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Review article

Artemisinin and its derivatives as promising therapies for autoimmune diseases

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ABSTRACT

Artemisinin, a traditional Chinese medicine with remarkable antimalarial activity. In recent years, studies demonstrated that artemisinin and its derivatives (ARTs) showed anti-inflammatory and immunoregulatory effects. ARTs have been developed and gradually applied to treat autoimmune and inflammatory diseases. However, their role in the treament of patients with autoimmune and inflammatory diseases in particular is less well recognized. This review will briefly describe the history of ARTs use in patients with autoimmune and inflammatory diseases, the theorized mechanisms of action of the agents ARTs, their efficacy in patients with autoinmmune and inflammatory diseases. Overall, ARTs have numerous beneficial effects in patients with autoimmune and inflammatory diseases, and have a good safety profile.

1. Introduction

Autoimmune diseases are diseases characterized by increased activity of the immune system, which shows reactivity to self-antigens, leading to tissue damage [1]. Currently, more than 80 types autoimmune diseases are known, some of which affect multiple organs (joint, kidney, brain, ect) like systemic lupus erythematosus, while others may only damage a single organ like type 1 diabetes. To date, about 5%–8% of the population worldwide suffer from autoimmune diseases which caused heavy health burden to patients and the society [2].

Artemisinins gained widespread acceptance as first-line antimalarial drugs after the emergence of chloroquine resistance in the 1950s [3]. Artemisinin, originally discovered by Youyou Tu in 1972, was isolated from Artemisia annua L. and contained a sesquiterpene trioxane skeleton [4]. Artemisinin-related studies have been extensively and intensively carried out over the past several decades. In recent years, ARTs have been proved to exhibit antiviral [5], anti-cancer [6], anti-inflammatory and immunomodulatory effects [7]. Besides, several artemisinin derivatives with improved bioactivity or solubility have been synthesized, such as artesunate, dihydro-artemisinin (DHA), and artemether, which extended the clinical applications of artemisinin to autoimmune diseases and inflammatory diseases [7]. However, the specific therapeutic mechanisms of ARTs in autoimmune diseases and inflammatory diseases remain unclear and need to be elucidated urgently.

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Table 1
The therapeutic benefits and pharmacological mechanisms of ARTs in autoimmune and inflammatory diseases.

Study	Disease	Intervention	Experimental models	Pharmacological mechanisms	Indication
Chen et al., 2021 [1]	SLE	Dihydroartemisinin (100 mg/kg/day, administration p.o lasted 2 months in vivo; a culture with 1 mg/ml DHA for 48 h in vitro)	BALB/c mice	Restores the Treg/Th17 balance; ⬇ Th17 cell differentiation; RORγt transcription ⬆ Treg cell differentiation; Foxp3 in lymphocytes; IL-17 and TGF-β levels	Alleviates the manifestations; Suppresses inflammation
Li et al., 2019 [2]	LN	Dihydroartemisinin (100 mg/kg/day, oral administration lasted 2 months)	BALB/c mice	Induces Nrf2/HO-1 pathway	Ameliorates the symptoms; Reverses MDSCs senescence
Dang et al., 2019 [3]	SLE	Artesunate (2.5 and 5 mg/kg, twice a day, oral adminisration lasted 8 weeks)	MRL/lpr mice	In the maintenance of the ratio of T follicular regulatory Tfr to Tfh; ⬇ IL-6; IFN-γ; IL-21; Tfh cells; JAK2 and STAT3 phosphorylation	Prolonges the survival of MRL/lpr mice; Decreases the levels of anti-dsDNA antibodies deposited in the kidney; Restores T-cell compartment
Feng et al., 2017 [4]	SLE	Artesunate (a culture medium containing artesunate at the concentration of 5 or 20 μmol/L for 12 h and 24 h; a culture medium containing artesunate at the concentration of 5 or 20 μM at 3×10^5 per well for 24 h)	SLE PBMCs and HUVECs	⬇ IFN inducible genes expressions; MIF production; p-STAT1 expression	Counteracts the effect of IFNα to inhibit MIF production by blocking STAT1 phosphorylation
Wu et al., 2016 [5]	SLE	SM934 (1.25, 2.5, and 5 mg/kg, twice-daily, oral i.g. from 9 weeks to 27 weeks of age; 10 μM, without cytotoxicity to splenic B cells, stimulate B cells in vitro for 48 h and 72 h; 60 μM, without cytotoxicity to PBMCs, stimulate PBMCs in vitro for 48 h or 6 d)	MRL/lpr mice and splenic; Human PBMCs from healthy donors	⬇ IL-6; IL-10; IL-21; B cell activation; plasma cell; antibody secretion; TLR7/9 mRNA expression; MyD88 protein expression; NF-kB phosphorylation; B cell activation; PC differentiation ⬆ quiescent B cell	Prolongs the life-span of MRL/lpr mice; Ameliorate the lymphadenopathy symptoms; Decreased the levels of serum anti-nuclear antibodies (ANAs); Restores the B-cell compartment; Maintains germinal center B-cell numbers
Huang et al., 2014 [6]	SLE	Dihydroartemisinin (a culture containing 0.1 μM, 1 μM, and 10 μM DHA for 24 h)	MRL/lpr mice (spleen cells)	⬇ TLR4 protein expression; IRF3 phosphorylation, IFN-β gene expression, release of IFN-α and IFN-β	Inhibits LPS-induced spleen cell proliferation
Hou et al., 2012 [7]	SLE	SM934 (3 mg/kg/day or 10 mg/kg/day, oral administration lasted 3 months or 6 months))	NZB/NZW F_1 mice	⬇ dsDNA IgG2a; IgG3 Abs; IL-17 accumulation of effector/memory T cells ⬆ anti-dsDNA IgG1 Ab; IL-10; IL-4; IL-10; apoptosis of CD4+T cells; development of regulatory T cells	Delays the progression of glomerulonephritis; Increases the survival rate of NZB/W F1 mice
Hou et al., 2011 [8]	SLE	SM934 (10 mg/kg/day and 2.5 mg/kg/day, oral administration lasted 4 weeks, for 6 consecutive days every week))	MRL/lpr mice	⬇ IFN-γ; IL-17; Th1; Th17; $CD3+B220+CD4^{-}CD8$ -T cells; STAT-1; STAT-3; STAT-5; IgG deposition ⬆ Treg cells	Decreases blood urea nitrogen; Decreases anti–dsDNA antibodies; Avoids severe proteinuria; Survived longer; Ameliorates proteinuria and renal lesion severity; Decreases spleen size
Wu et al., 2010 [9]	LN	Artemisinin (150 mg/kg/day, i.g. administration lasted 8 weeks)	B6D2F1 and DBA/2 mice	⬇ TNF-α; IL-6; NF-kBp 65 protein; NF-kB and TGF-β1 mRNA	Relieves the symptoms; Decreases the level of urine protein/24 h; Alleviates pathological renal lesions
Jin et al., 2009 [10]	SLE (LN)	Artesunate (125 mg/kg/day solved in 2 ml physiologic saline i.g. for 16 weeks)	MRL/lpr murine	⬇ MCP-1; pro-inflammation cytokine; major B cell activation factor (BAFF)	Increases the survival rate, body weight and blood leukocyte counts; Reduces the serum levels of ANA and anti-dsDNA antibody titer, 24 h urinary protein, and serum creatinine

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Table 1 (*continued*)

Study	Disease	Intervention	Experimental models	Pharmacological mechanisms	Indication
Li et al., 2006 [11]	SLE	Dihydroarteannuin (a culture containing 0.25 μM, 2.5 μM, 25 μM, and 250 μM for 2 h in vitro; at 5 mg/kg/day, 25 mg/kg/day, and 125 mg/kg/day for 10 days by i.g. in vivo)	BXSB mice (peritoneal macrophage)	⬇ TNF-α; NF-κBp65 expression; NF-κB activation; IκB-α protein degradation	Inhibites the nuclear translocation of NF-κB in peritoneal macrophages of BXSB mice in vitro; Inhibitory effects of DHA on TNF-alpha Production may result from the block in the NF-κB signaling pathway upstream of IκB degradation
Yang et al., 2023 [12]	IgAN	Artemisnin (46.6 mg/kg/day, gavaged for 8 weeks; a culture containing 12 μM artemisinin for 2 h in vivo)	BALB/c mice and mouse mesangial cells	⬇ LPS-induced oxidative stress and fibrosis	Improves renal injury and fibrosis in mice; Promotes AKT phosphorylation and Nrf2 nuclear translocation
Xia et al., 2020 [13]	IgAN	Dihydroartemisinin (a culture containing 0–15 μM DHA for 24 h)	HMCs	⬇ mTOR/S6K1 signaling pathway; cell proliferation ⬆ cell autophagy	Downregulates the mTOR/S6K1 signaling pathway; Promotes cell autophagy; Ameliorates cell proliferation in aIgA1-induced HMCs
Zhang et al., 2022 [14]	RA	Dihydroartemisinin (20 mg/kg/day, orally administration, from day 21 after the second immunization to the day 49; a culture containing 0.2 and 0.4 μM DHA for 24 h)	DBA/1J mice and inflammatory model in THP-1 cells	⬇ IL-1β; IL-6; hypoxia-inducible factor (HIF)-1α protein expression; NLRP3 expression; JAK3 phosphorylation; STAT3 protein expression	Alleviates paw edema; Reduces bone destruction; Inhibted inflammatory activation in THP-1 cells; Inhibits NLRP3 expression via the HIF1α and JAK3/STAT3 signaling pathway
Sun et al., 2021 [15]	RA	Artesunate (a culture containing 0.2 μM, 0.4 μM, 0.8 μM artesunate for 15 min, 48 h, and 7 d; a culture containing 0.2 μM, 0.4 μM, 0.8 μM artesunate for 15 min, 48 h, and 7 d)	Mouse bone marrow macrophages and rat	⬇ ROS production; HO-1 and NQO1 expression	Inhibits osteoclastogenesis and attenuate bone erosion; Suppresses the generation of ROS via activating p62/Nrf2
Ma et al., 2019 [16]	RA	Artesunate (a culture containing 60 μM artesunate for 24 h)	FLSs (obtained from active RA patients)	⬇ MMP-2 and MMP-9 production; PDK-1 expression; Akt and RSK2 phosphorylation	Inhibites the migration and invasion of RA-FLS in a dose-dependent manner
Feng et al., 2018 [17]	RA	Artesunate (20 mg/kg/day, i.g. for 12 days)	SD rats	⬇ PI3K, AKT, mTOR, p-PI3K, *p*-AKT, *p*-mTOR Bcl-2 and Bcl-xl expression, chondrocyte proliferation, ⬆ expressions of Bax, LC3ll/LC3l and Becline-1 protein expression, cell apoptosis and autophagy	Alleviates the inflammation; Don't produce any form of hepatotoxicity; Inhibites chondrocyte proliferation and accelerates cell apoptosis and autophagy via suppression of the PI3K/AKT/mTOR signaling pathway
Fan et al., 2018 [18]	RA	DC32 (12.5 mg/kg/day, 25 mg/kg/day, and 50 mg/kg/day, administrated p.o. from day 26–46; a culture containing 0.1 μM, 0.3 μM, and 1 μM DC32 for 12 h and 24 h)	DBA/1 mice; Lymphocytes and FLSs from rat with adjuvant arthritis	Restores the Treg/Th17 balance; ⬇ IL-6 transcription; MMPs (MMP-2, MMP-3) secretion; chemokines (CXCL12, CX3CL1) and IL-6 transcription	Inhibites footpad swelling and lymphocytic infiltration in mice with CIA; Inhibites the lymphocyte-induced invasion and migration of FLSs
Fan et al., 2018 [19]	RA	DC32 (12.5 mg/kg/day, 25 mg/kg/day, and 50 mg/kg/day, administrated by oral gavage from day 26–46; a culture containing 1 μM, 3 μM, 10 μM DC32 for 24 h)	DBA/1 mice; NIH-3T3 cells	⬇ cartilage degradation, Akt/mTOR and ERK activation ⬆ p62 transcription; Nrf2 transcripition, expression, and nuclear translocation; Keap-1 protein degradation; HO-1 and p62 expression	Activates Nrf2/HO-1 signaling pathway
Liu et al., 2017 [20]	RA	Artesunate (5 mg/kg/day, 10 mg/kg/day, and 20 mg/kg/day, i.g. for 0–142 days)	SD rat	⬇ Th17 cells; IL-17 ⬆ Treg cells; Foxp3 expression	Regulates the Th17/Treg balance by inducing Th17-mediated apoptosis
Lin et al., 2016 [21]	RA	SM934 (10 mg/kg/day, orally administered for consecutive 40 days)	DBA/1J mice	⬇ Tfh cells and Th17 cells development; pathogenic antibodies; inflammatory cytokines; prolarization of naïve $CD4^+$ T cells into Tfh cells; Bcl-6 expression; IL-21	Alleviates the severity of arthritis

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Table 1 (*continued*)

Study	Disease	Intervention	Experimental models	Pharmacological mechanisms	Indication
Hou et al., 2014 [22]	RA	Artesunate (i.p., 100 mg/kg, twice/day, for 2 weeks)	K/BxN mouse	⬇ GC B cells proliferation ⬆ Foxp3+CD25+Tregs	Suppresses the GC response through abrogating GC B cells
Li et al., 2013 [23]	RA	Artesunate (5 mg/kg/day, by gavage for 16 days)	Wistar rats	⬇ IL-1b; TNF-α; IL-17α; MMP-9 expression and activity; IkB degradation; extracellular signal-regulated kinase (ERK) and c-Jun N-terminal kinase	Ameliorates rat CIA; Inhibits the action of proinflammatory cytokines and the activity of MMP-9 via suppression of nuclear factor kappa B and mitogen-activated protein kinase signaling pathway
He et al., 2011 [24]	RA	Artesunate (a culture containing 5 μM, 10 μM, 20 μM artesunate for 24 h)	FLSs (obtained from patients with active rheumatoid arthritis)	⬇ VEGF and IL-8 secretion; HIF-1α nuclear expression and translocation	Inhibits angiogenic factor expression in RA FLS
Wang et al., 2008 [25]	CIA	SM905 (0.25 mg/kg/day and 0.5 mg/kg/day, orally administered once daily beginning 1 day before or alternatively 14 days after booster immunization till the end of the experiment)	DBA/1 mice	⬇ T cell proliferation; IL-17 production; IL-17A and RORgt mRNA expression	Suppresses inflammatory and pathogenic Th17 responses
Cuzzocrea et al., 2005 [26]	CIA	Artemether (3 mg/kg/day, intramusculary administration from day 25 postimmunization to 35)	Lewis rats	⬇ Inflammatory cell infiltrate; NO formation	Reduces tissue edema and bone erosion in the paws
Jia et al.,. 2022 [27]	UC	Artemisnin (administered with 100 mg/kg/day of artemisinin suspension for 14 days)	Wistar rats	⬇ IL-1β; IL-17 ⬆ PPAR-γ	Inhibites IL-17 signaling pathway
Yin et al., 2021 [28]	UC	Artesunate (30 mg/kg/day, i. p. for 7 days)	ICR mice	Maintaines the expression of claudin-1 and Muc2 in mucosal layer of colon; ⬇ PERK-eIF2α-ATF4-CHOP and IRE1α-XBP1 signaling pathways activation; ER-stress-associated apotosis; NF-κB activation; pro-inflammatory cytokines	Inhibites the occurrence of ER stress; Improves the clinical and histopathological alterations
Yang et al., 2021 [29]	UC	Artesunate (injected with 50 mg/kg/day, 100 mg/kg/day, and 150 mg/kg/day by gavage administration for 7 days; a culture containing 5, 10, and 20 μg/ml artesunate for 0–72 h)	RAW264.7 cells; BALB/c mice	⬇ Cell apopotosis; Pro-inflammatory factors and miR-155 expression; p–NF–κB expression ⬆ Cell viability	Alleviates the mice's survival; Alleviates the inflammatory response
Yin et al., 2020 [30]	UC	Artesunate (30 mg/kg/day, injected i.p. for 7 days)	ICR mice	⬇ Muc2 and claudin-1 loss; cleaved-caspase-3 expression; IκBα and NF-κBp65 phosphorylation; IL-1β, IL-6, and TNF-α expression ⬆ Bcl-2/Bax ratio; IL-10 expression	Alleviates DSS-induced clinical symptoms by relieving body weight loss, the disease activity index (DAI) score, and preventing colonic shortening; Protects the integrity of intestinal barrier through alleviating DSS-induced erosion of surface epithelial cells, reduction of goblet cells, and destruction of the crypt accompanied with inflammatory cells infiltration
Sun et al., 2020 [31]	Colitis	Artesunate (25 mg/kg/day, i.g. administered for 10 days in vivo; a culture containing 2.5 μg/ml, 5 μg/ml, 10 μg/ml, and 20 μg/ml artesunate for 24 h, 48 h, and 72 h in vitro)	Wild type C57BL/6 mice; $RAG^{-/-}$C57BL/6 mice; Murine bone marrow-derived DCs and human THP-1 MΦs	⬇ TNF-α; IL-12p40/70	In vivo, induces apoptosis of lamina propria MΦs and DCs; In vitro, induces a dose- and time-dependent apoptosis of murine bone marrow-derived DCs and human THP-1 MΦs, through the caspases-9-mediated intrinsic pathway

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Study	Disease	Intervention	Experimental models	Pharmacological mechanisms	Indication
Liang et al., 2020 [32]	Colitis	Dihydroartemisinin (10 mg/kg/day and 20 mg/kg/day, i.p. injection for 7 days)	C57BL/6 mice	⬇ IL-1β; IL-6; TNF-α; NLRP3 inflammasome; NF-κB p65 and p38 MAPK phosphorylation ⬆ PPARγ; Ki-67	Improves the clinical symptoms; Suppresses p38 activator-induced pro-inflammatory response
Lei et al., 2020 [33]	IBD	Dihydroartemisinin (150 mg/kg/day, i.g. administration at day 12–18)	C57BL/6 mice	⬇ TNF-α; IL-1β; IL-23; Bacteroidetes and Verrucomicrobia ⬆ cell junction-associated genes (EpCAM and Claudins); Firmicutes and Proteobacteria	Improves the diarrhea and bloody stool induced by DSS; Recovers the abundance of these gut bacteria altered by DSS
Lee et al., 2020 [34]	Colitis	Artemisinin (20 mg/kg/day, orally administered for 7 days)	C57BL/6 mice	⬇ lymphatic vessel endothelial hyaluronan receptor-1-positive LVD; inflammatory cytokines, VEGF-C, -D, and VEGFR-3 expression	Reduces the symptoms of colitis; Improves tissue histology; Relieves inflammatory edema; Relieves immunomodulatory cells infiltration
Yan et al., 2019 [35]	Colitis	Dihydroartemisinin (at 4, 8, or 16 mg/kg/day, intraperitioneally administered at 8, 24, and 48 h after OXA or TNBS infusion; a culture containing DHA 0.8 mg/ml for 72 h)	BALB/c mice	⬇ Th1 cells; Th17 cells; Th22 cells; $CD4^+$ T lymphocytes activation ⬆ Tregs; $CD4^+$ T apoptosis; HO-1 production	Ameliorates colitis signs; Reduces lymphocyte infiltration and tissue fibrosis; Restores Th/Treg balance
Li et al., 2019 [36]	Colitis	Dihydroartemisinin (10, 25, and 50 mg/kg/day, oral gavage administered for 7 days; a culture containing DHA 100 μM for 24 h)	C57BL/6J mice; Intestinal epithelial cell-6	⬇ proinflammatory cytokines expression and secretion; PI3K, AKT, IKKα, IκBα, and NF-κB (p65) phosphorylation	Ameliorates body weight loss; Shortens colon length; Increases DAI; Improves histological damage
Chen et al., 2019 [37]	UC	Artesunate (on day 11 after DSS induction, orally administered 10, 30, and 50 mg/kg/day for 5 days)	Sprague-dawley rats	⬇ pro-inflammatory mediators levels; myeloperoxidase (MPO) activity; inflammatory and apoptotic markers; TNF-α; IL-8; IFN-γ; TLR4; p–NF–κB; p-p38; Bax; caspase-9 ⬆ hemoglobin expression; Bcl-2 expression	Alleviates the UC symptoms; Lowers the DAI; Ameliorates pathological changes; Attenuates colon shortening; Inhibites the activity of the TLR4-NF-κB signaling pathway by reducing the expression levels of TLR4, p–NF–κB, p-p38, Bax and caspase-9, and increasing the expression of Bcl-2
Yan et al., 2018 [38]	UC	SM934 (a culture containing SM934 0.8, 8, and 80 μmol/L for 24 h; 3 and 10 mg/kg/day, orally administered for 1–10 days)	RAW264.7 and THP-1 cells; BALB/c mice	⬇ MPO activitity; macrophages; neutrophils; pro-inflammatory cytokines (IL-1β, IL-6 and TNF-α) mRNA and protein levels; pro-inflammatory mediators; NF-κB signaling activation	Restores DSS-induced body weight loss, colon shortening injury and inflammation scores; Reduces histopathological scores
Yang et al., 2012 [39]	Colitis	Artesunate (150 mg/kg/day, injected i.p. for 0–7 days; a culture containing artesunate 2.5, 5, 10, and 20 μg/ml for 16 h)	BALB/c mice and peritoneal macrophages from C57BL/6 mice	⬇ NF-κBp65 and *p*-IκB-α expression; IFN-γ; IL-17; TNF-α	Suppresses TNF-α expression in vitro and in vivo as well as Th1/Th17 responses in TNBS colitis model
Xie et al., 2023 [40]	Neuroinflammation	Artesunate (at 2, 5, 10, and 15 μM was added 24 h after Hb treatment in vitro; at 20, 50 or 70 mg/kg/day via i.p. injection for 3 consecutive days before intracerebral haemorrhage induction in vivo)	BV2 cells; SD rats	⬇ IL-1β; TNF-α; mTORC1 S6KP70 and 4E-BP1 phosphorylation; GPX4 expression ⬆ ROS generation; lipid oxidation; AMPK phosphorylation	Ameliorates intracerebral haemorrhage secondary injury; Induces microglial cell iron death; Modulates AMPK/mTORC1/GPX4 pathway
Zhao et al., 2022 [41]	AD1	Artemisnin (injected i.p. with 5 mg/kg/day artemisinin for one month; a culture containing 0.25–1 μM artemisinin)	C57BL/6J mice; BV2 cells	⬇ ROS; iNOS; IL-1β; TNF-α; IL-6	Attenuates amyloid-induced neuroinflammation and neuronal damage; Inhibits TLR4/NF-κB signaling pathway

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Table 1 (*continued*)

Study	Disease	Intervention	Experimental models	Pharmacological mechanisms	Indication
Zhang et al., 2021 [42]	Neuroinflammation	Artemisinin (a culture containing 10 μM and 100 μM artemisinin for 24 h)	BV2 cell line; C57BL/6 mice	⬇ pro-inflammatory factors NO; IL-1β; TNF-α ⬆ junction proteins ZO-1, Occludin, Claudin-5	Attenuates LPS-induced blood–brain barrier disruption in mice; Inhibites LPS-induced TLR4 dimerization and endocytosis in microglial BV-2 cells; Inhibits the TLR4-JNK signaling axis
Gao et al., 2020 [43]	Neuroinflammation	Dihydroartemisinin (40 mg/kg/day, injected i.p. for 19 days)	C57BL6 mice	⬇ IL-1β and IL-6 expression; P-PI3K/PI3K, TNF and P-AKT/AKT expression; cell reactivity	Reduces damaged cells in the hippocamal CA1, CA2, CA3 and DG regions
Okorji et al., 2016 [44]	Neuroinflammation	Artemether (a culture containing 5–40 μM artemether for 24 h)	BV2 mouse microglia cell line ICLCATL03001	⬇ pro-inflammatory mediators (NO/iNOS, PGE2/COX-2/mPGES-1, TNFα and IL-6); NF-κB and p38 MAPK signalling ⬆ HO-1, NQO1, and GSH levels; Nrf2 expression	Activates Nrf2 activity by increasing nuclear translocation of Nrf2 and its binding to antioxidant response elements in BV2 cells
Wang et al., 2015 [45]	Neuroinflammation	Artesunate (a culture containing 0–60 μM artesunate for 24 h)	Murine BV2 microglial cells	⬇ NO, iNOS, and IL-1β production; TLR4 and MyD88 expression; NF-κB activation; NF-κB (IκB) degradation	Attenuates the generation ofproinflammatory mediators on LPS-stimulated BV-2 microglial cells and this effect may be associated with the suppression of TLR4/MyD88/NF-κB signaling pathways
Okorji et al., 2014 [46]	AD[1]	Artesunate (a culture containing 0.5–4 μM artesunate for 24 h)	BV2 mouse microglia cell line ICLC ATL03001	⬇ PGE2, TNF-α and IL-6 production; COX-2 and mPGES-1 proteins; NF-κB-driven luciferase expression; IκB phosphorylation and degradation; IKK; p38 MAPK and its substrate MAPKAPK2 phosphorylation	Prevents neuroinflammation in BV2 microglia by interfering with NF-jB and p38 MAPK signalling
Shi et al., 2013 [47]	AD[1]	Artemisinin (40 mg/kg/day, i.p. injection for 30 days)	APPswe/PS1dE9 transgenic mice	⬇ β-secretase activity; NF-κB activity; NALP3 inflammasome activation	Decreases neuritic plaque burden; Regulates APP processing via inhibiting β-secretase activity
Zhu et al., 2012 [48]	Neuroinflammation	Artemisinin (a culture containing 2.5 μM, 5 μM, 10 μM, and 20 μM artemisinin for 1 h before incubating with LPS for 3 h)	Microglial BV2 cells from Sprague-Dawley rats	⬇ TNF-α, IL-6, MCP-1, and NO production; pro-inflammatory cytokines and inducible nitric oxide synthase (iNOS) mRNA and protein levels ⬆ IkB-α protein	Inhibites basal and LPS-induced migration of BV-2 microglia
Gan et al., 2023 [49]	OA	Artemisnin (a culture containing 50 μM artemisinin for 30 min)	Human endothelial HUVEC cells, ATDC5 chondrocyte-like cells, and MLO-Y4 osteoblast-like cells	⬇ Piezo1 expression; OA-related genes; p-PI3K; *p*-AKT	Ailevates OA lesions
Li et al., 2022 [50]	OA	Arteminsin (a culture containing 5 μm, 10 μm, and 20 μm artemisinin for 48 h)	Primary chondrocytes (from the knee joints normal Sprague Dawley rats)	⬇ TNFSF11 expression; ⬆ Mitochondrial autophagy activation	Relieves OA; Inhibites PI3K/AKT/mTOR signaling
Ma et al., 2021 [51]	OA	Dihydroartemisinin (1 mg/kg/2 days, injected i.p. for 8 weeks)	C57BL/6J mice	⬇ MMP-13 and VEGF expression; LIF secretion; sclerostin inhibition	Decreased OARSI scores; Rduces articular cartilage degeneration; Increases bone volume fractions (BV/TV) and bone mineral densities (BMD); Decreases the inhibition of sclerostin through reduction of LIF secretion by osteoclasts, hence, attenuates aberrant bone remodeling and inhibites angiogenesis in subchondral bone, further

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Table 1 (*continued*)

Study	Disease	Intervention	Experimental models	Pharmacological mechanisms	Indication
					reducing the progression of OA
Li et al., 2019 [52]	OA	DC32 (a culture containing 0.1 μm, 0.3 μm, and 1 μm DC32 for 12 h and 24 h; 6.25 mg/kg/day, 12.5 mg/kg/day, and 25 mg/kg/day, p.o. for 4 weeks on day 14)	FLSs of OA rats; Sprague-Dawley rats and C57BL/6J mice	⬇ IL-6, IL-1β, CXCL12 and CX3CL1 transcription; ERK and NF-κB pathway activation; Nrf2 and HO-1 expression; IκBα degradation and phosphorylation; NF-κBp65 phosphorylation; MMP2, MMP3, MMP13 and ADAMTS-5 expression; TNF-α ⬆ Type II collagen and aggrecan expression	Inhibites the invasion and migration of cultured OA-FLSs; Alleviates papain-induced mechanical allodynia, knee joint swelling and infiltration of inflammatory cell in synovium
Li et al., 2019 [53]	OA	Artesunate (25 mg/kg/day, 50 mg/kg/day, 100 mg/kg/day, and 200 mg/kg/day, injected i.p. for 60 days)	C57BL/6J mice	Improves the expression of lubricin and aggrecan; ⬇ collagen X (ColX) and MMP-13 expression; TGF-β/Smad 2/3 signaling; $CD31^{hi}Emcn^{hi}$ vessel formation; VEGF and angiogenin-1 expression	Lowers histologic scoring of OA and retards calcification of the cartilage zone; Sppresses osteoclastic bone resorption through regulating RANKL-OPG system; Restores coupled bone remodeling; Abrogates $CD31^{hi}Emcn^{hi}$ vessel formation via downregulating the expression of vascular endothelial growth factor (VEGF) and angiogenin-1 in subchondral bone
Li et al., 2019 [54]	OA	Artesunate (a culture containing 3.125 μM, 6.25 μM, and 12.5 μM artesunate for 24 h)	ATDC5 murine teratocarcinoma cell line; OA mouse	⬇ IL-1β; MMP-3 and MMP-13 overexpression; pro-apoptotic Bax, cleaved caspase-3 and cleaved caspase-7 expression; IκBα and p65 phosphorylation ⬆ cell viability; anti-apoptotic factor Bcl-2 expression	Blockes the advancement of the calcified cartilage zone and the loss of proteoglycan; Lowers histological scoring of OA in a mouse model
Bai et al., 2018 [55]	OA	Artesunate (300 mg/kg/day, gavage administration for 8 weeks)	Wistar rats	⬇ OPN and CTX-II levels ⬆ IGF-1 level	Inhibits OA development by elevating IGF-1 level and reducing OPN and CTX-II levels
Zhong et al., 2018 [56]	OA	Artemisinin (injected with 0.1 ml of artemisnin (4 μg/ml) into the articular cavity once a week for 6 weeks; a culture containing 4 μg/ml artemisinin for 48 h)	Articular chondrocytes (from the joints of SD rats or patients with OA)	⬇ pro-inflammatory chemokines and cytokines expression (IL-1β, IL-6, TNF-α, and MMP-13) ⬆ cell proliferation and viability	Inhibites OA progression and cartilage degradation via the Wnt/β-catenin signaling pathway; Increases glycosaminoglycan, deposition, prevention of chondrocyte apoptosis, and degeneration of cartilage
Zhao et al., 2017 [57]	OA	Artesunate (25 mg/kg/day, injected i.p. for consecutive 10 weeks starting from the first day of operation)	Wistar rats	⬇ osteoclastogenesis; angiogenesis; inflammatory response; JAK/STAT signaling activation	Relieves ACLT-induced osteoarthritis; Improves expression of pathological genes
Jiang et al., 2016 [58]	OA	Dihydroartemisinin (a culture containing 3.125 μM, 6.25 μM, and 12.5 μM DHA for 24 h)	SD rats	⬇ MMP-3 and -9, ADAMTS5, CCL-2 and -5, and CXCL1 expression; p65 and IκBα proteins nuclear translocation and degradation; catabolic and inflammatory factors levels; NF-κB pathway ⬆ LC3-II and ATG5 levels; autophagy	Suppresses the levels of catabolic and inflammatory factors in chondrocytes by promoting autophagy via NF-κB pathway inhibition
Khakzad et al., 2017 [59]	MS	Artemisinin (200 mg/kg/day and 600 mg/kg/day, injected daily i.p. for 15 days)	57BL6 mice	⬇ IFN-γ ⬆ IL-4	The mean weight of mice is significantly (p value < 0.05) higher; The mean EAE score of mice is significantly (p value < 0.05) lower; The brain histology shows the absence of plaque formation

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Table 1 (*continued*)

Study	Disease	Intervention	Experimental models	Pharmacological mechanisms	Indication
					in the artemisinin treated group
Thomé et al., 2016 [60]	EAE	Artesunate (3 mg/kg/day via i.p. for 5 consecutive days)	MOG_{35-55} induced EAE C57BL6 mice; $RAG2^{-/-}$mice	⬇ pathogenic T cells migration	Reduces the clinical signs of EAE and that correlated with a reduced infiltration of cells in the CNS; Reduces the severity of EAE
Li et al., 2013 [61]	EAE	SM934 (10 mg/kg/day, treated from day 1–18 i.p. in vivo; a culture containing 1 μM SM934 for 96 h in vitro)	MOG_{35-55} induced EAE C57BL6 mice	⬇ IL-2; IFN-γ; IL-17; IL-6; Th17; Th1; $CD4^+$ T cells ⬆ IL-10; TGF-β; Treg cells	Suppresses the Th17 and Th1 responses in the peripheral
Zhao et al., 2012 [62]	EAE	Dihydroartemisinin (injected with 25 mg/kg/day of DHA for 16 days; a culture containing 0.4 μM DHA in vitro)	C57BL/6 mice	⬇ Th cell differentiation ⬆ Treg cells	Attenunates mTOR signal in T cells
Wang et al., 2007 [63]	EAE	SM933 (administered at 400 μg per mouse i.p. daily from day 8 onwards in vivo; cultured for 24 h in the presence of 1 μg/ml SM933 in vitro)	C57BL/6 mice	⬇ NF-κB; CDK2; cyclin A ⬆ IκB; Rig-G; p27 degradation; cell cycle progression	Inhibites of encephalitogenic T cell responses; Exhibits a Th2 immune deviation; Reduces activity and concentration of NO and inducible NO synthase
Chen et al., 2020 [64]	Psoriasis	Dihydroartemisinin (25 mg/kg/day and 50 mg/kg/day, i.p. administered for 7 consecutive days)	BALB/c mice; NSG mice	⬇ $CD8^+$ central memory T (TCM); $CD8^+$ resident memory T (TRM) cells; IL-15; IL-17; Frequency and number of $CD8^+$; eomesodermin; BCL-6; CD8+CLA+, $CD8^+CD69^+$ or $CD8^+CD103+$ TRM cells	Ameliorates acute skin lesion of psoriatic mice; Alleviates its recurrence; Attenuates epidermal pathology and T-cell infiltration in the skin of IMQ-induced psoriatic mice
Huang et al., 2019 [65]	Psoriasis-like dermatitis	Artesunate (30 mg/kg/day and 60 mg/kg/day, injected i.p. respectively on day 0, continuing through day 6)	BALB/c mice	⬇ Ki-67; γδ T cells	Lowers cumulative score and epidermal thickening; Ameliorates mice from systemic inflammation
Wu et al., 2015 [66]	Psoriasis	Artemether (a culture containing 10 μg/ml, 20 μg/ml, 40 μg/ml, 80 μg/ml, 160 μg/ml, and 320 μg/ml artemether for 24 h, 48 h, and 72 h; at 1%, 3%, and 5% concentrations of topical creams for 4 weeks)	HaCaT cells; ICR mice	⬇ Proliferation of cultured HaCaT cells ⬆ HaCaT apoptosis	Increases the degree of orthokeratosis and the relative epidermal thickness of mouse tail skin
Bai et al., 2020 [67]	AD[2]	Artesunate (5 mg/kg/twice daily and 10 mg/kg/twice daily at 08:30 and 20:30, treated i.p. on day 21, 25, 28, 32, and 35)	BALB/c mice	⬇ IgE; TNF-α; IL-6; IL-17; IL-23; STAT3 phosphorylation; ROR-γt protein ⬆ TGF-β; SOCS3 protein	Improves atopic dermatitis symptoms; Decreases the dermatitis score, ear weight difference, spleen weight, and lymph node weigh; Reduces ear and skin epidermal thickness and mast cell infiltration
Meng et al., 2018 [68]	EAMG	Artesunate (i.g. treated with artesunate at doses of 10 mg/kg/day and 100 mg/kg/day until day 43 post immunization)	Lewis rats	Modulates Th1/Th2 cytokine expression levels; ⬇ lymphocyte proliferation; CD86; synthesis of anti-R97-116 IgG, IgG2a, and IgG2b antibodies ⬆ Treg cells	Exerts its immunomodulatory effects
Liu et al., 2017 [69]	AIT	Dihydroartemisinin (5 mg/kg/day, 10 mg/kg/day, and 20 mg/kg/day, administrated by oral gavage for 28 days in vivo; a culture containing 0 μM, 5 μM, and 10 μM DHA for 48 h in vitro)	C57BL/6J mice	⬇ Proliferation of lymphocytes, binding of C-X-C chemokine ligand 10 (CXCL10) and its receptor (C–X–C motif) receptor 3 (CXCR3); Calcium flow; PI3-kinase (PI3K); p-PI3K; Protein kinase B (AKT); *p*-AKT; Nuclear factor (NF)-κB/p65; p–NF–κB/p65	Reduces antithyroglobulin antibody and thyroid peroxidase antibody levels; Regulates Th1/Th2 imbalance

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Table 1 (*continued*)

Study	Disease	Intervention	Experimental models	Pharmacological mechanisms	Indication
Yang et al., 2021 [70]	DED	SM934 (0.1% and 0.5%; a culture containing SM934 10 μM)	SD rats; C57/BL6 mice; RAW 264.7 cells, a murine macrophage cell line	⬇ TNF-α; IL-6; IL-10; IL-1β; TLR4; Inflammasome; MyD88; NLRP3; Apoptosis-associated speck-like protein containing CARD (ASC); Cleaved caspase 1	Increases tear secretion; Maintains the number of conjunctival goblet cells; Reduces corneal damage; Upregulation of TLR4 and downstream NF-κB/NLRP3 signaling proteins
Chen et al., 2021 [71]	T1DM	Artesunate (50 and 100 mg/kg/day, i.g. for 4 weeks)	Sprague-Dawley rats	⬇ NF-κB; CD68; MMP1; MMP9; RAGE	Restrains diabetes-induced cardiovascular complications by maintaining heart and body weight while reducing blood glucose; Regulates blood lipid indicators to normal level
Li et al., 2019 [72]	T1DM	Artesunate (final concentration 1 mg/ml)	NOD mice	⬇ IFN-γ–producing T cells; TNF-α; IL-6 ⬆ IL-4–producing $CD4^+$ single-positive T cells and $CD8^+$ Tcells; Regulatory T cells	Promotes the functional maturity of β cells in vitro
Li et al., 2017 [73]	T1DM	Artemether (a culture containing 0–10 μM artemether for 72 h)	Cells from genetic models	⬇ Arx ⬆ GABAA receptor signaling	Repress Arx by causing its translocation to the cytoplasm; Mechanism of action of these molecules depends on the enhancement of GABAA receptor signaling

ARTs Artemisinin and its derivatives, *SLE* Systemic lupus erythematosus, *LN* Lupus nephritis, *RA* Rheumatoid arthritis, *CIA* Collagen-induced arthritis, *UC* Ulcerative colitis, *DSS* Dextran sodium sulphate, *IBD* Inflammatory bowel diseases, *AD^1* Alzheimer's disease, *OA* Osteoarthritis, *MS* Multiple sclerosis, *IgAN* IgA nephropathy, *EAE* Experimental autoimmune encephalomyelitis, *AD^2* Atopic dermatitis, *EAMG* Experimental autoimmune myasthenia gravis, *AIT* Autoimmune thyroiditis, *DED* Dry eye disease, *T1DM* Type 1 diabetes mellitus, *FLSs* Fibroblast-like synoviocytes, *HUVECs* Human umbilical vein endothelial cells, *PBMC* Peripheral blood mononuclear cells, *HMCs* human mesangial cells, *BMMs* Bone marrow macrophages, *MIF* Migration inhibitory factor, *i.g.* intragastric, *i.p.* intraperitoneal, *p.o.* per os.

In this review, we reviewed the effects of ARTs based on existing research, summarized their potential mechanisms of action (see Table 1), and provided some clues for clinicians to treat such diseases.

2. The role of ARTs in the treatment of autoimmune and inflammatory diseases

2.1. Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is an intractable lifelong chronic autoimmune disease characterized by loss of tolerance to autoantigens and persistent autoantibody production, which results in immune complex-mediated damage in multiple organs, including renal and skin injuries [8]. Lupus nephritis (LN), a type of glomerulonephritis, is one of the most severe organ manifestations of SLE [9], affecting approximately 30–60% of adults and up to 70% of children with SLE [10].

A study showed that artemisinin (150 mg/kg/day, intragastric (i.g.) administration lasted 8 weeks) could reduce TNF-α and IL-6 serum levels, NF-κBp65 protein expression, and NF-κB and TGF-β1mRNA expression in LN mice [11]. Artesunate (125 mg/kg/day solved in 2 ml physiologic saline i. g. for 16 weeks) down-regulated monocyte chemotactic protein-1 (MCP-1), pro-inflammatory cytokine and B cell activating factor (BAFF), and suppressed the production of antinuclear antibody (ANA) and anti-double-stranded DNA (anti-dsDNA) antibodies in SLE mice [12].

Moreover, macrophage migration inhibitory factor (MIF) is a key regulator of atherosclerosis and SLE, but the factors that lead to its overproduction are unknown. Feng et al. used two models of SLE peripheral blood mononuclear cells (PBMCs) (a culture medium containing artesunate at the concentration of 5 or 20 μmol/L for 12 h and 24 h) and human umbilical vein endothelial cells (HUVECs) (a culture medium containing artesunate at the concentration of 5 or 20 μM at 3×10^5 per well for 24 h) to explore the effect of artesunate on MIF levels and its underlying mechanism. They found that artesunate could down-regulate IFN inducible genes (LY6E and ISG15) expression and inhibit MIF production through restraining over-expression STAT1 phosphorylation (p-STAT1) in both HUVEC and PBMC cultures [13]. Artesunate (low-dose (2.5 mg/kg, twice a day) and high-dose (5 mg/kg, twice a day), oral administration lasted 8 weeks) treated groups suppressed T follicular helper (Tfh) cell differentiation, decreased Tfh cell count, and held the ratio of T follicular regulatory (Tfr) to Tfh cells to recover T cell subsets. Furthermore, artesunate changed the activation status of JAK2-STAT3 signaling pathway by inhibiting JAK2 phosphorylation and p-STAT3 [14].

SM934 (beta-aminoarteether maleate) is a water-soluble derivative of arteminisin [15]. SM934 (5 mg/kg, 2.5 mg/kg, and 1.25

mg/kg, twice-daily, oral i. g. from 9 weeks to 27 weeks of age) significantly extended the life-span of MRL/lpr mice, improved lymphadenopathy symptoms, and reduced serum levels of antinuclear antibodies (ANA) and disease-causing cytokines IL-6, IL-10, and IL-21. Futhermore, SM934 (10 μM, without cytotoxicity to splenic B cells, stimulate B cells in vitro for 48 h) restored the spleen B-cell compartment of MRL/lpr mice via increasing the number of resting B cells, sustaining the number of germinal center B cells, and decreasing the number of activated B cells and plasma cells [15]. The study claimed that SM934 (10 μM, without cytotoxicity to splenic B cells, stimulate B cells in vitro for 72 h) might distract the B-cell inherent pathway by downregulating the expression of TLR7/9 mRNA and MyD88 protein, and NF-κB phosphorylation [15]. As for human PBMCs, consistent with the results in MRL/lpr mice, SM934 (60 μM, without cytotoxicity to PBMCs, stimulate PBMCs in vitro for 48 h or 6 d) could retrain B cell activation and proliferation in PBMCs, inhibit plasma cells differentiation, and reduce antibody secretion [15]. In NZB/W F_1 mice, SM934 (3 mg/kg/day or 10 mg/kg/day, oral administration lasted 3 months or 6 months) reduced Th1-related anti-dsDNA IgG2a and IgG3 Abs, IL-17 serum level, and elevated Th2-related anti-dsDNA IgG1 Ab, IL-10, and IL-4 serum level [16]. Furthermore, SM934 (10 mg/kg/day, oral administration lasted 3 months) suppressed the accumulation of effector/memory T cells and induced the apoptosis of $CD4^+$ T cells, while enhancing the development of regulatory T cells in LN mice [16]. Hou et al. found that SM934 (10 mg/kg/day and 2.5 mg/kg/day, oral administration lasted 4 weeks, for 6 consecutive days every week) could reduce serum IFN-γ and anti-dsDNA IgG, especially IgG2a antibodies in vivo. In vitro, SM934 (10 mg/kg/day, oral administration lasted 4 weeks) inhibited the production of IFN-γ and IL-17, blocked the differentiation of naive $CD4^+$ T cells into Th1 and Th17, but not Treg cells. Ex vivo, SM934 (10 mg/kg/day of SM934, oral administration lasted 4 weeks) increased the percentage of Treg cells, inhibited the development of Th1 and Th17 cells, and retrained the comprehensive activation of STAT (STAT-1, STAT-3, and STAT-5) proteins in splenocytes of MRL/lpr mice [17].

Huang et al. discovered that DHA could inhibit LPS-induced TLR4-IRF signaling pathway, showing that DHA (a culture containing 0.1 μM, 1 μM, and10 μM DHA for 24 h) could inhibit spleen cell activation and proliferation by reducing LPS-induced TLR4 protein expression and IRF3 phosphorylation. Furthermore, DHA (a culture containing 10 μM DHA for 24 h) significantly reduced the expression of IFN-β gene, and the release of IFN-α and IFN-β [18]. Li et al. found that DHA strongly reduced TNF-α production in the culture supernatant of the peritoneal macrophages and in the sera of BXSB mice in vitro (mice peritoneal macrophage were prepared and co-cultured with DHA (0.25 μM, 2.5 μM, 25 μM, and 250 μM) for 2 h) or in vivo (DHA at 5 mg/kg/day, 25 mg/kg/day, and 125 mg/kg/day for 10 days by i. g.). What's more, DHA could suppress the degradation of IκB-α protein, the expression of NF-κB and NF-κBp65 of BXSB mice model in vivo (same as above), and the nuclear translocation of BXSB mice model in vitro (same as above) [19]. These observations suggested that the inhibitory effects of DHA on TNF-α production may result from the block in the NF-κB signaling pathway upstream of IκB degradation. In addition, myeloid-derived suppressor cells (MDSCs) senescence plays a crucial role in the pathogenesis of SLE. DHA (100 mg/kg/day, oral administration lasted 2 months) attenuated the symptoms of SLE mice through relieving MDSCs aging, which was involved in the induction of Nrf2/HO-1 pathway [20]. DHA alleviated the manifestations of pristane-induced SLE mice, suppressed inflammation, restored the Treg/Th17 balance in vivo (100 mg/kg/day, administration per os (p.o.) lasted 2 months), and inhibited Th17 cell differentiation, while inducing Treg cell differentiation in vitro (a culture with 1 mg/ml DHA for 48 h) [21].

Above all, the pathogenesis of SLE mainly involve increasing deposition of autoantibodies, abnormal activation of T cells and B cells, secretion of pathogenic factors by macrophages, and MDSCs senescence. In vitro and in vivo experiments have validated that ARTs can alleviate the development of SLE, relieve clinical symptoms, and prolong life span of SLE mice. It is speculated that the therapeutic mechanisms of ARTs against SLE may be related to inhibiting autoantibody production through downregulating BAFF, maintaining Tfr/Tfh ratio by inhibiting JAK2-STAT3 signaling pathway activation, and restoring Treg/Th17 balance possibly by suppressing Th17 cell differentiation and inducing Treg cell differentiation, and subsequently restoring T cell subpopulation to normal. Moreover, ARTs can restore B cell subpopulation to normal through blocking TLR-triggered B cell activation and plasma cell formation. ARTs can also hinder MDSCs senescence by inhibiting Nrf2/HO-1 pathway and impede the release of inflammatory factors via hampering NF-κB signaling pathway.

2.2. Immune-mediated kidney disease

Kidney is usually the target of pathogenic renal autoantigens or systemic autoimmune reactions [22]. Immunoglobulin A nephropathy (IgAN) is the most common form of primary glomerulonephritis worldwide, and one of the leading causes of chronic kidney disease, progressing to end-stage renal disease in up to 40% of patients [23].

DHA (a culture containing 0–15 μM DHA for 24 h) down-regulated the mammalian rapamycin/ribosomal protein S6 kinase β-1 (mTOR/S6K1) signaling pathway in human mesangial cells (HMCs). Thus, the drug might be a novel mTOR inhibitor, which could promote autophagy, inhibit HMCs cell proliferation, and provide another pathway for IgAN treatment [24]. In addition, Yang et al. found that artemisinin could improve renal injury and fibrosis in mice (46.6 mg/kg/day, gavaged for 8 weeks). It attenuated LPS-induced oxidative stress and fibrosis, promoted AKT phosphorylation, and Nrf2 nuclear translocation in vitro (a culture containing 12 μM artemisinin for 2 h) [25]. Therefore, artemisinin might reduce the level of fibrosis and oxidative stress with IgA nephropathy through the AKT/Nrf2 pathway, which provided an alternative treatment for IgAN.

2.3. Immune-and inflammation-mediated joint diseases

2.3.1. Rheumatoid arthritis

Rheumatoid arthritis (RA) is a heterogeneous and systemic autoimmune disease that causes polyarthritis mainly in small joints of the hands and feet [26].

Evidence based on animal models or patients has accumulated on the effectiveness of ARTs in the treatment of RA. Su et al. used mouse bone marrow macrophages (a culture containing 0.2 μM, 0.4 μM, 0.8 μM artesunate for 15 min, 48 h, and 7 d) and collagen-induced arthritis (CIA) rat models (7.5 mg/kg/day, 15 mg/kg/day, and 30 mg/kg/day, i. g. for 30 d) to investigate the effect of artesunate on the bone erosion during RA progression. The study suggested that artesunate might inhibit osteoclastogenesis and attenuate bone erosion through suppressing the generation of ROS via activating p62/Nrf2 [27]. Ma et al. conducted a study with fibroblast-like synoviocytes (FLS) from active RA patients, and found that artesunate (a culture containing 60 μM artesunate for 24 h) significantly suppressed PDK-1 expression and phosphorylation of AKT and RSK2, and inhibited the migration and invasion of RA-FLS as well as the expression of MMP-2 and MMP-9 [28]. Furthermore, artesunate (a culture containing 5 μM, 10 μM, and 20 μM artesunate for 24 h) could reduce the secretion of vascular endothelial growth factor (VEGF), IL-8, and HIF-1α in TNF-α- or hypoxia-induced RA FLS [29]. In rats with type II CIA, artesunate (20 mg/kg/day, i. g. for 12 days) not only inhibited the proliferation of chondrocytes and accelerated cell apoptosis and autophagy by inhibiting the PI3K/AKT/mTOR signaling pathway [30], but also (5 mg/kg/day, 10 mg/kg/day, and 20 mg/kg/day, i. g. for 0–142 days) regulated Th17/Treg cell balance in a dose-dependent manner by increasing the expression of forkhead/winged helix transcription factor (Foxp3) and decreasing the expression of IL-17 [31]. In K/BxN mouse model of RA, artesunate (intraperitoneal (i.p.), 100 mg/kg, twice/day, for 2 weeks) affected adaptive response via restraining germinal center (GC) B cell proliferation and differentiation, and reduced autoantibody production primarily by inhibiting adaptive immune response. These results identify GC B cells as a target of artesunate and provide a new rationale for using artemisinin analogues to treat autoimmune diseases mediated by autoantibodies [32]. Artesunate (5 mg/kg/day, by gavage for 16 days) could hinder NF-κB and mitogen-activated protein kinase (MAPK) signaling pathway by blocking the degradation of IκB and the activation of extracellular signal-regulated kinase (ERK) and c-Jun N-terminal kinase (JNK), and ultimately inhibit the expression of proinflammatory cytokines (IL-1β, TNF-α, IL-17α) and the activity of MMP-9 on type II CIA in rats [33]. DHA (20 mg/kg/day, orally administration, from day 21 after the second immunization to the day 49) could effectively alleviate the symptoms of inflammation and arthritis in CIA mice. It (a culture containing 0.2 and 0.4 μM DHA for 24 h) might inhibit the expression of NLRP3 through the hypoxia-inducible (HIF)-1α and JAK3/STAT3 signaling pathways, thereby partially reducing the inflammatory response in vitro [34].

DC32 [(9α, 12α-dihydroartemisinyl) bis (2′-chlorocinnmate)] [35], a DHA derivative. In CIA mice (12.5 mg/kg/day, 25 mg/kg/day, and 50 mg/kg/day, administrated by oral gavage from day 26–46) and cellular model of inflammation (a culture containing 1 μM, 3 μM, 10 μM DC32 for 24 h), DC32 alleviated footpad inflammation, reduced cartilage degradation by increasing the transcription and expression of p62 and Nrf2 through regulating the Nrf2-p62-Keap1 feedback loop, promoting Keap1 protein degradation, up-regulating HO-1 expression, and thereby significantly relieved RA [35]. Furthermore, DC32 (a culture containing 0.1 μM, 0.3 μM, and 1 μM DC32 for 12 h and 24 h) inhibited the lymphocyte-induced invasion and migration of FLSs by decreasing the secretion of MMPs (MMP-2, MMP-3) in vitro, and DC32 (12.5 mg/kg/day, 25 mg/kg/day, and 50 mg/kg/day, administrated p. o. from day 26–46) attenuated RA by restoring Treg/Th17 balance, and suppressed lymphocytic infiltration through downregulation of IL-6 in CIA mice [36]. Artemether (3 mg/kg/day, intramusculary administration from day 25 postimmunization to 35) reduced anti-CII antibody response, diminished inflammatory cell infiltration, and inhibited NO production, showed that artemether could improve the articular edema and bone erosion in Lewis rats with CIA and delay the progression of the disease [37]. In addition, in DBA/1J mice with CIA, SM934 (10 mg/kg/day, orally administered for consecutive 40 days) might alleviate RA by restraining the development of both Tfh cells and Th17 cells, the production of pathogenic antibodies, and a series of subsequent antibody-mediated immune responses [38]. SM905 [1-(12β-Dihydroartemisinoxy)-2-hydroxy-3-*tert*-butylaminopropane maleate; $C_{26}H_{43}NO_{10}$] [39] (0.25 mg/kg/day and 0.5 mg/kg/day, orally administered once daily beginning 1 day before or alternatively 14 days after booster immunization till the end of the experiment) inhibited CII-induced T cell proliferation, IL-17α production, mRNA expression of IL-17α and RORγt (a specific transcription factor for Th17), and inhibited the expression of pro-inflammatory mediators in arthritic joints, which indicated that SM905 had beneficial effects on CIA by suppressing inflammatory and pathogenic Th17 responses [40].

The above studies reveal the potential of ARTs in the treatment of RA, including reducing the incidence and severity of RA, improving articular edema and bone erosion, and inhibiting chondrocyte proliferation, accelerating apoptosis and autophagy, and thereby delaying progression of the disease. Moreover, the above studies show that ARTs can improve RA mainly by reducing the production of autoantibodies, suppressing the expression of pro-inflammatory cytokines, chemokines and chemokine receptors, maintaining the balance of lymphocytes, and regulating the disorder of lymphocytes activation.

2.3.2. Osteoarthritis

Osteoarthritis (OA) is a highly prevalent and disabling joint disease characterized by pathology of the entire joint including degeneration of articular cartilage, subchondral osteoporosis, and synovial inflammation [41].

OA-patient-derived chondrocytes and OA rats are common experimental models. Studies with related models show that artemisinin (injected with 0.1 ml of artemisnin (4 μg/ml) into the articular cavity once a week for 6 weeks) can enhance cell proliferation and viability, increase glycosaminoglycan deposition, and prevent chondrocyte apoptosis and cartilage degeneration. Artemisinin (a culture containing 4 μg/ml artemisinin for 48 h) relieved IL-1β-mediated inflammatory response, OA progression, and cartilage degradation via suppressing Wnt/β-catenin signaling pathway in vitro [42]. It has been reported that aberrant stress activation of Piezo1 leads to reduced chondrocyte activity or death and is strongly associated with cartilage damage [43,44]. Interestingly, Gan et al. have provided strong evidence supporting that artemisinin is a novel potent inhibitor of Piezo1 activation in primary OA-Human primary articular chondrocytes (HACs) and all cell lines examined, including human endothelial HUVEC cells, ATDC5 chondrocyte-like cells, and MLO-Y4 osteoblast-like cells [45]. In vitro, artemisinin (a culture containing 50 μM artemisinin for 30 min) reduced the Yoda1-induced increased in OA-related genes as well as p-PI3K and p-AKT protein levels in OA-HACs and attenuated DMM-induced OA injury in mice. Li et al. found that artemisinin (a culture containing 5 μm, 10 μm, and 20 μm artemisinin for 48 h)

relieved OA by activating mitochondrial autophagy by reducing TNFSF11 expression and inhibiting PI3K/AKT/mTOR signaling [46].

Artesunate (25 mg/kg/day, injected i. p. for consecutive 10 weeks starting from the first day of operation) inhibited the activation of JAK/STAT signal and improved the expression of pathological genes (ACTX-II, IL-6, and PEG2) in OA rats [47]. Moreover, it (25 mg/kg/day, 50 mg/kg/day, 100 mg/kg/day, and 200 mg/kg/day, injected i. p. for 60 days) inhibited osteoclast bone resorption by regulating RANKL-OPG system and restored bone remodeling by indirectly inhibiting TGF-β/Smad2/3 signaling pathway in OA mice [48]. Artesunate (300 mg/kg/day, gavage administration for 8 weeks) increased insulin-like growth fctor-1 (IGF-1) level and decreased osteopontin (OPN) and C-telopeptides of CTX-II levels in OA rats [49]. Artesunate suppressed osteoclast formation and abnormal angiogenesis by reducing the expression of vascular endothelial growth factor (VEGF), basic fibroblast growth factor (BFGF), and angiopoietin-1 (Ang-1) proteins [47,48].

In addition, DHA (1 mg/kg/2 days, injected i. p. for 8 weeks) could increase bone volume fraction and bone density, and lower the inhibition of sclerostin via reducing the secretion of leukemia inhibitory factor (LIF) by osteoclasts, and thus weaken the abnormal bone remodeling and inhibit angiogenesis in subchondral bones [50].

ARTs suppressed the activation of NF-κB and ERK signaling pathways by inhibiting the degradation and phosphorylation of IκBα and p65 proteins, thereby activated the autophagy of mouse chondrocytes via increasing the levels of autophagy markers such as LC3-II, ATG5, and the number of autophagosomes [51–53]. In addition, artesunate (a culture containing 3.125 μM, 6.25 μM, and 12.5 μM artesunate for 24 h) lowered the expression of pro-apoptotic Bax, cleaved caspase-3 and -7 in a dose-dependent manner and increased the expression of anti-apoptotic Bcl-2 in vitro [53]. ARTs exhibited potent anti-inflammatory effects by inhibiting the expression of pro-inflammatory factors (IL-1β, IL-6, TNF-α, and MMP-13) and promoting the expression of anti-inflammatory factors (IGF-1, IL-4, and TNF-β) [42,47,52]. ARTs up-regulated the expression of type II collagen and aggrecan [48,52], but down-regulated the expression of MMP-2, MMP-3, MMP-9, MMP-13, ADAMTS5, CCL-2, CCL-5, CXCL1, CXCL12, and CX3CL1 [42,47–53].

The currently known studies demonstrate that ARTs can alleviate pain, knee joint swelling, and infiltration of inflammatory cells in the synovium. Moreover, ARTs show favorable chondro-protective effect as evidence by enhancing cell proliferation and viability and increasing glycosaminoglycan deposition. These studies indicate that ARTs may be potential therapeutic agents for OA due to the abilities to inhibit OA progression, prevent chondrocyte apoptosis and articular cartilage degradation [42,47–53].

2.4. Immune-mediated skin diseases

2.4.1. Psoriasis

Psoriasis is a common and chronic popular squamous skin disease that can occur at any age and bring substantial burden to individuals and society [54]. The mechanism of its occurrence is abnormal hyperplasia of the dermis and epidermis [2].

Artemether inhibited the proliferation of HaCaT cell in a time-dependent (24 h, 48 h, and 72 h) and dose-dependent manner (a culture containing 10 μg/ml, 20 μg/ml, 40 μg/ml, 80 μg/ml, 160 μg/ml, and 320 μg/ml), and dose-dependently augmented the apoptosis of HaCaT cells. At 1%, 3%, and 5% concentrations of topical creams for 4 weeks, artemether suppressed the degree of keratinization, and the relative epidermal thickness of mice in dose-dependently in mice, and indicated a regulatory effect on keratinocyte differentiation activity [55]. For imiquimod-induced psoriasis-like dermatitis in mice, artesunate (30 mg/kg/day and 60 mg/kg/day, injected i. p. respectively on day 0, continuing through day 6) alleviated psoriatic dermatitis, reduced epidermal thickening, Ki-67 expression, and γδT cells in draining lymph nodes, which might be benefit the improvement of dermatitis [56]. In addition, DHA (25 mg/kg/day and 50 mg/kg/day, i. p. administered for 7 consecutive days) could not only ameliorate acute skin lesion of psoriatic mice, but also diminish recurrence by reducing $CD8^+$ central memory T (T_{CM}) and $CD8^+$ resident memory T (T_{RM}) cells, decrease epidermal pathology and T cell infiltration, and inhibit the expression of pro-inflammatory factors (IL-15, IL-17) [57].

2.4.2. Atopic dermatitis

Atopic dermatitis (AD) is a relapsing and chronic skin disease characterized by intense itching and a variety of clinical symptoms [58].

Artesunate (5 mg/kg/twice daily and 10 mg/kg/twice daily at 08:30 and 20:30, treated i. p. on day 21, 25, 28, 32, and 35) improved atopic dermatitis symptoms and mast cell infiltration, mainly by inhibiting the level of IgE and TNF-α, decreasing the expression of IL-6, IL-17 and IL-23, promoting SOCS3 protein and significantly restraining ROR-γt protein and STAT3 protein phosphorylation. These results indicated that ARTs might alleviate atopic dermatitis by inhibiting the release of inflammatory cytokines and down-regulating the response of Th17 cells in atopic dermatitis mice [59].

In summary, these studies indicate that ARTs may attenuate both psoriasis and AD by inhibiting immune cells such as $CD8^+$ memory T cells, γδ T/Th17 cells and mast cells, and diminishing the level of inflammatory cytokines.

2.5. Immune-mediated Gastrointestinal System diseases

Inflammatory bowel disease (IBD) is a chronic inflammatory bowel disorder mediated by autoimmunity. Traditionally, IBD is classified into ulcerative colitis (UC) and Crohn's disease (CD) according to its phenotypic characteristics [60]. Experimental UC models are commonly established for the study of IBD.

In mouse models of dextran sulfate sodiumn (DSS)-induced UC, artesunate (30 mg/kg/day, i. p. for 7 days) inhibited the occurrence of endoplasmic reticulum (ER) stress via preventing the activation of PERK-eIF2α-ATF4-CHOP and IRE1α-XBP1 signaling pathways, simultaneity ER-stress-associated apoptosis in colon tissues [61]. In addition, ARTs remarkably suppressed the activation of NF-κB, PI3K/AKT, and p38 MAPK signaling pathways, the expression levels of pro-inflammatory cytokines (IL-1β,IL-6,TNF-α, IL-23,IL-8,

IL-17, and IFN-γ) and Th1/T17 [61–70], and improved the clinical and histopathological alterations as well as maintained the expression of Claudin-1 and Muc2 in mucosal layer of colon [61,62]. Moreover, artemisinin (administered with 100 mg/kg/day of artemisinin suspension for 14 days) could downregulate the expression of proinflammatory cytokines such as IL-1β and IL-17 in the IL-17 signaling pathway and upregulate the expression ofthe anti-inflammatory cytokine PPAR-γ in UC rats [71].

Artesunate (30 mg/kg/day, injected i. p. for 7 days) significantly protected the integrity of intestinal barrier through alleviating DSS-induced erosion of surface epithelial cells, reducing goblet cells, and destructing inflammatory-cell-infiltrated crypts [62]. The immunomodulatory mechanism of artesunate involved a novel and potent intrinsic apoptosis pathway for inducing proliferation of macrophages and dendritic cells and suppressing IL-12 and TNF-α both in vivo (125 mg/kg/day, i. g. administered for 10 days) and in vitro (a culture containing 2.5 μg/ml, 5 μg/ml, 10 μg/ml, and 20 μg/ml artesunate for 24 h, 48 h, and 72 h) [63].

DHA (150 mg/kg/day, i. g. administration at day 12–18) could up-regulated the expression of EpCAM, Claudins and other cell junction-associated genes, and restored the abundance of intestinal flora altered by DSS [65]. Furthermore, DHA (at 4, 8, or 16 mg/kg/day, intraperitioneally administered at 8, 24, and 48 h after OXA or TNBS infusion) treatment ameliorated colitis signs, reduced lymphocyte infiltration and tissue fibrosis in vivo. It (a culture containing DHA 0.8 mg/mL for 72 h) also promoted heme oxygenase-1 (HO-1) production in vivo and vitro, accompanied with $CD4^+$ T cell apoptosis and restored the Th/Treg balance [72]. Artemisinin (20 mg/kg/day, orally administered for 7 days) improved inflammation-driven lymphangiogenesis via VEGF-C/VEGFR-3 signaling pathway in a mouse model of experimental colitis, suggested that VEGF-C/VEGFR-3 signaling pathway might be a potential target for the treatment of IBD [73].

Taken together, treatment with ARTs significantly relieve clinical symptoms and inflammatory edema, improve histopathological, and modulate immune-inflammatory responses induced by DSS in mice such as restoring weight loss, preventing colon shorten, reducing disease activity index scores, histopathological scores and myeloperoxidase activity, and enhancing hemoglobin expression. These studies suggest that ARTs can protect the integrity of intestinal barrier by maintaining the expression of intestinal mucosal barrier related proteins, restoring the abundance of intestinal flora, inhibiting apoptosis, and exerting immunomodulatory and anti-inflammatory effects, thereby indicate that ARTs have potential to treat IBD.

2.6. Immune- and inflammation-mediated neurological diseases

2.6.1. Multiple sclerosis

Experimental autoimmune encephalomyelitis (EAE) is the most commonly used model for multiple sclerosis (MS) [74]. EAE is a complex disease in which interactions of multiple immunopathological and neuropathological mechanisms lead to the key pathological features of MS, including inflammation, demyelination, axonal loss, and gliosis [74].

In mice with myelin oligodendrocyte glycoprotein (MOG) $_{35\text{-}55}$ peptide-induced EAE, artemisinin (200 mg/kg/day and 600 mg/kg/day, injected daily i. p. for 15 days) reduced the concentration of IFN-γ and increased the concentration of IL-4, thereby transformed the immune response from Th1 to Th2 and reduced the severity of disease [75]. Furthermore, artesunate (3 mg/kg/day via i. p. for 5 consecutive days) could reduce the clinical symptoms of autoimmune encephalomyelitis by inhibiting the migration and infiltration of pathogenic T cells to the central nervous system [76]. SM934 (10 mg/kg/day, treated day 1–18 i. p.) ameliorated murine EAE via enhancing the expansion and function of Treg cells and strongly suppressed Th17 and Th1 in vivo and in vitro (a culture containing 1 μM SM934 for 96 h) [77]. Analogously, DHA (injected with 25 mg/kg/day of DHA for 16 days) significantly decreased Th but increased Tregs without apparent global immune suppression in vivo. In vitro, DHA (a culture containing 0.4 μM DHA) promoted the growth of Tregs through dose-dependent TGF-βR/Smad signal. Moreover, DHA modulated the mTOR pathway, because mTOR signal was attenuated in T cells upon DHA treatment. These results implied a novel immune regulatory function of DHA in reciprocally regulated Th and Tregs generation through modulating mTOR pathway [78]. Ethyl 2-[4-(12-β-artemisininoxy)]phenoxylpropionate (SM933) is a novel derivative of artemisinin [79]. The main anti-inflammatory features of SM933 are inhibition of brain-derived T-cell responses, namely Th2 immune bias, and reduction of the activity and concentration of NO and iNOs via NF-κB and Rig-G/JAB1 signaling pathways in vivo (administered at 400 μg per mouse i. p. daily from day 8 onwards) and in vitro (cultured for 24 h in the presence of 1 μg/ml SM933) [79].

These studies suggest that ARTs are novel anti-inflammatory agents acting through defined signaling mechanisms to modulate Th1/Th2 balance, inhibiting the production and differentiation of Th17.

2.6.2. Autoimmune myasthenia gravis

Autoimmune encephalomyelitis (MG) is an autoimmune disorder characterized by dysfunction of neuromuscular junction transmission [80].

In rats with experimental autoimmune myasthenia gravis (EAMG), artesunate treatment (i.g. treated with artesunate at doses of 10 mg/kg/day and 100 mg/kg/day until day 43 post immunization), especially in low doses, played an immunosuppressant role by inhibiting lymphocyte proliferation and the expression of costimulatory molecule CD86, regulating the expression level of Th1/Th2 cytokines, and enhancing the levels of Tregs. Ultimately, artesunate reduced the synthesis of anti-R97-116 IgG, IgG2a, and IgG2b antibodies, hence it might improve clinical symptoms and block the development of EAMG [80]. These data implied that artesunate might be a potential drug for the treatment of human myasthenia gravis (MG).

2.6.3. Neuroinflammation

Neuroinflammation is one of the host defense mechanisms by which the nervous system protects itself from pathogens and infectious damage. It occurs as one of the most common pathological outcomes in various neurological disorders and becomes the

promising therapeutic target [81].

In microglial BV2 cells (a culture containing 2.5 μM, 5 μM, 10 μM, and 20 μM artemisinin for 1 h before incubating with LPS for 3 h) and mice (40 mg/kg/day, i. p. injection for 30 days) with neuroinflammation, artemisinin attenuated proinflammatory responses via inhibiting NF-κB signaling pathway and NLRP3 inflammasome activation82,83. Moreover, artemisinin (a culture containing 10 μM and 100 μM artemisinin for 24 h) might inhibit the TLR4-JNK signaling axis and block pro-inflammatory cytokines by targeting Toll-like receptor TLR4 co-receptor MD2 and suppressing LPS-induced TLR4 dimerization and endocytosis in microglial BV-2 cells [82]. Futhermore, Artemisinin (injected i. p. with 5 mg/kg/day artemisinin for one month) attenuated amyloid-induced neuroinflammation and neuronal damage by modulating the TLR4/NF-κB signaling pathway in Alzheimer's disease (AD) model mice [83].

Similar to artemisinin, artesunate (a culture containing 0–60 μM artesunate for 24 h) inhibited the expression of TLR4 and MyD88, and the activation of NF-κB via blocking the degradation of IκB, suggested that artesunate might inhibit the production of pro-inflammatory mediators by suppressing TLR4/MyD88/NF-κB signaling pathway [84]. What's more, artesunate ameliorated intracerebral haemorrhage (ICH) secondary injury in vitro (at 2, 5, 10, and 15 μM was added 24 h after Hb treatment) and in vivo (rats received artesunate at 20, 50 or 70 mg/kg/day via i. p. injection for 3 consecutive days before ICH induction) by inducing microglial cell iron death and further inhibiting inflammation mainly through the AMPK/mTORC1/GPX4 pathway [85]. This finding may provide a new target for the treatment of ICH. Artesunate (a culture containing 0.5–4 μM artesunate for 24 h) restrained PGE_2 production by reducing protein expression of COX-2 and mPGES-1, and prevented neuroinflammation in BV2 microglia through interfering with NF-κB and p38 MAPK signalling [86].

Artemether is a lipid-soluble derivative of artemisinin. Artemether (a culture containing 5–40 μM artemether for 24 h) has been reported to inhibit NF-κB and p38 MAPK signals and induce Nrf2 expression, which mediates the anti-inflammatory effect of BV2 microglia [87]. Unlike artemether, DHA (40 mg/kg/day, injected i. p. for 19 days) hindered LPS-induced inflammation by inhibiting PI3K/AKT pathway. Moreover, DHA alleviated LPS-induced behavior and memory impairments via reducing the amount of LPS-induced cell damage in the CA1, CA2, CA3, and DG regions of the hippocampus [88].

Taken together, ARTs significantly block the expression of pro-inflammatory mediators (TNF-α, IL-6, IL-1β, MCP-1, NO/iNOs, and PGE2/COX-2/MPGES-1) and the activation of NALP3 inflammasome, and alleviate neurodegeneration development, LPS-induced behavioral and memory impairments, neuroinflammation, and amyloidosis in mice [82,89,90,84,86–88]. Furthermore, ARTs increase junction proteins ZO-1, Occludin, and Claudin-5 in primary brain microvessel endothelial cells, and alleviate LPS-induced blood-brain barrier disruption [82,89,90,84,86–88]. Therefore, ARTs may be beneficial as potential therapeutic interventions for inflammatory central nervous system diseases (Alzheimer's disease, Parkinson's disease, and Huntington's disease) by inhibiting nervous system responses [91].

2.7. Immune- and inflammatory- mediated endocrine diseases

2.7.1. Type 1 diabetes

Type 1 diabetes (T1D) results from the autoimmune destruction of insulin-producing β cells in the pancreas [92]. Therefore, a major goal of T1D research is to develop new methods to increase β cells mass and control autoreactive T-cell responses. Previous studies have shown that γ-Aminobutyric acid (GABA) inhibits pro-inflammatory $CD4^+$ T cell responses in vitro [93]. In the islets, β cells express both $GABA_A$ receptors ($GABA_A$-Rs) and $GABA_B$-Rs. $GABA_A$-Rs are promising drug targets in both respects due to their ability to promote β cells replication and survival, as well as suppress autoreactive T cell responses [94].

In a genetic model, as small molecules, artemether (a culture containing 0–10 μM artemether for 72 h) could enhance gephyrin-mediated $GABA_A$ signaling by increasing gephyrin enzymatic activity in α cells. Enhanced $GABA_A$ signaling functionally hindered Arx by translocating Arx into the cytoplasm [95]. Deletion of the master regulatory transcription factor Arx is sufficient to induce the conversion of α cells to functional β-like cells [96], thus increasing β cells mass. Through the above studies, gephyrin can be used as a druggable target for α cells to regenerate pancreatic β cells clusters.

A large number of studies have shown that among $CD4^+$ T cells, Th1 cells are pathogenic, while Th2 and Treg cells are protective in disease [97–99]. Th1 and Th2 cells secrete the iconic cytokines, IFN-γ and IL-4, respectively, involving in the development of T1D [100]. However, Li et al.' findings demonstrated that artesunate (final concentration 1 mg/ml) administration significantly prevented the incidence of T1D in mice by reducing autoimmune T cells (IFN-γ–producing T cells) and increasing protective T cells (IL-4–producing $CD4^+$ single-positive T cells, $CD8^+$ T cells, and Tregs), and promoting the functional maturity of β cells in vitro [101]. Interestingly, Chen et al. found that artesunate had a hypoglycemic effect at high concentration (100 mg/kg/day, i. g. for 4 weeks) and a preventive effect against cardiovascular complications at low concentration (50 mg/kg/day, i. g. for 4 weeks). Artesunate might restrain diabetes-induced cardiovascular complications by improving heart and body weight while reducing blood glucose and regulating blood lipids to normal level. Moreover, the expression levels of NF-κB, CD68, MMP1, MMP9, and RAGE were decreased, indicating that artesunate might play its protective role against diabetes-associated cardiovascular complications by inhibiting proteins expression in the RAGE/NF-κB signaling pathway and diminishing inflammatory factors [102].

In general, ARTs can not only diminish the incidence of T1D, but also play a therapeutic role in T1D and prevent cardiovascular complications caused by T1D. The main mechanisms involve enhancing the function of B cells, increasing the number of B cells by transforming α cells to functional β-like cells, reducing blood glucose, regulating the balance of T cells, and inhibiting inflammation.

2.7.2. Autoimmune thyroiditis

Autoimmune thyroiditis (AIT) is a common organ-specific autoimmune disease and a type of autoimmune thyroid disease (AITD) [103]. DHA (5 mg/kg/day, 10 mg/kg/day, and 20 mg/kg/day, administrated by oral gavage for 28 days) could reduce the levels of

anti-thyroglobulin antibody and thyroid peroxidase antibody in experimental AIT mice, maintain the balance of Th1/Th2, and dose-dependently decrease the proliferation of lymphocytes. Furthermore, DHA (a culture containing 0 μM, 5 μM, and 10 μM DHA for 48 h) inhibited the binding of C-X-C chemokine ligand 10 (CXCL10) and its receptor 3 (CXCR3), hence it restrained calcium flow and reduced the expression levels of PI3K, p-PI3K, AKT, NF-κBp65, and p-NF-κBp65. Therefore, DHA might be a therapeutic agent for AIT by inhibiting the CXCR3/PI3K/AKT/NF-KB signaling pathway [103].

2.8. Immune-mediated exocrine disease

Dry eye disease (DED) is caused by a variety of factors, including inflammation and injury of cornea and conjunctiva, neurosensory abnormalities, and high osmotic pressure [104].

One study using scopolamine hydrobromide (SCOP)-induced rodent model (SD rats and C57/BL6 mice) and benzalkonium chloride (BAC)-induced rat model showed that SM934 (0.1% and 0.5%) increased tear secretion, maintained the number of conjunctiva cup cells, alleviated corneal damage, reduced the levels of inflammatory mediators (TNF-α, IL-6, IL-10, and IL-1β), diminished the accumulation of macrophages expressing TLR4 in the conjunctiva, and suppressed the expression of inflammasome components (MyD88, NLRP3, ASC, and cleaved caspase 1). In LPS-treated RAW 264.7 cells, pretreatment with SM934 (a culture containing SM934 10 μM) hindered the upregulation of TLR4 and down-regulated NF-κB/NLRP3 signaling proteins. Therefore, the study suggests that SM934 simultaneously preserved the structural integrity of the ocular surface and prevent corneal and conjunctiva inflammation to treat DED [105].

3. Conclusion and future directions

Autoimmune diseases are increasing dramatically in many parts of the world, likely due to changes in our exposure to environmental factors. Autoimmune diseases have a significant impact on the individuals and families they affect, as well as on our society and healthcare costs, and current projections indicate that they may soon become one of the leading medical illnesses [106]. Long-term use of conventional immunosuppressants brings a huge financial burden to patients with autoimmune diseases or organ transplantation, and is accompanied by some complications, including infections, tumors, and lymphoproliferative diseases. Therefore, there is an urgent need to find a cost-effective and effective treatment with few side effects.

In recent years, the research on ARTs in the treatment for autoimmune and inflammatory diseases has developed rapidly. Current studies suggest that ARTs have favorable immunomodulatory and anti-inflammatory effects, with broad benefits for autoimmune and inflammatory diseases. ARTs have been widely used in humans for treating malaria with only mild side effects [107]. As the effective doses of artemisinin-type drugs against different diseases may differ, the safety profile of artemisinins in malaria treatment may not be identical for other diseases. Cancer treatments require fairly high doses of artemisinin, but preliminary clinical trials have also shown it to be well tolerated [108–111]. What's more, currently available data from experiments using ARTs to treat mouse models of inflammatory and autoimmune diseases have not reported mmajor side effects [112].

In short, ARTs are a highly valuable class of drugs with high potentials for the treatment of inflammatory and autoimmune diseases. The existing data in the literature demonstrate the need for further studies, particularly randomized clinical trials. Elucidating the mechanism of action of ARTs may open up new avenues for the prevention, diagnosis, and treatment of autoimmune and inflammatory diseases.

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CRediT authorship contribution statement

Kaidi Xie: Writing – original draft, Formal analysis, Data curation. **Zhen Li:** Writing – review & editing. **Yang Zhang:** Writing – review & editing. **Hao Wu:** Writing – review & editing. **Tong Zhang:** Writing – review & editing. **Wen Wang:** Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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