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.

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