worldwide. However, partially owing to their unclear mechanism and undefined active components, their effectiveness and applications are far from being accepted. In early 2018, an article on “why Chinese medicine is heading for clinics around the world” was reported in *Nature*. For the first time, the World Health Organization (WHO) recognized traditional medicine as an influential global medical compendium^[10]. More attractively, it has been shown that the application of traditional Chinese medicine (TCM) results in better clinical outcomes for patients with COVID-19 after evaluation of the report focused on outcomes from the reports as well as from 12 randomized controlled trials that had been registered and published^[10]. However, compared with the definite advantages for patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, the benefits of herbal medicines for the prevention and protection from SARS-CoV-2 infection are largely unknown. Normally, to

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block pathogen inbreak, the treatment should enhance the immune system of the body to defend the “enemy” strongly and immediately; herbal medicines have a long and promising history in this regard. The regulation of the immune system by herbal medicines, including anti-inflammation, regulation of innate immunity, and balancing of cytokine levels, has also been widely observed in COVID-19^[11]. However, several knowledge gaps remain in terms of our understanding of herbal medicines in relation to immune reactivity during COVID-19 vaccination. This article provides an overview of the immune response during vaccination and the potential role of medicinal herbs in promoting effective immune responses during vaccination, which may be beneficial for COVID-19 vaccination in the future.

Vaccine strategy of SARS-CoV-2

Vaccines play vital roles in the prevention of diseases and the reduction of morbidity and mortality caused by viral or bacterial infections^[12–13]. During the pandemic COVID-19, extensive efforts have been made to develop and manufacture COVID-19 vaccines. Traditionally, a vaccine contains a carefully chosen molecular entity called the vaccine antigen(s), which is the target of vaccination-induced immune response^[14–15]. Consistently, vaccines of SARS-CoV-2 frequently use spike (S) protein or its S1 subunit, or the receptor binding domain (RBD) in S1 as vaccine antigens because of their ability to induce neutralizing antibody production, which may block host cell entry and inhibit infection. Two mRNA-based vaccines (Pfizer-BioNTech BNT162b2 and Moderna mRNA-1273) encoded with the stabilized ectodomain version of the S protein showed more than 94% efficacy in preventing COVID-19^[16–19], and elicited natural antibodies^[20,21]. Ideally, a designed vaccine is desired to induce complete protection or sterile immunity; however, due to possible safety concerns, it may have issues with incomplete immune induction^[22]. Thus, improving immunity is considered an effective strategy to reduce susceptibility to disease and increase bodily defenses against pathogen invasion^[23–24]. In addition, viral evolution has occurred during the high global burden of SARS-CoV-2 transmission. Numerous SARS-CoV-2 variants have emerged during the COVID-19 pandemic^[25]. The Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1) Delta (B.1.617.2), and Omicron (B.1.1.529) variants were successively reported between late 2020 and 2021^[26–27]. Currently, Omicron (BA.4 and BA.5) is the latest variant of concern (VOC) and has become dominant globally since early 2022. The virologic and immunological features associated with VOCs indicate that a larger number of specific mutations in S proteins lead to increased infectious and transmissibility and/or easy escape of vaccination-induced immune responses^[28]. Evaluation of herbal regulations on host immunity, especially during COVID-19 vaccination, may also help respond to the adaptive system induced by different vaccine platforms.

Immune responses to vaccination

The human immune system is a complex and well-organized system that supports and protects the body against foreign substances called pathogens^[29–30] through two basic elements: the innate and adaptive immune systems^[31].

Similarly, when vaccinating, the whole immune response is experienced, as stimulated by the antigens received from vaccines that carry epitopes with strong antigenicity but low titer^[32]. To avoid an improper response when the body encounters viruses for the first time, vaccination is highly recommended to pre-educate cells of the immune system. At the early stage of the response to the antigen, pre-existing immune cells such as macrophages, natural killer (NK) cells, and neutrophils in the blood and tissues are the first to identify, capture, and destroy invading pathogens in a rapid response to virtually all pathogens, and consequently initiate inflammation at the local infectious site^[33]. Subsequently, the adaptive immune system is activated, providing long-term systemic protection. A set of leukocytes and lymphocytes, T and B cells, are responsible for the adaptive responses^[34]. The cellular immune response in infected cells is mediated by T lymphocytes. Helper T cells are involved in the overall adaptive immune response, and cytotoxic T cells play a significant role in the clearance of pathogen-infected cells^[35–36]. Additionally, B cell-derived plasma cells produce antibodies, particularly neutralizing antibodies specific to the antigen that will effectively prevent the pathogens from entering the host cells, thus limiting the infection and protecting the body from further infection at a later stage^[9].

Herbal medicines regulate the immune system and may contribute to the vaccination

Researchers are attempting to strengthen the human immune system against infections and prevent pathogens from invading. Herbal medicines and their natural bioactive components exhibit various immune regulatory activities through distinct interactions with immune cells. (Table 1)

Innate immune system

NK cells

NK cells are cytotoxic granular lymphoid cells that play a key role in initiating the primary immune response^[37–38]. When viruses or bacteria infect, NK cells are immediately activated by the release of cytolytic granules containing inflammatory cytokines and chemokines^[39]. During vaccination, NK cells are also involved and affected^[40–43]. The secreted factors may further recruit components that subsequently activate innate and adaptive immune responses. It is known that ligand–receptor interactions between NK cell surfaces and pathogens control and mediate NK activation^[44]. The major receptors responsible for NK cell recognition include NKp46, NKp30, NKp44, and NKG2D^[45].

Several herbal medicines have exhibited their ability to stimulate NK cell proliferation and enhance NK cell toxicity. *Polygonum cuspidatum* is widely distributed in China and Japan owing to its lipid regulation, anti-infection, and anti-inflammatory effects^[46]. The crude extract of *P. cuspidatum* has been found to stimulate immune responses in BALB/c mice by increasing splenic NK cell cytotoxicity. It also helps NK cells destroy the targeted YAC-1 cells^[47]. A flavonoid component from the seeds of *Astragalus complanatus* upregulates the expression of NKG2D and NKp44 in NK cells, which in turn stimulates NK-92 cells and serves as an immune

Table 1**The regulation of herbs in modulation of the immune cells**

No	Herbal Plant Species	Active Compounds	target cell	Mechanism of Action	Related vaccines/disease	References
1	<i>Polygonum cuspidatum</i>	Crude extract	NK cell	It has been found that the crude extract of <i>Polygonum cuspidatum</i> stimulated immune responses in normal BALB/c mice partly by increasing splenic NK cell cytotoxicity. It also helped NK cells isolated from mouse spleen destroy target YAC-1 cells.	Not mentioned	[45, 46]
2	The seeds of <i>Astragalus complanatus</i>	Flavonoid		It has been shown that the flavonoid component from the seeds of <i>Astragalus complanatus</i> up-regulated the expression of NK-92 cell activating receptor NKG2D and NKp44, which in turn affects NK-92 cells, serving as an immune stimulator of NK cells for therapeutic treatment.	Tumor	[47]
3	Shengmai injection	Not mentioned		Shenmai injection increased the activity of NK cells for patients	Gastric cancer	[48, 49]
4	Peanuts, blueberries and some other berries	Resveratrol	Macrophage	Resveratrol enhanced immune responses by up-regulation of CD86 and MHC-II expressions in macrophages of immunized mice, and the levels of TLR4 and IKK, I κ B α , NF- κ B and JNK4 proteins were significantly increased in the resveratrol-treated group	PRV vaccines	[58, 59]
5	<i>Cordyceps militaris</i>	Polysacchari-des		Polysaccharides isolated from <i>Cordyceps militaris</i> activated macrophages through NF- κ B and MAPK pathways via macrophage receptors DECIN-1 and TLR2. They up-regulated the uptake of NO, ROS, TNF- α and phagocytosis in mouse peritoneal macrophages and RAW264.7 macrophages, indicating a role on modulation of the immune response.	melanoma solid tumor	[60, 61]
6	<i>Citrus unshiu</i> peel	Polysacchari-de		The polysaccharide isolated from <i>Citrus unshiu</i> peel activated signaling of MAPK and NF- κ B and produced the cytokines of IL-6, IL-12 and TNF- α in RAW 264.7 cells, which were completely inhibited by JNK inhibitors. In addition, neutralizing antibody experiments showed that TLR2 and TLR4 were involved in the polysaccharide-stimulated RAW 264.7 cells.	Not mentioned	[62]
7	<i>Ganoderma atrum</i>	Polysacchari-de		<i>Ganoderma atrum</i> polysaccharide has been demonstrated to induce immune response by recognition of mannose receptor and TLR4 and through NF- κ B pathway in macrophages.	Not mentioned	[63]
8	Dried 'Shixia' longan pulp	Polysacchari-de		The polysaccharide from dried 'Shixia' longan pulp significantly enhanced the phagocytic function of macrophages and promoted the production of NO, IL-1 β , IL-6 and TNF α via Ca ²⁺ and and CR3-mediated MAPKs and PI3K-AKT signaling pathways.	Not mentioned	[64]
9	<i>Astragalus membranaceus</i>	Polysacchari-des		<i>Astragalus</i> polysaccharides activated key nodes in TLR4/MyD88-dependent signaling pathways of RAW 264.7 macrophages, including TLR4, MyD88, TRAF-6, NF- κ B, and AP-1, both <i>in vivo</i> and <i>in vitro</i>	Not mentioned	[65]
11	<i>Rhynchosia minima</i> root	Polysacchari-de		Polysaccharides from <i>Rhynchosia minima</i> root remarkably enhanced the phagocytic ability of macrophages and promoted the release of NO and the secretion of cytokines (TNF- α , IL-6, and MCP-1) from macrophages. Simultaneously, the polysaccharides activated macrophages through the TLR4-NF- κ B pathway. It is a promising immune enhancer that can be used in functional foods or drugs	Not mentioned	[66, 67]
12	Persimmon	Polysacchari-des		The polysaccharides can activate TLR2-mediated NF- κ B activation upregulates the expression of iNOS, TNF- β , IL-1 β and IL-6 genes, which can act as an immunostimulator	Not mentioned	[68, 69]
13	<i>Bupleurum falcatum</i> L.	Saikosaponin-d	DC T cell	Saikosaponin-d reduced the differentiation of DCs, as evidenced by decreased expression levels of cluster of differentiation (CD)1a, CD80 and CD86 molecules and increased CD14 expression. Expression levels of the mannose receptor and CD32 were also significantly elevated. Saikosaponin-d treatment promoted DC maturation	Not mentioned	[73–75]

(Continued)

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No	Herbal Plant Species	Active Compounds	target cell	Mechanism of Action	Related vaccines/disease	References
14	Carrot	Crude polysacchari-des		Crude polysaccharides derived from carrot pomace increased the fraction of CD11c+MHCII+ cells and the expression of co-stimulatory molecules CD40 and CD80, in bone marrow-derived dendritic cells (BMDC). Moreover, innate myeloid cells in polysaccharides derived from carrot pomace-fed mice showed evidence of phenotypic modification <i>via</i> markedly enhanced IL-12 and IFN- γ production in response to LPS stimulation <i>ex vivo</i> .	Not mentioned	[76]
15	<i>Rehmannia glutinosa</i> polysaccharide	Polysacchari-de		The dendritic morphology of MDDCs was substantially altered the expression of co-stimulatory molecules in MDDCs was increased after <i>Rehmannia glutinosa</i> polysaccharide-treatment. Furthermore, the activation of MDDCs by <i>Rehmannia glutinosa</i> polysaccharide was dependent on the ERK, p38, and JNK signaling pathways CP induced DC maturation <i>via</i> the activation of MAPK and NF- κ B signaling pathways	Cancer and infectious diseases	[77,78]
16	<i>Chrysanthemum zawadskii</i> Herbich var. latilobum leaves	Polysacchari-de		CP induced DC maturation <i>via</i> the activation of MAPK and NF- κ B signaling pathways	Not mentioned	[79]
17	<i>Astragalus membranaceus</i> , <i>Ganoderma lucidum</i> and <i>Radix ophiopogonis</i>	Polysacchari-de		Three polysaccharides with immunoactivities showed elongated dendrites, decreased phagocytic abilities, phenotypic changes (CD40/MHCII/CD80/CD86) and increased level of nitric oxide (NO) in a dose dependent manner. Interestingly, blockage of NO by iNOS inhibitor slightly decreased CD40 and MHCII but not CD80/CD86 expression induced by polysaccharides	Not mentioned	[80]
18	leaves of <i>Annona muricata</i> L	Polysacchari-des		Polysaccharides isolated from leaves of <i>Annona muricata</i> L functionally induced DC maturation by up-regulating the secretion of Th1 polarizing pro-inflammatory cytokines, the expression of surface molecules, and antigen presenting ability, which is dependent on the activation of the MAPK and NF- κ B signaling pathways	Not mentioned	[81]
19	<i>Radix Glycyrrhizae</i>	Polysacchari-des		<i>Radix Glycyrrhizae</i> polysaccharide activate dendritic cells through TLR4 signaling.	Not mentioned	[82]
20	the seeds of <i>Plantago asiatica</i> L.	Polysacchari-des		The polysaccharide purified from the seeds of <i>Plantago asiatica</i> L. activate dendritic cells through TLR4 signaling.	Not mentioned	[83]
21	<i>Pleurotus ferulae</i>	Water extract		<i>Pleurotus ferulae</i> water extract activate dendritic cells through TLR4 signaling.	Not mentioned	[84]
22	<i>Ganoderma lucidum</i>	Polysacchari-des		<i>Ganoderma lucidum</i> polysaccharide activate dendritic cells through TLR4 signaling.	Not mentioned	[85]
23	Grapes and peanuts	Resveratrol		Resveratrol increasing the number of T lymphocytes	pseudorabies virus vaccine	[95]
24	Astragalus,	Astragalus polysacchari-de, epimedium polysacchari-de, propolis flavone, ginsenosides		The Chinese herbal medicinal ingredients have been found to enhance immune response through promotion of T lymphocyte proliferation of and up-regulation of IFN- γ and IL-10 mRNA expressions	rabbit hemorrhagic disease vaccine	[96]
25	epimedium, propolis, ginseng <i>Lentinus edodes</i>	A polysacchari-de-peptide complex		Data showed that the production of IL-2 and TNF- α in murine spleen mononuclear cells and human peripheral blood mononuclear cells were all significantly augmented, indicates its regulatory effect on Th immune responses.	Not mentioned	[97]
26	Yanyankang Powder	Not mentioned		regulates relationships of Th1/Th2, and then reduces the occurrence of uveitis.	Experimental Autoimmune Uveitis	[98,99]

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Table 1

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No	Herbal Plant Species	Active Compounds	target cell	Mechanism of Action	Related vaccines/disease	References
27	<i>Scolopendra subspinipes mutilans</i> L. Koch	a polysacchari-de-protein complex		It has been reported that <i>Scolopendra subspinipes mutilans</i> L. Koch increased the ratio of Th1/Th2 cytokines and percentage of CD4 ⁺ T cells that contributed to its antitumor and immunostimulatory activity.	Not mentioned	[100]
28	Shashen Maidong Decoction	Not mentioned		Shashen Maidong Decoction regulated the immune imbalance of Th1/Th2 by increasing IFN- γ concentration and decreasing IL-4 concentration.	Not mentioned	[101]
29	<i>Lycium barbarum</i> L.	Polysacchari-des		It has been found that <i>Lycium barbarum</i> polysaccharide played a variety of immune-modulatory functions through activation of CXCR5+PD-1+ Tfh cells and induce IL-21 secretion.	Recombinant vaccine	[102]
30	<i>Rhynchosia minima</i>	Polysacchari-des		Polysaccharides from <i>Rhynchosia minima</i> significantly up-regulated CD3 ⁺ , CD4 ⁺ T lymphocyte percentage and splenocyte CD4 ⁺ /CD8 ⁺ ratio, effectively alleviating cyclophosphamide-induced immunosuppression in mice	Not mentioned	[103]
31	<i>Astragalus</i> , <i>Epimedium</i> , <i>Paeonia lactiflora</i> , and <i>Ophiopogon japonicus</i>	Not mentioned		The Chinese herbal formula significantly increased the CD4/CD8 ratio and enhanced the humoral and cellular immune functions of immunosuppressed mice.	Not mentioned	[104]
32	Fuzheng Qingjie granule	Not mentioned		Fuzheng Qingjie granule significantly increased the ratio of CD4 ⁺ /CD8 ⁺ T cells and the serum level of TNF- α , and also increased the expression of CD69 in tumor tissue.	Not mentioned	[105]
33	inulin	Polysacchari-des(Advax TM)	B cell	A natural polysaccharide-derived Advax TM adjuvant showed its immunologically active that mice immunized with inactivated influenza virus vaccine in Advax TM had significantly higher frequencies of influenza-specific B cells secreting IgG and IgM in bone marrow and spleen when compared to mice immunized with vaccine alone.	Influenza vaccine	[107]
34	Isatis indigotica root	Polysacchari-des(IIP-A-1, IIP-2)		The polysaccharide IIP-A-1 has been reported to activate influenza H1N1 and hepatitis B surface antigen vaccines. Another polysaccharide IIP-2 enhanced the titer of neutralizing antibody, promoted the activation of lymph node B cells and promoted the recruitment of B cells in the blood. The administration of inactivated rabies virus mixed with IIP-2 provided completed protection against HuNPB3 rabies infection.	rabies virus	[108,109]
35	<i>Radix Platycodon grandiflorum</i>	Polysacchari-de		Polysaccharide isolated from <i>Radix Platycodon grandiflorum</i> was found to markedly increase polyclonal IgM antibody production and B cell proliferation	Not mentioned	[110]
36	<i>Coriolus versicolor</i> mushroom	Polysacchari-des		It has been demonstrated that <i>Coriolus versicolor</i> mushroom polysaccharides binded and induced B cell activation using membrane Ig and TLR-4 as potential immune receptors. <i>Coriolus versicolor</i> mushroom polysaccharides inactivates mouse B cells through the MAPK and NF- κ B signaling pathways	Not mentioned	[111]
37	Alfalfa grass	Polysacchari-des		Polysaccharide extracted from Alfalfa grass activated splenic B cells by TLR4 via the MAPK/p38 pathway, and it selectively improved the cell viability and IgM production of B cells.		[112]
38	the roots of <i>Acanthopanax koreanum</i> , <i>Platyloden grandiflorum</i> , and <i>Acanthopanax senticosus</i>	Polysacchari-des		Polysaccharides found in the roots of <i>Acanthopanax koreanum</i> , <i>Platyloden grandiflorum</i> , and <i>Acanthopanax senticosus</i> , stimulated B cells through CD19 and CD79b, which suggested the possibility that these polysaccharides might directly bind to the mlg of B cells	Not mentioned	[113-115]

stimulator of NK cells for therapeutic treatment^[48]. Commercial Shenmai injection is a TCM that was officially included in the 2015 edition of the *Chinese Pharmacopoeia*. It has been reported that Shenmai injection in patients with gastric cancer significantly increased the activity of NK cells in serum^[49]. Recently, the availability of Shenmai injections for COVID-19 has been evaluated by molecular docking and network pharmacology. Data showed that 22 compounds and 16 targets were predicted in the Shenmai injection that was shared with COVID-19^[50].

Macrophages

Macrophages represent the first line of host defense behind the epithelial barrier, with a variety of complex bactericidal functions, including surveillance, chemotaxis, phagocytosis, and destruction of target organisms^[51–52]. Similar to the recognition of NK cells by receptors, macrophage activation is mainly achieved through specific receptors. There are three types of receptors on macrophages, including pattern recognition receptors (eg, toll-like receptors (TLRs), dectin-1, and mannose receptors)^[53], opsonizing receptors (eg, complement receptors)^[54], and antigen presentation-related molecules (eg, MHC I/MHC II and co-stimulatory molecules CD80 and CD86)^[55–56]. As a result of binding and medication, multi-signaling pathways such as Nuclear factor kappa B (NF- κ B), Mitogen-activated Protein Kinase (MAPK), and phosphatidylinositol 3 kinase (PI3K) /protein kinase B (AKT) are involved and activated in the host defense following vaccination.

Resveratrol is a natural compound widely distributed in the red grape skin, Japanese knotweed (*P. cuspidatum*), peanuts, and blueberries^[57]. It has been reported that resveratrol enhances the immune response by upregulation of CD86 and MHC-II expression in macrophages from a vaccine of pseudorabies virus-immunized mice, and the expression of TLR4, inhibitor of kappa B kinase (IKK), I κ B α , NF- κ B, and c-Jun N-terminal kinase 4 (JNK4) were all significantly increased in the resveratrol-treated group^[58]. *Cordyceps militaris* is a medicinal herb with a variety of functions, such as anti-inflammatory activity^[59]. Pharmacological research has shown that polysaccharides isolated from *C. militaris* upregulated the uptake of Nitric Oxide (NO), Reactive Oxygen Species (ROS), and Tumor Necrosis Factor (TNF- α), promoted phagocytosis, and activated NF- κ B and MAPK pathways through receptors DECIN-1 and TLR2 in mouse peritoneal and RAW264.7 macrophages, indicating a role in immune modulation^[60]. The polysaccharides isolated from *Citrus unshiu* induced the production of cytokines Interleukin-6 (IL-6), Interleukin-12 (IL-12), and TNF- α in RAW 264.7 cells through activation of MAPK and NF- κ B signaling^[61]. *Ganoderma atrum* polysaccharides have been demonstrated to induce an immune response by recognizing the mannose receptor and TLR4 through the NF- κ B pathway in macrophages^[62]. Another polysaccharide from dried “Shixia” longan pulp significantly enhanced the phagocytic function of macrophages and promoted the production of NO, IL-1 β , IL-6 and TNF α via Ca²⁺

and CR3-mediated MAPKs and PI3K-AKT signaling pathway^[63]. *Astragalus* polysaccharides, the main active extract from *Astragalus membranaceus*, have been reported to activate the TLR4/MyD88-dependent signaling pathway in RAW 264.7 macrophages and in TLR4+ and MyD88+ mice^[64]. *Rhynchosia minima* root, a medicinal herb in southern China, has been used to inhibit upper respiratory infections in folk medicine for years^[65]. Polysaccharides from *R. minima* root remarkably enhanced the phagocytic ability of macrophages and promoted NO release and secretion of TNF- α , IL-6, and MCP-1, and are thus considered promising immune enhancers used in functional foods or drugs^[66]. Persimmon leaves are commonly used to treat infectious diseases^[60]. One study showed that polysaccharides from persimmon leaves activated TLR2-mediated NF- κ B activation and upregulated the expression of iNOS, TNF- β , IL-1 β , and IL-6 in macrophages, which indicated their role as immune stimulators^[67].

Dendritic cells

Dendritic cells (DCs) are crucial for linking innate to specific adaptive immunity, which is associated with their activation and maturation status^[68]. As bone marrow-derived cells, DCs may be generated from multiple precursor cells including lymphoid and myeloid progenitors. Before activation, DCs reside in the periphery, where they take up antigens. Once activated, they migrate to lymphoid organs and present processed antigens to T cells^[69]. By upregulating co-stimulatory and surface molecule expression and inducing pro-inflammatory cytokines, DCs elicit a potent immune response^[70–71]. Given the central role of DC in controlling the immune response, DCs are considered a critical cell type and potential target when vaccine injection is completed.

Saikosaponin-d is a triterpenoid saponin derived from *Bupleurum falcatum* L. Its anti-inflammatory, antibacterial, and antiviral properties have been demonstrated in carrageenan-induced paw edema in rats and acetic acid-induced vascular permeability in mice, cellular RAW 264.7, and cancer cells^[72–73]. Saikosaponin-d reduced the differentiation of human monocyte-derived DCs isolated from patients with condylomata acuminata by downregulating CD1a, CD80, and CD86 expression and upregulating CD14, CD32, and mannose receptor expression^[74]. Saikosaponin-d also highly promoted DC maturation by increasing the expression of CD40, CD83, CD80, and CD86, whereas the function of mature DCs, including IL-12 secretion and lymphocyte growth stimulation, was significantly elevated in response to Saikosaponin-d treatment^[74]. Polysaccharides are a series of compounds that have attracted considerable attention because of their intrinsic immunomodulatory characteristics^[75]. Data have shown that crude polysaccharides derived from carrot pomace increased both the fraction of CD11c⁺ MHCII⁺ cells and the expression of CD40 and CD80 in bone marrow-derived dendritic cells (BMDCs) and augmented the frequencies of splenic DCs and vaccine-specific antibody titers in cyclophosphamide-induced immunosuppressed mice when experiencing an influenza vaccine challenge^[76]. A polysaccharide derived from *Rehmannia glutinosa* has been found to induce the

activation and maturation of DCs with altered dendritic morphology and increased expression of co-stimulatory molecules^[77-78]. Furthermore, the activation of DCs by *R. glutinosa* polysaccharides was dependent on the ERK, p38, and JNK signaling pathways^[78]. Similarly, it has been reported that a polysaccharide isolated from *Chrysanthemum zawadskii* Herbich var. *latilobum* leaves induced the maturation of DCs through the activation of MAPK and NF- κ B signaling pathways, which subsequently activate naive T cells to polarize CD4⁺ and CD8⁺ T cells and induce the production of IFN- γ and IL-2 *in vitro*^[79]. Three types of polysaccharides isolated from *A. membranaceus*, *Ganoderma lucidum*, and *Radix ophiopogonis* were characterized and tested for their immunactivities. They significantly elongated dendrites, reduced their phagocytic abilities, and altered the phenotypic CD40/MHCII/CD80/CD86 expression in BMDCs^[80]. Polysaccharides isolated from *Annona muricata* L also functionally induced DC maturation by upregulating Th1 polarizing cytokine secretion and surface molecule expression, which in turn enhanced the antigen-presenting ability^[81]. Similar to macrophages, DCs have important toll-like receptors on their membranes. Distinct polysaccharides purified from *R. Glycyrrhizae*^[82], seeds of *Plantago asiatica* L.^[83], *Pleurotus ferulae*^[84], and *G. lucidum*^[85] activated DCs through TLR4 signaling.

Adaptive immune system

The adaptive immune system is the second line of defense that defends against pathogen-specific invasion, mainly through T and B lymphocytes. Briefly, T lymphocytes function by mediating cellular immunity and adjusting immunity, whereas B lymphocytes mainly participate in humoral immunity. In contrast to immediate innate immunity, adaptive immunity develops upon pathogen exposure and is long-lasting and sustained by memory cells.

T lymphocytes

T lymphocytes (also referred to as T cells) are pluripotent stem cells derived from the bone marrow, where pre-T cells migrate and mature in the thymus and export to the periphery^[86]. Diverse T cell types are involved in the immune system. Naive T cells are first activated by either antigen-specific signals delivered by the T cell receptor or by the interaction of CD28 on T cells and CD80 or CD86 on antigen-presenting cells^[87]. Once activated, naive T cells rapidly differentiate into helper T cells (CD4⁺ T cells/Th cells), cytotoxic T cells (CD8⁺ T cells), and regulatory T cells. More subsets of CD4⁺ T cells, including T helper 1 (Th1), T helper 2 (Th2), and follicular helper T cells (Tfh)^[88], are differentiated with multiple functions. Th1 cells have the ability to promote the proliferation, differentiation, and maturation of CD8⁺ T cells and enhance the phagocytosis of macrophages and cytolytic autologous antigen-presenting cells^[88-89]. Th2 cells provide an excellent auxiliary function for antibody production by B cells, especially IgE antibodies^[89-90]. Tfh cells differentiate into antibody-secreting plasma cells and memory B cells^[90]. Unlike assisted CD4⁺ T cells, CD8⁺ T cells directly kill infected cells, clear intracellular pathogens,

and secrete cytokines such as IFN- γ and TNF α ^[91]. The dynamic balances of Th1/Th2 and CD4⁺/CD8⁺ ratios are thus considered remarkable markers of immune status and body homeostasis maintenance^[92-93].

Many herbal medicines enhance immunity by regulating T-cell-related functions. A series of natural compounds isolated from medicinal herbs, such as astragalus polysaccharides, epididymal polysaccharides, propolis flavonoids, and ginsenosides, have been reported to promote T lymphocyte proliferation^[94]. The widely distributed compound resveratrol^[57] also increases the number of T lymphocytes when used as an immune adjuvant in a pseudorabies virus vaccine^[58]. The differentiation and ratio of subsets in CD4⁺ T cells have also been investigated when drugs are administered. A Chinese commercial medicine named Yanyankang powder inhibited the differentiation of Th0 to Th1 cells but promoted Th0 to Th2 cells in autoimmune uveitis rats through downregulation of Th1-secreted IFN- γ but upregulation of Th2 secreted IL-10, which finally reduced the ratio of Th1/Th2^[95-96]. Herbal *Scolopendra subspinipes mutilans* L. *Koch* has been used for cancer treatment for hundreds of years in China, and its immunostimulatory activity has been shown to accelerate the Th1/Th2 ratio and increase the number of CD4⁺ T cells^[97]. Similarly, Shashen Maidong decoction, a representative prescription for nourishing *Yin* and generating body fluid, blocked the Th1/Th2 imbalance by increasing IFN- γ and decreasing IL-4^[98]. In addition, the antigen-specific Tfh response plays a vital role in enhancing the protective effects of vaccines. It has been found that a *Lycium barbarum*-derived polysaccharide played a variety of immune-modulatory functions through activation of CXCR5⁺ PD-1⁺ Tfh cells, as well as induction of IL-21 secretion^[99]. The CD4⁺/CD8⁺ ratio was observed in herb-regulated immune responses. Polysaccharides from *R. minima* significantly upregulated both the percentage of CD4⁺ T lymphocytes and splenocyte CD4⁺/CD8⁺ ratio, which effectively alleviated cyclophosphamide-induced immunosuppression in mice^[66]. A Chinese herbal formula composed of *Astragalus*, *Epimedium*, *Paeonia lactiflora*, and *Ophiopogon japonicus* increased the CD4⁺/CD8⁺ ratio and enhanced humoral and cellular immune functions in immunosuppressed mice^[100]. Another report showed a similar effect of a commercialized Fuzheng Qingjie granule on upregulation of the serum CD4⁺/CD8⁺ ratio in hepatocellular H22 tumor-bearing mice^[101].

B lymphocytes

One of the main protective processes induced by vaccines is antibody production from B lymphocytes (B cells), which can directly recognize extracellular antigenic moieties of pathogens through their immunoglobulin B-cell receptor present in the outer membrane and become activated and differentiate into plasma cells to produce specific antibodies^[102]. The association between antibody response to different vaccines and dynamic immune repertoire changes in different cell subsets may not be equal, and there are several host- and vaccine-specific factors modulating an antibody response in B cells, which may contribute to the loss of vaccine efficacy^[103].

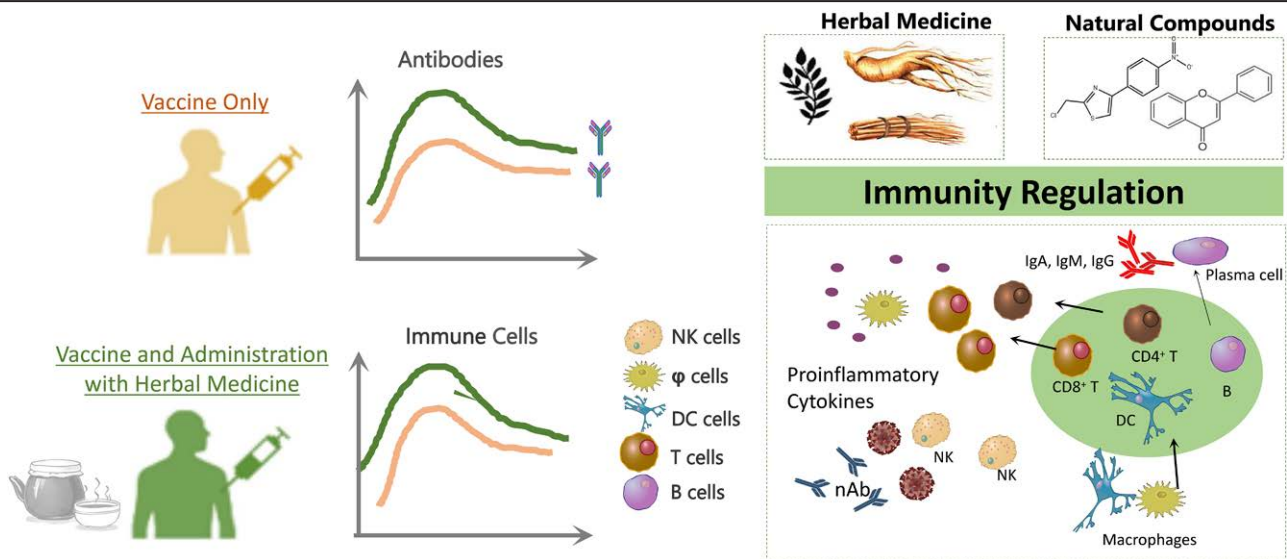


Figure 1. Main immune cell targets of herbal medicines in regulation of the immune system. Macrophages, NKs, and DCs in the innate immune system, and T lymphocytes and B lymphocytes and their subtype transformation in the adaptive immune system are highly involved in and contribute to the assistance of herbal medicine toward the protective effects of vaccines. DC: Dendritic cell; NK: Natural killer; Th: T helper.

Several studies have shown that B cells are the major target cells of herbal medicines. A natural polysaccharide-derived Advax™ adjuvant showed its immunologically activity that mice immunized with inactivated influenza virus vaccine in Advax™ had significantly higher frequencies of influenza-specific B cells secreting IgG and IgM in the bone marrow and spleen than mice immunized with vaccine alone^[104]. Polysaccharide IIP-A-1 isolated from the Chinese herb *Isatis indigotica* root has been reported to activate influenza H1N1 and hepatitis B surface antigen vaccines^[105]. Another polysaccharide, IIP-2, isolated from *I. indigotica* root, enhanced the titer of neutralizing antibodies and promoted the activation of lymph node B cells and the recruitment of B cells in the serum. Administration of inactivated rabies virus mixed with IIP-2 provided complete protection against HuNPB3 rabies infection^[106]. A polysaccharide isolated from *R. P. grandiflorum* markedly increased polyclonal IgM production and B-cell proliferation^[107]. It has been demonstrated that *Coriolus versicolor* mushroom polysaccharides bound and induced B cell activation using membrane Ig and TLR4 as potential immune receptors. *C. versicolor* mushroom polysaccharides activate mouse B cells through the MAPK and NF-κB signaling pathways^[108]. Polysaccharides extracted from alfalfa grass activated splenic B cells by TLR4 through the MAPK/p38 pathway, and selectively improved the cell viability and IgM production of B cells but did not affect T cell viability^[109]. Polysaccharides separated from the roots of *Acanthopanax koreanum*, *P. grandiflorum*, and *Acanthopanax senticosus* stimulate B cells through CD19 and CD79b, suggesting that these polysaccharides may directly bind to the mIg of B cells^[110–112].

The potential roles of herbal medicines in the regulation of COVID-19 vaccination

The information described earlier shows that herbal medicines modulate the immune response in multiple ways on different scales, which may help to generate

or optimize vaccine strategies (Figure 1). When a novel vaccine market is available, its protective function, associated immune response, and vaccination schedules are evaluated. COVID-19 vaccines have been designed and marketed by numerous countries and companies worldwide to overcome the COVID-19 pandemic. However, the dynamic immune responses and protective effects of vaccines remain elusive. Researchers have been devoted to uncovering the immune responses after COVID-19 vaccination. A study in China found that the inactivated virus COVID-19 vaccine CoronaVac had 65.9% effectiveness against COVID-19, 90.3% against intensive care, and 86.3% against death^[113] through induction of robust circulating and memory B cell and T cell responses^[114]. In a prospective cohort of 100 individuals who received SARS-CoV-2 CoronaVac^[114], spike-specific IgG responses peaked after two doses and rapidly declined in 8 to 10 weeks after the booster dose. Spike-specific circulating and memory B cells were effectively induced, followed by a decrease after 8 to 10 weeks, as well. SARS-CoV-2-specific circulating CD4⁺ T cells and CD8⁺ T cells were detected 2 weeks after the booster dose and sustained over time, and memory CD4⁺ T cells and CD8⁺ T cells were identified as SARS-CoV-2-specific 8 to 10 weeks after the booster dose. Another study performed head-to-head comparisons of T cells, B cells, and antibody responses, with a particular interest in immune memory, to four diverse vaccines, namely, Moderna mRNA-1273, Pfizer/BioNTech BNT162b2, Janssen Ad26. COV2.S, and Novavax NVX-CoV2373 in humans^[8]. The results showed that immunological responses on memory CD4⁺ T cells were consistent, whereas other responses varied, which may be dependent on distinct vaccine design insights. For example, cTfh and CD4-CTL were highly expressed after mRNA or NVX30CoV2373 vaccination, comparable CD8⁺ T cell frequencies were induced by mRNA and Ad26. COV2.S vaccines, and mRNA vaccines had substantial declines in neutralizing antibodies, whereas memory

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T cells and B cells were comparatively stable over 6 months. Importantly, the issue of protective immunity against different variants was evaluated. Studies on the impact of a large panel of variants on memory T and B cells, particularly in the context of COVID-19 vaccination, have shown that T cells of vaccines recognize SARS-CoV-2 variants, including Omicron, in which B cell RBD memory recognition of Omicron is reduced. A median of 11 CD4 and 10 CD8 spike epitopes have been recognized in vaccines^[115]. One of the definite responses is the normal immune reaction that helps produce pre-existing immune cells and antibodies. Several studies on SARS-CoV-2 immunity have reported the occurrence of pre-existing immunity against SARS-CoV-2 in the population, including pre-existing antibodies and immune cells, especially specific memory T cells^[116–119].

The understanding and evidence of herbal medicines in the regulation of COVID-19 vaccines are still unclear, and their potential effects and anticipated benefits have not been thoroughly considered. However, previous findings of herbs suggest that herbal medication enhances the human immune abilities with vaccine immunization, which seems to greatly affect body defense and may benefit from their definite regulation of immunity. It may strengthen the innate immune system by NK and macrophage proliferation or secretion, reinforce the DC function to bridge the innate and adaptive immune system, or alter the patterns of evolution of antibodies arising from specific and defined antigens, such as delivery systems with T or B lymphocytes or adjuvantation to target and trigger effective adaptive immunity of the COVID-19 vaccine. In addition, it affects the response among individuals in a variation in the degree of disease, and some individuals with herbal assistants may exhibit a better response to vaccination, such as significant increases in serum nAb responses against vaccine-matched and emerging variants.

Conclusion

Although a large knowledge gap remains to be filled in herb-regulated vaccine responses, the advances discussed in this article have expanded our insights into numerous applications, including COVID-19 vaccines. This review may provide a framework for understanding herbs in vaccine strategies, and the limitations of vaccines may be alleviated the immunoregulatory activities of medicinal herbs. The COVID-19 vaccination currently requires further identification and confirmation, which is a result of increased interest and encouraged research efforts.

Conflict of interest statement

The authors declare no conflict of interests.

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Author contributions

Lin Li and Lin Miao conceived the project. Xuan Li, Xiuping Liu, and Huimin Yan searched for and collected published data from the PubMed database. Xuan Li, Xiuping Liu, Huimin Yan, and Lin Miao wrote the manuscript. Nuttapon Wichai and Jiabao Wang constructed the figures. Yu Wang, Lin Li, Mingchi Luo, Shengyuan Zhou, and Kai Wang revised the manuscript. All authors read, contributed to, and approved the manuscript.

Ethical approval of studies and informed consent

Not applicable.

Data availability

The database of the literature cited in the review is published on the PubMed website with the Research Topic or keywords “Immune, vaccination, herbs, herbal medicine, and COVID-19.”

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