Traditional Medicine Combination Therapy Is A Promising Strategy for MRSA Infection

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Abstract

Methicillin-resistant Staphylococcus aureus (MRSA) is a superbug that often causes serious inflammation-related injuries. Host immune defense against MRSA infection and MRSA immune evasion strategies are the main mechanisms of these injuries. Conventional drugs, such as antibiotics, optimized antibiotics and vaccines, can treat MRSA infections, but their use is limited because of drug-resistance and impairment of immunity. Traditional medicine (TM) therapies, presently used to address these unmet clinical needs and treat injuries, are regarded as a potential solution to combat MRSA infection. This review systematically summarizes the immune mechanisms of MRSA infection, analyzes the efficacy characteristics and corresponding mechanisms of conventional and TM therapies in treating injuries, and discusses the potential advantages of combined therapy. Furthermore, several appropriate immune responses-related conditions that could be treated with the combination therapy were summarized, and new perspectives on the clinical and basic research on this combination therapy were proposed. This review lays a foundation for the development of anti-MRSA therapies and provides novel strategies and methods for the treatment of inflammation-related injuries caused by multiple drug-resistant bacteria.

1 Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA), a worldwide prevalent superbug, usually causes immune injuries[1]. These immune injuries are attributed to the interaction between the host's immune responses and MRSA immune evasion[2]. Conventional drugs, such as antibiotics, optimized antibiotics and vaccines, are currently used to treat injuries. Since the emergence of resistant strains and immune evasion, the efficacy of antibiotics has decreased and their adverse effects limit their use [3, 4]. Optimized antibiotics are new favorite in drug research due to their superior potency, efficacy, and specificity. However, high production costs hinder its extensive use. Vaccine development often suffers from challenges in technique, cost, and other difficulties. It is therefore a burning issue to improve treatment methods for MRSA immune injuries.

Traditional medicine (TM) is used to treat bacterial infection and immune injuries, because it not only inhibits and kills bacteria, but also relieves immune injuries, partly overcomes drug resistance, and alleviates the adverse effects caused by conventional therapies[5-8]. Studies have shown that TM enhances host immunity. For example, it activates Peyer's batches and regulates neutrophil phagocytosis [9-11]. A study has suggested that herbal formulae combined with antibiotics exert better bacteriostatic efficacy than antibiotic use alone[12].

This study aims to review the efficacies and corresponding mechanisms of both conventional drugs and TM in combating MRSA, and to explore the potential of their combination. Additionally, the research ideas and

methods on the combination medication are discussed. This review will lay a foundation for the development of a new strategy to treat MRSA infection.

2 MRSA infection and its immune mechanisms

MRSA infection has three stages: colonization, adaptation and invasion. Its high pathogenicity is attributed to the invasiveness, virulence and variability [13]. MRSA has virulence factors that increase its invasiveness, allowing the bacteria to adhere and invade to host cells [14]. The variability of MRSA includes antigenic variation and phase variation. Antigenic variation enables resistance to commonly used antibiotics without reducing the pathogenicity of MRSA, and can alter the immunoreactivity of its encoded products, thereby evading the host's immune response[15, 16]. Phase variation helps MRSA immune evasion by promoting MRSA biofilm (MRSA-BF) formation and assisting bacteria survival within the "Trojan horse"[17]. In MRSA infection, the human immune system evolves several efficient mechanisms to eliminate MRSA, and MRSA evolves immune evasion strategies against host immunity (Fig. 1)[2].

2.1 Host immune defense against MRSA infection

As shown in Fig. 1, there are three lines of defense against MRSA infection, the body's mucosal immune system (MIS), the innate immune system (IIS) and the adaptive immune system (AIS). As a physical and immune defense barrier, MIS maintains immune homeostasis in the vast epithelial surface areas from the nasal cavity and respiratory tract to the intestine [18]. The formation of secretory IgA (SIgA) is the key strategy of the MIS [19]. SIgA is released into the nasal passage and intestinal tract, binding and "coating" offending pathogens, thus blocking pathogens invasion (Fig. 1) [20]. The IIS is rapidly triggered during infections, which involves the activation of the complement system and the recruitment and activation of dedicated immune cells such as neutrophils and macrophages (Fig. 1) [21]. The activated complement system usually exerts phagocytosis by binding with the complement receptor (CR), and it triggers serial chemotactic and proinflammatory responses to facilitate neutrophil migration to the infection site [22, 23]. Neutrophils are activated and stimulate bacterial clearance by phagocytosis and bactericide[24, 25]. As pathogens are degraded, antigenic peptides are processed by specific antigen-presenting cells such as DCs and Mφs, further triggering the AIS, which plays a major role in both the treatment and control of chronic infections (Fig. 1)[26, 27].

2.2 MRSA immune evasion

To establish infection successfully, MRSA deploys several immune evasion strategies to prevent the host's three lines of defense. (Table 1.). The analysis of molecular structures reveals the mechanism by which a bacterial pathogen evades SIgA-mediated immunity via Staphylococcal superantigen-like protein-7 (SSL-7) in the mucosal immune response, which facilitates survival in mucosal environments and then contributes to systemic infections [28].

To evade attack from innate immune responses, MRSA secretes virulence factors that prevent complement initiation, digest complements and inhibit the cleavage of complement cleavage fragments, further evading opsonization of the complement system and causing inhibition of subsequent neutrophil effects (Table 1) [25, 29-38]. Other virulence factors prevent neutrophils from functioning by blocking them from arriving at infected sites, inhibiting their phagocytosis, and even killing them [32, 39-41]. MRSA also impairs macrophages mainly via the formation of mature MRSA-BF[40, 42]. It survives in macrophages and enters the general circulation, leading to other tissue damage, which is called the "Trojan horse" [43]. Finally, MRSA directly causes macrophage death through pore-forming toxins (PFTs), particularly PVL. MRSA also manipulates the AIS, for example, interfering with B-cell activation and proliferation, and impeding the humoral response[44, 45].

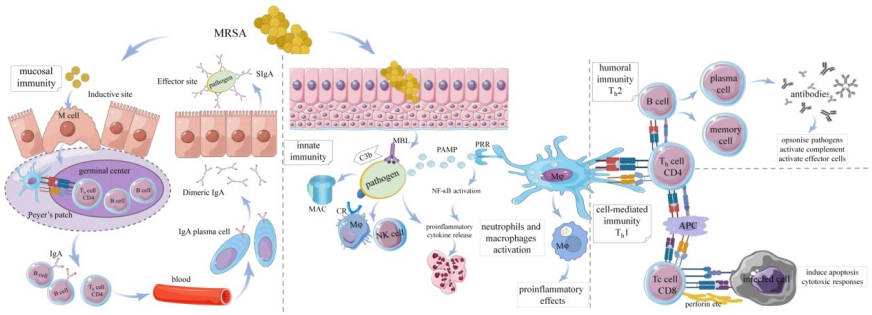


Figure 1. Overview of immune response mechanisms during MRSA infection. The body has three lines of defense against MRSA infections. (A) Mucosal immune response. The mucosal surface is in direct contact with pathogens. The key strategy of the mucosal immune response is to generate antigen-specific IgA antibodies in the external secretions. This process occurs at Peyer's patches (PP), and its key function is the sampling of antigens. To facilitate this sampling, microfold (M) cells, specialized phagocytic cells in the PP, can directly swallow and transport antigens in the nasal or intestinal cavity to DCs via phagocytosis. In the PP, through antigen presentation, IgA-committed B-cell (IgA+ B cells) are induced to develop and finally produce dimeric (or polymeric) forms of IgA after proliferation and differentiation at effector sites. Ultimately, these forms of IgA become secretory IgA by binding to polymeric Ig receptors (SCs). SIgAs are then released into the nasal passage and intestinal tract, binding and "coating" offending pathogens, thus blocking pathogen invasion. (B) Innate immune response. The complement system is activated through the classical pathway, lectin pathway and alternative pathway. Some complement fragments, such as C3b formed by C3 convertases cleaving the C3 protein, can exert phagocytosis through binding with the complement receptor (CR). The membrane attack complex (MAC) is formed and directly leads to cell lysis. Moreover, other complement fragments, such as C3a and C5a, can trigger a series of chemotactic and proinflammatory responses to facilitate neutrophil migration to the site of infection. Neutrophils recruit and migrate to infection sites along a concentration gradient of chemokines secreted or released by activated host cells or complement components such as C5a. Finally, neutrophils are primed, activated and stimulate bacterial clearance by phagocytosis and bactericide. Gradually, the invading bacteria are killed, and any remaining neutrophils die off via apoptosis and are cleared by macrophages. (C) Adaptive immune response. As pathogens are degraded, antigenic peptides can be presented by dedicated antigen-presenting cells, such as DCs and Mφs, to T-lymphocytes, further activating the host adaptive immune response. When stimulated directly or indirectly, B cells differentiate and produce antibodies, which specifically bind with bacteria to eliminate pathogens. When bacteria enter the cells, antigen-specific T cells are stimulated and differentiate into CD8+ T cells. These cells recognize and specifically bind to infected cells (targeted cells) invaded by antigens, activate lysosomal enzymes in targeted cells, and finally lead to the lysis and death of targeted cells. The antigens in the cells lose are bound and immobilized by the antibodies and are then phagocytosed. Ultimately, MRSA infection is inhibited.

Table 1. MRSA virulence factors that contribute to immune evasion and their functions in host immune responses

Evasion proteins against mucosal immune
Staphylococcal superantigen-like protein-7 (SSL-7)
Evasion proteins against innate immune
Proteins including extracellular adherence protein (Eap), collagen-binding protein (Cna) and serine-aspartate repeat protein
Staphylococcal Protein A (SpA)
Staphylococcal complement inhibitor (SCIN)
Extracellular fibrinogen-binding protein (Efb); its homolog extracellular complement-binding protein (Ecb)

Evasion proteins against mucosal immune
Second Immunoglobulin-binding protein (Sbi)
Factor I Staphylokinase (SAK) chemotaxis inhibitory protein of staphylococci (CHIPS)
Staphylococcal superantigen-like protein-7 (SSL-7) Proteases, e.g., staphopain A (Scp A), aureolysin (Aur)
Staphylococcal superantigen-like 5 (SSL5) Proteins including extracellular adherence protein (Eap) *Staphylococcal* complement inhibitor (SCIN), chemotaxis inhibitory protein of staphylococci (CHIPS) Nuc Panton-Valentine leukocidin (PVL) Phenol-soluble-modulins (PSMs)

3 Challenges of conventional drugs for the treatment of MRSA infection

3.1 Antibiotics

Antibiotics are used for MRSA infection. Long-term use of antibiotics causes resistance, which is due to the immune evasion strategies of bacteria. The use of antibiotics also impairs phagocytic bactericidal functions and weakens the host's immunity [3]. Additionally, oral antibiotic treatment can disrupt the normal intestinal flora, affecting lung or other tissue immunity to bacteria[53]. Antibiotic resistance and side effects limit its utilization.

3.2 Optimized antibiotics

Optimized antibiotics, including antibody-antibiotic conjugate (AAC) and antibiotic adjuvants, have been proposed to combat MRSA infection[16, 54]. AAC is an anti-MRSA antibody linked to an antibiotic using a protease-sensitive linker[55]. When MRSA is opsonized by the antibody and is phagocytized by immune cells, the linker is cleaved by host cell proteases, and the antibiotic is released close to the bacteria and in the compartment with antibiotic tolerant bacteria[55]. Optimized antibiotics, with superior potency, efficacy, and specificity, are more effective the antibiotics alone for the treatment of secondary MRSA infection[55]. Moreover, AAC can combat antibiotic-tolerant bacteria more effectively and can improve the permeability of antibiotics into host cells. However, high production costs hinder their clinical translation [56]. Antibiotic adjuvant (AA) is another strategy for developing novel antibiotics. To date, AAs mainly contain efflux pump inhibitors and β -lactamase inhibitors[16]. Efflux pumps can actively extrude antibiotics, increasing their minimum inhibitory concentration (MIC) or even losing their antimicrobial activity. Using efflux pumps as therapeutic targets, efflux pump inhibitors (EPIs) were developed. EPIs, with no antibacterial activity on their own, inhibit efflux pumps by interfering with efflux gene expression, adding functional groups to the drug substrate, and developing small-molecules as substrate analogues to hinder identification, or to interfere with the assembly of channel proteins [57]. EPIs can increase the activity of antibacterial drugs subject to efflux, maintain the drug concentration at the therapeutic dose and shorten the treatment duration[58]. However, its use requires high-dose administration, which could be toxic [16]. This high-dose administration makes it difficult to widely develop EPIs.β -Lactamase can deactivate antibiotics[16]. Thus, β -lactamases inhibitors (BLIs), capable of inactivating mostβ -lactamases, are a proper antibiotic adjuvant. These inhibitors are mainly used in treating G- bacterial infection, while their use in G+ bacteria still needs to be developed[59].

3.3 Vaccines

Vaccination to prevent MRSA infection acquisition is the main treatment strategy. Vaccination can decrease the occurrence and transmission of resistant strains [60]. Vaccines usually induce the immune system to react to multiple targets, which makes it more difficult for bacteria to evade the immune response induced by vaccination, namely, it restricts the mutation of bacterial resistance genes [61]. Vaccines do not increase antibiotic resistance, and most vaccines still work after long-term use. Moreover, vaccination can restrict the ability of bacteria to colonize and establish an infection by enhancing immunity [62]. However, these vaccines have had limited or no success in human trials[63, 64].

4 TM for anti-MRSA infection

TM has exerted its unique efficacies in inhibiting MRSA infection[6, 12]. However, the bacteriostatic ability of TM is weaker than that of antibiotics.TM regulation of the body's immunity might be a promising strategy to combat MRSA infection. In TM, single herbs and their active components as well as formulae play a key role in regulating host immunity. The mechanisms of these herbs and formulae were systematically analyzed and summarized (Table 3, Fig. 2).

4.1 Single Herbs and active components

4.1.1 *Glycyrrhiza glavra* (*Glycyrrhiza* polysaccharides)

Glycyrrhiza glavra (*G. glavra* , licorice) is an herbal medicine with various bioactivities. It has been used to treat lung injury and bacterial infection [65]. Its components including glycyrrhizin (GL) and its hydrolysis product 18-β-glycyrrhetinic acid (18-β-GA), as well as licorice flavonoids, can restrain bacterial infection [65]. GL has anti-inflammatory and immunomodulatory activities[66]. Neutrophils are its primary targets. By down-regulating the expression of endothelial adhesion molecules in neutrophils (ICAM-1 and P-selectin), GL prevents neutrophil adhesion, partly curbing local injuries [67]. It also decreases myeloperoxidase (MPO) levels. MPO, an enzyme mainly stored in azurophilic neutrophil granules, has potent antibacterial activity, and it is a marker of neutrophil migration and infiltration, as well inflammation and tissue injury [66, 68, 69]. GL can inhibit neutrophil phagocytosis, and it can treat the initial phase of lung inflammation. It decreases the secretion of inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2) and pro-inflammatory cytokines (TNF-α, IL-1α, IL-6) by regulating NF-ϰB signaling molecules[66]. Both iNOS and COX-2 are induced by inflammatory stimuli and play important roles in MRSA pneumonia[70]. Altogether, GL inhibits MRSA pneumonia in the initial phase, mainly by preventing the adhesion, migration, recruitment, infiltration and phagocytosis of neutrophils.

18-β-GA can combat MRSA immune evasion and improve host immunity[71]. It markedly reduces MRSA immune evasion to alleviate infection via down-regulating the key virulence factors, saeR, hla, RNAIII, mecA, and sbi [72]. Additionally, it can regulate the functions of neutrophils and DCs. In a mouse model of MRSA skin infection, 18-β-GA reduces neutrophil recruitment by down-regulating KC and granulocyte colony-stimulating factor (G-CSF) to alleviate skin infection [72]. It also activates adaptive immune responses to anti-MRSA infection by targeting DCs[73]. In a mouse model of lipopolysaccharide (LPS)-induced inflammation, at doses of 1 mg/mL and 10 mg/mL, 18-β-GA increases CD40 expression levels in DCs [73]. The interaction of CD40 and its ligand CD40L can promote T cells activation and inflammatory cytokine (IL-1, IL-6 and IL-12) production and induce DC maturation and activation, thereby promoting immune responses[73].18-β-GA modulates the Th1/Th2 response through up-regulating Th1 responses. During the Th1 response, it also enhances the secretion of IL-10 by CD4+ T cells, and IL-10 limits Th1 responses in a regulatory-feedback loop [73, 74]. This process suggests that 18-β-GA may suppress excessive inflammatory-responses or terminate immune responses after pathogen eradication by upregulating IL-10. These results shed new light on the possibilities of exploiting these herbs and compounds for the treatment of infectious diseases by regulating DC maturation and T-cell differentiation. Besides its single use, GL exerts synergistic effects when combined with antibiotics. Licorice flavonoids can increase the sensitivity of MRSA strains to oxacillin, a β -lactam antibiotic[75].

4.1.2 *Panax ginseng* (Ginseng polysaccharide)

Panax ginseng (Pg) is known for invigorating and maintaining physical vitality [76]. Pg contains ginsenoside, polysaccharides and peptides. It exerts antibacterial and immunoregulatory functions and has been widely used for the treatment of infectious diseases [76]. Heat-processed Pg (at 100 °C) enhances the antimicrobial activity against *S. aureus* , which is due to increased levels of the ginsenoside Rg3, a major compound against *S. aureus* infection [77]. HPLC analysis shows that Rg3 penetrates the bacterial cell membrane more easily than other compounds, thereby inhibiting bacterial growth[77, 78]. Pg is an adjuvant for pneumococcal vaccines, which can enhance vaccine efficacy and increase the survival rate after lethal bacterial challenge [79]. Pg extracts and Rb1 ginsenosides also show an adjuvant effect on immunization against MRSA. Rb1 can promote both lymphocyte proliferation and antibody production specific for MRSA antigens[80].

Ginsan is a polysaccharide extracted from Pg [81]. It can protect mice from *S. aureus* -induced sepsis by bidirectionally modulating the IIS, mainly phagocytosis. It suppresses MRSA-induced sepsis by increasing the bactericidal activity of macrophages by increasing nitric oxide (NO) levels. Moreover, it restricts excessive inflammation by suppressing TLR2, TLR4, TLR9 and MyD88 levels, decreasing related downstream molecule (p38 MAPK and JNK1/2) phosphorylation, and reducing NF-ϰB activation and inflammatory cytokine (TNF-α, IL-1β and IL-6) levels. In conclusion, ginsan not only enhances immune responses but also avoids the pathologic inflammatory response to increase survival in MRSA-infected mice[81, 82]. It also induces a high humoral immune response against *S. typhimurium* with increasing serum IgG1, IgG2 and SIgA levels [8]. Western blot and RT-PCR confirmed that combined with an orally delivered antigen, ginsan specifically up-regulates the expression of COX-1, COX-2 and CCL3 mRNA in Peyer's patches [8]. COX-1 and COX-2 are two inflammation mediators and can modulate MRSA inflammation[70]. They promote DC migration to the Peyer's patch via CCL3, a chemo attractant for DCs [8]. Consequently, ginsan may serve as a potent vaccine supplement for oral immunization.

Ginsenoside, another ingredient of Pg, combats MRSA infection by stimulating immune responses and disrupting immune evasion. A Pg extract mainly consisting of ginsenoside can modulate the mRNA levels of TLR2/4, trigger the activation of the MyD88-dependent pathway and NF-ϰB signaling, and increase the mRNA levels of TNF-α and IL-1α, finally promoting monocytes-macrophage recruitment to combat the infection[83]. Ginsenosides isolated from Korean red ginseng can disrupt the structure of bacterial BFs and inhibit MRSA immune evasion [84]. The combination of ginsenosides and kanamycin/cefotaxime (conventional antibiotics) elicits synergistic or additive effects according to FICI indexes, which can be linked to altered cell membrane permeability [85]. When ginsenosides interact with MRSA-BF, the permeability of the plasma membrane to kanamycin could be increased [85]. Ginsenoside not only attenuates bacterial toxicity but also promotes the influx of antibiotics, which effectively inhibits immune evasion.

Ginseng oligopeptides (GOP), a dietary supplement derived from Pg, has immunomodulatory activities [86]. Oral administration of GOP can enhance the IIS and AIS, which may be due to increased macrophage phagocytosis and NK cell activity and the stimulation of Th cells (Th1 and Th2 cells) followed by antibody production (serum IgA, IgG1, IgG2b and intestinal SIgA) and cytokine secretion. Increased Th1 responses trigger IL-2 and IL-12 secretion, increased Th2 responses trigger IL-6 secretion and increased proportions of Tregs inhibit TNF-α [86].

4.1.3 *Panax quinquefolius* (aqueous extract of *P. quinquefolius*)

A patented aqueous extract from *Panax quinquefolium* (*P. quinquefolius*), CVT-E002, is used to treat upper respiratory tract infection [87]. An *in vivo* study showed that it can improve the function of immune organs. It increases the NK cell numbers in mouse spleen and bone marrow [88, 89]. It also stimulates the proliferation of B-lymphocytes in the spleen of mice, and at doses of 10–500 Ag/mL, it increases IL-2 and IFN-γ levels in the spleen in a dose-dependent manner[87, 90]. In addition, it activates peritoneal exudate macrophages (PEM), leading to increases in NO, IL-1, IL-6 and TNF-α levels [90]. Additionally, it stimulates*in vivo* IgG production in treated mice[90].

4.1.4 *Ophiopogon japonicus* (*O. japonicus*)

Ophiopogon japonicus (*O. japonicus*) has various bioactivities, including anti-inflammatory and immunoreg-

ulatory activities. Its rhizome, as the primary medical portion, has been used to treat inflammatory diseases [91].

Ruscogenin (RUS) is a major effective steroidal sapogen in *O. japonicus* [92]. It exerts immunoregulatory activities mainly by inhibiting neutrophil infiltration and phagocytosis as well as blocking cell apoptosis, thus alleviating acute lung injury (ALI) and pneumonia caused by committee- or hospital-acquired MRSA (CA- or HA-MRSA) infection [93]. At doses of 0.3 kg/mL, 1.0 kg/mL and 3.0 kg/mL, RUS reduces neutrophil infiltration by decreasing MPO levels, thus inhibiting LPS-induced ALI in mice[94]. Additionally, it inhibits neutrophil phagocytosis [94]. This process might be associated with the suppression of NF-ϰB p65 phosphorylation and activation [94, 95]. Moreover, RUS inhibits the apoptosis of cells. Apoptosis is a common inflammatory characteristic of MRSA pneumonia and is critical for improving MRSA clearance as well as alleviating lung injuries [96, 97]. At a dose of 1 mg/kg, RUS inhibits LPS-induced apoptosis of pulmonary endothelial cells (PECs) by suppressing Bax and cleaved caspase-3 levels and by up-regulating Bcl-2 [96]. The high ratio of Bax/Bcl-2 is a well-recognized indicator of apoptosis. Bax accelerates apoptosis, and Bcl-2 inhibits apoptosis [98]. Cleaved caspase-3 is a pro-apoptosis marker [98]. The anti-apoptotic effects of RUS on PECs are accomplished by restraining NF-ϰB activation. This action occurring by inhibiting TLR4 and MyD88 expression, which then inhibits NO, IL-6 and TNF-α production[96]. TLR4 and its adapter protein MyD88 play an important role in the pulmonary inflammatory response[93]. MyD88 deletion can weaken the endocytosis of pathogens by neutrophils and decrease ROS and cytokines levels[99]. Taken together, RUS combats MRSA infection, especially MRSA-induced lung injuries by blocking neutrophil function and exerting anti-apoptosis effects.

Ophiopogon polysaccharide (OPS), another ingredient of O. japonicus, exhibits immune-enhancing activity in which macrophages are its main targets. It can induce the migration and recruitment of immune cells to infected sites by up-regulating IL-1β, TNF-α and other cytokines [100]. Additionally, it enhances the phagocytic function of macrophages by increasing iNOS and NO levels, ultimately enhancing the ability to kill pathogens[100]. Furthermore, OPS induces CD14 and MHC-II expression to promote macrophage activation and exert antigen-presenting functions, thus accelerating the initiation of the AIS[100]. Recently, immunological enhancement of OPS was markedly promoted by a drug delivery system via encapsulation with liposomes (OPS liposomes, OPSLs) [100].

4.1.5 *Cordyceps sinensis* and *Cordyceps militaris* (*C. sinensis* , *C. militaris*)

Cordyceps sinensis (*C. sinensis*) and *Cordyceps militaris* (*C. militaris*) are representative species of*Cordyceps* mushrooms [101, 102]. *C. sinensis* exerts anti-inflammatory and immunoregulatory properties[101]. It can attenuate LPS-induced pulmonary inflammation and fibrosis *in vivo* [101]. In LPS-induced ALI mice, *C. sinensis* extract (CSE) can improve pathological damage of lung tissue and reduce the degree of pulmonary edema in a dose-dependent manner. It reduces the number of neutrophils and macrophages, as well as MPO levels, thus alleviating inflammatory cell exudation, which is related to NF-ϰB signaling[101]. By inhibiting the phosphorylation of NF-ϰB p65 and downstream factors of NF-ϰB signaling (COX-2, iNOS), CSE down-regulates NO, TNF-α, IL-6 and IL-1β, thus inhibiting the inflammatory response [101].

C. militaris is another representative species of this genus and shows immunomodulatory effects [102]. Cordycepin (Cor) is the representative component [102]. Cor regulates the secretion of inflammatory mediators and pro-inflammatory cytokines by affecting the TLR4/NF-ϰB pathway in macrophages[103]. It can inhibit neutrophil exudation and phagocytosis by decreasing MPO levels and down-regulating iNOS/NO expression and improve lung edema and inflammatory responses by regulating inflammatory cytokines, including TNF-α, IL-6, HMGB1 and IL-10. This regulation occurs through the up-regulation of heme oxygenase-1 (HO-1) in a dose-dependent manner [104, 105]. HO-1, an antioxidative enzyme, can reduce free hemoglobin with pro-inflammatory activity *in vivo* , and produce by-products possessing anti-inflammatory activities [106]. Cor can increase the mRNA and protein levels and enzymatic activity of HO-1 in a dose-dependent manner, inhibiting inflammatory responses[105]. HO-1 can further attenuate inflammation and injuries in the lung through down-regulating TNF-α, IL-6 and HMGB1 and up-regulating IL-10 [105]. IL-10 can inhibit

inflammation [104]. HO-1 and IL-10 promote each other's expression and cooperate to inhibit inflammation. HMGB1, an inflammatory cytokine, is recognized by TLR4 and induces inflammation, which is promoted by nucleocytoplasmic translocation of HMGB1[107]. In conclusion, Cor exerts a protective effect by increasing Nrf2/HO-1 signaling and decreasing NF-ϰB signaling[104, 105]. Nrf2 is an upstream regulator of HO-1. The expression of Nrf2 in the cytoplasm and nucleus before and after Cor intervention shows that Nrf2 activation and transformation from the cytoplasmic into the nucleus are the mechanisms for the induction of HO-1 expression [104, 105].

4.1.6 *Atractylodes* species Atractylodis Rhizoma (Atractylodes macrocephala polysaccharide)

Atractylodes species are composed of two major groups,*Atractylodes lancea* (Thunb.) DC. (*A. lancea*) and*Atractylodes macrocephala* Koidz. (*A. macrocephala*). Extracts from Atractylodes species including lactones and polysaccharides, exert anti-inflammatory, antibacterial and immunomodulatory activity and improve gastrointestinal function[108]. *A. macrocephala* extract at 1.562 mg/mL, 3.125 mg/mL and 6.25 mg/mL concentrations can inhibit MRSA in a dose-dependent manner [109]. Atractylenolide I (AO-I), a major bioactive component isolated from *A. macrocephala* , has anti-inflammatory effects[110]. It exerts a protective effect on LPS-induced ALI mice by inhibiting the phagocytic activity of neutrophils and macrophages [110]. By inhibiting TLR4, NF-ϰB activation and IϰB-α degradation, it decreases MPO levels, thus suppressing the numbers and phagocytic activities of neutrophils and macrophages in the BALF. Finally, AO-I exerts anti-inflammatory activity by inhibiting TNF-α, IL-1β, IL-6, IL-13 and macrophage migration inhibitory factor (MIF) [110]. IL-13, a Th2 cytokine, induces airway inflammation [111]. MIF is released by bacterial antigen-stimulated macrophages, promoting infiltration and phagocytosis of macrophages in response to airway inflammation [112]. Notably, MIF shows greater deleterious effects in chronic inflammation than in acute one[113]. Hence, it is necessary for anti-inflammatory agents to inhibit these cytokines. Additionally, AO-I can directly up-regulate IL-10 to promote inflammation resolution[110]. It also inhibits antibiotic-induced dysbiosis of the intestinal microbiome [114]. Hence, it may be a promising method to combine *A. macrocephala*with antibiotics for MRSA infection, because it not only enhances the ability to resist pathogens but also reduces the disruption to the normal intestinal flora by antibiotics. *A. macrocephala*polysaccharides (AMPS), another component in *A. macrocephala* , exert immunoregulatiory activity. In contrast to AO-I, AMPS induces IϰB degradation, activates NF-ϰB and then up-regulates NO and TNF-α, thus improving the phagocytic activities of macrophages and enhancing the IIS in a dose-dependent manner [115, 116].

In *A. lancea* , an acidic polysaccharide (ALP-3) is a component deserving attention. It can modulate macrophage functions, including promoting macrophage proliferation and phagocytosis, and releasing NO, TNF-α and IL-6. In addition, it exerts intestinal immune activities[117]. It can directly stimulate myeloid cell proliferation in Peyer's patch cells and induce them to enhance the production of hematopoietic growth factors (HGF). HGF acts on the impaired intestinal mucosa and promotes intestinal mucosal repair[117]. Briefly, *A. lancea* and *A. macrocephala* provide a protective effect on MRSA infection, especially on pulmonary injuries mainly by inhibiting inflammation and improving MIS.

4.2 Formulae

4.2.1 Zhenqi Capsule

Zhenqi capsule (ZQ) is composed of *Astragalus membranaceus*(*A. membranaceu*) and *Ligustrum lucidum* . It is commonly used to improve immunity, increase leukocyte numbers, and promote the recovery of normal functions after surgical operation, radiotherapy, or chemotherapy [118]. An analysis of the tissue distribution of the main bioactive components of ZQ suggests that these components show overall high levels in the spleen and thymus, suggesting that these components mainly accumulate in organs associated with the immune response, confirming their immune effect[118]. Of these components, astragaloside IV with its higher tissue concentration and bioavailability *in vivo* , has become an index of quality control of ZQ [118]. The extract from *Ligustrum* lucidum contains potent immune stimulants and influences immune restoration[119].

Astragali Radix (AR) is one of the major tonics in TM. AR polysaccharide (ARPS), the representative component of AR, has effects on immune regulation and inflammation [120]. In an*Aeromonas hydrophila* -infected

mouse model, ARPS balances the inflammatory status in infected sites. It enhances the phagocytic activities of phagocytes by stimulating macrophage and NK cell activity. It also inhibits neutrophil phagocytic activity and reduces MPO levels, preventing potential poor prognosis due to excessive neutrophil infiltration [68]. Additionally, its immunostimulatory activity is involved in activating T-helper cells and stimulating cell division and transformation in lymphocytes[68]. It lowers the proportion of CD8+ T cells and increases the ratio of CD4+/CD8+ T cells, representing an increase in immunity [68]. ARPS induces the activation of CD4+ T cells in mice with *P. aeruginosa* infection[121].

4.2.2 Yupingfeng San

Yupingfeng San (YPFS) is composed of AR, *A. macrocephala* and*Saposhnikoviae Radix* (SR). Clinically, YPFS has beneficial immune-modulatory effects and has been used to prevent and treat bacterial infection as well as upper respiratory tract infection[122]. Based on its network pharmacology analysis, it is associated with the bacterial invasion of epithelial cells and other bacterial infections, which is consistent with its clinical uses[123]. It is also linked with aminoacyl-tRNA biosynthesis, which is a representative pathway to reflect the inhibitory effect of an herbal formula in combination with antibiotics on MRSA-BF infection [12, 123]. Furthermore, it is involved in the NF-ϰB signaling pathway, chemokine signaling pathway, leukocyte trans-endothelial migration, endocytosis and antigen processing and presentation [123, 124].

The bidirectional regulatory effect on the expression of inflammatory factors is one of the features of this formula. It helps the immune system achieve a balance between the expression of pro-inflammatory and anti-inflammatory cytokines in the process of combating MRSA infection. In acute inflammation models (LPS-induced for 3 hours), YPFS activates NF-ϰB by enhancing the degradation of IϰB-α, inducing the mRNA and protein expression of pro-inflammatory cytokines (IL-1β, IL-6 and TNF-α) in a dose-dependent manner, with maximal induction reaching approximately 2- to 20- fold of the original[124]. However, when in chronic inflammation models (for 24 hours), it suppresses these cytokines, exerting anti-inflammatory effects [124]. In this process, it is key events to bidirectionally regulate these inflammation mediators (iNOS, COX-2) [125]. It depresses iNOS and COX-2 levels in macrophages at the 3-hour time point; however, at the 24-hour time point, it exerts the opposite[125]. The iNOS, an enzyme in macrophages, assists macrophages in combating pathogens. However, when MRSA-BF is formed after 24 hours, it helps MRSA evade attack by the immune system, which promotes macrophages toward anti-inflammatory or profibrotic M2 phenotype polarization [42, 126]. One of the features of a typical M2 macrophage response is decreased iNOS levels, which promotes profibrotic responses and abscess production during chronic MRSA infection [42, 127]. Similarly, COX-2 is an inducible enzyme, and its expression is up-regulated in the initial stages of inflammation and tissue injury such as MRSA-induced acute skin injury. If this high expression continuously occurs, it can lead to severe damage to the body [70]. Therefore, moderate expression of iNOS and COX-2 plays a protective role against MRSA infection. Overall, YPFS balances complex immune responses against MRSA infection by exerting bidirectional modulating functions, which is hardly found in conventional drugs [128].

In addition, AR, *A. macrocephala* and SR have bidirectional regulatory effects on cytokines, including COX-2 and iNOS[124, 129]. The glycoprotein derived from *A. macrocephala* stimulates TNF-α production in splenocytes, yet other components of *A. macrocephala* , AO-I and III, exert anti-inflammatory activities by suppressing TNF-α production[130, 131]. SR water extracts can up-regulate iNOS. However, the other three SR-derived active ingredients inhibit iNOS expression [125, 132]. Thus, a single herb may exhibit a greater immune stimulation effect than YPFS. Bidirectional regulation is a unique advantage of herbal formulae. Apart from enhancing the IIS, YPF-PS derived from YPFS enhances T lymphocyte proliferation. It promotes lymphocyte entry into S and G2/M phases, and thus effectively increases the percentages of CD4+ and CD8+ T cells, greatly potentiating the cell immune responses[133].

4.2.3 Shengmai San

Shengmai San (SMS) is composed of Pg, *O. japonicas* and*Schisandra chinensis* (*S. chinensis*)[134]. It is a classic tonic prescription for chronic pulmonary diseases, such as syndromes of weakness and shortness of breath, with powder and injection commonly used clinically[135, 136]. SMS combats MRSA infection by

regulating immunity and inflammation. It is highly recommended for use in combination with antibiotics for CA-MRSA in clinical guidelines, with an effective rate up to more than 80% [137]. A meta-analysis showed that when treating chronic obstructive pulmonary disease (COPD), SMS combined with Western medicine has greater efficacy than Western medicine alone, which provides a partial basis for SMS combined with conventional therapies in the treatment of MRSA infection[138]. It can also combat sepsis by protecting the MIS of mice [139]. At a dose of 1.5 mL/kg, SMS regulates NF-κB and decreases IFN-γ, TNF-α and IL-2 levels, thus inhibiting excessive inflammation and exerting its anti-septic activity[139]. Metabolomics analysis suggests that the key mechanism of this activity is embodied in SMS regulating taurine and taurine metabolism, as well as arginine and proline metabolism[139]. These metabolic processes have also been regulated in Reyanning combined with linezolid against MRSA-BF infection[12, 140]. These effects of SMS are echoed by network pharmacology analysis in which SMS can regulate the processes of immunity and inflammation [141].

S. chinensis is one of the herbs in this formula. Schisantherin A (SA), isolated from the fruit of *S. chinensis* , shows a protective effect on acute inflammatory lung injuries by improving the IIS[142]. It inhibits neutrophil and macrophage activities and reduces neutrophil infiltration[143]. Besides, it inhibits NF-κB signaling and MAPKs signaling, and then it decreases TNF-α, IL-6 and IL-1β levels in the BALF, thus exerting anti-inflammatory effects and improving pulmonary injuries [143].

4.2.4 Buzhongyiqi Tang (Hochu-ekki-to, TJ-41)

Buzhongyiqi Tang, known as Hochuekkito (HET), TJ-41, is a formula in both traditional Chinese medicine and Japanese Kampo medicine. This formula comprises 10 herbs, including AR, Pg, *A. lancea* ,*Angelicae radix* , *Zizyphi fructus* , *Aurantii nobilis pericarpium* , *Bupleuri radix* , *G. glavra* , *Cimicifugae rhizome* and *Zingiberis rhizome* [144]. HET has anti-infection and anti-inflammatory effects and exerts trophic support functions [145]. It not only directly reduces or prevents MRSA colonization, but also combats MRSA infection by regulating the MIS. In a small-scale clinical trial for MRSA carriers' patients, HET eradicated MRSA successfully with no side effects [144]. It also prevents MRSA colonization by improving serum nutrition levels and enhancing the IIS[144, 145]. HET also up-regulates the activity of splenocytes, which is the major immunomodulation system of anti-bacterial infection [144].*Atractylodes* rhizome, *Zingiberis rhizoma* and*Bupleuri radix* promote the immunostimulation of spleen cells.*Atractylodes* rhizome extract promotes T-cell activity by expressing CD28 in T cells in the spleen [144].*Zingiberis rhizoma* extract stimulates CD8+ T cells of splenocytes[144]. *Bupleuri radix* extract has antimicrobial activity [146]. In addition, it also promotes B-cell mitogenic activity in spleen cells[144]. Thus, for MRSA carriers who are not recommended to use conventional drugs, HET seems to be a more effective option. Additionally, HET decreases vulnerability to MRSA infection[147].

Furthermore, HET exerts immunomodulation by regulating the MIS in the upper respiratory or intestinal tract to resist bacterial infection. Specifically, oral administration of HET can increase IgA levels in intestinal, which is the key indicator to evaluate mucosal antibody responses [148]. It can directly enhance mucosal IgA antibodies by modulating cytokine secretion by intestinal epithelial cells (IECs). Additionally, it is inferred that HET could increase SIgA secretion and enhance immune responses [9, 148]. DNA microarray and flow cytometry analyses show that oral administration of HET increases the proportion of L-selectin-positive cells in B lymphocytes in Peyer's patch cells and peripheral blood mononuclear cells [148]. L-selectin promotes the recruitment of B-lymphocytes to the non-intestinal mucosal effector site, which partly explains the reason for the enhancement of the IgA immune response in the nasal mucosa [148]. In summary, HET exerts anti-MRSA efficacy by regulating immune organs and the MIS.

Table 2. The effect of TM therapies on host immunity and MRSA immune evasion.

Name of TM	Active Ingredient	Model	Dosing concentration	Targets and indicators	Immunomodulatory action	Ref.
G. glavra	Glycyrrhizin (GL)	Male CD mice (20–25 g)	10 mg/kg	ICAM-1, P-selectin	It decreases the degree of positive staining and densitometry for ICAM-1 and P-selectin.	[67]
		Male specific pathogen-free BALB/c mice (6 weeks)	50 mg/kg	neutrophils, macrophages, MPO, CD11b positive cells	It reduces the numbers of total cells, neutrophils, and macrophages, and decreases MPO and CD11b levels to inhibit the migration and infiltration of immune cells.	[66, 67]
				TNF-α, IL-1α, IL-6, COX-2, iNOS, NF-κB	It decreases the levels of pro-inflammatory cytokines (TNF-α, IL-1α, IL-6) and pro-inflammatory mediators (COX-2, iNOS, NF-κB).	[66, 67]
	18β-Glycyrrhetinic Acid (GA)	Female Crl; SKH1-hrBR hairless mice, subcu-taneously inoculated with MRSA	600 μg/mL	saeR, Hla, RNAIII, mecA, sbi	It reduces MRSA immune evasion by down-regulating MRSA virulence factors (saeR, Hla, RNAIII, mecA, sbi).	[72]

Name of TM	Active Ingredient	Model	Dosing concentration	Targets and indicators	Immunomodulatory action	Ref.
				KC, G-CSF	It reduces the levels of inflammatory cytokines (KC, G-CSF).	[72]
		Male BALB/c and C57BL/6 mice (6 weeks)	1 and 10 mg/mL for 14 hours	co-stimulatory molecules CD40, CD86, MHC class II	It induces phenotypic maturation of DCs by increasing CD40, CD86 and MHC-II expression in DCs.	[73]
				IL-12, IFN-γ	It increases IL-12 levels to promote DC maturation and activates T cells to differentiate into IFN-γ producing Th1 cells.	[73]
				IL-10	It suppresses excessive inflammatory responses or terminates the immune responses after pathogen eradication by increasing IL-10 levels.	[73]

Name of TM	Active Ingredient	Model	Dosing concentration	Targets and indicators	Immunomodulatory action	Ref.
P. ginseng (Pg)	Ginsan	Male pyrogen-free BALB/c mice (5–7 weeks, 18–22 g); S. aureus 25923 or E. coli	0.012, 0.025, 0.5, 25, and 250 mg/kg (intravenous injection)	Macrophage, TLR2, TLR4, TLR9, MyD88, MAPK, JUN 1/2, NF-κB, TNF-α, IL-1β, IL-6, IL-12	It induces resistance to MRSA septicemia by modulating monocyte/macrophage-mediated innate immunity.	[82]
		BALB/c mice	100 mg/kg (intraperitoneally introduced, once a day)	Serum antibodies, Peyer's patches, COX-1, COX-2, CCL3	It effectively enhances the humoral immune response to orally delivered antigen, mediated by CCL3 via COX-1 and COX-2.	[8]
	Pg extract, such as ginsenoside	Female mouse mastitis model (lactating mice)	3, 10, 50 mg/mL	Macrophage, TLR2, TLR4, NF-κB	Pg extracts trigger and induce the inflammatory response. Pg modulates the mRNA levels of TLR2 and TLR4, triggers the activation of the MyD88-dependent pathway and then leads to the liberation of the NF-κB transcription factor.	[83]

Name of TM	Active Ingredient	Model	Dosing concentration	Targets and indicators	Immunomodulatory action	Ref.
	Ginsenoside	MRSA strains: bacterial cells cultured in a Mueller–Hinton broth	100 mg/mL	MRSA biofilm	It not only attenuates bacterial toxicity but also promotes the influx of antibiotics.	[85]
	ginseng oligopeptides (GOP)	420 Female healthy BALB/c mice	0.0375, 0.075, 0.15, 0.3 and 0.6 g/kg for 30 days (intragastrically administered)	Macrophage, NK cell, T and Th cells	It increases macrophage phagocytosis capacity and NK cell activity, and enhances T and Th cells, as well as IL-2, IL-6 and IL-12 secretion and IgA, IgG1 and IgG2b production.	[86]
P. quinquefolius	aqueous extract of the *P. quinquefolius* (CVT-E002)	Old mice (8–9 weeks)	80 mg chow/mouse daily	NK cell in spleen and bone marrow	It augments the absolute numbers of NK cells in the spleen and bone marrow.	[88]
		C57 BL/6 mice	10, 100, 500 Ag/mL	B-lymphocyte in the spleen	It increases IL2 and IFN-γ levels in B-lymphocytes in a dose-dependent manner.	[87]
		C57 BL/6 mice (6–8 weeks)	500, 100 and 10 μg/mL	Peritoneal exudate macrophages (PEM)	It stimulates NO, IL-1, IL-6 and TNF-α levels in PEM.	[90]
		BALB/c mice (1 week)	18, 6 mg per mouse	Plasma cells	It increases IgG levels.	[90]

Name of TM	Active Ingredient	Model	Dosing concentration	Targets and indicators	Immunomodulatory action	Ref.
O. japonicas	OPS, OPL	Peritoneal macrophages isolated from ICR mice (18–22 g)	62.5, 31.25, 15.625, 7.813 and 3.907 g/mL	Phagocytes, NO, iNOS	It improves immune function of macrophages by enhancing phagocytic function and increasing NO and iNOS levels, finally enhancing the ability of sterilization.	[100]
				IL-1β, TNF-α, MCP-1, MIP1β	It exerts immune activity by promoting IL-1β, TNF-α, MCP-1 and MIP-1β levels in macrophages.	[100]
			31.25, 15.625 and 7.813 g/mL	CD14, MHC-II	It induces CD14 and MHC-II to promote macrophages activation and maturation.	[100]
	Ruscogenin (RUS)	Male ICR mice (6–8 weeks)	0.3, 1.0 and 3.0 mg/kg	MPO	It reduces neutrophil infiltration by decreasing MPO levels.	[94]

Name of TM	Active Ingredient	Model	Dosing concentration	Targets and indicators	Immunomodulatory action	Ref.
			1.0 and 3.0 mg/kg	iNOS, NF-ϰB	It suppresses the inflammatory response by decreasing iNOS levels, which might be linked with the down-regulation of NF-ϰB.	[94]
		Male C57BL/6 mice (18-22 g)	0.3 and 1 mg/kg	NO, IL-6, TNF-α	It alleviates lung injury and inflammation by decreasing NO, IL-6 and TNF-α levels.	[96]
			0.1, 0.3 and 1 mg/kg	Bax, cleaved caspase-3, Bcl-2	It inhibits PEC apoptosis by decreasing Bax and cleaved caspase-3 levels and by increasing Bcl-2 levels.	[96]
			0.3 and 1 mg/kg	TLR4, MYD88, NF-ϰB p65	It attenuates LPS-induced PEC apoptosis and exerts a protective effect on lung injury and inflammation by suppressing the TLR4/MYD88/NF-ϰB pathway.	[96]

Name of TM	Active Ingredient	Model	Dosing concentration	Targets and indicators	Immunomodulatory action	Ref.
Cordyceps mushrooms-C. sinensis	*Cordyceps sinensis* extract (CSE)	Sixty male adult BALB/c mice (8 weeks, 20 ± 2 g)	10, 30 and 60 mg/kg	Neutrophils, macrophages, MPO	It alleviates inflammatory cell exudation by decreasing the numbers of neutrophils and macrophages, as well as MPO levels.	[101]
				NF-κB p65, COX-2, iNOS, NO, TNF-α, IL-6, IL-1β	It down-regulates NO, TNF-α, IL-6 and IL-1β by inhibiting the phosphorylation of NF-κB p65 and COX-2, iNOS.	[101]
Cordyceps mushrooms-C. militaris	cordycepin	Male specific pathogen-free Wistar rats (8–10 weeks)	1, 10 and 30 mg/kg	TNF-α, IL-6, HMGB1, IL-10, TLR4	It alleviates anti-oxidative stress injuries by down regulating TNF-α, IL-6 and HMGB1 as well up-regulating IL-10, which is associated with inhibiting TLR4 signaling.	[104, 105]

Name of TM	Active Ingredient	Model	Dosing concentration	Targets and indicators	Immunomodulatory action	Ref.
				Neutrophils, MPO, NO, iNOS, LDH	It attenuates inflammation by decreasing the neutrophil number and inhibiting their exudation by suppressing MPO, NO, iNOS and LDH levels.	[105]
				Nrf2, HO-1	It stimulates HO-1 production and alleviates lung injuries by promoting Nrf2 activation and inducing nuclear translocation of Nrf2.	[104, 105]
		Male BALB/c mice (6-8 weeks)	50, 100 and 200 mg/kg	NF-ϰB, IϰB	It prevents IϰB phosphorylation and NF-ϰB release to achieve anti-inflammatory effect.	[104]
Atractylodes species- *A. macrocephala*	Atractylenolide I (AO-I)	Male BALB/c mice (20-24 g)	5, 10 and 20 mg/kg	Neutrophils, macrophages, MPO	It decreases neutrophil and macrophage numbers in BALF and inhibits neutrophil infiltration by reducing MPO levels.	[110]

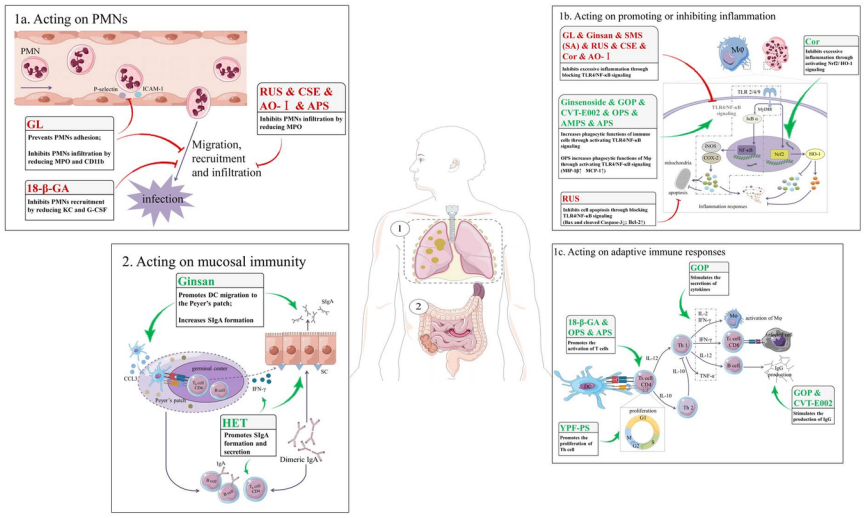
Name of TM	Active Ingredient	Model	Dosing concentration	Targets and indicators	Immunomodulatory action	Ref.
				TNF-α, IL-6, IL-1β, IL-13, MIF, IL-10	It decreases TNF-α, IL-6, IL-1β, IL-13 and MIF levels, as well as increases IL-10 levels in a dose-dependent manner.	[110]
				TLR4, NF-ϰB, IϰBα	It exerts a protective effect on ALI-induced mice by inhibiting TLR4, NF-ϰB activation and IϰBα degradation.	[110]
	Atractylodes macro-cephala polysaccha-rides (AMPS)	The murine macrophage cell line RAW264.7	25, 50, 100 and 200 lg/mL	Macrophages, NO, TNF-α	It stimulates macrophages to promote phagocytic activity and the productions of NO and TNF-α.	[115, 116]
				NF-ϰB, IϰB	It induces IϰB degradation and the activation of NF-ϰB.	[115, 116]
Atractylodes species- *A. lancea*	A neutral polysaccha-ride (ALP-1), an acidic polysaccha-ride (ALP-3)	The murine RAW264.7 macrophage cell line, Specific pathogen free BALB/C mice (6-8 weeks)	50, 100, 250, 500, 1000 and 2000 mg/mL for 18h	Macrophages, NO, TNF-α, IL-6	They promote macrophages phagocytosis and the release of NO, TNF-α and IL-6.	[117]

Name of TM	Active Ingredient	Model	Dosing concentration	Targets and indicators	Immunomodulatory action	Ref.
				HGF	They modulate the intestinal immune system by stimulating Peyer's patch cells to induce HGF production.	[117]
	water extracts of *A. macrocephala* and *A. lancea*	Murine normal colonic epithelial cell-line MCE301 cells	100 μg/mL	G-CSF	They promote the intestinal immune system by promoting G-CSF.	[149]
Zhenqi Fuzheng granule (ZQ)	Astragalus polysaccharides (APS)	Male MF1albino mice (5-6 weeks)	250 mg APS/kg/week for four consecutive weeks	Spleen, neutrophil and ROS in intestinal	It increases both in the phagocytic ability of neutrophils and the intestinal ROS production.	[68]
Yu Ping Feng San (YPFS)	water-soluble extracts of YPFS	RAW 264.7 murine macrophages	1/mL	macrophage	It increases the phagocytic activity of macrophages.	[124]
			1mg/mL; 3h	IL-1β, IL-6, TNF-α	It suppresses the production of pro-inflammatory cytokines in LPS-induced cultured macrophages.	[124]
			0.03, 0.1, 0.3, 1, 3 mg/mL; 24h	IL-1β, IL-6, TNF-α	It induces the production of pro-inflammatory cytokines.	[124]

Name of TM	Active Ingredient	Model	Dosing concentration	Targets and indicators	Immunomodulatory action	Ref.
			1mg/mL; 3h & 24h	iNOS, COX-2	It reduces iNOS and COX-2 levels in macrophages at 3-hour time points. However, it induces the two at 24-hour time points.	[125]
SMS	Filtered SMS solutions	Healthy specific pathogen-free ICR mice (20–22 g, 6–8 weeks)	0.375, 0.75 and 1.5 mL/kg	IFN-γ, TNF-α, IL-2, NF-κB	It inhibits excessive inflammation by regulating NF-κB and decreasing IFN-γ, TNF-α and IL-2 levels.	[137]
	Schisantherin A	Male BALB/c mice, (6–8 weeks)	10, 20 and 40 mg/kg	MPO, neutrophils, macrophages	It improves inflammatory cell infiltration in pulmonary tissue by inhibiting neutrophils and macrophages, as well as MPO levels.	[143]
				TNF-α, IL-6, IL-1β in the BALF	It exerts an anti-inflammatory effect through decreasing TNF-α, IL-6 and IL-1β levels in the BALF.	[143]

Name of TM	Active Ingredient	Model	Dosing concentration	Targets and indicators	Immunomodulatory action	Ref.
				NF-ϰB p65, IϰB-α, JNK, ERK, p38	It inhibits the phosphorylation of p65, ERK, p38, JNK, and the degradation of IϰB-α in a dose-dependent manner.	[143]
Buzhongyiqitang (Hochuekkito)	Hochuekkito extract (HET)	Female BALB/c mice (6 weeks)	3.4 g/kg/day	MRSA, splenocyte	It inhibits MRSA and promotes murine splenocyte immunological activity in dose-dependent manners.	[144]
		73 acute stroke patients (41 HET-treated and 32 non-HET-treated)	7.5 g/day, three divided doses for three months	serum nutritional markers	It improves levels of serum nutritional markers by supporting nutrition and enhancing innate immunity.	[145]
		Female C3H/HeJ mice (6-8 weeks)	1000 mg/kg/day	mucosal IgA antibody	It enhances the IgA immune response.	[148]

(A) Targets of immune responses in the host's immune defenses.



(B) Targets of immune responses in MRSA immune evasion strategies.

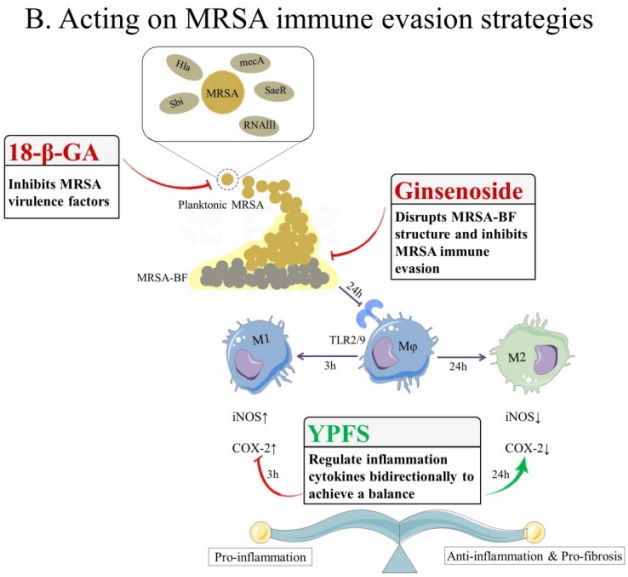


Figure 2. Main mechanisms of TCM therapies against MRSA infections. (A) Targets of immune responses in the lung and mucosa. 1a. Acting on PMNs; 1b. Acting on promoting or inhibiting inflammation; 1c. Acting

on adaptive immune responses. 2. Acting on mucosal immunity. (B) Targets of immune responses in MRSA immune evasion strategies. PMN, polymorphonuclear leukocyte. ICAM-1, Intercellular adhesion molecule 1. GL, glycyrrhizin. 18-β -GA, 18-β -glycyrrhetinic acid. RUS, Ruscogenin. CSE, *C. sinensis* extract. AO-I,*Atractylenolide* I. APS, *Astragalus* polysaccharides. SMS (SA), Shengmai San (*Schisantherin A*). Cor, cordycepin. GOP, Ginseng oligopeptides. CVT-E002, a patented aqueous extract from*Panax quinquefolium* (*P. quinquefolius*). OPS, Ophiopogon polysaccharide. AMPS, *A. macrocephala* polysaccharides. Mφ, macrophage. HET, Hochuekkito. YPF-PS, polysaccharides derived from Yupingfeng San. Green arrows represent promotion. Red arrows represent inhibition.

Briefly, MRSA infection is closely associated with neutrophil function, inflammation, immune responses, and MRSA immune evasion. In this section, the main mechanisms of TCM immune therapies for anti-MRSA infection are summarized and analyzed, suggesting that they can regulate multiple biological processes to modulate the host's immune responses and MRSA immune evasion (Fig. 2). As is shown in Fig 2. 1a, regarding the aspects of regulating the function of PMNs, GL and 18-β-GA inhibit PMN adhesion and recruitment [67, 72]. RUS, CSE, AO-I and APS inhibit PMN infiltration by reducing MPO levels[68, 94, 101, 110]. With respects to modulating inflammation, various TM therapies exert their therapeutic effect on MRSA infection by regulating TLR4/NF-ϰB signaling (Fig. 2. 1b). Ginsenoside, AMPS, CVT-E002 and other therapies increase the phagocytic functions of immune cells to promote inflammation through activating TLR4/NF-ϰB signaling. OPS also contributes to enhancing the functions of macrophages. GL, Cor, CSE, RUS, SMS and other active compounds inhibit excessive inflammation by blocking this signaling. In addition, RUS inhibits cell apoptosis by blocking this signaling to improve MRSA clearance and alleviate lung injuries. Cor also inhibits excessive inflammation by activating Nrf2/HO-1 signaling. These herbs and formulae exhibit anti-MRSA infection functions by regulating inflammation (Fig 2. 1b). Besides innate immune responses, TM therapies act on the adaptive immune response (Fig 2. 1c). For example, GOP plays immunomodulatory activities by stimulating the secretion of cytokines and the production of antibodies. YPF-PS significantly enhances T lymphocyte proliferation to potentiate cell immune responses. Moreover, ginsan and HET act on mucosal immunity to promote SIgA formation and secretion, significantly preventing MRSA invasion (Fig. 2. 2). Apart from regulating host immunity, TCM therapies act on MRSA virulence factors (Fig 2. 1d). 18-β-GA directly inhibits MRSA virulence factors. Ginsenoside can disrupt MRSA-BF structure and inhibit MRSA immune evasion against MRSA infection.

5 Combination therapy with conventional and TM immune therapies

The effects characteristics and mechanisms of conventional and TM immune therapies against MRSA infection are comprehensively analyzed and summarized here. In the prevention phase of MRSA infection, vaccination is the main measure. However, no safe and effective vaccine for MRSA infection is currently available. Some herbs or formulae, such as HET, can prevent MRSA colonization by modulating the mucosal immune response. In the treatment phase, conventional therapies usually focus on inhibiting or killing bacteria. TM immune therapies usually account for both killing bacteria and regulating host immunity to combat MRSA immune injuries. In the recovery phase, TM therapies exert immune enhancement function to help MRSA infection recovery. As shown in Table 3, these two therapies show different mechanisms. Hence, it is inferred that combined conventional and TM therapies hold great potential for the treatment of MRSA infection.

Table 3. Differences in the mechanisms of the two therapies

	Conventional Therapies	TM Immune Therapies
Mucosal immune response	Oral vaccines have not been developed.	They enhance Peyer's batches activation and increase the production of IgA+B cells and SIgA.

	Conventional Therapies	TM Immune Therapies
Innate immune response	(a) The development and research of vaccines are mainly based on inhibiting the bacterial immune evasion from innate immune responses, for example, targeting virulence factors by blocking the complement system and killing neutrophils. (b) AAC therapy facilitates bacterial uptake by phagocytic cells through opsonizing by antibodies.	(a) Targeting the complement system: They influence the complement system to regulate the development of MRSA infection. (b) Targeting neutrophil phagocytosis: They act on neutrophil migration and recruitment, chemokine expression, macrophage activity and antigen presentation.
Adaptive immune response	The development and research of passive immunotherapy also targets the molecules or components mediated immune evasion.	(a) Targeting T-cell activation: They stimulate T-cell activation and enhancing T-lymphocyte proliferation. (b) Targeting antibodies: They increase B-cell activation and antibody titers. (c) Targeting MRSA immune evasion strategies: They inhibit the formation of bacterial BFs.

6 Conclusion and Prospective Studies

Conventional therapies are insufficient to treat MRSA infection, and are even likely to weaken host immunity. TM therapies can regulate the host's immune responses independently to combat MRSA infection. The combination of two therapies is a promising strategy and may display greater efficacy in bacterial infection treatment (Table. 2).

What conditions can combination therapy be used for? Generally, combination therapy can be used to prevent MRSA infection in specific populations. For HA-MRSA patients, especially permanent users of medical devices, removing contaminated devices may lead to the risk of bacterial infection. Combination therapy can reduce this risk. For the population with weakened immune systems, such as neonates and the elder. TM therapies can enhance their immunity. For patients with congenital and acquired diseases caused by impaired neutrophils number and function, combination therapy can increase the number and function of neutrophils[150]. Combination therapy can also prevent MRSA colonization. It can also be used for the treatment of MRSA infection. It can treat patients with low immunity who are infected by MRSA[68, 86, 145]. Additionally, combination therapy is a promising therapy for MRSA-BF infection[5, 6, 12].

Current findings have confirmed the synergistic effects of combination therapy [7, 8, 85]. However, most of these studies were performed *in vitro* and in animal models. Few clinical studies have been performed. Moreover, the corresponding mechanisms of combination therapy are not revealed. Real-world, multiple-center, international large-sample randomized controlled clinical trials should be conducted. In these trials, populations of different ethnicities are enrolled, and internationally unified efficacy evaluation standards and evaluation norms are adopted, which will aid the global recognition of this research. Network pharmacology techniques based on big data and multi-omics integration analysis approaches have marked advantages for revealing the mechanism of action of these herbs and formulae by integrating and analyzing the relationships among proteins, genes and metabolites. In summary, combination therapy is a promising immunotherapy strategy for MRSA infection, and the mechanisms need to be further elucidated.

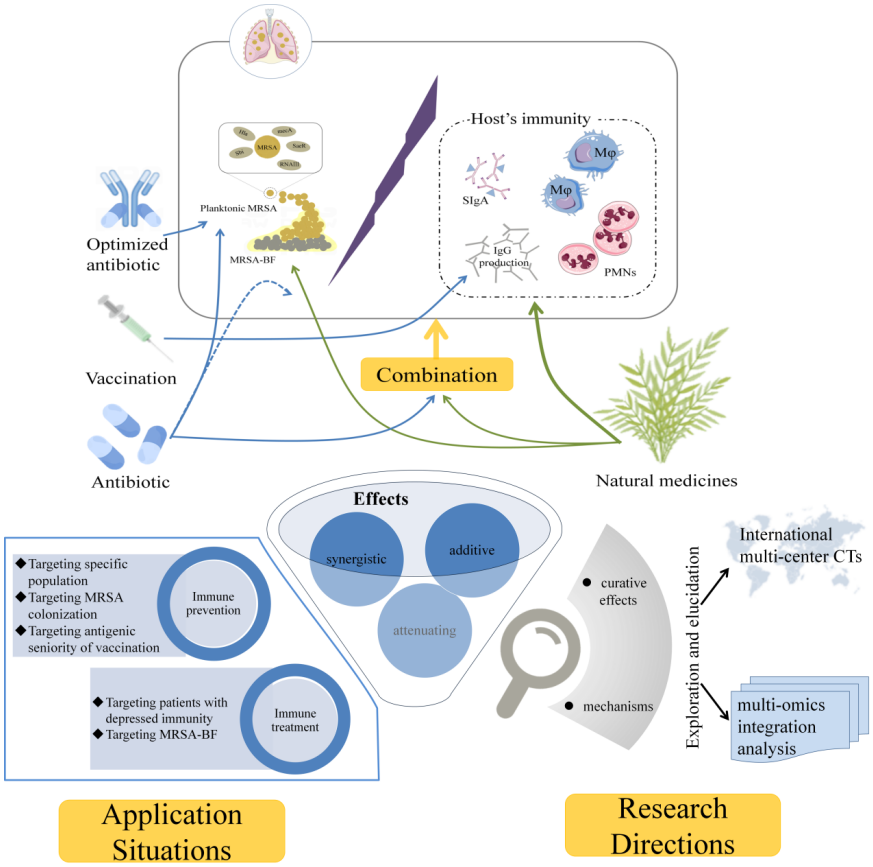


Figure 3. Overview of the combined efficacy of conventional therapies and TM therapies against MRSA infection. Combination with conventional therapies and TM therapies combats MRSA infection not only by inhibiting planktonic MRSA and MRSA-BF but also by regulating host immunity. The combination therapy may exert three effects: additive, synergistic and attenuating. Combination therapy can be used for both MRSA infection prevention and treatment. Furthermore, international multi-center CTs should be performed to confirm curative effects and multi-omics integration analysis should be used to elucidate the corresponding mechanisms.

References:

1. Tong SY, Davis JS, Eichenberger E, Holland TL, Fowler VG, Jr.**Staphylococcus aureus infections: epidemiology, pathophysiology, clinical manifestations, and management** . *Clin Microbiol Rev*2015; 28(3):603-661.

2. Buchan KD, Foster SJ, Renshaw SA. **Staphylococcus aureus: setting its sights on the human innate immune system** .*Microbiology (Reading)* 2019; 165(4):367-385.

3. Yang JH, Bhargava P, McCloskey D, Mao N, Palsson BO, Collins JJ.**Antibiotic-Induced Changes to the Host Metabolic Environment Inhibit Drug Efficacy and Alter Immune Function** . *Cell Host Microbe* 2017; 22(6):757-765 e753.

4. Cunha CB, Opal SM. **Antibiotic Stewardship: Strategies to Minimize Antibiotic Resistance While Maximizing Antibiotic Effectiveness** . *Med Clin North Am* 2018; 102(5):831-843.

5. Zhang L, Liang E, Cheng Y, Mahmood T, Ge F, Zhou K, et al. **Is combined medication with**

natural medicine a promising therapy for bacterial biofilm infection? *Biomed Pharmacother* 2020; 128:110184.

6. Zhang L, Wen B, Bao M, Cheng Y, Mahmood T, Yang W, et al.**Andrographolide Sulfonate Is a Promising Treatment to Combat Methicillin-resistant Staphylococcus aureus and Its Biofilms** .*Front Pharmacol* 2021; 12:720685.

7. Zhou Y, Zong Y, Liu Z, Zhao H, Zhao X, Wang J. **Astragalus Polysaccharides Enhance the Immune Response to OVA Antigen in BALB/c Mice** . *Biomed Res Int* 2021; 2021:9976079.

8. Na HS, Lim YJ, Yun YS, Kweon MN, Lee HC. **Ginsan enhances humoral antibody response to orally delivered antigen** . *Immune Netw* 2010; 10(1):5-14.

9. Liu L, Hu L, Yao Z, Qin Z, Idehara M, Dai Y, et al. **Mucosal immunomodulatory evaluation and chemical profile elucidation of a classical traditional Chinese formula, Bu-Zhong-Yi-Qi-Tang** . *J Ethnopharmacol* 2019; 228:188-199.

10. van Kessel KP, Bestebroer J, van Strijp JA.**Neutrophil-Mediated Phagocytosis of Staphylococcus aureus** .*Front Immunol* 2014; 5:467.

11. Krishna S, Miller LS. **Innate and adaptive immune responses against Staphylococcus aureus skin infections** . *Semin Immunopathol* 2012; 34(2):261-280.

12. Zhang L, Yang W, Chu Y, Wen B, Cheng Y, Mahmood T, et al.**The Inhibition Effect of Linezolid With Reyanning Mixture on MRSA and its Biofilm is More Significant than That of Linezolid Alone** .*Front Pharmacol* 2021; 12:766309.

13. Cheung GYC, Bae JS, Otto M. **Pathogenicity and virulence of Staphylococcus aureus** . *Virulence* 2021; 12(1):547-569.

14. Ji N, Yang J, Ji Y. **Determining Impact of Growth Phases on Capacity of Staphylococcus aureus to Adhere to and Invade Host Cells** .*Methods Mol Biol* 2020; 2069:187-195.

15. Bateman SL, Seed PC. **Procession to pediatric bacteremia and sepsis: covert operations and failures in diplomacy** . *Pediatrics*2010; 126(1):137-150.

16. Annunziato G. **Strategies to Overcome Antimicrobial Resistance (AMR) Making Use of Non-Essential Target Inhibitors: A Review** . *Int J Mol Sci* 2019; 20(23).

17. Gor V, Ohniwa RL, Morikawa K. **No Change, No Life? What We Know about Phase Variation in Staphylococcus aureus** .*Microorganisms* 2021; 9(2).

18. McGhee JR, Fujihashi K. **Inside the mucosal immune system** .*PLoS Biol* 2012; 10(9):e1001397.

19. Tian C, Hromatka BS, Kiefer AK, Eriksson N, Noble SM, Tung JY, et al. **Genome-wide association and HLA region fine-mapping studies identify susceptibility loci for multiple common infections** . *Nat Commun* 2017; 8(1):599.

20. Palm NW, de Zoete MR, Cullen TW, Barry NA, Stefanowski J, Hao L, et al. **Immunoglobulin A coating identifies colitogenic bacteria in inflammatory bowel disease** . *Cell* 2014; 158(5):1000-1010.

21. de Vor L, Rooijakkers SHM, van Strijp JAG. **Staphylococci evade the innate immune response by disarming neutrophils and forming biofilms** . *FEBS Lett* 2020; 594(16):2556-2569.

22. Dasari P, Nordengrun M, Vilhena C, Steil L, Abdurrahman G, Surmann K, et al. **The Protease SplB of Staphylococcus aureus Targets Host Complement Components and Inhibits Complement-Mediated Bacterial Opsonophagocytosis** . *J Bacteriol* 2022; 204(1):e0018421.

23. Ricklin D, Reis ES, Mastellos DC, Gros P, Lambris JD.**Complement component C3 - The "Swiss Army Knife" of innate immunity and host defense** . *Immunol Rev* 2016; 274(1):33-58.

24. Kraus RF, Gruber MA. **Neutrophils-From Bone Marrow to First-Line Defense of the Innate Immune System** . *Front Immunol*2021; 12:767175.

25. Teng TS, Ji AL, Ji XY, Li YZ. **Neutrophils and Immunity: From Bactericidal Action to Being Conquered** . *J Immunol Res* 2017; 2017:9671604.

26. Zarrin AA, Bao K, Lupardus P, Vucic D. **Kinase inhibition in autoimmunity and inflammation** . *Nat Rev Drug Discov* 2021; 20(1):39-63.

27. Drasler B, Karakocak BB, Tankus EB, Barosova H, Abe J, Sousa de Almeida M, et al. **An Inflamed Human Alveolar Model for Testing the Efficiency of Anti-inflammatory Drugs in vitro** . *Front Bioeng Biotechnol* 2020; 8:987.

28. Bestebroer J, Aerts PC, Rooijakkers SH, Pandey MK, Kohl J, van Strijp JA, et al. **Functional basis for complement evasion by staphylococcal superantigen-like 7** . *Cell Microbiol* 2010; 12(10):1506-1516.

29. Grousd JA, Rich HE, Alcorn JF. **Host-Pathogen Interactions in Gram-Positive Bacterial Pneumonia** . *Clin Microbiol Rev* 2019; 32(3).

30. Wojcik-Bojek U, Rozalska B, Sadowska B. **Staphylococcus aureus-A Known Opponent against Host Defense Mechanisms and Vaccine Development-Do We Still Have a Chance to Win?** *Int J Mol Sci*2022; 23(2).

31. Zhao Y, van Kessel KPM, de Haas CJC, Rogers MRC, van Strijp JAG, Haas PA. **Staphylococcal superantigen-like protein 13 activates neutrophils via formyl peptide receptor 2** . *Cell Microbiol* 2018; 20(11):e12941.

32. do Vale A, Cabanes D, Sousa S. **Bacterial Toxins as Pathogen Weapons Against Phagocytes** . *Front Microbiol* 2016; 7:42.

33. Kumar D, Romero Y, Schuck KN, Smalley H, Subedi B, Fleming SD.**Drivers and regulators of humoral innate immune responses to infection and cancer** . *Mol Immunol* 2020; 121:99-110.

34. Mues N, Chu HW. **Out-Smarting the Host: Bacteria Maneuvering the Immune Response to Favor Their Survival** . *Front Immunol* 2020; 11:819.

35. Irmscher S, Doring N, Halder LD, Jo EAH, Kopka I, Dunker C, et al.**Kallikrein Cleaves C3 and Activates Complement** . *J Innate Immun* 2018; 10(2):94-105.

36. Woehl JL, Ramyar KX, Katz BB, Walker JK, Geisbrecht BV. **The structural basis for inhibition of the classical and lectin complement pathways by S. aureus extracellular adherence protein** . *Protein Sci* 2017; 26(8):1595-1608.

37. Sage MAG, Cranmer KD, Semeraro ML, Ma S, Galkina EV, Tran Y, et al.**A Factor H-Fc fusion protein increases complement-mediated opsonophagocytosis and killing of community associated methicillin-resistant Staphylococcus aureus** . *PLoS One* 2022; 17(3):e0265774.

38. Pietrocola G, Nobile G, Rindi S, Speziale P. **Staphylococcus aureus Manipulates Innate Immunity through Own and Host-Expressed Proteases** . *Front Cell Infect Microbiol* 2017; 7:166.

39. Guerra FE, Borgogna TR, Patel DM, Sward EW, Voyich JM. **Epic Immune Battles of History: Neutrophils vs. Staphylococcus aureus** .*Front Cell Infect Microbiol* 2017; 7:286.

40. Pivard M, Moreau K, Vandenesch F. **Staphylococcus aureus Arsenal To Conquer the Lower Respiratory Tract** . *mSphere* 2021; 6(3).

41. Yao Z, Cary BP, Bingman CA, Wang C, Kreitler DF, Satyshur KA, et al.**Use of a Stereochemical Strategy To Probe the Mechanism of Phenol-Soluble Modulin alpha3 Toxicity** . *J Am Chem Soc* 2019; 141(19):7660-7664.

42. Thurlow LR, Hanke ML, Fritz T, Angle A, Aldrich A, Williams SH, et al. **Staphylococcus aureus biofilms prevent macrophage phagocytosis and attenuate inflammation in vivo** . *J Immunol* 2011; 186(11):6585-6596.

43. Zhu H, Jin H, Zhang C, Yuan T. **Intestinal methicillin-resistant Staphylococcus aureus causes prosthetic infection via 'Trojan Horse' mechanism: Evidence from a rat model** . *Bone Joint Res* 2020; 9(4):152-161.

44. Falugi F, Kim HK, Missiakas DM, Schneewind O. **Role of protein A in the evasion of host adaptive immune responses by Staphylococcus aureus** . *mBio* 2013; 4(5):e00575-00513.

45. Pauli NT, Kim HK, Falugi F, Huang M, Dulac J, Henry Dunand C, et al.**Staphylococcus aureus infection induces protein A-mediated immune evasion in humans** . *J Exp Med* 2014; 211(12):2331-2339.

46. Smith EJ, Visai L, Kerrigan SW, Speziale P, Foster TJ. **The Sbi protein is a multifunctional immune evasion factor of Staphylococcus aureus** . *Infect Immun* 2011; 79(9):3801-3809.

47. Nasser A, Moradi M, Jazireian P, Safari H, Alizadeh-Sani M, Pourmand MR, et al. **Staphylococcus aureus versus neutrophil: Scrutiny of ancient combat** . *Microb Pathog* 2019; 131:259-269.

48. Laarman AJ, Mijnheer G, Mootz JM, van Rooijen WJ, Ruyken M, Malone CL, et al. **Staphylococcus aureus Staphopain A inhibits CXCR2-dependent neutrophil activation and chemotaxis** . *EMBO J*2012; 31(17):3607-3619.

49. Rigby KM, DeLeo FR. **Neutrophils in innate host defense against Staphylococcus aureus infections** . *Semin Immunopathol*2012; 34(2):237-259.

50. Herzog S, Dach F, de Buhr N, Niemann S, Schlagowski J, Chaves-Moreno D, et al. **High Nuclease Activity of Long Persisting Staphylococcus aureus Isolates Within the Airways of Cystic Fibrosis Patients Protects Against NET-Mediated Killing** . *Front Immunol*2019; 10:2552.

51. Schilcher K, Andreoni F, Uchiyama S, Ogawa T, Schuepbach RA, Zinkernagel AS. **Increased neutrophil extracellular trap-mediated Staphylococcus aureus clearance through inhibition of nuclease activity by clindamycin and immunoglobulin** . *J Infect Dis* 2014; 210(3):473-482.

52. Loffler B, Hussain M, Grundmeier M, Bruck M, Holzinger D, Varga G, et al. **Staphylococcus aureus panton-valentine leukocidin is a very potent cytotoxic factor for human neutrophils** . *PLoS Pathog*2010; 6(1):e1000715.

53. Edwards MR, Walton RP, Jackson DJ, Feleszko W, Skevaki C, Jartti T, et al. **The potential of anti-infectives and immunomodulators as therapies for asthma and asthma exacerbations** . *Allergy* 2018; 73(1):50-63.

54. Rowe SE, Beam JE, Conlon BP. **Recalcitrant Staphylococcus aureus Infections: Obstacles and Solutions** . *Infect Immun* 2021; 89(4).

55. Lehar SM, Pillow T, Xu M, Staben L, Kajihara KK, Vandlen R, et al.**Novel antibody-antibiotic conjugate eliminates intracellular S. aureus** . *Nature* 2015; 527(7578):323-328.

56. Mariathasan S, Tan MW. **Antibody-Antibiotic Conjugates: A Novel Therapeutic Platform against Bacterial Infections** . *Trends Mol Med* 2017; 23(2):135-149.

57. Kumar S, Mukherjee MM, Varela MF. **Modulation of Bacterial Multidrug Resistance Efflux Pumps of the Major Facilitator Superfamily** .*Int J Bacteriol* 2013; 2013.

58. Adams KN, Szumowski JD, Ramakrishnan L. **Verapamil, and its metabolite norverapamil, inhibit macrophage-induced, bacterial efflux pump-mediated tolerance to multiple anti-tubercular drugs** . *J Infect Dis* 2014; 210(3):456-466.

59. Bonomo RA. **beta-Lactamases: A Focus on Current Challenges** .*Cold Spring Harb Perspect Med* 2017; 7(1).

60. Jansen KU, Knirsch C, Anderson AS. **The role of vaccines in preventing bacterial antimicrobial resistance** . *Nat Med* 2018; 24(1):10-19.

61. Kennedy DA, Read AFJPotRSBBS. **Why does drug resistance readily evolve but vaccine resistance does not?** 2017; 284(1851):20162562.

62. Buchy P, Ascioglu S, Buisson Y, Datta S, Nissen M, Tambyah PA, et al. **Impact of vaccines on antimicrobial resistance** . *Int J Infect Dis* 2020; 90:188-196.

63. Fattom A, Matalon A, Buerkert J, Taylor K, Damaso S, Boutriau D.**Efficacy profile of a bivalent Staphylococcus aureus glycoconjugated vaccine in adults on hemodialysis: Phase III randomized study** . *Hum Vaccin Immunother* 2015; 11(3):632-641.

64. Fowler VG, Allen KB, Moreira ED, Moustafa M, Isgro F, Boucher HW, et al. **Effect of an investigational vaccine for preventing Staphylococcus aureus infections after cardiothoracic surgery: a randomized trial** . *JAMA* 2013; 309(13):1368-1378.

65. Zhang QH, Huang HZ, Qiu M, Wu ZF, Xin ZC, Cai XF, et al.**Traditional Uses, Pharmacological Effects, and Molecular Mechanisms of Licorice in Potential Therapy of COVID-19** . *Front Pharmacol* 2021; 12:719758.

66. Lee SA, Lee SH, Kim JY, Lee WS. **Effects of glycyrrhizin on lipopolysaccharide-induced acute lung injury in a mouse model** . *J Thorac Dis* 2019; 11(4):1287-1302.

67. Menegazzi M, Di Paola R, Mazzon E, Genovese T, Crisafulli C, Dal Bosco M, et al. **Glycyrrhizin attenuates the development of carrageenan-induced lung injury in mice** . *Pharmacol Res* 2008; 58(1):22-31.

68. Abuelsaad AS. **Supplementation with Astragalus polysaccharides alters Aeromonas-induced tissue-specific cellular immune response** . *Microb Pathog* 2014; 66:48-56.

69. Sun S, Wang J, Wang J, Wang F, Yao S, Xia H. **Maresin 1 Mitigates Sepsis-Associated Acute Kidney Injury in Mice via Inhibition of the NF-kappaB/STAT3/MAPK Pathways** . *Front Pharmacol* 2019; 10:1323.

70. Cai JY, Hou YN, Li J, Ma K, Yao GD, Liu WW, et al.**Prostaglandin E2 attenuates synergistic bactericidal effects between COX inhibitors and antibiotics on Staphylococcus aureus** .*Prostaglandins Leukot Essent Fatty Acids* 2018; 133:16-22.

71. Wahab S, Annadurai S, Abullais SS, Das G, Ahmad W, Ahmad MF, et al.**Glycyrrhiza glabra (Licorice): A Comprehensive Review on Its Phytochemistry, Biological Activities, Clinical Evidence and Toxicology** . *Plants (Basel)* 2021; 10(12).

72. Long DR, Mead J, Hendricks JM, Hardy ME, Voyich JM.**18beta-Glycyrrhetinic acid inhibits methicillin-resistant Staphylococcus aureus survival and attenuates virulence gene expression** . *Antimicrob Agents Chemother* 2013; 57(1):241-247.

73. Bordbar N, Karimi MH, Amirghofran Z. **Phenotypic and functional maturation of murine dendritic cells induced by 18 alpha- and beta-glycyrrhetinic acid** . *Immunopharmacol Immunotoxicol* 2014; 36(1):52-60.

74. Li XL, Zhou AG. **Evaluation of the immunity activity of glycyrrhizin in AR mice** . *Molecules* 2012; 17(1):716-727.

75. Wu SC, Yang ZQ, Liu F, Peng WJ, Qu SQ, Li Q, et al.**Antibacterial Effect and Mode of Action of Flavonoids From Licorice Against Methicillin-Resistant Staphylococcus aureus** .*Front Microbiol*

2019; 10:2489.

76. Ratan ZA, Haidere MF, Hong YH, Park SH, Lee JO, Lee J, et al.**Pharmacological potential of ginseng and its major component ginsenosides** . *J Ginseng Res* 2021; 45(2):199-210.

77. Na S, Kim JH, Rhee YK, Oh SW. **Enhancing the antimicrobial activity of ginseng against Bacillus cereus and Staphylococcus aureus by heat treatment** . *Food Sci Biotechnol* 2018; 27(1):203-210.

78. Xue P, Yao Y, Yang XS, Feng J, Ren GX. **Improved antimicrobial effect of ginseng extract by heat transformation** . *J Ginseng Res* 2017; 41(2):180-187.

79. Lee SO, Lee S, Kim SJ, Rhee DK. **Korean Red Ginseng enhances pneumococcal Deltapep27 vaccine efficacy by inhibiting reactive oxygen species production** . *J Ginseng Res* 2019; 43(2):218-225.

80. Prenafeta A, March R, Foix A, Casals I, Costa L. **Study of the humoral immunological response after vaccination with a Staphylococcus aureus biofilm-embedded bacterin in dairy cows: possible role of the exopolysaccharide specific antibody production in the protection from Staphylococcus aureus induced mastitis** . *Vet Immunol Immunopathol* 2010; 134(3-4):208-217.

81. Ahn JY, Song JY, Yun YS, Jeong G, Choi IS. **Protection of Staphylococcus aureus-infected septic mice by suppression of early acute inflammation and enhanced antimicrobial activity by ginsan** . *FEMS Immunol Med Microbiol* 2006; 46(2):187-197.

82. Ahn JY, Choi IS, Shim JY, Yun EK, Yun YS, Jeong G, et al.**The immunomodulator ginsan induces resistance to experimental sepsis by inhibiting Toll-like receptor-mediated inflammatory signals** .*Eur J Immunol* 2006; 36(1):37-45.

83. Silvestrini P, Beccaria C, Pereyra EAL, Renna MS, Ortega HH, Calvinho LF, et al. **Intramammary inoculation of Panax ginseng plays an immunoprotective role in Staphylococcus aureus infection in a murine model** . *Res Vet Sci* 2017; 115:211-220.

84. Alsayari A, Muhsinah AB, Almaghaslah D, Annadurai S, Wahab S.**Pharmacological Efficacy of Ginseng against Respiratory Tract Infections** . *Molecules* 2021; 26(13).

85. Sung WS, Lee DG. **The combination effect of Korean red ginseng saponins with kanamycin and cefotaxime against methicillin-resistant Staphylococcus aureus** . *Biol Pharm Bull*2008; 31(8):1614-1617.

86. He LX, Ren JW, Liu R, Chen QH, Zhao J, Wu X, et al. **Ginseng (Panax ginseng Meyer) oligopeptides regulate innate and adaptive immune responses in mice via increased macrophage phagocytosis capacity, NK cell activity and Th cells secretion** . *Food Funct* 2017; 8(10):3523-3532.

87. Wang M, Guilbert LJ, Li J, Wu Y, Pang P, Basu TK, et al. **A proprietary extract from North American ginseng (Panax quinquefolium) enhances IL-2 and IFN-gamma productions in murine spleen cells induced by Con-A** . *Int Immunopharmacol* 2004; 4(2):311-315.

88. Miller SC, Ti L, Shan J. **Dietary supplementation with an extract of North American ginseng in adult and juvenile mice increases natural killer cells** . *Immunol Invest* 2012; 41(2):157-170.

89. Mancuso C, Santangelo R. **Panax ginseng and Panax quinquefolius: From pharmacology to toxicology** . *Food Chem Toxicol* 2017; 107(Pt A):362-372.

90. Wang M, Guilbert LJ, Ling L, Li J, Wu Y, Xu S, et al.**Immunomodulating activity of CVT-E002, a proprietary extract from North American ginseng (Panax quinquefolium)** . *J Pharm Pharmacol* 2001; 53(11):1515-1523.

91. Zhao JW, Chen DS, Deng CS, Wang Q, Zhu W, Lin L. **Evaluation of anti-inflammatory activity of compounds isolated from the rhizome of Ophiopogon japonicas** . *BMC Complement Altern Med* 2017; 17(1):7.

92. Lei F, Weckerle CS, Heinrich M. **Liriopogons (Genera Ophiopogon and Liriope, Asparagaceae): A Critical Review of the Phytochemical and Pharmacological Research** . *Front Pharmacol*2021; 12:769929.

93. Li L, Li Y, Zhu F, Cheung AL, Wang G, Bai G, et al. **New Mechanistic Insights into Purine Biosynthesis with Second Messenger c-di-AMP in Relation to Biofilm-Related Persistent Methicillin-Resistant Staphylococcus aureus Infections** . *mBio* 2021; 12(6):e0208121.

94. Sun Q, Chen L, Gao M, Jiang W, Shao F, Li J, et al.**Ruscogenin inhibits lipopolysaccharide-induced acute lung injury in mice: involvement of tissue factor, inducible NO synthase and nuclear factor (NF)-kappaB** . *Int Immunopharmacol* 2012; 12(1):88-93.

95. Song J, Kou J, Huang Y, Yu B. **Ruscogenin mainly inhibits nuclear factor-kappaB but not Akt and mitogen-activated protein kinase signaling pathways in human umbilical vein endothelial cells** . *J Pharmacol Sci* 2010; 113(4):409-413.

96. Wu Y, Wang Y, Gong S, Tang J, Zhang J, Li F, et al.**Ruscogenin alleviates LPS-induced pulmonary endothelial cell apoptosis by suppressing TLR4 signaling** . *Biomed Pharmacother*2020; 125:109868.

97. Kitur K, Parker D, Nieto P, Ahn DS, Cohen TS, Chung S, et al.**Toxin-induced necroptosis is a major mechanism of Staphylococcus aureus lung damage** . *PLoS Pathog* 2015; 11(4):e1004820.

98. Xu X, Yan G, Chang J, Wang P, Yin Q, Liu C, et al.**Comparative Transcriptome Analysis Reveals the Protective Mechanism of Glycyrrhinic Acid for Deoxynivalenol-Induced Inflammation and Apoptosis in IPEC-J2 Cells** . *Oxid Med Cell Longev* 2020; 2020:5974157.

99. Miyake T, Wang D, Matsuoka H, Morita K, Yasuda H, Yatera K, et al.**Endocytosis of particulate matter induces cytokine production by neutrophil via Toll-like receptor 4** . *Int Immunopharmacol* 2018; 57:190-199.

100. Sun W, Hu W, Meng K, Yang L, Zhang W, Song X, et al.**Activation of macrophages by the ophiopogon polysaccharide liposome from the root tuber of Ophiopogon japonicus** . *Int J Biol Macromol* 2016; 91:918-925.

101. Fu S, Lu W, Yu W, Hu J. **Protective effect of Cordyceps sinensis extract on lipopolysaccharide-induced acute lung injury in mice** . *Biosci Rep* 2019; 39(6).

102. Lee CT, Huang KS, Shaw JF, Chen JR, Kuo WS, Shen G, et al.**Trends in the Immunomodulatory Effects of Cordyceps militaris: Total Extracts, Polysaccharides and Cordycepin** . *Front Pharmacol*2020; 11:575704.

103. Choi YH, Kim GY, Lee HH. **Anti-inflammatory effects of cordycepin in lipopolysaccharide-stimulated RAW 264.7 macrophages through Toll-like receptor 4-mediated suppression of mitogen-activated protein kinases and NF-kappaB signaling pathways** . *Drug Des Devel Ther* 2014; 8:1941-1953.

104. Lei J, Wei Y, Song P, Li Y, Zhang T, Feng Q, et al.**Cordycepin inhibits LPS-induced acute lung injury by inhibiting inflammation and oxidative stress** . *Eur J Pharmacol* 2018; 818:110-114.

105. Qing R, Huang Z, Tang Y, Xiang Q, Yang F. **Cordycepin alleviates lipopolysaccharide-induced acute lung injury via Nrf2/HO-1 pathway** . *Int Immunopharmacol* 2018; 60:18-25.

106. Trindade-da-Silva CA, Clemente-Napimoga JT, Abdalla HB, Rosa SM, Ueira-Vieira C, Morisseau C, et al. **Soluble epoxide hydrolase inhibitor, TPPU, increases regulatory T cells pathway in an**

arthritis model . *FASEB J* 2020; 34(7):9074-9086.

107. Leelahavanichkul A, Huang Y, Hu X, Zhou H, Tsuji T, Chen R, et al.**Chronic kidney disease worsens sepsis and sepsis-induced acute kidney injury by releasing High Mobility Group Box Protein-1** .*Kidney Int* 2011; 80(11):1198-1211.

108. Jun X, Fu P, Lei Y, Cheng P. **Pharmacological effects of medicinal components of Atractylodes lancea (Thunb.) DC** . *Chin Med* 2018; 13:59.

109. Xu Z, Cai Y, Fan G, Liu X, Dai YJPe. **Application of Atractylodes Macrocephala Koidz Extract in Methicillin-Resistant Staphylococcus Aureus** . 2017; 174:410-415.

110. Zhang JL, Huang WM, Zeng QY. **Atractylenolide I protects mice from lipopolysaccharide-induced acute lung injury** . *Eur J Pharmacol* 2015; 765:94-99.

111. Karo-Atar D, Bordowitz A, Wand O, Pasmanik-Chor M, Fernandez IE, Itan M, et al. **A protective role for IL-13 receptor alpha 1 in bleomycin-induced pulmonary injury and repair** . *Mucosal Immunol*2016; 9(1):240-253.

112. de Souza HS, Tortori CA, Lintomen L, Figueiredo RT, Bernardazzi C, Leng L, et al. **Macrophage migration inhibitory factor promotes eosinophil accumulation and tissue remodeling in eosinophilic esophagitis** . *Mucosal Immunol* 2015; 8(5):1154-1165.

113. Zhang S, Zis O, Ly PT, Wu Y, Zhang S, Zhang M, et al.**Down-regulation of MIF by NFkappaB under hypoxia accelerated neuronal loss during stroke** . *FASEB J* 2014; 28(10):4394-4407.

114. Liu P, Zhao G, Zhang L, Gong Y, Gu Y. **Atractylenolide I inhibits antibiotic-induced dysbiosis of the intestinal microbiome** .*Ann Transl Med* 2021; 9(20):1539.

115. Ji GQ, Chen RQ, Zheng JX. **Macrophage activation by polysaccharides from Atractylodes macrocephala Koidz through the nuclear factor-kappaB pathway** . *Pharm Biol* 2015; 53(4):512-517.

116. Li BX, Li WY, Tian YB, Guo SX, Huang YM, Xu DN, et al.**Polysaccharide of Atractylodes macrocephala Koidz Enhances Cytokine Secretion by Stimulating the TLR4-MyD88-NF-kappaB Signaling Pathway in the Mouse Spleen** . *J Med Food* 2019; 22(9):937-943.

117. Qin J, Wang HY, Zhuang D, Meng FC, Zhang X, Huang H, et al.**Structural characterization and immunoregulatory activity of two polysaccharides from the rhizomes of Atractylodes lancea (Thunb.) DC** .*Int J Biol Macromol* 2019; 136:341-351.

118. Liu XH, Zhu RJ, Hu F, Guo L, Yang YL, Feng SL. **Tissue distribution of six major bio-active components after oral administration of Zhenqi Fuzheng capsules to rats using ultra-pressure liquid chromatography-tandem mass spectrometry** . *J Chromatogr B Analyt Technol Biomed Life Sci* 2015; 986-987:44-53.

119. Liu J, Mao JJ, Li SQ, Lin H. **Preliminary Efficacy and Safety of Reishi & Privet Formula on Quality of Life Among Non-Small Cell Lung Cancer Patients Undergoing Chemotherapy: A Randomized Placebo-Controlled Trial** . *Integr Cancer Ther* 2020; 19:1534735420944491.

120. Jin M, Zhao K, Huang Q, Shang P. **Structural features and biological activities of the polysaccharides from Astragalus membranaceus** . *Int J Biol Macromol* 2014; 64:257-266.

121. Liu QY, Yao YM, Yu Y, Dong N, Sheng ZY. **Astragalus polysaccharides attenuate postburn sepsis via inhibiting negative immunoregulation of CD4+ CD25(high) T cells** . *PLoS One* 2011; 6(6):e19811.

122. Song T, Hou X, Yu X, Wang Z, Wang R, Li Y, et al. **Adjuvant Treatment with Yupingfeng Formula for Recurrent Respiratory Tract Infections in Children: A Meta-analysis of Randomized Controlled Trials** . *Phytother Res* 2016; 30(7):1095-1103.

123. Zuo H, Zhang Q, Su S, Chen Q, Yang F, Hu Y. **A network pharmacology-based approach to analyse potential targets of traditional herbal formulas: An example of Yu Ping Feng decoction** . *Sci Rep*2018; 8(1):11418.

124. Du CY, Choi RC, Zheng KY, Dong TT, Lau DT, Tsim KW. **Yu Ping Feng San, an ancient Chinese herbal decoction containing Astragali Radix, Atractylodis Macrocephalae Rhizoma and Saposhnikoviae Radix, regulates the release of cytokines in murine macrophages** . *PLoS One* 2013; 8(11):e78622.

125. Du CY, Choi RC, Dong TT, Lau DT, Tsim KW. **Yu Ping Feng San, an ancient Chinese herbal decoction, regulates the expression of inducible nitric oxide synthase and cyclooxygenase-2 and the activity of intestinal alkaline phosphatase in cultures** . *PLoS One* 2014; 9(6):e100382.

126. Masters EA, Ricciardi BF, Bentley KLM, Moriarty TF, Schwarz EM, Muthukrishnan G. **Skeletal infections: microbial pathogenesis, immunity and clinical management** . *Nat Rev Microbiol* 2022.

127. Scherr TD, Roux CM, Hanke ML, Angle A, Dunman PM, Kielian T.**Global transcriptome analysis of Staphylococcus aureus biofilms in response to innate immune cells** . *Infect Immun* 2013; 81(12):4363-4376.

128. Yu S, Guo Z, Guan Y, Lu YY, Hao P, Li Y, et al. **Combining ZHENG Theory and High-Throughput Expression Data to Predict New Effects of Chinese Herbal Formulae** . *Evid Based Complement Alternat Med*2012; 2012:986427.

129. Hoo RL, Wong JY, Qiao C, Xu A, Xu H, Lam KS. **The effective fraction isolated from Radix Astragali alleviates glucose intolerance, insulin resistance and hypertriglyceridemia in db/db diabetic mice through its anti-inflammatory activity** . *Nutr Metab (Lond)* 2010; 7:67.

130. Kim KA, Son YO, Kim SS, Jang YS, Baek YH, Kim CC, et al.**Glycoproteins isolated from Atractylodes macrocephala Koidz improve protective immune response induction in a mouse model** .*Food Sci Biotechnol* 2018; 27(6):1823-1831.

131. Novianti E, Katsuura G, Kawamura N, Asakawa A, Inui A.**Atractylenolide-III suppresses lipopolysaccharide-induced inflammation via downregulation of toll-like receptor 4 in mouse microglia** . *Heliyon* 2021; 7(10):e08269.

132. Khan S, Shin EM, Choi RJ, Jung YH, Kim J, Tosun A, et al.**Suppression of LPS-induced inflammatory and NF-kappaB responses by anomalin in RAW 264.7 macrophages** . *J Cell Biochem* 2011; 112(8):2179-2188.

133. Fan W, Zheng P, Wang Y, Hao P, Liu J, Zhao X. **Analysis of immunostimulatory activity of polysaccharide extracted from Yu-Ping-Feng in vitro and in vivo** . *Biomed Pharmacother* 2017; 93:146-155.

134. Zhuang W, Fan Z, Chu Y, Wang H, Yang Y, Wu L, et al.**Chinese Patent Medicines in the Treatment of Coronavirus Disease 2019 (COVID-19) in China** . *Front Pharmacol* 2020; 11:1066.

135. Fu S, Zhang J, Gao X, Xia Y, Ferrelli R, Fauci A, et al.**Clinical practice of traditional Chinese medicines for chronic heart failure** . *Heart Asia* 2010; 2(1):24-27.

136. Huang X, Duan X, Wang K, Wu J, Zhang X. **Shengmai injection as an adjunctive therapy for the treatment of chronic obstructive pulmonary disease: A systematic review and meta-analysis** .*Complement Ther Med* 2019; 43:140-147.

137. Lu J, Yu Y, Wang XJ, Chai RP, Lyu XK, Deng MH, et al.**Mechanism of Shengmai Injection () on Anti-Sepsis and Protective Activities of Intestinal Mucosal Barrier in Mice** . *Chin J Integr Med* 2021.

138. Li DM, Qi RH, Zhang HC, Liao X, Xie YM, Zhang JH, et al.[**Clinical application evaluation and revision suggestions of clinical practice guideline on traditional Chinese medicine therapy alone or combined with antibiotics for community acquired pneumonia**] .*Zhongguo Zhong Yao Za Zhi* 2018; 43(24):4759-4764.

139. Skwarczynski M, Zhao G, Boer JC, Ozberk V, Azuar A, Cruz JG, et al.**Poly(amino acids) as a potent self-adjuvanting delivery system for peptide-based nanovaccines** . *Sci Adv* 2020; 6(5):eaax2285.

140. Chai R, Zhang Y, Lu J, Wang T, Chen XJCJPE. **Research on mechanism of shengmai injection in the treatment of sepsis based on metabolomics** . 2019; 14:30-34.

141. Lu J, Lyu X, Chai R, Yu Y, Deng M, Zhan X, et al.**Investigation of the Mechanism of Shengmai Injection on Sepsis by Network Pharmacology Approaches** . *Evid Based Complement Alternat Med* 2020; 2020:4956329.

142. Azoulay E, Russell L, Van de Louw A, Metaxa V, Bauer P, Povoa P, et al. **Diagnosis of severe respiratory infections in immunocompromised patients** . *Intensive Care Med* 2020; 46(2):298-314.

143. Zhou E, Li Y, Wei Z, Fu Y, Lei H, Zhang N, et al.**Schisantherin A protects lipopolysaccharide-induced acute respiratory distress syndrome in mice through inhibiting NF-kappaB and MAPKs signaling pathways** . *Int Immunopharmacol* 2014; 22(1):133-140.

144. Minami M, Konishi T, Makino T. **Effect of Hochuekkito (Buzhongyiqitang) on Nasal Cavity Colonization of Methicillin-Resistant Staphylococcus aureus in Murine Model** . *Medicines (Basel)* 2018; 5(3).

145. Kitahara M, Takayama S, Akaishi T, Kikuchi A, Ishii T.**Hochuekkito can Prevent the Colonization of Methicillin-Resistant Staphylococcus aureus in Upper Respiratory Tract of Acute Stroke Patients** . *Front Pharmacol* 2021; 12:683171.

146. Yang F, Dong X, Yin X, Wang W, You L, Ni J. **Radix Bupleuri: A Review of Traditional Uses, Botany, Phytochemistry, Pharmacology, and Toxicology** . *Biomed Res Int* 2017; 2017:7597596.

147. Ogawa-Ochiai K, Ishikawa H, Li H, Vu Quang L, Kimoto I, Takamura M, et al. **Immunological and Preventive Effects of Hochuekkito and Kakkonto Against Coronavirus Disease in Healthcare Workers: A Retrospective Observational Study** . *Front Pharmacol* 2021; 12:766402.

148. Matsumoto T, Noguchi M, Hayashi O, Makino K, Yamada H.**Hochuekkito, a Kampo (traditional Japanese herbal) Medicine, Enhances Mucosal IgA Antibody Response in Mice Immunized with Antigen-entrapped Biodegradable Microparticles** . *Evid Based Complement Alternat Med* 2010; 7(1):69-77.

149. Shimato Y, Ota M, Asai K, Atsumi T, Tabuchi Y, Makino T.**Comparison of byakujutsu (Atractylodes rhizome) and sojutsu (Atractylodes lancea rhizome) on anti-inflammatory and immunostimulative effects in vitro** . *J Nat Med* 2018; 72(1):192-201.

150. Miller LS, Fowler VG, Shukla SK, Rose WE, Proctor RA.**Development of a vaccine against Staphylococcus aureus invasive infections: Evidence based on human immunity, genetics and bacterial evasion mechanisms** . *FEMS Microbiol Rev* 2020; 44(1):123-153.

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Traditional Medicine Combination Therapy Is A Promising Strategy for MRSA Infection

Table 1. MRSA virulence factors that contribute to immune evasion and their functions in host immune responses

Evasion proteins against mucosal immune	Target	Function/ effect on immune system	Ref.
Staphylococcal superantigen-like protein-7 (SSL-7)	SIgA	It enhances the ability to colonize in mucosal environments such as the nasal passage by binding to SIgA.	[1]
Evasion proteins against innate immune	**Target**	**Function/ effect on immune system**	**Ref.**
Proteins including extracellular adherence protein (Eap), collagen-binding protein (Cna) and serine-aspartate repeat protein E (SdrE)	C1q in classical pathway, lectin pathway, alternative pathway	They inhibit the activation of the complement system by blocking these three pathways.	[2-4]
Staphylococcal Protein A (SpA)	IgG	It results in the inverted tagging and blocking of the C1q binding sites, preventing complement initiation.	[5]
	B cells	It interferes in B-cells activation and proliferation, reducing the phagocytosis of MRSA, impeding antibody production and causing disordered activation, finally leading to the death of the B cells.	[6, 7]

Staphylococcal complement inhibitor (SCIN)	C3 convertases	It binds and stabilizes C3 convertases, interfering with the activation of the complement system.	[8]
Extracellular fibrinogen-binding protein (Efb); its homolog extracellular complement-binding protein (Ecb)	C3	They prevent C3 from recognition by macrophages.	[9]
Second Immunoglobulin-binding protein (Sbi)	IgG	It avoids neutrophil-mediated opsonophagocytosis.	[10]
	C3	It binds to complement, leading to the cleavage and consumption of complement Factor C3.	[11]
Factor I	C3b	It mediates C3b cleavage to iC3b, inhibiting initiation of the alternative pathway as well the activation of the terminal complement cascade.	[12]
Staphylokinase (SAK)	Complement	It digests IgG and complement.	[13]
chemotaxis inhibitory protein of staphylococci (CHIPS)	C5aR	It binds to C5aR to evade complement.	[14]
	FPR1	It binds to FPR1 to block the chemotaxis of neutrophils.	[15]
Staphylococcal superantigen-like protein-7 (SSL-7)	C5	It inhibits the opsonization of bacteria by inhibiting the cleavage of C5.	[16]
Proteases, e.g., staphopain A (Scp A), aureolysin	Complement	They degrade complement preventing opsonization and bacteria	[5]

(Aur)		lysis.	
	Neutrophils	ScpA inhibits the chemotaxis and activation of neutrophils.	[17]
Staphylococcal superantigen-like 5 (SSL5)	P-selectin glycoprotein ligand 1 (PSGL-1)	It binds to PSGL-1 of sialyl Lewis X, thus blocking PSGL-1 interaction with the natural ligand P-selectin and abrogating neutrophil rolling on endothelial cells.	[18]
Proteins including extracellular adherence protein (Eap)	Intercellular adhesion molecule 1 (ICAM-1)	It binds to ICAM-1, blocking the neutrophil recruitment to the infection site.	[8]
Staphylococcal complement inhibitor (SCIN), chemotaxis inhibitory protein of staphylococci (CHIPS)	Neutrophils	They impair neutrophil recruitment as chemotaxis inhibitors.	[19]
Nuc	NETs	It is a nuclease produced by MRSA to evade NETs.	[20, 21]
Panton-Valentine leukocidin (PVL)	Neutrophils	It causes neutrophil lysis at the dose of 0.04 μg/mL.	[22]
Phenol-soluble-modulins (PSMs)	Neutrophils	They directly kill neutrophils mainly by disrupting the membrane.	[23]

Table 2. The effect of TM therapies on host immunity and MRSA immune evasion.

Name of TM	Active Ingredient	Model	Dosing concentration	Targets and indicators	Immunomodulatory action	Ref.
G. glavra	Glycyrrhizin (GL)	Male CD mice (20–25 g)	10 mg/kg	ICAM-1, P-selectin	It decreases the degree of positive staining and densitometry for ICAM-1 and P-selectin.	[24]
		Male specific pathogen-free BALB/c mice (6 weeks)	50 mg/kg	neutrophils, macrophages, MPO, CD11b positive cells	It reduces the numbers of total cells, neutrophils, and macrophages, and decreases MPO and CD11b levels to inhibit the migration and infiltration of immune cells.	[24, 25]
				TNF-α, IL-1α, IL-6, COX-2, iNOS, NF-κB	It decreases the levels of pro-inflammatory cytokines (TNF-α, IL-1α, IL-6) and pro-inflammatory mediators (COX-2, iNOS, NF-κB).	[24, 25]
	18β-Glycyrrhetinic Acid (GA)	Female Crl; SKH1-hrBR hairless mice, subcutaneously inoculated with MRSA	600 μg/mL	saeR, Hla, RNAIII, mecA, sbi	It reduces MRSA immune evasion by down-regulating MRSA virulence factors (saeR, Hla, RNAIII, mecA, sbi).	[26]
				KC, G-CSF	It reduces the levels of inflammatory cytokines (KC, G-CSF).	[26]

				co-stimulatory molecules CD40, CD86, MHC class II	It induces phenotypic maturation of DCs by increasing CD40, CD86 and MHC-II expression in DCs.	[27]
		Male BALB/c and C57BL/6 mice (6 weeks)	1 and 10 mg/mL for 14 hours	IL-12, IFN-γ	It increases IL-12 levels to promote DC maturation and activates T cells to differentiate into IFN-γ producing Th1 cells.	[27]
				IL-10	It suppresses excessive inflammatory responses or terminates the immune responses after pathogen eradication by increasing IL-10 levels.	[27]
P. ginseng (Pg)	Ginsan	Male pyrogen-free BALB/c mice (5–7 weeks, 18–22 g); S. aureus 25923 or E. coli	0.012, 0.025, 0.5, 25, and 250 mg/kg (intravenous injection)	Macrophage, TLR2, TLR4, TLR9, MyD88, MAPK, JUN 1/2, NF-κB, TNF-α, IL-1β, IL-6, IL-	It induces resistance to MRSA septicemia by modulating monocyte/macrophage-mediated innate immunity.	[28]

			12		
	BALB/c mice	100 mg/kg (intraperitoneally introduced, once a day)	Serum antibodies, Peyer's patches, COX-1, COX-2, CCL3	It effectively enhances the humoral immune response to orally delivered antigen, mediated by CCL3 via COX-1 and COX-2.	[29]
Pg extract, such as ginsenoside	Female mouse mastitis model (lactating mice)	3, 10, 50 mg/mL	Macrophage, TLR2, TLR4, NF-κB	Pg extracts trigger and induce the inflammatory response. Pg modulates the mRNA levels of TLR2 and TLR4, triggers the activation of the MyD88-dependent pathway and then leads to the liberation of the NF-κB transcription factor.	[30]
Ginsenoside	MRSA strains: bacterial cells cultured in a Mueller–Hinton broth	100 mg/mL	MRSA biofilm	It not only attenuates bacterial toxicity but also promotes the influx of antibiotics.	[31]
ginseng oligopeptides	420 Female healthy	0.0375, 0.075, 0.15, 0.3 and 0.6	Macrophage, NK cell, T	It increases macrophage phagocytosis capacity and NK cell activity, and	[32]

	(GOP)	BALB/c mice	g/kg for 30 days (intragastrically administered)	and Th cells	enhances T and Th cells, as well as IL-2, IL-6 and IL-12 secretion and IgA, IgG1 and IgG2b production.	
P. quinquefolius	aqueous extract of the *P. quinquefolius* (CVT-E002)	Old mice (8–9 weeks)	80 mg chow/mouse daily	NK cell in spleen and bone marrow	It augments the absolute numbers of NK cells in the spleen and bone marrow.	[33]
		C57 BL/6 mice	10, 100, 500 Ag/mL	B-lymphocyte in the spleen	It increases IL2 and IFN-γ levels in B-lymphocytes in a dose-dependent manner.	[34]
		C57 BL/6 mice (6–8 weeks)	500, 100 and 10 μg/mL	Peritoneal exudate macrophages (PEM)	It stimulates NO, IL-1, IL-6 and TNF-α levels in PEM.	[35]
O. japonicas	OPS, OPL	BALB/c mice (1 week)	18, 6 mg per mouse	Plasma cells	It increases IgG levels.	[35]
		Peritoneal macrophages isolated from ICR mice (18–22 g)	62.5, 31.25, 15.625, 7.813 and 3.907 g/mL	Phagocytes, NO, iNOS	It improves immune function of macrophages by enhancing phagocytic function and increasing NO and iNOS levels, finally enhancing the ability of sterilization.	[36]
				IL-1β, TNF-	It exerts immune activity by promoting IL-	[36]

				α, MCP-1, MIP1β	1β, TNF-α, MCP-1 and MIP-1β levels in macrophages.	
			31.25, 15.625 and 7.813 g/mL	CD14, MHC-II	It induces CD14 and MHC-II to promote macrophages activation and maturation.	[36]
			0.3, 1.0 and 3.0 mg/kg	MPO	It reduces neutrophil infiltration by decreasing MPO levels.	[37]
		Male ICR mice (6–8 weeks)	1.0 and 3.0 mg/kg	iNOS, NF-κB	It suppresses the inflammatory response by decreasing iNOS levels, which might be linked with the down-regulation of NF-κB.	[37]
	Ruscogenin (RUS)		0.3 and 1 mg/kg	NO, IL-6, TNF-α	It alleviates lung injury and inflammation by decreasing NO, IL-6 and TNF-α levels.	[38]
		Male C57BL/6 mice (18−22 g)	0.1, 0.3 and 1 mg/kg	Bax, cleaved caspase-3, Bcl-2	It inhibits PEC apoptosis by decreasing Bax and cleaved caspase-3 levels and by increasing Bcl-2 levels.	[38]
			0.3 and 1 mg/kg	TLR4, MYD88, NF-κB p65	It attenuates LPS-induced PEC apoptosis and exerts a protective effect on lung injury and inflammation by suppressing the TLR4/MYD88/NF-κB pathway.	[38]
Cordyceps mushrooms- C.	*Cordyceps sinensis* extract	Sixty male adult BALB/c	10, 30 and 60 mg/kg	Neutrophils, macrophages,	It alleviates inflammatory cell exudation by decreasing the numbers of neutrophils	[39]

sinensis	(CSE)	mice (8 weeks, 20 ± 2 g)		MPO	and macrophages, as well as MPO levels.	
				NF-κB p65, COX-2, iNOS, NO, TNF-α, IL-6, IL-1β	It down-regulates NO, TNF-α, IL-6 and IL-1β by inhibiting the phosphorylation of NF-κB p65 and COX-2, iNOS.	[39]
				TNF-α, IL-6, HMGB1, IL-10, TLR4	It alleviates anti-oxidative stress injuries by down regulating TNF-α, IL-6 and HMGB1 as well up-regulating IL-10, which is associated with inhibiting TLR4 signaling.	[40, 41]
Cordyceps mushrooms- militaris	C. cordycepin	Male specific pathogen-free Wistar rats (8–10 weeks)	1, 10 and 30 mg/kg	Neutrophils, MPO, NO, iNOS, LDH	It attenuates inflammation by decreasing the neutrophil number and inhibiting their exudation by suppressing MPO, NO, iNOS and LDH levels.	[40]
				Nrf2, HO-1	It stimulates HO-1 production and alleviates lung injuries by promoting Nrf2 activation and inducing nuclear translocation of Nrf2.	[40, 41]
		Male BALB/c mice (6-8	50, 100 and 200 mg/kg	NF-κB, IκB	It prevents IκB phosphorylation and NF-κB release to achieve anti-inflammatory	[41]

		weeks)			effect.
Atractylodes species- *A. macrocephala*	Atractylenolide I (AO-I)	Male BALB/c mice (20-24 g)	5, 10 and 20 mg/kg	Neutrophils, macrophages, MPO	It decreases neutrophil and macrophage numbers in BALF and inhibits neutrophil infiltration by reducing MPO levels. [42]
				TNF-α, IL-6, IL-1β, IL-13, MIF, IL-10	It decreases TNF-α, IL-6, IL-1β, IL-13 and MIF levels, as well as increases IL-10 levels in a dose-dependent manner. [42]
				TLR4, NF-κB, IκBα	It exerts a protective effect on ALI-induced mice by inhibiting TLR4, NF-κB activation and IκBα degradation. [42]
	Atractylodes macrocephala polysaccharides (AMPS)	The murine macrophage cell line RAW264.7	25, 50, 100 and 200 lg/mL	Macrophages, NO, TNF-α	It stimulates macrophages to promote phagocytic activity and the productions of NO and TNF-α. [43, 44]
				NF-κB, IκB	It induces IκB degradation and the activation of NF-κB. [43, 44]
Atractylodes species- *A. lancea*	A neutral polysaccharide (ALP-1), an acidic polysaccharide (ALP-3)	The murine RAW264.7 macrophage cell line, Specific pathogen free	50, 100, 250, 500, 1000 and 2000 mg/mL for 18h	Macrophages, NO, TNF-α, IL-6	They promote macrophages phagocytosis and the release of NO, TNF-α and IL-6. [45]
				HGF	They modulate the intestinal immune system by stimulating Peyer's patch cells to induce HGF production. [45]

		BALB/C mice (6-8 weeks)				
	water extracts of *A. macrocephala* and *A. lancea*	Murine normal colonic epithelial cell-line MCE301 cells	100 µg/mL	G-CSF	They promote the intestinal immune system by promoting G-CSF.	[46]
Zhenqi Fuzheng granule (ZQ)	Astragalus polysaccharides (APS)	Male MF1albino mice (5-6 weeks)	250 mg APS/kg/week for four consecutive weeks	Spleen, neutrophil and ROS in intestinal	It increases both in the phagocytic ability of neutrophils and the intestinal ROS production.	[47]
			1/mL	macrophage	It increases the phagocytic activity of macrophages.	[48]
Yu Ping Feng San (YPFS)	water-soluble extracts of YPFS	RAW 264.7 murine macrophages	1mg/mL; 3h	IL-1β, IL-6, TNF-α	It suppresses the production of pro-inflammatory cytokines in LPS-induced cultured macrophages.	[48]
			0.03, 0.1, 0.3, 1, 3 mg/mL; 24h	IL-1β, IL-6, TNF-α	It induces the production of pro-inflammatory cytokines.	[48]
			1mg/mL; 3h & 24h	iNOS, COX-2	It reduces iNOS and COX-2 levels in macrophages at 3-hour time points. However, it induces the two at 24-hour	[49]

					time points.	
	Filtered SMS solutions	Healthy specific pathogen-free ICR mice (20–22 g, 6–8 weeks)	0.375, 0.75 and 1.5 mL/kg	IFN-γ, TNF-α, IL-2, NF-κB	It inhibits excessive inflammation by regulating NF-κB and decreasing IFN-γ, TNF-α and IL-2 levels.	[50]
SMS				MPO, neutrophils, macrophages	It improves inflammatory cell infiltration in pulmonary tissue by inhibiting neutrophils and macrophages, as well as MPO levels.	[51]
	Schisantherin A	Male BALB/c mice, (6–8 weeks)	10, 20 and 40 mg/kg	TNF-α, IL-6, IL-1β in the BALF	It exerts an anti-inflammatory effect through decreasing TNF-α, IL-6 and IL-1β levels in the BALF.	[51]
				NF-κB p65, IκB-α, JNK, ERK, p38	It inhibits the phosphorylation of p65, ERK, p38, JNK, and the degradation of IκB-α in a dose-dependent manner.	[51]
Buzhongyiqitang (Hochuekkito)	Hochuekkito extract (HET)	Female BALB/c mice (6 weeks)	3.4 g/kg/day	MRSA, splenocyte	It inhibits MRSA and promotes murine splenocyte immunological activity in dose-dependent manners.	[52]
		73 acute stroke	7.5 g/day, three	serum	It improves levels of serum nutritional	[53]

	patients (41 HET-treated and 32 non-HET-treated)	divided doses for three months	nutritional markers	markers by supporting nutrition and enhancing innate immunity.	
	Female C3H/HeJ mice (6-8 weeks)	1000 mg/kg/day	mucosal IgA antibody	It enhances the IgA immune response.	[54]

Table 3. Differences in the mechanisms of the two therapies

	Conventional Therapies	TM Immune Therapies
Mucosal immune response	Oral vaccines have not been developed.	They enhance Peyer's batches activation and increase the production of IgA+B cells and SIgA.
Innate immune response	(a) The development and research of vaccines are mainly based on inhibiting the bacterial immune evasion from innate immune responses, for example, targeting virulence factors by blocking the complement system and killing neutrophils. (b) AAC therapy facilitates bacterial uptake by phagocytic cells through opsonizing by antibodies.	(a) Targeting the complement system: They influence the complement system to regulate the development of MRSA infection. (b) Targeting neutrophil phagocytosis: They act on neutrophil migration and recruitment, chemokine expression, macrophage activity and antigen presentation.
Adaptive immune response	The development and research of passive immunotherapy also targets the molecules or components mediated immune evasion.	(a) Targeting T-cell activation: They stimulate T-cell activation and enhancing T-lymphocyte proliferation. (b) Targeting antibodies: They increase B-cell activation and antibody titers. (c) Targeting MRSA immune evasion strategies: They inhibit the formation of bacterial biofilms.

References:

1. Bestebroer J, Aerts PC, Rooijakkers SH, Pandey MK, Kohl J, van Strijp JA, et al. **Functional basis for complement evasion by staphylococcal superantigen-like 7**. *Cell Microbiol* 2010; 12(10):1506-1516.
2. Pietrocola G, Nobile G, Rindi S, Speziale P. **Staphylococcus aureus Manipulates Innate Immunity through Own and Host-Expressed Proteases**. *Front Cell Infect Microbiol* 2017; 7:166.
3. Sage MAG, Cranmer KD, Semeraro ML, Ma S, Galkina EV, Tran Y, et al. **A Factor H-Fc fusion protein increases complement-mediated opsonophagocytosis and killing of community associated methicillin-resistant Staphylococcus aureus**. *PLoS One* 2022; 17(3):e0265774.
4. Woehl JL, Ramyar KX, Katz BB, Walker JK, Geisbrecht BV. **The structural basis for inhibition of the classical and lectin complement pathways by S. aureus extracellular adherence protein**. *Protein Sci* 2017; 26(8):1595-1608.
5. Wojcik-Bojek U, Rozalska B, Sadowska B. **Staphylococcus aureus-A Known Opponent against Host Defense Mechanisms and Vaccine Development-Do We Still Have a Chance to Win?** *Int J Mol Sci* 2022; 23(2).
6. Falugi F, Kim HK, Missiakas DM, Schneewind O. **Role of protein A in the evasion of host adaptive immune responses by Staphylococcus aureus**. *mBio* 2013; 4(5):e00575-00513.
7. Pauli NT, Kim HK, Falugi F, Huang M, Dulac J, Henry Dunand C, et al. **Staphylococcus aureus infection induces protein A-mediated immune evasion in humans**. *J Exp Med* 2014; 211(12):2331-2339.
8. do Vale A, Cabanes D, Sousa S. **Bacterial Toxins as Pathogen Weapons Against Phagocytes**. *Front Microbiol* 2016; 7:42.
9. Kumar D, Romero Y, Schuck KN, Smalley H, Subedi B, Fleming SD. **Drivers and regulators of humoral innate immune responses to infection and cancer**. *Mol Immunol* 2020; 121:99-110.
10. Smith EJ, Visai L, Kerrigan SW, Speziale P, Foster TJ. **The Sbi protein is a multifunctional immune evasion factor of Staphylococcus aureus**. *Infect Immun* 2011; 79(9):3801-3809.
11. Mues N, Chu HW. **Out-Smarting the Host: Bacteria Maneuvering the Immune Response to Favor Their Survival**. *Front Immunol* 2020; 11:819.
12. Irmscher S, Doring N, Halder LD, Jo EAH, Kopka I, Dunker C, et al. **Kallikrein Cleaves C3 and Activates Complement**. *J Innate Immun* 2018; 10(2):94-105.
13. Teng TS, Ji AL, Ji XY, Li YZ. **Neutrophils and Immunity: From Bactericidal Action to Being Conquered**. *J Immunol Res* 2017; 2017:9671604.
14. Grousd JA, Rich HE, Alcorn JF. **Host-Pathogen Interactions in Gram-Positive Bacterial Pneumonia**. *Clin Microbiol Rev* 2019; 32(3).
15. Nasser A, Moradi M, Jazireian P, Safari H, Alizadeh-Sani M, Pourmand MR, et al. **Staphylococcus aureus versus neutrophil: Scrutiny of ancient combat**. *Microb Pathog* 2019; 131:259-269.
16. Zhao Y, van Kessel KPM, de Haas CJC, Rogers MRC, van Strijp JAG, Haas PA. **Staphylococcal superantigen-like protein 13 activates neutrophils via formyl peptide receptor 2**. *Cell Microbiol* 2018; 20(11):e12941.
17. Laarman AJ, Mijnheer G, Mootz JM, van Rooijen WJ, Ruyken M, Malone CL, et al. **Staphylococcus aureus Staphopain A inhibits CXCR2-dependent neutrophil activation and chemotaxis**. *EMBO J* 2012; 31(17):3607-3619.
18. Guerra FE, Borgogna TR, Patel DM, Sward EW, Voyich JM. **Epic Immune Battles of History: Neutrophils vs. Staphylococcus aureus**. *Front Cell Infect Microbiol* 2017; 7:286.
19. Rigby KM, DeLeo FR. **Neutrophils in innate host defense against Staphylococcus**

aureus infections. *Semin Immunopathol* 2012; 34(2):237-259.
20. Herzog S, Dach F, de Buhr N, Niemann S, Schlagowski J, Chaves-Moreno D, et al. **High Nuclease Activity of Long Persisting Staphylococcus aureus Isolates Within the Airways of Cystic Fibrosis Patients Protects Against NET-Mediated Killing**. *Front Immunol* 2019; 10:2552.
21. Schilcher K, Andreoni F, Uchiyama S, Ogawa T, Schuepbach RA, Zinkernagel AS. **Increased neutrophil extracellular trap-mediated Staphylococcus aureus clearance through inhibition of nuclease activity by clindamycin and immunoglobulin**. *J Infect Dis* 2014; 210(3):473-482.
22. Loffler B, Hussain M, Grundmeier M, Bruck M, Holzinger D, Varga G, et al. **Staphylococcus aureus panton-valentine leukocidin is a very potent cytotoxic factor for human neutrophils**. *PLoS Pathog* 2010; 6(1):e1000715.
23. Yao Z, Cary BP, Bingman CA, Wang C, Kreitler DF, Satyshur KA, et al. **Use of a Stereochemical Strategy To Probe the Mechanism of Phenol-Soluble Modulin alpha3 Toxicity**. *J Am Chem Soc* 2019; 141(19):7660-7664.
24. Menegazzi M, Di Paola R, Mazzon E, Genovese T, Crisafulli C, Dal Bosco M, et al. **Glycyrrhizin attenuates the development of carrageenan-induced lung injury in mice**. *Pharmacol Res* 2008; 58(1):22-31.
25. Lee SA, Lee SH, Kim JY, Lee WS. **Effects of glycyrrhizin on lipopolysaccharide-induced acute lung injury in a mouse model**. *J Thorac Dis* 2019; 11(4):1287-1302.
26. Long DR, Mead J, Hendricks JM, Hardy ME, Voyich JM. **18beta-Glycyrrhetinic acid inhibits methicillin-resistant Staphylococcus aureus survival and attenuates virulence gene expression**. *Antimicrob Agents Chemother* 2013; 57(1):241-247.
27. Bordbar N, Karimi MH, Amirghofran Z. **Phenotypic and functional maturation of murine dendritic cells induced by 18 alpha- and beta-glycyrrhetinic acid**. *Immunopharmacol Immunotoxicol* 2014; 36(1):52-60.
28. Ahn JY, Choi IS, Shim JY, Yun EK, Yun YS, Jeong G, et al. **The immunomodulator ginsan induces resistance to experimental sepsis by inhibiting Toll-like receptor-mediated inflammatory signals**. *Eur J Immunol* 2006; 36(1):37-45.
29. Na HS, Lim YJ, Yun YS, Kweon MN, Lee HC. **Ginsan enhances humoral antibody response to orally delivered antigen**. *Immune Netw* 2010; 10(1):5-14.
30. Silvestrini P, Beccaria C, Pereyra EAL, Renna MS, Ortega HH, Calvinho LF, et al. **Intramammary inoculation of Panax ginseng plays an immunoprotective role in Staphylococcus aureus infection in a murine model**. *Res Vet Sci* 2017; 115:211-220.
31. Sung WS, Lee DG. **The combination effect of Korean red ginseng saponins with kanamycin and cefotaxime against methicillin-resistant Staphylococcus aureus**. *Biol Pharm Bull* 2008; 31(8):1614-1617.
32. He LX, Ren JW, Liu R, Chen QH, Zhao J, Wu X, et al. **Ginseng (Panax ginseng Meyer) oligopeptides regulate innate and adaptive immune responses in mice via increased macrophage phagocytosis capacity, NK cell activity and Th cells secretion**. *Food Funct* 2017; 8(10):3523-3532.
33. Miller SC, Ti L, Shan J. **Dietary supplementation with an extract of North American ginseng in adult and juvenile mice increases natural killer cells**. *Immunol Invest* 2012; 41(2):157-170.
34. Wang M, Guilbert LJ, Li J, Wu Y, Pang P, Basu TK, et al. **A proprietary extract from North American ginseng (Panax quinquefolium) enhances IL-2 and IFN-gamma productions in murine spleen cells induced by Con-A**. *Int Immunopharmacol* 2004; 4(2):311-315.
35. Wang M, Guilbert LJ, Ling L, Li J, Wu Y, Xu S, et al. **Immunomodulating activity of CVT-E002, a proprietary extract from North American ginseng (Panax quinquefolium)**.

J Pharm Pharmacol 2001; 53(11):1515-1523.
36. Sun W, Hu W, Meng K, Yang L, Zhang W, Song X, et al. **Activation of macrophages by the ophiopogon polysaccharide liposome from the root tuber of Ophiopogon japonicus**. *Int J Biol Macromol* 2016; 91:918-925.
37. Sun Q, Chen L, Gao M, Jiang W, Shao F, Li J, et al. **Ruscogenin inhibits lipopolysaccharide-induced acute lung injury in mice: involvement of tissue factor, inducible NO synthase and nuclear factor (NF)-kappaB**. *Int Immunopharmacol* 2012; 12(1):88-93.
38. Wu Y, Wang Y, Gong S, Tang J, Zhang J, Li F, et al. **Ruscogenin alleviates LPS-induced pulmonary endothelial cell apoptosis by suppressing TLR4 signaling**. *Biomed Pharmacother* 2020; 125:109868.
39. Fu S, Lu W, Yu W, Hu J. **Protective effect of Cordyceps sinensis extract on lipopolysaccharide-induced acute lung injury in mice**. *Biosci Rep* 2019; 39(6).
40. Qing R, Huang Z, Tang Y, Xiang Q, Yang F. **Cordycepin alleviates lipopolysaccharide-induced acute lung injury via Nrf2/HO-1 pathway**. *Int Immunopharmacol* 2018; 60:18-25.
41. Lei J, Wei Y, Song P, Li Y, Zhang T, Feng Q, et al. **Cordycepin inhibits LPS-induced acute lung injury by inhibiting inflammation and oxidative stress**. *Eur J Pharmacol* 2018; 818:110-114.
42. Zhang JL, Huang WM, Zeng QY. **Atractylenolide I protects mice from lipopolysaccharide-induced acute lung injury**. *Eur J Pharmacol* 2015; 765:94-99.
43. Ji GQ, Chen RQ, Zheng JX. **Macrophage activation by polysaccharides from Atractylodes macrocephala Koidz through the nuclear factor-kappaB pathway**. *Pharm Biol* 2015; 53(4):512-517.
44. Li BX, Li WY, Tian YB, Guo SX, Huang YM, Xu DN, et al. **Polysaccharide of Atractylodes macrocephala Koidz Enhances Cytokine Secretion by Stimulating the TLR4-MyD88-NF-kappaB Signaling Pathway in the Mouse Spleen**. *J Med Food* 2019; 22(9):937-943.
45. Qin J, Wang HY, Zhuang D, Meng FC, Zhang X, Huang H, et al. **Structural characterization and immunoregulatory activity of two polysaccharides from the rhizomes of Atractylodes lancea (Thunb.) DC**. *Int J Biol Macromol* 2019; 136:341-351.
46. Shimato Y, Ota M, Asai K, Atsumi T, Tabuchi Y, Makino T. **Comparison of byakujutsu (Atractylodes rhizome) and sojutsu (Atractylodes lancea rhizome) on anti-inflammatory and immunostimulative effects in vitro**. *J Nat Med* 2018; 72(1):192-201.
47. Abuelsaad AS. **Supplementation with Astragalus polysaccharides alters Aeromonas-induced tissue-specific cellular immune response**. *Microb Pathog* 2014; 66:48-56.
48. Du CY, Choi RC, Zheng KY, Dong TT, Lau DT, Tsim KW. **Yu Ping Feng San, an ancient Chinese herbal decoction containing Astragali Radix, Atractylodis Macrocephalae Rhizoma and Saposhnikoviae Radix, regulates the release of cytokines in murine macrophages**. *PLoS One* 2013; 8(11):e78622.
49. Du CY, Choi RC, Dong TT, Lau DT, Tsim KW. **Yu Ping Feng San, an ancient Chinese herbal decoction, regulates the expression of inducible nitric oxide synthase and cyclooxygenase-2 and the activity of intestinal alkaline phosphatase in cultures**. *PLoS One* 2014; 9(6):e100382.
50. Lu J, Yu Y, Wang XJ, Chai RP, Lyu XK, Deng MH, et al. **Mechanism of Shengmai Injection () on Anti-Sepsis and Protective Activities of Intestinal Mucosal Barrier in Mice**. *Chin J Integr Med* 2021.
51. Zhou E, Li Y, Wei Z, Fu Y, Lei H, Zhang N, et al. **Schisantherin A protects lipopolysaccharide-induced acute respiratory distress syndrome in mice through inhibiting NF-kappaB and MAPKs signaling pathways**. *Int Immunopharmacol* 2014; 22(1):133-140.

52. Minami M, Konishi T, Makino T. **Effect of Hochuekkito (Buzhongyiqitang) on Nasal Cavity Colonization of Methicillin-Resistant Staphylococcus aureus in Murine Model**. *Medicines (Basel)* 2018; 5(3).
53. Kitahara M, Takayama S, Akaishi T, Kikuchi A, Ishii T. **Hochuekkito can Prevent the Colonization of Methicillin-Resistant Staphylococcus aureus in Upper Respiratory Tract of Acute Stroke Patients**. *Front Pharmacol* 2021; 12:683171.
54. Matsumoto T, Noguchi M, Hayashi O, Makino K, Yamada H. **Hochuekkito, a Kampo (traditional Japanese herbal) Medicine, Enhances Mucosal IgA Antibody Response in Mice Immunized with Antigen-entrapped Biodegradable Microparticles**. *Evid Based Complement Alternat Med* 2010; 7(1):69-77.