The immunosuppressive activity of artemisinin-type drugs towards inflammatory and autoimmune diseases

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Abbreviations: α-SMA, α-smooth muscle actin; AaE, Artemisia annua ethanolic extract; ACLT, anterior cruciate ligament transection; ACLT+MMx, OA model rats constructed by anterior cruciate ligament transection and medial meniscus resection in the joints; ACT, artemisinin-based combination therapy; AHR, airway hyper-responsiveness; AKI, septic acute kidney injury; AKT, AKT serine/threonine kinase; ALP, alkaline phosphatase; ALT, activating protein 1; ARE, androgen responsive element; ASM, Airway smooth muscle; AST, aspartate aminotransferase; ATC, nuclear factor of activated T cells c1; NFκB cells; NLRP3, nucleotide-binding domains and leucine-rich repeat pyrin domains containing 3 inflammasome; NO, nitric oxide; NOX, NADPH oxidase; NRFκBα, NFκB inhibitor protein; IKK, IkB kinase; INOS, inducible nitric oxide synthase; IRF-3, interferon regulatory factor 3; JAK, janus kinase; JUN, JUN-activating binding protein; JUN, JUN oncogenic transcription factor; KEAP, Kelch Like ECH Associated Protein; KEAP, potassium-stimulated insulin secretion; LDH, lactate dehydrogenase; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinase; MIF, macrophage migration inhibitory factor; MIP-2, macrophage inflammatory protein 2; MMP, matrix metalloprotein; MMS, medial meniscus resection; MOG, myelin oligodendrocyte glycoprotein; MPO, myeloperoxidase; MSU, monosodium urate; mTOR, mammalian target of rapamycin; MUC, mucin; MyD88, myd-88; NADPH oxidase; NFκB, nuclear factor of activated T cells c1; NFκB, nuclear factor κ B cells; NLRRP-3, nucleotide-binding domains and leucine-rich repeat pyrin domains containing 3 inflammasome; NO, nitric oxide; NOX, NADPH oxidase; NQO1, NAD(P)H quinone dehydrogenase 1; RORγt, retinoic acid receptor; SOD, superoxide dismutase; SYK, spleen tyrosine kinase; TLR, toll-like receptor; TRAcP, tartrate-resistant acid phosphatase; TRAF, TNF receptor-associated factor; TRAF, TNF receptor-associated factor 2/6; TRAP, tartrate-resistant acid phosphatase; VEGF, vascular endothelial growth factor; VSMCs, vascular smooth muscle cells; YM-2, chitinase 3-like protein 4.
Abstract
The sesquiterpene lactone artemisinin from *Artemisia annua* L. is well established for malaria therapy, but its bioactivity spectrum is much broader. In this review, we give a comprehensive and timely overview of the literature regarding the immunosuppressive activity of artemisinin-type compounds toward inflammatory and autoimmune diseases. Numerous receptor-coupled signaling pathways are inhibited by artemisinins, including the receptors for interleukin-1 (IL-1), tumor necrosis factor-α (TNF-α), β3-integrin, or RANKL, toll-like receptors and growth factor receptors. Among the receptor-coupled signal transducers are extracellular signal-regulated protein kinase (ERK), c-Jun N-terminal kinase (JNK), phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K), AKT serine/threonine kinase (AKT), mitogen-activated protein kinase (MAPK)/extracellular signal regulated kinase (ERK) kinase (MEK), phospholipase C γ1 (PLCγ), and others. All these receptors and signal transduction molecules are known to contribute to the inhibition of the transcription factor nuclear factor κ B (NF-κB). Artemisinins may inhibit NF-κB by silencing these upstream pathways and/or by direct binding to NF-κB. Numerous NF-κB-regulated downstream genes are down-regulated by artemisinin and its derivatives, for example, cytokines, chemokines, and immune receptors, which regulate immune cell differentiation, apoptosis genes, proliferation-regulating genes, signal transducers, and genes involved in antioxidant stress response. In addition to the prominent role of NF-κB, other transcription factors are also inhibited by artemisinins (mammalian target of rapamycin [mTOR], activating protein 1 [AP1]/FBJ murine osteosarcoma viral oncogene homologue [FOS]/JUN oncogenic transcription factor [JUN]), hypoxia-induced factor 1α (HIF-1α), nuclear factor of activated T cells c1 (NF-ATC1), Signal transducers and activators of transcription (STAT), NF E2-related factor-2 (NRF-2), retinoic-acid-receptor-related orphan nuclear receptor γ (ROR-γt), and
forkhead box P-3 (FOXP-3). Many in vivo experiments in disease-relevant animal models demonstrate therapeutic efficacy of artemisinin-type drugs against rheumatic diseases (rheumatoid arthritis, osteoarthritis, lupus erythematosus, arthrosis, and gout), lung diseases (asthma, acute lung injury, and pulmonary fibrosis), neurological diseases (autoimmune encephalitis, Alzheimer's disease, and myasthenia gravis), skin diseases (dermatitis, rosacea, and psoriasis), inflammatory bowel disease, and other inflammatory and autoimmune diseases. Randomized clinical trials should be conducted in the future to translate the plethora of preclinical results into clinical practice.

**KEYWORDS**
arthritis, asthma, dermatitis, immunity, inflammatory bowel disease, natural product, neuroinflammation, traditional Chinese medicine

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1 | **INTRODUCTION**

While traditional Chinese medicine (TCM) represents a holistic medical system that is fundamentally different from Western academic medicine, there is increasing interest since the late 20th century to understand the pharmacological mechanisms of Chinese phytotherapy by using modern scientific methods such as phytochemistry, molecular pharmacology, and biology. A showcase example in this context is *Artemisia annua* L. (Sweet Wormwood, Chinese: *qinghao*), which has been used in TCM for about two millennia. According to the Chinese Pharmacopoeia, *Artemisia annua* has flavors of bitter, pungent, and cold and belongs to the meridians of liver and gallbladder. It mainly has activities of eliminating summer-heat and preventing malaria for treating summer heat evil-induced fever, *yin*-deficiency-induced fever, malaria-induced chill and fever, and jaundice with damp-heat pathogen.\(^1\) In the early 1970s, artemisinin has been isolated from *A. annua* as active principle against malaria. In the past decades, artemisinin-based therapies saved the life of millions of malaria patients worldwide. In the year 2015, Youyou Tu was awarded with the Nobel Prize in Medicine or Physiology for her eminent achievements on *A. annua* and artemisinin. This honor not only appreciated her personal achievements in science but also brought Chinese science in general to the international scientific frontline.\(^2\) On the other hand, the scientific community was made aware of the potential of the therapeutic potential of medicinal plants and isolated phytochemicals isolated thereof. In this respect, artemisinin and *A. annua* demonstrated that the clinical activity of TCM herbal remedies is also successfully provable with measures of western academic medicine.

In general, natural products do not act in a mono-specific manner but in a multi-specific fashion.\(^3\) Therefore, it does not come as a surprise that artemisinins’ spectrum of activities is not limited to malaria. Since the 1990s, it became more and more clear that artemisinin and its derivatives are not only active against *Plasmodia*, but that other diseases such as cancer and viral diseases are also susceptible to this type of sesquiterpenoids.\(^4,5\) It is reasonable to hypothesize that large portions of the populations in East and West might benefit from the use of artemisinin-type drugs to meet the challenge posed by the worldwide threat of inflammatory and autoimmune diseases.
The criteria to extract the relevant literature for this focused review article were as follows: The PubMed database was screened for articles related to artemisinin/artesunate and inflammatory/autoimmune diseases until July 30, 2020. Some exclusion criteria were defined as follows: Combination therapies of artemisinin and its derivatives and other established or investigational drugs were excluded. Only experimental studies regarding monotherapies with artemisinin-type drugs were considered in the present review article. Another exclusion criterion was the focus on the anti-inflammatory activity independent of infectious diseases. As infectious diseases caused by microbial pathogens may be accompanied by inflammation. In such cases, the anti-inflammatory activity of artemisinins cannot be clearly separated from their anti-infective effects. Therefore, we exclusively focused on anti-inflammatory and autoimmune disease without contribution of communicable diseases to solely and undoubtedly elaborate the immunosuppressive molecular mechanisms.

Looking into the future, another intention of this review was to provide comprehensive preclinical information stimulate the conductance of clinical trials to prove the therapeutic potential of artemisinin and its derivatives in clinical settings.

2 | RHEUMATIC DISEASES

Among the long list of rheumatic disorders, artemisinin derivatives (artemisinin, artesunate, artemether, dihydroartemisinin, and the semisynthetic derivatives DC32, SM 903, and SM934) have been investigated in rheumatic arthritis, osteoarthritis, and osteoporosis as well as lupus erythematosus and gout (Table 1).

2.1 | Rheumatoid arthritis

Rheumatoid arthritis is a frequent inflammatory disease of the joints associated with pain, swelling, and stiffness of the joints. This is an autoimmune disease, which affects Caucasians less than other populations. Mis-regulated immune cells migrate into the joints and release proinflammatory cytokines (e.g., interleukin-1β [IL-1β], IL-6, tumor necrosis factor-α [TNF-α]) leading to osteoclast activation and cartilage inflammation. The function of regulatory T cells (Treg) is dampened in dependency of forkhead box P3 (FOXP3) activity and elevated TNF-α levels. Synovitis is also frequently observed. Cytokines also induce tumor-like proliferation at the synovia. This tumor-like tissue is called pannus, which contributes to the destruction of bone and cartilage by necrosis-inducing collagenases and other proteolytic enzymes. Rheumatoid arthritis-specific fibroblasts spread from the synovia into the body via the blood vessel system and lead to a generalization of the disease.

Therapy options are nonsteroidal antiphlogistic drugs (NSAIDs) and glucocorticoids against inflammation, disease-modifying anti-rheumatic drugs (DMARDs), including methotrexate (as gold standard), azathioprine, hydroxychloroquine, and the therapeutic biologicals anakinra, tocilizumab, adalimumab, infliximab etc.) as well as analgetic drugs against pain. Rheumatoid arthritis is difficult to be treated, because many patients do not respond and high side effects hamper treatment success (e.g., diarrhea, nausea and vomiting, gastrointestinal bleeding, headache, dizziness, edema, increased risk for ulcers). Therefore, novel therapeutic strategies are urgently required and artemisinin-type drugs may offer promising alternatives.

The majority of experimental data have been raised in animal models of rheumatoid arthritis with well-established models such as type II collagen-induced arthritis (CIA) or Freud’s complete adjuvant (FCA)-induced arthritis in mice or rats (Table 1). Some authors also applied experimental in vitro settings by using lipopolysaccharide (LPS)-stimulated murine macrophages or fibroblast-like synoviocytes isolated from rheumatoid arthritis patients. Synovial tissue biopsies from rheumatoid patients also have been investigated. Using appropriate experimental models, which are established in the scientific community of rheumatoid research, represents an important prerequisite to estimate the therapeutic effect of artemisinin-type drugs in an objective manner.
| Compound            | Model                                      | Mode of action                                                                 | Reference                  |
|---------------------|--------------------------------------------|--------------------------------------------------------------------------------|-----------------------------|
| **Rheumatoid arthritis** |                                            |                                                                                |                             |
| Di-ART-GPC liposomes (derivative) | Inflammatory cell model | Better the ankle swelling rate, anti-inflammatory response and inhibition of proinflammatory cytokine secretion than artemesunate | Zhang et al.⁶              |
| Artesunate          | Synovial tissue biopsies from RA patients | Migration↓, MMP-2↓, MMP-9↓, PDK-1↓, pAKT↓, pRSK-2↓ | Ma et al.⁷                 |
| Artesunate          | CIA in rats                                | Inflammation↓, PI3K↓, AKT↓, mTOR↓, pPI3K↓, pAKT↓, pmTOR↓, BCL-2↓, BCL-x↓, BAX↑, LC3II/LC3II↑, Beclin-1↑, chondrocyte proliferation↓, apoptosis↑, autophagy↑ | Feng and Qiu⁸              |
| DC32 (derivative)   | CIA in in DBA/1 mice                       | Footpad inflammation↓, reduce cartilage degradation↓, NRF-2/HO-1 signaling↑, p62↑ | Fan et al.⁹                |
| NIH-3T3             |                                            | NRF-2 expression and nuclear translocation↑, KEAP-1↓, HO-1↑, p62↑, activation of AKT/mTOR and ERK↑ |                             |
| DC32 (derivative)   | CIA in in DBA/1 mice                       | Foot pad swelling↓, lymphocytic infiltration↓, restoration of Treg/Th17 balance, IL-6↓, lymphocyte-induced invasion and migration↓, MMP-2 and MMP-3 secretion↓, CXCL-12↓, CX3CL-1↑ | Fan et al.¹⁰               |
| Artesunate          | CIA in Sprague-Dawley rats                 | Th17 cells↓, Treg cells↑, FOXP-3↓, IL-17↑ | Liu et al.¹¹               |
| Artesunate          | CIA in Wistar rats                         | Pannus formation↓, erosion of cartilage↓, bone lesions↓, FOXP-3↑ | Zhu et al.¹²               |
| SM934 (derivative)  | CIA in in DBA/1 mice                       | In vivo: joint swelling↓, bone erosion and destruction↓, Tfh cells↓, Th17 cells↓, pathogenic antibodies↓ | Lin et al.¹³               |
|                     |                                            | Ex vivo: proliferation↓, inflammatory cytokine secretion↓ |                             |
|                     |                                            | In vitro: polarization of naive CD4+ T cells into Tfh cells↓; BCL-6↓, IL-21-producing CD4 T cells↓, STAT-3 signaling downstream of IL-21↓ |                             |
| Artesunate          | FCA-induced arthritis in rats              | Joint inflammation↓, functional parameters (stair climbing ability, motility, suppression of mechanical allodynia)↑, nitric oxide↓, neutrophil influx↓, COX-2↓, apoptosis↓ | Guruprasad et al.¹⁴        |
| Artesunate          | K/BxN mice                                 | Germinal center B cells↓ | Hou et al.¹⁵               |

(Continues)
| Compound     | Model                      | Mode of action                                                                 | Reference |
|--------------|----------------------------|--------------------------------------------------------------------------------|-----------|
| Artesunate   | CIA in rats                | Inflammation symptoms ↓, cartilage and bone destruction ↓, proinflammatory cytokines (IL-1β, TNF-α, IL-17α) ↓, MMP-9 ↓, iκB degradation ↓, ERK activation ↓ | Li et al.16 |
| LPS-stimulated RAW264.7 macrophages | Proinflammatory cytokines (IL-1β, TNF-α, IL-17α) ↓, MMP-9 ↓, iκB degradation ↓, ERK activation ↓ |          |
| Artesunate   | CIA in Wistar rats         | TNF-α ↓, MCP-1 ↓, RANTES ↓                                                   | Mo et al.17 |
| Dihydroartemisinin | CIA in Wistar rats        | Inflammation ↓, bone erosion ↓, proliferation of fibrous connective tissue and blood capillary ↓, clarity of articular cavity ↑ | Wang et al.18 |
| Artesunate   | RA-FLS from patients       | VEGF and IL-8 secretion ↓, TNF-α- or hypoxia-induced nuclear expression and translocation of HIF-1α ↓, pAKT ↓ | He et al.19  |
| SM905 (derivative) | CIA in in DBA/1 mice    | Arthritis incidence and severity ↓, Pro-inflammatory cytokines, chemokines and chemokine receptors in draining lymph nodes ↓, IL-17A in T cells ↓, ROR-γt ↓ | Wang et al.20 |
| Artesunate   | RA-FLS from patients       | IL-1β ↓, TNF-α ↓, IL-6 ↓, nuclear NFκB translocation, DNA-binding and transcriptional activity ↓, iκBα phosphorylation and degradation ↓ | Xu et al.21  |
| Artesunate   | CIA in in Lewis rats       | Paw edema ↓, anti-collagen II Abs ↓, bone erosion ↓                           | Mirshafiey et al.22 |
| Artemether   | CIA in in Lewis rats       | Paw edema ↓, inflammatory cell infiltrate ↓, anti-collagen II Abs ↓, NO formation ↓ | Cuzzocrea et al.23 |

**Systemic lupus erythematosus**

| Dihydroartemisinin | Pristane-induced lupus in female BALB/c mice | Myeloid-derived suppressor cell senescence ↓, senescence-associated secretory phenotype ↓, ageing-related proteins (p21, p53, p16) ↓, NRF-2/HO-1 pathway ↑ | Li et al.24  |
| Artesunate | Lupus-prone MRL/lpr mice | Survival ↑, lupus nephritis symptoms ↓, anti-dsDNA antibodies in kidney ↓, IL-6 ↓, IFN-γ ↓, IL-21 ↓, Tfh cells in spleen ↓, ratio of Tfr to Tfh cells maintained, phosphorylation of JAK2 and STAT3 ↓ | Dang et al.25  |
| Artesunate | HUVEC and SLE PBMC | IFN-inducible genes (LY6E, ISG-15) ↓, MIF ↓, IFNα-1b-induced pSTAT1 ↓ | Feng et al.26  |
| Compound          | Model                        | Mode of action                                                                 | Reference |
|-------------------|------------------------------|---------------------------------------------------------------------------------|-----------|
| SM934 (derivative) | Lupus-prone MRL/lpr mice    | In vivo: survival↑, lymphadenopathy↓, serum ANA↓, IL-6↓, IL-10↓, IL-21↓,       | Wu et al.27 |
|                   |                              | quiescent B cells↑, germinal center B-cell number maintained, activated          |           |
|                   |                              | B-cells↓, plasma cells↓                                                         |           |
|                   | Ex vivo: TLR-triggered       | activation↓, TLR7/9↓, MyoD88↓, pNF-κB↓, TLR-associated B-cell activation↓,      |           |
|                   |                              | plasma cell differentiation↓                                                    |           |
|                  |                              | [45x599] Dihydroartemisinin Spleen cells from lupus-prone MRL/lpr mice          |           |
|                  |                              | LPS-induced spleen cell proliferation↓, LPS-induced protein expression of        |           |
|                  |                              | TLR-4↓, pIRF-3↑, IFN-α↑, IFN-β↑                                                 | Huang et al.28 |
|                  |                              | Artemisinin Female lupus nephritis mice Transcriptional coactivator P300/CBP    | Wu et al.29 |
|                  |                              | protein in renal tissue↑, Gα receptor in PBMC↑, Gβ receptor in PBMC↓           |           |
|                  |                              | SM934 (derivative) Female lupus-prone NZB × NZW F1 mice                       | Hou et al.30 |
|                  |                              | Survival↑, glomerulonephritis progression↓, Th1-related anti-dsDNA↓, IgG2a and |           |
|                  |                              | IgG3 Abs↓, serum IL-4/10↑, serum IL-17↓, Th2-related anti-dsDNA IgG1 Abs↑,     |           |
|                  |                              | effector/memory T cells↓, apoptosis of CD4(+) T cells↑, Treg cells↑,            |           |
|                  |                              | IL-10 production of macrophages↑                                               |           |
|                  |                              | SM934 (derivative) Lupus-prone MRL/lpr mice                                   | Hou et al.31 |
|                  |                              | Survival↑, spleen size↓, proteinuria, renal lesion severity↓, Treg cells↑,     |           |
|                  |                              | Th1 cells↓, Th17 cells↓, serum anti-double-stranded DNA antibodies↓, blood     |           |
|                  |                              | urea nitrogen↓, IFN-γ↑, IL-17↓, STAT-1, -3, -5↓                                |           |
|                  |                              | Artemisinin Lupus nephritis mice Symptoms↓, renal lesions↓, 24 h urinary      | Wu et al.32 |
|                  |                              | protein level↓, expression of TNF-α, IL-6, NF-κB, TGF-β1 in renal tissue↓     |           |
|                  |                              | Artesunate Lupus-prone MRL/lpr mice                                            | Jin et al.33 |
|                  |                              | Survival↑, body weight↑, blood leukocyte count↓, 24 h urinary protein level↓, |           |
|                  |                              | serum ANA↓, serum anti-dsDNA Abs↓, serum creatinine↓, MCP-1 in serum, urine    |           |
|                  |                              | and kidney↓, BAFF↓                                                             |           |
|                  |                              | Dihydroartemisinin Lupus nephritis in BXSB mice                               | Li et al.34 |
|                  |                              | TNF-α↓, nuclear NF-κB translocation↓, IκBa degradation↓                        |           |
|                  |                              | Dihydroartemisinin Lupus nephritis in BXSB mice                               | Dong et al.35 |
|                  |                              | renal pathology↓, anti-dsDNA Abs↓, TNF-α↓                                    |           |

Arthrosis (Continues)
At the phenotypic level in vivo, which compares to some extend to the clinical symptoms of patients, artemisinin-type drugs led to improvements. We did not find papers reporting no effect or worsening of rheumatoid arthritis symptoms. Symptomatic improvements of the disease were decreased joint and food pad inflammation and swelling, decreased pannus formation, reduced cartilage and bone erosion, reduced paw edema as well as improved functional parameters (stair climbing ability, motility, suppression of mechanical allodynia) and improved clarity of articular cavity (Table 1).6–23

At the microscopic level, reduced proliferation of fibrous connective tissue, chondrocytes, and blood capillaries were observed upon treatment with artemisinins. The infiltration of inflamed tissue areas with lymphocyte and germinal center B cells went down and the balance of Treg and Th17 cells was restored. Regulatory T cells (Treg; formerly termed T-helper suppressor cells, Th3) exert anti-inflammatory and antiapoptotic properties. Their accumulation in arthritic tissues upon artemisinin treatment supports the healing process. Th17 cells are proinflammatory helper cells that produce interleukin 17 (IL-17). Th17 cells inhibit Treg cells and thereby promote inflammation. In rheumatoid arthritis, the Treg counts are decreased, while Th17 counts are increased. Furthermore, the polarization of naïve CD4+ T cells into T-follicular helper cells (Tfh) cells was suppressed by artemisinin-type compounds (Table 1). Tfh cells aggravate antibody-mediated autoimmune reactions.

At the molecular level, a plethora of results provided details of the molecular mechanisms and signaling pathways involved in the anti-rheumatic activity of artemisinin and its derivatives (Table 1). These compounds inhibited the secretion of proinflammatory cytokines and chemokines, that is, TNF-α, IL-1β, IL-6, IL-8, IL-17a, C-X-C:

| Compound   | Model                                           | Mode of action                                                                 | Reference |
|------------|------------------------------------------------|-------------------------------------------------------------------------------|-----------|
| Artesunate | Primary human fibroblasts, surgery-induced knee arthrofibrosis in male New Zealand rabbits | Autophagy↑, mTOR signaling by PI3K/AKT/mTOR and AMPK/mTOR pathways↓          | Wan et al.36 |
| Artesunate | Male New Zealand rabbits, primary human fibroblasts | Collagen content↓, fibroblast viability and proliferation↓, fibroblast apoptosis↑, ERS-related CHOP and proapoptotic BAX proteins↑, BCL-2↓, pERK pathway↑, p-eIF2α↑ | Chen et al.37 |
| Artemisinin| LPS- and MSU-treated human U937 cells            | NLRP-3↓, caspase-1↓, IL-1β↓, interaction NLRP-3 and NEK-7 in NLRP-3 inflammasome activation↓, K+ efflux↓ | Kim et al.38 |

Abbreviations: AKT, AKT serine/threonine kinase; BCL-2, breakpoint cluster lymphoma 2; BCL-X, BCL-2 X gene; CIA, collagen-induced arthritis; COX-2, cyclooxygenase 2; CXCL-12, C-C chemokine ligand 12; ERK, extracellular signal-regulated protein kinase; ERS, endoplasmic reticulum stress; FCA, Freund’s complete adjuvant; FLS, fibroblast-like synoviocytes; FOXP-3, forkhead box P-3; HO-1, heme oxygenase 1; IL-1β, interleukin-1β; IFN-γ, interferon regulatory factor 3; JAK-2, janus kinase 2; KEAP, kelch like ECH associated protein; LPS, lipopolysaccharide; MCP-1, monocyte chemoattractant protein 1; MMP, matrix metalloproteinases; MIF, macrophage-migration inhibitory factor; mTOR, mammalian target of rapamycin; MSU, monosodium urate; NFκB, nuclear factor kappa-light-chain-enhancer of activated B cells; PDK-1, pyruvate dehydrogenase kinase 1; PI3K, phosphatidylinositol 3-kinase; pRSK-2, ribosomal protein S6 kinase; STAT, signal transducer and activator of transcription; TNF-α, tumor necrosis factor-α; TLR, toll-like receptor; VEGF, vascular endothelial growth factor.
chemokine ligand (CXCL-12), CX3CL-1, the leucocyte activator RANTES and the macrophage activator monocyte chemoattractant protein 1 (MCP-1). (COX-2) is a well-known mediator of inflammation, which is induced upon exposure of cells to TNF-α and IL-1β. COX-2 is upregulated in rheumatoid arthritis, and artemisinin-type drugs downregulated its activity. Several signal transduction pathways involved in inflammation were downregulated by these drugs, for example, the expression and/or phosphorylation of signal transducers (e.g., AKT serine/threonine kinase (AKT), phosphatidylinositol 3-kinase (PI3K), extracellular signal-regulated protein kinase (ERK)), and activation and/or nuclear translocation of transcription factors (e.g., retinoic acid receptor-related orphan nuclear receptor γ [ROR-γt], nuclear factor κ B (NF-κB) as important inflammatory regulator and FOXP-3, which is important for T-cell regulation). Oxidative stress represents an important trigger of inflammation. Artemisinin and its derivatives counteracted oxidative stress in rheumatoid arthritis by upregulating NF E2-related factor-2 (NRF-2), kelch like ECH associated protein 1 (KEAP-1), and heme oxygenase 1 (HO-1) and downregulating HIF-1α. Matrix metalloproteinases are expressed in inflammatory conditions and regulate the bioavailability and activity of inflammatory cytokines. Matrix metalloproteases (MMP-2) and MMP-9 were downregulated upon exposure to artemisinin-type drugs. Furthermore, artemisinin and its derivatives induced apoptosis and autophagy. While antiapoptotic breakpoint cluster lymphoma 2 (BCL-2) and BCL-X were downregulated, the proapoptotic BAX was upregulated. The autophagy markers Beclin-1 and LC3 were upregulated by artemisinins (Table 1).

In summary, the synopsis of published data reveals quite an interesting picture that artemisinin and its derivatives were indeed able to inhibit inflammation in experimental settings of rheumatoid arthritis.

### 2.2 Lupus erythematosus

Lupus erythematosis is an autoimmune disease characterized by a hyperactive immune system, which attacks healthy tissues. The disease typically affects joints, skin, kidney, blood cells, heart, and lungs. The most common and severe form is systemic lupus erythematosus (SLE). SLE therapy comprises of methotrexate, immunosuppressive drugs (corticosteroids, hydroxychloroquine, and antibody therapy (e.g., belimumab, which inhibits the B-cell activating factor, BAFF). Clinical symptoms of lupus erythematosus improved after application of artemisinin-type drugs, that is, the survival of animals increased, lymphadenopathy was reduced, the glomerulonephritic lesions, the 24 h urinary proteins levels, the renal and serum anti-dsDNA antibodies, and the serum creatinine levels all decreased (Table 1).

Considerable immune cell alterations were observed, for example, the Tfh cell counts in the spleen and the effector/memory T-cell counts decreased, while the Treg and quiescent B cell numbers and the plasma cell differentiation increased. The LPS-induced spleen cell proliferation also went down (Table 1).

The decrease in cellular senescence and senescence-associated secretory phenotype was linked to reduced expression of p53, p21, and p16. Th1 cell-related anti-dsDNA IgG2a and IgG3 antibody production was suppressed, while Th2-cell-related anti-dsDNA IgG1 generation was activated. Proinflammatory cytokine production was suppressed (TNF-α, IL-6, IL-10, IL-17, IL-21), while anti-inflammatory cytokines were more abundant (IL-4 and IL-10). The drop in IFN-γ was associated with a downregulation of IFN-inducible genes (LY6E and ISG-15), while interferon-α (IFN-α) and IFN-β were upregulated. Relevant signaling pathways were shut down by artemisinins, that is, there was a downregulation of the toll-like receptor (TLR-4), TLR-7, and TLR-9 pathways as well as the NF-κB pathway. The phosphorylation of interferon regulatory factor 3 (IRF-3), janus kinase 2 (JAK-2), signal transducer and activator of transcription 1 (STAT-1), and STAT-3 went down. The transcriptional coactivator P300/CBP protein in renal tissue and the GCα and GCβ receptors were activated in PBMC. MyoD88 and macrophage-migration inhibitory factor (MIF) as SLE markers were also suppressed by artemisinins. Inflammatory oxidative stress was reduced by activation of the NRF-2/NO-1 pathway (Table 1).
In sum, these data show that artemisinin and derivates corrected the immune cells and cytokine imbalances and related deregulations in signal transduction leading to SLE.

### 2.3  |  Arthrosis and gout

While rheumatic arthritis and lupus erythematosus are inflammatory diseases without tissue destruction, osteoarthritis and arthrosis belong to the destructive rheumatic diseases. Gout is categorized as metabolic disease associated with rheumatic complaints.

A main factor of arthrosis is the deposition of urate crystals in the joints. Arthrosis is associated with osteoporosis and painful joint deformation. Drug therapy comprises of glucocorticoids, nonsteroidal antiphlogistic drugs, and others. The therapeutic effects of artesunate include a decrease of collagen content and reduced fibroblast viability and proliferation and increased apoptosis at the same time. Associated ERK and PI3K/AKT/mTOR and AMPK/mTOR signaling was also suppressed by artesunate (Table 1).

Inflammatory arthritis with swollen joints is also indicative for gout. This disease is caused by elevated uric acid levels. The uric acid crystals deposit in joints, tendons, and surrounding tissues and cause the typical gout attacks. These crystals provoke inflammatory reactions of macrophages, which are initiated by the nucleotide-binding domains and leucine-rich repeat pyrin domains containing 3 (NLRP-3) inflammasome protein complex. NLRP-3 binds and activates caspase 1, which cleaves pro-IL-1β to IL-1β as main player in the inflammatory cascade. Gout treatment consists of application of NSAIDS, glucocorticoids, low-dose colchicine, as well as allopurinol, probenecid and the IL-1 inhibitor canakinumab, all of which are associated with side effects.

Artemisinin-type drugs have been not well analyzed in gout as of yet. In monosodium urate-induced gout in mice, food and ankle swelling was reduced by artemisinin and NLRP-3 inflammasome activation was suppressed. This was associated with a decrease in IL-1β and caspase 1 (Table 1). As numerous encouraging results are available for the other rheumatic diseases discussed above, more investigations on the therapeutic potential of artemisinin in gout should be encouraged.

### 3  |  LUNG DISEASES

#### 3.1  |  Asthma

Asthma represents a long-term airway inflammation with airflow obstruction and bronchospasms. Affected patients suffer from symptoms such as coughing, wheezing, shortness of breath, and chest tightness. Chronically inflamed bronchi and bronchioles induce increased contractility of the surrounding smooth muscles, which narrows the airways. Participating immune cells in this process are eosinophils, T lymphocytes, macrophages, and neutrophils. Asthma is reversible (in contrast to chronic obstructive pulmonary disease, COPD). Asthma cannot be cured. It can be attempted to prevent the disease from progression and to relieve the symptoms. Standard medications include short- or long-acting β2 adrenoreceptor agonists (SABA, LABA), corticosteroids for long-term control, leukotriene receptor antagonists, and beta blocker (propranolol).

Ovalbumin- or cigarette smoke-treated mice were used for in vivo experimentation to mimic asthma. In vitro, bronchial epithelial cells treated with cigarette smoke and TNF-α as well as primary airway smooth muscle cells from asthmatic patients were investigated (Table 2).

Artemisinin-type compounds relieved the asthma symptoms in mice. Traction force and airway pressure decreased upon drug treatment. Sneezing, rubbing, mucus secretion, and methacholine-induced airway hyper-responsiveness also were less in treated animals. Relieving the symptoms were due to decreased histamine and IgE release and resulted in a regain of body weight and improved survival rates.
| Compound       | Model                          | Mode of action                                                                 | Reference |
|----------------|--------------------------------|--------------------------------------------------------------------------------|-----------|
| **Asthma**     |                                |                                                                                 |           |
| Artesunate     | OVA-treated mice               | EOS number in BALF ↓, EOS apoptosis ↑, FAS ↑, BCL-2 ↓                          | Wang et al.51 |
| Artesunate     | OVA- and aluminium hydroxide-treated BALB/c mice | Infiltration of inflammatory cells around the bronchus and blood vessels ↓, mucus secretion ↓ | Wang et al.52 |
| Artesunate     | Airway smooth muscle cells     | Traction force ↓ and Ca^{2+} influx ↑ by TAS2R signalling                       | Wang et al.52 |
|                | OVA-treated BALB/c mice        | Airway resistance ↓                                                           | Zhu et al.53 |
| Dihdroartemisinin | OVA-treated BALB/c mice           | Body weight ↑, survival rate ↑, airway pressure ↓, Th17 cells ↓, IL-6/STAT-3 pathway ↓, miR-183C ↓, FOXO-1 ↑ | Li et al.54 |
| Artesin         | OVA-treated allergic rhinitis mice | Sneezing ↓, rubbing ↓, Histamine ↓, IgE ↓, inflammatory factors (TNF-α ↓, INF-γ, IL-1β, IL-10) ↓, Treg ↑, pERK ↓ | Wei et al.59 |
| Artesunate     | Human bronchial epithelial cells | Nuclear NRF-2 ↑                                                              | Ravindra et al.55 |
| Artesunate     | Cigarette smoke- and OVA-treated BALB/c mice | Methacholine-induced airway hyperresponsiveness ↓, pulmonary inflammation cell recruitment ↓, IL-4 ↓, IL-8 ↓, IL-13 ↓, TNF-α ↓, PI3Kδ/AKT ↓, HDAC-2 ↑ | Luo et al.56 |
|                | Cigarette smoke- and TNF-α-treated BEAS-2B cells | IL-8 ↓, HDAC-2 ↑     |           |
| Artesunate     | Primary ASM cells from asthmatic and non-asthmatic donors | Mitogen-stimulated increases ↓, cyclin D1 ↓, pAKT ↓, pp70(S6K) ↓ | Tan et al.57 |
|                | OVA-treated BALB/c mice        | Area of α-smooth muscle actin-positive cells, cyclin D1 ↓                     |           |
| Artesunate     | Cigarette smoke-induced acute lung injury in BALB/c mice, bronchial epithelial BEAS-2B cells | BAL fluid total and differential cell counts ↓; IL-1β ↓, MCP-1 ↓, IP-10 ↓, KC ↓, oxidative biomarkers 8-isoprostane ↓, 8-OHdG ↓, 3-nitrotyrosine ↓, catalase, NOX2 | Ng et al.58 |
| Dihdroartemisinin | OVA-treated BALB/c mice          | Infiltrating inflammatory cells ↓, mucus hypersecretion ↓, Th2 cytokines ↓, OVA-specific IgE and AHR ↓, MUC-5ac ↓, YM-2 ↓, ERK ↓, pMAPK p38 ↓, NF-κB activation ↓ by JkB-α ↓ | Wei et al.59 |
| Artesunate     | OVA-treated mice               | Total cells ↓, eosinophils ↓, neutrophils ↓, iNOS ↓, NOX1-4 ↓, p22phox ↓, p67phox ↓, SOD ↓, catalase ↓, NRF-2 ↑ | Ho et al.60 |
**Table 2** (Continued)

| Compound       | Model                                      | Mode of action                                                                 | Reference                     |
|----------------|--------------------------------------------|---------------------------------------------------------------------------------|-------------------------------|
| Artesunate     | OVA-treated BALB/c mice                    | Total and eosinophil counts ↓, IL-4 ↓, IL-5 ↓, IL-13 ↓, Muc5ac ↓ in lung tissues, AHR to metacholine ↓ | Cheng et al.61               |
|                | Normal human bronchial epithelial cells    | EGF-induced pAKT ↓, tuberin ↓, p70S6 kinase ↓, 4E-binding protein 1 ↓           |                               |
| Dihdroartemisinin | LPS-induced ALI                          | Infiltration of inflammatory cells ↓, MPO ↓, oxidative stress ↓, Pro-inflammatory cytokines (IL-1β, TNF-α, IL-6) ↓, IκB degradation ↓, nuclear translocation of NFκB/p65 ↓, NRF-2 pathway ↑ | Huang et al.62              |
| Artesunate     | RIR-mediated ALI                          | Inflammatory cell count ↓, inflammatory cytokines in BALF ↓, F4/80-positive cells ↓, MPO ↓, caspase-1 ↓, NLRP-3 activation ↓, hypoxia/reoxygenation-mediated AM activation ↓ | Liu et al.63                |
| Artesunate     | RIR-mediated ALI                          | Serum and pulmonary NOX ↓, MDA ↓, IL-6 ↓, MIP-2 ↓, PGE-2 ↓, MPO ↓, total cell number ↓, protein concentration in BALF enhanced after RIR stimulation ↓, pulmonary pNFκB ↓, HO-1 pathway ↑ | Liu et al.64                |
| Artesunate     | LPS-induced ALI                           | Inflammatory cells ↓, lung edema ↓, MPO ↓, MDA ↓, TNF-α ↓, IL-6 ↓, IL-1β ↓, IL-6 ↓, TLR4 ↓, NF-κB activation ↓, NRF-2 ↑, HO-1 ↑ | Zhao et al.65               |
| Liposomal artesunate | LPS-induced ALI                          | TNF-α ↓, IL-6 ↓                                                             | Hu et al.66                   |
| Artesunate     | CLP-induced septic lung injury            | Mortality ↓, lung pathology ↓, neutrophil infiltration ↓, TNF-α and IL-6 in serum and BALF ↓, COX-2 ↓, iNOS ↓, NF-κB activation ↓, NRF-2 ↑, HO-1 ↑ | Cao et al.67                |
| Artesunate     | Paraquat-intoxicated Sprague-Dawley rats  | TGF-β1 ↓, IL-10 ↓, TNF-α ↓                                                   | Jiang et al.68               |

**Acute lung injury**

**Pulmonary fibrosis**

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**Abbreviations:** α-SMA, α-smooth muscle actin; AKT, AKT serine/threonine kinase; COX-2, cyclooxygenase 2; CLP, cecal ligation and puncture; EOS, eosinophil; ERK, extracellular signal-regulated protein kinase; FAS, fas cell surface death receptor; HO-1, heme oxygenase 1; IL-1β, interleukin-1β; INF-γ, interferon-γ; iNOS, inducible nitric oxide synthase; MCP-1, monocyte chemoattractant protein 1; MDA, malondialdehyde; MIP-2, macrophage inflammatory protein 2; MPO, myeloperoxidase; NLRP-3, nucleotide-binding domains and leucine-rich repeat pyrin domains containing 3 inflammasome; NRF-2, NF E2-related factor-2; NF-κB, nuclear factor κ B; OVA, ovalbumin; pAKT, phosphorylated AKT; PGE-2, prostaglandin E2; PI3K, phosphatidylinositol-4,5-bisphosphate 3-kinase; RIR, renal ischemia-reperfusion; SOD, superoxide dismutase; TNF-α, tumor necrosis factor-α; TGF-β1, tumor growth factor β1,STAT, Signal transducers and activators of transcription.
bronchoalveolar lavage were less infiltrated with inflammatory cells (eosinophils, neutrophils, and Th17 cells) upon exposure to artemisinins (Table 2).

The levels of various cytokines (TNF-α, IFN-γ, IL-1β, IL-8, IL-10, IL-13, MCP-1) and proliferative (cyclin D1) dropped down. Apoptosis was enhanced in eosinophilic leukocytes with increased fas cell surface death receptor (FAS) and decreased BCL-2 expression. Furthermore, oxidative stress markers related to inflammation also went down (e.g., 8-isoprostane, 8-OhdG, 3-nitrotyrosine, catalase, NADPH oxidase (NOX-2), superoxide dismutase (SOD), inducible nitric oxide synthase [iNOS], and NOX-1, -2, -3, -4), while NRF-2 was activated. Asthma-related signal transduction was also silenced by artemisinin and its derivatives, that is, TAS2R signaling, IL-6/STAT-3, pathway, PI3K/AKT, ERK, mitogen-activated protein kinase (MAPK) signaling, and the NF-κB pathway (Table 2).

In conclusion, there are numerous in vitro and in vivo results demonstrating that artemisinin-type drugs have the potential to treat asthma.

3.2 | Acute lung injury and pulmonary fibrosis

Acute lung injury or pneumonia represents a systemic inflammatory response in the lungs with short breath and bluish skin coloration without participation of heart failure. Lungs may collapse and low oxygen blood levels may occur. Immune cells (neutrophils, T-lymphocytes, and eosinophils) migrate into the inflamed lung tissue and enhance the phenomenon. The therapeutic value of corticosteroids and NO is not established and critically discussed.

The treatment with artemisinin and its derivatives of acute lung injury in experimental animal models demonstrated an improvement of the disease symptoms. Lung edema disappeared and the inflammatory cell count downs went down. The release of proinflammatory cytokines (TNF-α, IL-1β, IL-6) was suppressed by artemisinin-type drugs. Toll-like receptor 4 (TLR-4) signaling, which is important for innate immune responses and the NF-κB pathway, was silenced by artemisinins. Typical inflammation mediators such as malondialdehyde (MDA), macrophage inflammatory protein 2 (MIP-2), prostaglandin E2 (PGE-2), and COX-2 were downregulated. The activation of the NLRP-3 inflammasome was ceased. Markers of inflammation-related oxidative stress were also improved by artemisinins, that is, the NO content and MPO activity decreased, while the activities of NRF-2 and HO-1 increased (Table 2).

Among the symptoms of pulmonary fibrosis are short breathing, dry cough, respiratory failure, pneumothorax, and others. A typical feature is that normal lung tissue is transiently and irreversibly exchanged with fibrotic scarred tissue. Curative therapies are not available and current treatment concepts aim to slow down the progression of scar development by pirfenidone to downregulate growth factors and procollagens 1 and 2 and by corticosteroids as immunosuppressive therapy.

A well-known side effect of cancer therapy with bleomycin is the occurrence of lung fibrosis. Therefore, bleomycin can be experimentally used to mimic pulmonary fibrosis in vivo. Treatment of bleomycin-induced lung fibrosis with dihydroartemisinin was characterized by decreased levels of TGF-β1, TNF-α, α-smooth muscle actin (α-SMA), and NF-κB in lung tissues. Reductions of collagen synthesis and fibroblast proliferation also improved the symptoms pulmonary fibrosis (Table 2).

4 | NEUROLOGICAL DISEASES

4.1 | General neuroinflammation

Among other factors, neuroinflammation may be caused by autoimmune reactions or mechanic brain traumata. Microglia cells as innate immune cells are activated in response to inflammatory stimuli in the brain without peripheral immune response. During this process, proinflammatory cytokines (IL-6, IL-1β, and TNF-α) are produced,
| Compound     | Model                              | Mode of action                                                                 | Reference          |
|--------------|------------------------------------|-------------------------------------------------------------------------------|--------------------|
| **Neuroinflammation** |                                    |                                                                               |                    |
| Dihydroartemisinin | LPS-treated mice                   | Escape latency ↓, movement length ↓, open field activities ↑, hippocampal cell damage ↓, IL-1β ↓, IL-6 ↓, GFAP ↓, pPI3K ↓, IL-6, TNF-α, and pAKT ↓ | Gao et al.76       |
| Artesunate    | Experimental surgical TBI          | NF-κB ↓, Pro-inflammatory cytokines (IL-1β and TNF-α) ↓, NLRP3 inflammasome ↓, activation of astrocytes and microglia (GFAP, IBA-1) ↓, modulation of neurotrophic factors (BDNF, GDNF, NT-3) | Gugliandolo et al.77 |
| Artemether    | LPS-stimulated BV2 microglia/HT22 neuron cell coculture | Pro-inflammatory mediators (NO/iNOS, PGE2/COX-2/mPGES-1, TNF-α, IL-6) ↓, Aβ ↓, BACE-1 ↓, NF-κB and p38 MAPK signalling ↓, HO-1 ↑, NQO-1 ↑, GSH ↑, nuclear NRF-2 translocation ↑ | Okorji et al.77     |
| Artesunate    | LPS-stimulated BV2 microglia       | NO ↓, INOS ↓, IL-1β ↓, TLR-4 ↓, MyD-88 ↓, NF-κB ↓, IκB degradation ↓, TLR-4/MyD-88/NF-κB signalling pathways ↓ | Wang et al.78       |
| Artesunate    | LPS + IFNγ-activated BV2 microglia  | PGE2 ↓, COX-2 ↓, PGES-1 ↓, TNF-α ↓, IL-6 ↓, NF-κB activity ↓, IκB phosphorylation and degradation ↓, IKK ↓, pp38 MAPK ↓, pMAPKAP2K2 ↓ | Okorji et al.79     |
| Artesunate    | LPS-stimulated BV2 microglia       | NRF-2-ARE pathway ↑, HO-1 ↑, ERK pathway ↑ | Lee et al.80        |
| Artemisinin   | LPS-stimulated BV2 microglia       | microglia cell migration ↓, TNF-α ↓, IL-6 ↓, MCP-1 ↓, NO ↓, iNOS ↓, IκB-α ↑, NF-κB binding activity ↓ | Zhu et al.81        |
| **Autoimmune encephalitis** |                                    |                                                                               |                    |
| Artemisinin   | C57BL6 mice                        | EAE score ↓, plaque formation ↓, IFN-γ ↓, IL-4 ↑ | Khakzad et al.82    |
| Artesunate    | MOG35-55 peptide-induced EAE in C57BL6 mice | Immune cell infiltration into CNS ↓ | Thomé et al.83      |
| SM934 (derivative) | MOG35-55 peptide-induced EAE in C57BL6 mice | CD4(+) T cell infiltration in spinal lesions ↓, Treg cells ↑, Th17 cells ↓, Th1 cells ↓, IL-17 ↓, IL-2 ↓, IFN-γ ↓, IL-6 ↓, TGF-β ↑, IL-10 ↑ | Li et al.84        |
| Dihydroartemisinin | CD4cre:Smad2fl/fl C57BL/6 mice     | Th cell differentiation ↓, Treg cells ↑, TGF-βR:SMAD signalling ↑, mTOR signalling ↓ | Zhao et al.85       |
which may first cause neurotoxicity, but later on contribute to the repair of damaged neuronal tissue. These factors may also compromise the blood–brain barrier leading to the migration of immune cells (macrophages, T and B cells) from the periphery into the brain, which further enhance neuroinflammation and favor neurodegeneration.75

Symptomatic and histological investigations revealed that artemisinins contribute to a normalization of behavioral deficits and protect from hippocampal cell damage. The release of proinflammatory cytokines (TNF-α, IL-1β, IL-6, MCP-1) was reduced by artemisinin-type drugs. Oxidative stress, which also plays an important role in neuroinflammation, was suppressed by these drugs, as indicated by nuclear NRF-2 translocation and activation of the NRF-2/ARE pathway as well as increased levels of HO-1, NAD(P)H quinone dehydrogenase 1 (NQO-1), and GSH. Inflammatory signaling pathways were downregulated, for example, the NF-κB and TLR-4 pathways and the

| Compound | Model | Mode of action | Reference |
|----------|-------|----------------|-----------|
| SM933 (derivative) | MOG35-55 peptide-induced EAE in C57BL6 mice | Th2 activity↓, NF-κB activity↓, IkB↑, RIG-G↑, nuclear JAB-1 translocation↓, CDK-2↓, cyclin A↓, | Wang et al.86 |

**Alzheimer’s disease**

| Artemisinin | dihydroartemisinin, artesunate, artmether | hIAPP inhibition and disaggregation | Xu et al.87 |
|------------|------------------------------------------|----------------------------------|-----------|
| Artemisin B | Injection of Aβ25-35 into lateral ventricle of KM mice, LPS-stimulated BV2 microglia | Spatial memory↑, pathological features in hippocampus and cortex↓, NO↓, proinflammatory cytokines (IL-1β, IL-6, TNF-α)↓, MyD-88↓, NF-kB↓, TLR4↓, TLR4/MyD-88/NF-κB pathway↓ | Qiang et al.88 |
| Artemisin | APPswe/PS1dE9 double transgenic mice | Neuritic plaque burden↓, β-secretase activity↓, NF-kB↓, NALP-3 inflammasome activation↓ | Shi et al.89 |

**Myasthenia gravis**

| Artesunate | EAMG Lewis rats | Lymphocyte proliferation↓, costimulatory CD86↓, modulating Th1/Th2 cytokine expression, Treg cells↑, synthesis of anti-R97-116 IgG, IgG2a, and IgG2b antibodies↓ | Meng et al.90 |
|------------|----------------|----------------------------------|-----------|
| Artemisin | EAMG rats | TNF-α↓, IL-17+ mononuclear cells↓, TGF-β1↑, Treg cells↑ | Chen et al.91 |

Abbreviations: BDNF, brain derived neurotrophic factor; CNS, central nervous system; COX-2, cyclooxygenase 2; EAE, experimental autoimmune encephalitis; EAMG, experimental allergic encephalomyelitis; ERK, extracellular signal-regulated protein kinase; GDNF, glial cell derived neurotrophic factor; GFAP, glial fibrillary acidic protein; HO-1, heme oxygenase 1; IL-17, interleukin-17; iNOS, inducible nitric oxide synthase; JAB-1, JUN-activating binding protein; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor κ B; NLRP3, nucleotide-binding domains and leucine-rich repeat pyrin domains containing 3 inflammasome; NQO-1, NAD(P)H quinone dehydrogenase 1; pAKT, phosphorylated AKT; PGE-2, prostaglandin E2; PGES, prostaglandin E synthase; PI3K, phosphatidylinositol-4,5-bisphosphate 3-kinase; RIG-G, retinoic acid-induced gene G protein; TNF-α, tumor necrosis factor-α; TGF-β1, tumor growth factor β1.
ERK and MAPK pathways. A number of proinflammatory mediators were also suppressed (NO, iNOS, MyD-88, PGE-2, COX-2, and mPGES) (Table 3).76–81,92

4.2 | Autoimmune encephalitis, alzheimer's disease, and myasthenia gravis

Autoimmune encephalitis is a heterogeneous group of neurological disorders associated with changes in consciousness, cognitive decline, seizure, abnormal movements.93,94 Experimental models to test the activity of artemisinin-type drugs included treatment with MOG35-55 and specific genetically modified mouse strains. MOG35-55 is a peptide covering the residues 35-55 of the myelin oligodendrocyte glycoprotein, which is important for myelinization of central nervous system (CNS) nerves. Upon treatment with artemisinin-type drugs, the disease score and plaque formation decreased. Furthermore, the infiltration of immune cells into the CNS and spinal lesions was less. The T-helper cell (Th1, Th2, Th17) counts and activity decreased and the Treg cell count increased. In line with this, proinflammatory cytokines (IL-2, IL-6, IL-17, IFN-γ) decreased, while anti-inflammatory ones (TGF-β and IL-10) increased. The proliferative markers CDK-2 and cyclin A were less expressed, while the antiproliferative marker retinoic acid-induced gene G protein (RIG-G) went up. Signal transduction involving mTOR, NF-κB, JAB-1 was suppressed (Table 3).82–86

The appearance of neurofibrillary tau protein complexes and β-amyloid plaques is typical in Alzheimer’s disease.95 Furthermore, neuroinflammation is also involved in this disease.96 Microglia cells activated by proinflammatory cytokines are unable to clear up β-amyloid, which leads to plaque formation. Increased IL-1β production is associated with decreased synaptophysin contents and synaptic loss. Satisfying drug treatments are not yet available.97 There are also clues that artemisinin and its derivatives may be helpful for the treatment of Alzheimer’s disease. These compounds improved spatial memory, the neuritic plaque burden decreased pathological features in hippocampus and cortex improved and the β-secretase activity went down upon treatment. Furthermore, NALP-3 inflammasome activity was inhibited, and the amyloid polypeptide (hIAPP) was disaggregated and inhibited. Moreover, proinflammatory cytokines (IL-1β, IL-6, TNF-α) and the TLR4/MyD-88/NF-κB signaling pathway was suppressed (Table 3).87–89

Myasthenia gravis is a neuromuscular autoimmune disease affecting muscles of the eyes, face, and swallowing. The disease results from antibodies that lead to the decoy of nicotinic acetylcholine receptors between muscles and nerves, thus preventing muscle contraction.98 Drugs to treat myasthenia gravis are acetylcholine esterase inhibitors (neostigmine and pyridostigmine) and immunosuppressants (prednisone and azathioprine).99 Investigations on artemisinins to treat myasthenia gravis are still in its infancy. Nevertheless, some hints are available. Artemisinin and artesunate decreased lymphocyte proliferation, modulated Th1/Th2 cytokine expression, increased Treg cell counts, and the production of anti-R97 immunoglobulin antibodies (Table 3).90,91

5 | SKIN DISEASES

5.1 | Dermatitis

Dermatitis (or eczema) is a form of skin inflammation, which appears in three common forms: atopic, contact, seborrheic dermatitis. It is characterized by red skin, itchiness, and rash. Inflammatory cells such as Langerhans cells, inflammatory dendritic epidermal cells, and plasmacytoid dendritic cells migrate into the epidermis and generate edema.100 Therapeutic medications include corticosteroids (hydrocortisone), antihistaminic drugs, and immunosuppressants (tacrolimus).101
| Compound       | Model                                                                 | Mode of action                                                                 | Reference |
|---------------|------------------------------------------------------------------------|---------------------------------------------------------------------------------|-----------|
| **Dermatitis**|                                                                        |                                                                                 |           |
| Artesunate    | DNCB-induced atopic dermatitis in BALB/c mice                          | Symptoms↓, dermatis score↓, ear weight difference↓, spleen weight↓, lymph node weight↓, skin epidermal thickness↓, mast cell infiltration↓, IgE levels ↓, Th17 cell-related factors (IL-6, IL-17, IL-23, STAT-3, ROR-γt)↓, TGF-β and SOCS-3↑ | Bai et al. 102 |
| Artemisinin   | TPA-induced skin inflammation in mice                                  | NF-κB reporter gene expression↓, TNF-α induced phosphorylation and degradation of IκBα and p65 nuclear translocation↓, upstream signaling of IKK ↓ by adaptors proteins, TRAF-2 and RIP-1↓, TNF-α-induced expression of NF-κB target genes, such as antiapoptosis (c-IAP-1, BCL-2, FLIP), proliferation (COX-2, cyclin D1), invasion (MMP-9), angiogenesis (VEGF), and major inflammatory cytokines (TNF-α, iNOS, MCP-1), TNF-α-induced apoptosis↑ | Wang et al. 103 |
| Artemisinin   | Concavalin A-induced contact hypersensitivity                         | Treg generation↑, Th17 development↓, p38 MAPK activation↑, IL6↓, IL-17↓, TGF-β↑, STAT-3 activation↓ | Li et al. 104 |
| Artesunate    | Allergic contact dermatitis                                            | Ear swelling↓, spleen index↓, inflammatory cell infiltration↓, IFN-γ↓, NF-κB p65↓ | Li et al. 105 |
| Artemisinin   | Contact sensitivity in female hairless guinea pigs                    | Elicitation reaction↓                                                             | Chena and Maibach, 106 |
| **Rosacea**   |                                                                        |                                                                                 |           |
| Artemether    | open-label trial (130 patients)                                        | Significantly lower papule and pustule scores and comparable erythema scores compared with patients with metronidazole treatment for 4 weeks | Wang et al. 107 |
| Artemisinin   | LL37-induced rosacea-like mice                                         | Angiogenesis↓, proinflammatory cytokines (IL-1β, IL-6, TNF-α)↓, chemokines (CXCL-10, CCL-20, CCL-2 and CXCL-2)↓, TLR-2↓, infiltration of T cells, macrophages, and neutrophils. | Yuan et al. 108 |
| Artesunate    | Demodex folliculorum and LL-37 stimulated HaCaT cells                | Proinflammatory cytokines (TNF-α, IL-6, IL-8, MCP-1)↓                            | Li et al. 109 |
| **Psoriasis** |                                                                        |                                                                                 |           |
| Artesunate    | Imiquimod-induced psoriasis                                           | Systemic inflammation↓, γδ T cell number in draining lymph nodes↓, cumulative score↓, epidermal thickening↓, Ki-67 expression↓ | Huang et al. 110 |

Abbreviations: COX-2, cyclooxygenase 2; CXCL-10, C-X-C chemokine ligand 10; DNCB, dinitrochlorobenzene; EAMG, experimental allergic encephalomyelitis; GFAP, glial fibrillary acidic protein; IL-17, interleukin-17; iNOS, inducible nitric oxide synthase; LPS, lipopolysaccharide; MCP-1, monocyte chemotractant protein 1; MMP, matrix metalloproteases; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor κ B; NLRP3, nucleotide-binding domains and leucine-rich repeat pyrin domains containing 3 inflammasome; STAT, signal transducer and activator of transcription; TAP, tetradecanoylphorbol-acetate; TNF-α, tumor necrosis factor–α; TGF-β1, tumor growth factor β1.
Typical symptoms were reduced or disappeared by artemisinins in dinitrochlorobenzene (DNCB)-, tetradecanoylphorbol-acetate (TPA)- or concavalin A-induced dermatitis in animals (e.g., decreased dermatitis scores, ear, spleen, and lymph node weights, skin epidermal thickness as well as decreased IgE levels). The tissue infiltration of inflammatory cells was reduced, the counts of Th7 cells decreased, while that of Treg cells increased. Th17 cell-related factors (IL-6, IL-17, IL-23, STAT-3, ROR-γt) were downregulated, whereas the expression TGF-β and SOCS-3 was upregulated. SOCS-3 is a suppressor of cytokine signaling, which acts like TGF-β in an anti-inflammatory fashion. TNF-α-induced activation of the NF-κB pathway with subsequent expression of NF-κB downstream genes was suppressed by artemisinin, for example, genes coding for antiapoptosis proteins (c-IAP-1, BCL-2, and FLIP), proliferation proteins (COX-2 and cyclin D1), invasion proteins (MMP-9), angiogenesis proteins (VEGF), and major inflammatory cytokines (TNF-α, iNOS, MCP-1) (Table 4).102–106

5.2 | Rosacea and psoriasis

Rosacea is an autoimmune disease which affects Caucasians more than other populations. Typical symptoms are pimples, skin swelling, redness, and others.111 Established medications are antibiotics such (e.g., metronidazole, doxycycline, and tetracycline) and ivermectin.112 Demodex folliculorum- and LL37-stimulated HaCat cells as rosacea-mimicking in vitro cell model released several proinflammatory cytokines (TNF-α, IL-6, IL-8, and MCP-1). Interestingly, an open label trial with 130 rosacea patients showed significantly lower papule and pustule scores and comparable erythema scores compared with patients with standard metronidazole treatment for 4 weeks (Table 4).107–109

Another autoimmune disease of skin is psoriasis, where immune cells react again skin cells. Psoriasis is characterized by premature maturation of excessively growing keratinocytes in response to inflammation. Dendritic cells, macrophages, and T-cells release cytokines (IFN-γ, TNF-α, IL-1β, IL-6, and IL-22), which stimulate the growth of epidermal skin layer cells. Defective Treg cells and inappropriate IL-1β release as well as DNA release from dying cells further increase inflammation and stimulate IFN-α release of dendritic cells. The stimulated and proliferating keratinocytes and psoriatic T cells also release proinflammatory cytokines (IL-1β, IL-6, IL-27, IL-22, and TNF-α).113 The available therapeutic options may relieve the symptoms of psoriasis, but do not lead to satisfying curative effects. Treatment is attempted with steroids and NSAIDs, methotrexate, UV-light plus psoralen, the TNF-α-inhibitory antibodies infliximab and adalimumab and the TNF-α decoy receptor eternacept. Efalizumab and alefacept are also used, which are directed against T-cells.114 Therapeutic options for psoriasis have not been investigated in detail yet. Imiquimod-induced experimental psoriasis was treated with artesunate leading to beneficial results: systemic inflammation, T-cell numbers in draining lymph nodes, cumulative score, epidermal thickening, and proliferation rate (Ki-67 expression) all went down upon artesunate treatment (Table 4).110

6 | INFLAMMATORY BOWEL DISEASE

Ulcerative colitis and Crohn’s disease are common forms of inflammatory bowel disease (IBD), which occur in the colon and small intestine. Typical IBD symptoms are ulcers, abdominal pain, diarrhea, rectal bleeding, weight loss, and others. Multiple pathophysiological factors lead to inflammatory responses.115,116 Several treatment strategies have been recommended for IBD, for example, mesalazine, immunosuppressants (prednisone azathioprine, methotrexate, and TNF-α inhibitors), which partly can exert harsh adverse effects.117 There are many results showing improvements of clinical IBD symptoms by treatment with artemisinin-based drugs, for example, the body weight regained towards normal levels, the disease activity index was improved, colonic shortening was stopped, the gastric juice parameters normalized, and diarrhea and rectal bleeding were
### TABLE 5  Anti-inflammatory activity of artemisinin-type drugs against inflammatory bowel disease

| Compound          | Model                                                                 | Mode of action                                                                                         | Reference |
|-------------------|-----------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|-----------|
| Artesunate        | DSS-induced ulcerative colitis in wildtype and T cell-deficient RAG mice (RAG-/-) | Apoptosis of lamina propria MΦs and DCs, mucosal TNF-α and IL-12p70, apoptosis of human THP-1 MΦs, secretion of IL-12p40/70 by DCs and TNF-α by MΦs. | Sun et al.^{118} |
| Artesunate        | DSS-induced ulcerative colitis                                        | Body weight↑, DAI score↑, colon shortening↓, erosion of surface epithelial cells, goblet cells, crypt destruction↓, inflammatory cells infiltration↓, loss of MUC2 and claudin-1, Bcl-2/Bax ratio↑, cleaved-caspase-3, pIkBα, pNF-κB p65, IL-1β, IL-6, TNF-α, IL-10↑ | Yin et al.^{119} |
| Dihydroartemisinin| OXA- and TNBS-induced colitis in mice                                 | Colitis signs↓, lymphocyte infiltration↓, tissue fibrosis, numbers of Th1, Th17, Th9, and Th22, restoration of Th/Treg balance, activation of CD4 + T lymphocytes, apoptosis induction↑, HO-1↑ | Yan et al.^{120} |
| Artesunate        | DSS-induced ulcerative colitis, RAW264.7 cells                       | DAI score↑, pathological changes, pro-inflammatory mediators (TNF-α, IFN-γ, IL-1β, IL-6), MPO, hemoglobin expression↑, apoptosis markers (BAX, caspase-9), pp38↓ | Chen et al.^{121} |
| Dihydroartemisinin| DSS-induced ulcerative colitis in male C57 mice, intestinal epithelial cell-6 | Body weight↑, colon shortening↓, DAI score↑, pro-inflammatory cytokines (TNF-α, IFN-γ, IL-1β, IL-6), phosphorylation of PI3K, AKT, IKKa, IkBa, and NF-κB (p65), PI3K/AKT and NF-κB signaling pathways↓ | Li et al.^{122} |
| Artesunate        | Aspirin-induced gastric injury in fasted Wistar rats                  | Oxidative stress markers (GSH, MDA, SOD), mediators of inflammation (myeloperoxidase and TNF-α), inflammation markers (IL-1β, IL-6, NF-κB (p65) and COX-2)↓ | Verma and Kumar^{123} |
| SM934 (derivative) | DSS-induced ulcerative colitis                                       | Body weight↑, colon shortening, injury and inflammation, DAI score, MPO activity, inflammatory cytokines (IL-1β, IL-6 and TNF-α), macrophages and neutrophils↓ | Yan et al.^{124} |
| Dihydroartemisinin| DSS-induced ulcerative colitis in Sprague-Dawley rats                | IBD-related bone loss, osteoclast formation, DAI score, TNF-α, RANKL, RANK, TRAF-6, FRA-1, NF-ATC1, P1NP↑ | Ge et al.^{125} |

(Continues)
reduced. Histologically, artemisinins reduce the erosion of surface epithelial cells, crypts were less destructed and less inflammatory cells infiltrated the colonic tissue (macrophages, dendritic cells, CD4+ T cells, Th1 cells, Th17 cells, Th9 cells, Th22 cells, and neutrophils). The mucosal markers mucin 2 (MUC-2) and claudin 1 were less expressed upon artemisinin-based treatment. The healthy histological architecture was restored with less fibrosis and less inflamed gastric mucosa (Table 5).118–128

At the mechanistic level, the release of several proinflammatory cytokines (TNF-α, IFN-γ, IL-1β, IL-6, IL-8, IL-12, IL-17) was suppressed by artemisinin and its derivatives, while the release of IL-10 as anti-inflammatory cytokine was boosted. The activity of COX-2 as inflammatory mediator was suppressed. IBD-related apoptosis in colonic tissues was reduced as indicated by reduced expression of BAX, caspase 9 and phosphorylated p38 MAPK. Inflammation-related oxidative stress was also reduced by artemisinin and its derivatives, because the expression and activity of SOD, MDA MPO and glutathione decreased, while that of HO-1 increased. IBD-associated signaling was considerably affected by artemisinin and its derivatives. The signaling routes of NF-κB, TLR-4, RANK/RANKL, PI3K/AKT, FRA, and NF-ATC1 were all downregulated (Table 5).

### 7 | OTHER DISEASES

Kidney inflammation (nephritis) can affect tubules, glomeruli (glomerulonephritis), and the interstitial tissue in between (interstitial nephritis).129–131 SLE can be associated with lupus nephritis. The inflammatory processes cause reduced renal blood flow and thus reduced urine production. Hematuria and proteinuria may also result from renal inflammation.

In animal models, an improvement of renal function associated with a decrease of tubulointerstitial inflammation, fibrosis, and proteinurea was reported. A number of proinflammatory cytokines and chemokines reduced.

### TABLE 5 (Continued)

| Compound       | Model                        | Mode of action                                                                 | Reference                  |
|----------------|------------------------------|--------------------------------------------------------------------------------|----------------------------|
| Artemisinin    | LS174T cells                 | Activation of DNA-binding capacity of PXR for the CYP-3A4 element              | Hu et al.127               |
| Artemisinin    | DSS-induced ulcerative colitis in mice | Body weight ↓, diarrhea ↓, rectal bleeding ↓, colon shortening ↓, colonic inflammation ↓ by PXR-mediated activation of CYP-3A expression |                           |
| Artesunate     | DSS-, or OXA-, or TNBS-induced ulcerative colitis in mice | DSS-colitis, TNBS-colitis, (but not OXA-induced colitis) ↓, weight loss ↓, disease activity ↓, NF-κBp65 ↓, plkBα ↓, IFN-γ ↓, IL-17 ↓, TNF-α ↓ | Yang et al.128             |

Abbreviations: COX-2, cyclooxygenase 2; DSS, dextran sulfate sodium; EAMG, experimental allergic encephalomyelitis; GFAP, glial fibrillary acidic protein; HO-1, heme oxygenase 1; IL-17, interleukin-17; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinase; MDA, malondialdehyde; NF-κB, nuclear factor κ B; NLRP3, nucleotide-binding domains and leucine-rich repeat pyrin domains containing 3 inflammasome; PI3K, phosphatidylinositol-4,5-bisphosphate 3-kinase; SOD, superoxide dismutase; TRAF-6, TNF receptor-associated factor 6; TGF-β1, tumor growth factor β1.
| Compound                | Model                                                                 | Mode of action                                                                                                                                                                                                 | Reference |
|-------------------------|-----------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|
| **Nephritis**            |                                                                       |                                                                                                                                                                                                             |           |
| Dihydroartemisinin      | LPS-induced AKI in male C57BL/6 mice                                  | Renal function (serum creatinine and blood urea nitrogen)↑, pathological injury ↓, tubular cell apoptosis ↓ (cleaved caspase 3↑, APAF-1↑), inflammatory response ↓ (IL-1β↓, IL-5↓, IL-6↓, IL-17A↓, IFN-γ↓, TNF-α↓, CXCL-1↓, MCP-1↓), NF-κB signaling pathway↓, oxidative stress↓ | Liu et al.,132 |
| Artemisinin             | Subtotal nephrectomized (SNx) rats                                    | Renal function↑, tubulointerstitial inflammation and fibrosis↓                                                                                                                                              | Wen et al.,133 |
|                         | Ang II-induced injury of the human kidney 2 (HK-2) cells             | NLRP-3 inflammasome and NF-κB activation↓                                                                                                                                                                    |           |
| Artesunate              | High glucose-treated rat HBZY-1 mesangial cells                       | ECM production↓, ROS↓, MDA↓, SOD↑, TLR-4↓, MyD-88↓, NF-κB↓, NLRP-3↓                                                                                                                                         | Sun et al.,133 |
| Artesunate              | Pristine-induced nephritis in female BALB/c mice                      | Renal function↑, proteinuria↓, TNF-α↓, IL-6↓, α-SMA↓, TLR-4↓, MyD-88↓, NF-κB p65↓, TGFB1↓                                                                                                                  | Wan et al.,134 |
| Artesunate              | IgA nephropathy rat model                                            | Renal function↑, MCP-1↓                                                                                                                                                                                       | Mi et al.,135 |
| **Type 1 diabetes mellitus** |                                                                     |                                                                                                                                                                                                             |           |
| Artesunate              | NOD mice                                                             | Prevention of type 1 diabetes, IL-4-producing CD4+ single-positive T cells and CD8+ T cells↑, IFN-γ producing T cells↓, Treg cells↑                                                                                                                                 | Li et al.,136 |
| Artesunate              | Glucagon-CreERT2; Rosa-LSL-eYFP mice                                  | No effect on α-to-β cell transdifferentiation nor insulin secretion                                                                                                                                         | Ackermann et al.,137 |
| Artemisinin, artemether, artemesate and derivatives | Murine β Min6 cells, αTC1 cells, GFPMCherry zebrafish                | Transdifferentiation of glucagon-producing α cells into insulin-producing β cells, cytoplasmic translocation of ARX                                                                                           | Li et al.,138 |
| Artesunate              | IL-1β-treated pancreatic β cells                                     | GSIS↑, KSIS↑, IL-1β-induced apoptosis↓, NF-κB↓, iNOS↓, NO↓, SIRT-1↑                                                                                                                                          | Yu et al.,139 |
| **Autoimmune hepatitis** |                                                                     |                                                                                                                                                                                                             |           |
| Artesunate              | Con A-induced autoimmune liver injury                                | Serum transaminases (ALT, AST)↓, pro-inflammatory cytokines(TNF-α, IFN-γ, IL-6, IL-17)↓, anti-inflammatory cytokines (IL-10)↑, pNF-κB p65 and pIKB-α↓,                                                                 | Cao et al.,140 |

(Continues)
Table 6 (Continued)

| Compound          | Model                          | Mode of action                                                                 | Reference       |
|-------------------|--------------------------------|--------------------------------------------------------------------------------|-----------------|
| Artesunate        | Con A-induced autoimmune liver injury | Serum transaminases↓, pro-inflammatory cytokines (TNF-α, IFN-γ, IL-6, IL-17)↓, anti-inflammatory cytokines (IL-10)↑, phosphorylation of ERK, JNK, p38 MAPK, NF-κB p65 and κB-α↓ | Zhao et al.,141 |

Autoimmune thyroiditis

| Dihydroartemisinin | Porcine Tg-immunized female C57BL/6J mice | Antithyroglobulin antibody and thyroid peroxidase antibody levels↓, Th1/Th2 imbalance normalized, calcium flow ↓ by CXCL-10 binding to CXR-3↓, pI3K↓, pAKT↓, pAKT↑, NF-κB↓, pNF-κB↓ | Liu et al.,142 |

Atherosclerosis

| Artesunate        | TNF-α-stimulated primary rat VSMCs | Proliferation↓, PCNA↓, MMP-2 and MMP-9↓, NO↓, PGE-2↓, COX-2↓, iNOS↓, NF-κB p65↓ | Cao et al.,143 |

Multiorgan failure by hemorrhagic shock

| Artesunate        | Experimental HS in male Wistar rats | Multiple organ injury and dysfunction↓, pAKT↑, peNOS↓, pGSK-3B↑, NF-κB↓, iNOS↓, pro-inflammatory cytokines (TNF-α, IL-6)↓ | Sordi et al.,144 |

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; COX-2, cyclooxygenase 2; CXCL-10, C-X-C chemokine ligand 10; EAMG, experimental allergic encephalomyelitis; GFAP, glial fibrillary acidic protein; IL-6, interleukin-6; iNOS, inducible nitric oxide synthase; LPS, lipopolysaccharide; MCP-1, monocyte chemoattractant protein 1; MAPK, mitogen-activated protein kinase; MDA, malondialdehyde; NLRP-3, nucleotide-binding domains and leucine-rich repeat pyrin domains containing 3 inflammasome; NF-κB, nuclear factor κ B; NLRP3, nucleotide-binding domains and leucine-rich repeat pyrin domains containing 3 inflammasome; pAKT, phosphorylated AKT; PGE-2, prostaglandin E2; PI3K, phosphatidylinositol-4,5-bisphosphate 3-kinase; SOD, superoxide dismutase; TLR, TLR, toll-like receptor; TNF-α, tumor necrosis factor–α; TGF-β1, tumor growth factor β1.

((IL-1β, IL-5, IL-6, IL-17A, IFN-γ, TNF-α, CXCL-1, MCP-1) as well as inflammatory mediators (α-SMA, TLR4, MyD-88, NF-κB p65) were downregulated. NLRP-3 inflammasome and NF-κB activation was shut down and inflammation-related oxidative stress markers were normalized (suppression of ROS and MDA and enhancement of SOD activity) (Table 6).132–135,145

Type 1 diabetes mellitus is characterized by a lack of pancreatic insulin production in juvenile patients. In contrast to type 2 diabetes, the underlying mechanisms of type 1 diabetes led to an autoimmune-regulated destruction of the insulin-producing β-cells. Autoantibodies have been identified and characterized. Insulin substitution is indispensable for patients’ survival.146

Artemisinin and its derivatives have been investigated in diverse genetic animal models in vivo and β-cells in vitro. Artesunate prevented the onset of type 1 diabetes mellitus. Glucose-stimulated and potassium-stimulated insulin secretions (GSIS and KSIS) were both increased by artemether and a transdifferentiation from of glucagon-producing α cells into insulin-producing β cells was induced by artemether. This effect was associated with cytoplasmic translocation of the transcription factor ARX. In contrast to these positive results, other authors did not observe any effect on α-to-β cell transdifferentiation or insulin secretion (Table 6).136–139
Liver inflammation can be acute or take a chronic course. A specific chronic form is **autoimmune hepatitis**, which is an autoimmune reaction directed against hepatocytes. Common auto-antibodies are the anti-nuclear antibody (ANA), smooth muscle antibody (SMA), and atypical perinuclear antineutrophil cytoplasmic antibody (p-ANCA). Patients with autoimmune hepatitis have an increased risk for the development of liver cirrhosis and liver cancer.\textsuperscript{147}

Artesunate has been used to treat concavalin A-induced autoimmune liver injury.\textsuperscript{140,141} As a result, the liver transaminases in the serum decreased, less proinflammatory cytokines (TNF-\(\alpha\), IFN-\(\gamma\), IL-6, IL-17) and more anti-inflammatory cytokines (IL-10) were determined, and the phosphorylation of several signal transducers (ERK, JNK, p38 MAPK, NF-\(\kappa\)B p65, and I\(\kappa\)B-\(\alpha\)) was inhibited (Table 6).

In **autoimmune thyroiditis**, antibodies against thyroid cells are produced, which destroy these cells.\textsuperscript{148} Dihydroartemisinin treatment inhibited antithyroglobulin antibody and thyroid peroxidase antibody production in a mouse model of autoimmune thyroiditis.\textsuperscript{142} This observation was associated with a normalization of the Th1/Th2 imbalance, decreased calcium flow by CXCL-10 binding to CXR-3 and a suppression of expression and phosphorylation several signaling molecules (PI3K, AKT, and NF-\(\kappa\)B) (Table 6).

**Atherosclerosis** is characterized by plaque formation and deposition. Autoimmune processes contribute to atherosclerosis and monocytes and basophils attack the arterial endothelia.\textsuperscript{149,150} TNF-\(\alpha\)-stimulated primary rat vascular smooth muscle cells were treated with artesunate. Their proliferation was inhibited and several inflammatory-related proteins were downregulated (MMP-2, MMP-9, PGE-2, COX-2, iNOS, and NF-\(\kappa\)B).\textsuperscript{143} (Table 6).

**Multiorgan failure** by hemorrhagic shock is also associated with inflammatory processes.\textsuperscript{151,152} Although the experimental evidence for the activity of artemisinin-type compounds is still weak in this context, artesunate improved multiple organ injury and dysfunction in an experimental rat model of hemorrhagic shock.\textsuperscript{144} This effect was correlated with a decrease of the proinflammatory TNF-\(\alpha\) and IL-6, decreased activities of endothelial and inducible nitric oxide synthases (eNOS, iNOS) as well as of NF-\(\kappa\)B (Table 6).

8 | **TOXICOLOGY OF ARTEMISININ-TYPE DRUGS**

Although the toxicity of artemisinins have been well-investigated in preclinical and clinical malaria studies and this type of drugs are generally accepted to be relatively safe, toxicological issues are still in the focus of interest. Since artemisinins have been recently considered for other diseases than malaria, this issue has to be considered again. This is true for inflammatory and autoimmune diseases as discussed in the present review article but also for all other discussed disease indications (e.g., cancer schistosomiasis, trypanosomiasis etc.), where longer treatment durations might be necessary to observe clinically visible therapeutic effects. Therefore, we give here an update of the past decade on our comprising review on the toxicity of artemisinin-type drugs.\textsuperscript{153}

8.1 | **Neurotoxicity**

Among the most reported toxicities regarding therapeutic use of artemisinins is neurotoxicity, which is dependent of the duration of treatment. In animal experiments, behavioral changes, balance and coordination disturbances, eye reflex and auditory loss were investigated. The lowest observed neurotoxic effect levels (LONEL) of artheether have been determined in the plasma of monkeys, rats, and dogs.\textsuperscript{154} The authors observed that the exposure time to provoke minimal neurotoxicity was longest in monkeys and shortest in rats, indicating that LONEL values are lower in primates (including human beings) than in rodents. Another observation was that orally administered artelinic acid needed longer exposure times to provoke neurotoxicity than intramuscularly applied arteether, which indicates that the application route and the water solubility of artemisinin-type drugs play an important role. In dogs, artemether
induced neuropathic CNS changes with motor and motor neuron damages, but no disturbances in behavior. By contrast, artesunate did not provoke neurotoxicity.\textsuperscript{155}

Neurotoxicity was rarely seen in malaria patients, which is probably due to the fact that the common duration of therapy for only 3–5 days seems to be safe.

8.2 | Hematotoxicity

Hematotoxicity can appear in the erythropoietic and leukopoietic differentiation lineages, and erythropoietic toxicities by artemisinins are much better documented that the leukopoietic one.\textsuperscript{153} If disturbances occur in erythropoiesis in maternal or fetal organisms, embryotoxicity may appear (see below). A frequently used parameter for erythrocytic toxicity is the determination of reticulocyte count. Reticulocytes in the peripheral blood are bone marrow–derived precursor cells. Reduced reticulocyte counts frequently occur, but mostly with mild to moderate courses, which are reversible after the end of therapy.

\textit{Erythropoietic lineage}: Interesting results were reported by using K562 leukemia cells as suitable model to study erythroblastic differentiation. A panel of artemisinin derivatives except deoxyartemisinin inhibited erythroid differentiation of K562 cells, reinforcing the peroxide moiety in the chemical scaffold of artemisinins for erythroblastic toxicity. The most active compound in this series was the active metabolite dihydroartemisinin, which decreased Glycophorin A and \(\gamma\)-globin expression, caused S-phase arrest in the cell cycle, induced apoptosis of early erythroblasts.\textsuperscript{156,157} In dogs, artemether and artesunate induced anemia, concurrent extramedullary hematopoiesis in the spleen and suppressed bone marrow erythropoiesis.\textsuperscript{155} A 10-years follow-up study among Nigerian children revealed that anemia is common pre- and early posttreatment without significant increase under artemisinin-based combination therapy (ACT), but single injections caused declines in hematocrit values.\textsuperscript{158} In a clinical pilot Phase I–II trial with 23 colorectal carcinoma, two patients experienced reversible anemia and neutropenia.\textsuperscript{159}

\textit{Leukopoietic lineage}: Artesunate induced clastogenic and aneugenic effects caused by oxidative and nitrosative stress and thereby caused apoptosis in human lymphocytes.\textsuperscript{160} While artemisinins alone or malaria-related ACTs may cause only mild to moderate hematotoxicity, this cannot be taken for granted for all combination therapies. The compassionate application of dichloroacetate and artesunate by alternative practitioner resulted in the death of a glioblastoma patient. The patient experienced bone marrow toxicity (leukopenia and thrombocytopenia) and hepatotoxicity and died 10 days after the infusion.\textsuperscript{161}

8.3 | Embryotoxicity and teratogenicity

The inhibition of erythropoiesis fired discussions on a potential risk for embryotoxicity of artemisinin-type drugs.\textsuperscript{162} However, embryos may get lost during the first weeks of pregnancy without becoming aware to the women knowing about their pregnancy in this early stage. Malformation of damaged but surviving animals can also not be determined with convincing certainty. Therefore, WHO warned on the use of artemisinins within the first three trimester.\textsuperscript{163} The potential embryotoxic risk is further aggravated by the fact that embryotoxic effects of artemisinins have been documented in preclinical studies in mice, rats, rabbits, and monkeys.\textsuperscript{153}

A recent investigation confirmed the embryotoxic risk of artesunate at high doses (8 mg/kg) in rats regarding several parameters: the gravid uterine weight and fetus weights decreased, the number of fetal deaths and post-implantation losses increased. There were also more malformations of the embryos.\textsuperscript{164} Therefore, embryotoxicity is an important aspect to be considered if it comes to the development of novel artemisinin derivatives. The synthetic tetraoxane drug candidate (RKA182) and a trioxolane equivalent (FBEG100) revealed embryotoxicity and erythroblasts depletion in rodents.\textsuperscript{165} The novel derivative artefenomel and artesunate as positive control drug were similarly embryotoxic in rats regarding cardiovascular defects and fetal resorption. Both compounds depleted
embryonic erythroblasts and reduced maternal reticulocyte counts. However, artefenomel was ∼250-fold less embryotoxic in vitro than dihydroartemisinin, the active metabolite of artesunate. Lipid nanoparticles containing artemether and clindamycin caused ∼90% fetal resorptions, but no postimplantation losses or fetal malformations. Nevertheless, should this nanoparticle formulation be further developed as drug, its use in pregnancy must be excluded.

8.4 | Cardiotoxicity

Cardiotoxicity is a well-known side effects of anthracyclines because of the generation of radical oxygen species (ROS), which cannot be sufficiently detoxified in cardiac tissues. As ROS are also produced by artemisinin-type drugs, the question arises whether or not cardiotoxicity also applies for this drug class. Cardiotoxicity has been reported in animals, while clinical trials in human malaria patients did not show alerting signs of cardiotoxicity in the past.

In dogs, artemether provoked a prolongation of frequency-correct Q-wave T-wave interval (QTC) intervals on electrocardiograms, while artemunate decreased the heart rate. In another study, artesunate decreased the heart rate in vitro, but not in vivo.

In a Zebrafish model to study cardiotoxicity, low dose artesunate protected from verapamil-induced heart failure. Cardiac malformation was prevented by artesunate. Furthermore, Verapamil-induced venous stasis, cardiac output decrease, and blood flow dynamics reduction were restored by artesunate in zebrafish. Monitoring of biomarkers for cardiotoxicity by RNA-sequencing revealed that the gene for frizzled receptor 7a (fzd7a) was upregulated in zebrafish with verapamil-induced heart failure but downregulated upon artesunate. As frizzled receptors belong to the Wnt signaling pathway, artesunate may confer cardioprotection via this pathway. By contrast, high artesunate concentrations exerts cardiotoxic effects. While this kind of biphasic effects are well documented in the literature and referred to as hormesis, this is the first report for hormetic effects of artemisinin-type drugs.

8.5 | Other toxicities

Nephrotoxicity: While renal failure and tubular necrosis have been occasionally reported with artemisinins in the past, another previous report on histopathological examinations of adult rodents treated with artemether-loaded lipid nanoparticles did not find signs of nephrotoxic changes.

Gastrointestinal toxicity: Upon artesunate application, the gastric pH increased, and the volume of gastric secretions decreased at supra-therapeutical doses. However, the treatment of malaria patients with artemisinin-piperazine combination therapy at high doses produced symptoms of gastrointestinal toxicity such as decreased food consumption and loss of body weight, which indicates that monitoring gastrointestinal toxicity is not outside of the scope. In a pilot Phase I–II trial on cervical carcinoma, 5/10 patients had abdominal pain (or headache or transient flu-like-symptoms). Severe adverse events did not appear.

Hepatotoxicity: While liver damage has not been seen as considerable source of toxicity associated with artemisinins in the past, treatment outside the officially approved treatment guidelines led to the appearance of hepatotoxic reactions. During the past years, artemisinin and its derivatives became popular for out-of-treatment patients in complementary and alternative medicine. The treatment of a glioblastoma patient with dichloroacetate and artesunate by an alternative practitioner resulted in a fatal outcome for the patient because of acute liver damage and bone marrow toxicity 10 days after intake. Another glioblastoma patient took artesunate and a cocktail of Chinese herbs (Coptis chinensis, Siegesbeckia orientalis, Artemisia scoparia, Dictamnus dasycarpus) in addition to standard radiochemotherapy including ondansetron, valproic acid, levetiracetam, lorazepam, and
clobazam. The patient suffered from a dramatic increase of liver enzymes. This reaction was reversible upon cessation of artesunate and the Chinese herbal decoction.\textsuperscript{176}

**Reproductive toxicity:** In healthy rats not suffering from malaria, artemisinin suppressed the levels of follicle-stimulating hormone, while it increased those of progesterone.\textsuperscript{177} In addition to hormonal imbalance in female organisms, artesunate also exerted reproductive toxicity in males. Artesunate decreased epididymal sperm count and increased the number of sperms with abnormal head morphology. In addition, spermatozoa of artesunate-treated mice had significantly more DNA strand breaks than untreated control animals, indicating that artesunate crossed the blood-testis barrier.\textsuperscript{178}

**Reduction of toxicity induced by xenobiotic compounds:** Interestingly, artemisinin-type drugs have not only been subject to unravel toxic reactions but also whether or not this drug class is capable to reduce the toxicity induced by other xenobiotic compounds such as anticancer drugs. This is a new aspect in toxicological research on artemisinins, which deserves further attention in the future. Doxorubicin caused hyperemia and hemorrhages in the liver and heart of rats, which was associated with increased caspase-3, TNF-α, iNOS, and NF-κB expression. Artemisinin suppressed the expression of these proteins, indicating cardio- and hepatoprotective effects of artemisinin.\textsuperscript{179} Activated NRF2 signaling is related with tissue-protection. Artemisitene is an NRF-2 inducer, which protected from bleomycin-induced lung injury.\textsuperscript{180}

**9 | SYNOPSIS OF DATA AND FUTURE PERSPECTIVES**

There is no doubt that the spectrum of bioactivities of artemisinin-type drugs is much broader than initially expected. This type of compounds is not only active against malaria but also other infectious and vector-borne diseases as well as cancer.\textsuperscript{181–184} In the present review, the focus is on inflammatory and autoimmune diseases.

The question may arise, whether or not such broad spectrum of activities is realistic, and if so, how specific such drugs could be in terms of disease relevant target proteins as underlying molecular mechanisms. There is an overwhelming number of publications pointing to the transcription factor NF-κB as possible common mode of action of artemisinin and its derivatives, because NF-κB plays a role in many of the diseases, where artemisinins exert inhibitory activity. As a matter of fact, NF-κB is involved in the pathology of viral diseases,\textsuperscript{5,184–187} cancer,\textsuperscript{188,189} and even malaria.\textsuperscript{190–192} The central role of NF-κB for innate and acquired immune functions is well-studied. It regulates the expression of proinflammatory cytokine- and chemokines and thereby drives the activation, proliferation, and differentiation of immune cells.\textsuperscript{193,194} A majority of published literature indeed speaks for the inhibition of NF-κB as major mechanism explaining the activity of artemisinin and its derivatives against inflammatory and autoimmune diseases (Figure 1). NF-κB is a dimer formed by several protein that share a Rel binding domain. Known proteins with a Rel domain are NF-κB1 (p50 and p105), NF-κB2 (p52 and p100), RelA (p65), and RelB: The NF-κB signaling is a tightly controlled process. In the cytoplasm, NF-κB is inactive and complexed with IκB. IκB kinase (IKK) phosphorylates IκB-α, which is thereby degraded. Cleavage of the NF-κB/IκB complex activates NF-κB, which is then translocated to the nucleus. Numerous regulatory gene sequences contain a κB motif. Binding of the NF-κB dimer to this binding motif actives the transcription of NF-κB downstream genes. In rare cases, repression of transcription has been observed. Many of the NF-κB regulated genes are involved in regulating the immune system.\textsuperscript{195}

A synopsis of all published studies on the activity of artemisinin-type drugs against inflammatory and autoimmune diseases allows to compile a hypothetical network, how artemisinin and its derivatives inhibit signaling in inflammatory and autoimmune diseases (Figure 2). There are numerous receptor-coupled signaling pathways that have been described to be inhibited by artemisinins, including the receptors for IL-1, TNF-α, β3-integrin, or RANKL as well as toll-like receptors and growth factor receptors. Among the signal transducers are well-known molecules such as ERK, JNK, PI3K, AKT, MEK, phospholipase C γ1 (PLC-γ1), and others. All these receptors and signal transduction molecules are known to contribute to the inhibition of NF-κB. This network compilation also
demonstrates that artemisinin-type drugs may not only inhibit NF-κB by direct binding but by silencing the upstream pathways of NF-κB. Upon artemisinin-induced inhibition of NF-κB transcriptional activity, a large number of NF-κB-regulated downstream genes are downregulated. Among them are genes with diverse cellular functions such as cytokines, chemokines, and immune receptors, which regulate immune cell differentiation, apoptosis genes, and inflammatory and autoimmune diseases.

**FIGURE 1** Treatment of inflammatory and autoimmune diseases by artemisinin-type drugs. Artemisinins presumably bind to the transcription factor NF-κB. As a consequence, the expression of NF-κB-regulated downstream genes is suppressed, which leads to beneficial therapeutic effects toward inflammatory and autoimmune diseases. NF-κB, nuclear factor κ B [Color figure can be viewed at wileyonlinelibrary.com]
proliferation-regulating genes, signal transducers, and genes involved in antioxidant stress response. It is important to mention that NF-κB is not the only transcription factor whose activity is inhibited by artemisinin and its derivatives. These drugs also inhibit the activity of mTOR, activating protein 1 (AP1)/FBJ murine osteosarcoma viral oncogene homologue (FOS)/JUN oncogenic transcription factor (JUN), HIF-1α, NF-ATC1, STAT, NRF-2, RORγt, and FOXP-3 either directly or by involvement of the large NF-κB network.

As outlined in the Section 1, we explicitly excluded inflammatory conditions related to infectious diseases from the literature survey. The intention was to separate anti-inflammatory of artemisinins from their antimicrobial activity, because microbial infections frequently also cause inflammation. The cure from microbes and other parasites by artemisinins may lead to a reduction of accompanied inflammation in affected tissues. However, from a practical point of view it does not matter that much, whether or not anti-inflammatory treatment effects of artemisinin-type drugs occur in a primary or secondary manner. In fact, there are several reports reporting on the improvement of inflammation in the course of infectious diseases. After having dissected the anti-inflammatory molecular mechanisms of artemisinins in the chapters above, it is now interesting to have a look at infectious conditions that simultaneously cause inflammations. Some authors reported on the improvement of nephritis in the course of malaria treatment.196–198 A myasthenia gravis patient suffering from severe malaria experienced favorable outcome for both conditions from artesunate treatment.199 This anti-inflammatory effect has not only been observed for Plasmodia but also for other protozoa such as Naegleria fowleri, which causes meningoencephalitis.200,201 Comparable anti-inflammatory effects of artemisinins also have been described for bacteria-induced arthritis202 and viruses, for example, the reduction of human herpesvirus 6 (HHV-6)-caused fulminant or acute viral myocarditis203 or of hepatitis B virus-induced liver inflammation.204
Another aspect to be considered is that artemisinin and its derivatives would probably not be used as mono-therapy for the treatment of inflammatory and autoimmune diseases, if they ever reach clinical routine. Rather, they would be combined with other established drugs. Therefore, it is interesting to know whether or not drug combinations involving artemisinins act in an additive or synergistic manner, or whether even antagonistic effects have to be considered. There are only very few hints as yet for additive or synergistic immunosuppressive effects.

The combination of artesunate with an immunomodulator (methotrexate/triptolide/azathioprine) exhibited superior induction of macrophage apoptosis than each drug applied alone.205 There are a few more clues from the literature that artemisinin-based combination treatments (ACT) may result in synergies to treat malaria, for example, the approved artemether–lumefantrine combination.206 An ACT against malaria containing methylene blue as investigational drug as well as the combination of artesunate and curcumin were also described in this context.207,208 The combination of artesunate with hydroxychloroquine improved renal function in immunoglobulin A-induced nephropathy.209,210

Synergies of artemisinin-type drugs are also known for chemotherapy, radiotherapy, antibody therapy of cancer cells,211–216 and anti-schistosomiasis therapy.217 Drug combinations may not always be beneficial, and in rare cases toxic reactions may be provoked.218 These few examples of potential synergistic or even antagonistic reactions of ACTs highlight the importance also to investigate drug combinations with artemisinins for inflammatory and autoimmune diseases in the future.

During the past two decades, many groups including our own scientifically substantiated the wisdom of TCM handed over for millennia by (1) identification of the bioactive chemical compounds in medicinal plants (e.g., artemisinin in Artemisia annua) and (2) unraveling the molecular and cellular mechanisms of Chinese herbal medicine with modern scientific methods.219–224 Based on the achievements in phytochemistry and phytopharmacology, the isolated chemical structures may also serve as lead compounds the development of novel (semi)synthetic derivatives. A plethora of artemisinin derivatives have been already described in the literature. It is reasonable to assume that specific artemisinin derivatives are not only active against diverse inflammatory and autoimmune diseases, but that different derivatives may be identified with specific activity against each different disease.

Novel artemisinin derivatives have been investigated for their activity against malaria,225–228 viral infections,229,230 and schistosomiasis.231–233 A huge number of artemisinin derivatives was investigated for anticancer effects in vitro and in vivo.234–238 On the other hand, the efforts in medicinal chemistry may also open new avenues for the synthesis of novel artemisinin-based derivatives with improved anti-inflammatory and immunosuppressive properties.

A major issue in drug development is the related to safety and toxicity and the vast majority of novel compounds drop out from the developmental pipeline because of toxic effects to normal organs and tissues. Artemisinins are generally considered as safe in malaria treatment, although cases of toxicity also have been documented.153,178,239 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.

Considerably higher drug doses of artemisinins are necessary in cancer therapy. Preliminary clinical trials also indicate good tolerability, but again cases of toxic reactions became aware.159,168,240–242 As of yet, it is not known, which side effects would appear, if artemisinin-type drugs will be used for the treatment of anti-inflammatory or autoimmune diseases. Therefore, the conductance of preclinical toxicity studies and clinical Phase 1 trials are mandatory for the further development of artemisinin-type compounds to treat inflammatory and autoimmune diseases. However, the currently available data from mouse experiments did not report on major side effects. With all caution, it could thus be assumed that artemisinins may be also well tolerable to treat inflammatory or autoimmune diseases as described for malaria therapy.

Nevertheless, reports on toxic reactions should be taken seriously. Relatively low concentrations are applied for a few days only for malaria therapy. Hence, drug accumulation over prolonged periods of time, which are frequently responsible for toxic side effects, is less probable. Furthermore, oral application is safer than intravenous or intramuscular injections. The best doses, treatment duration, and applicationroutes have not been elaborated for
inflammatory and autoimmune diseases. Another rather unexpected aspect is that the combination of artemisinin with other drugs may not only lead to synergistic therapeutic effects toward the disease but may also cause antagonistic effects concerning toxicity, that is, to reduce side effects of other drugs.\textsuperscript{179,180} All these aspects have to be carefully studied in clinical trials to come up with optimized treatment regimens against inflammatory and autoimmune diseases. In basic research, there are important tasks to be done. As exemplarily shown for some artemisinin-derived synthetic compounds,\textsuperscript{166} it is within the scope of expectations to develop novel chemical entities with less toxicity. Hence medicinal chemistry should systematically investigate possibilities to generate novel artemisinin-related compounds with improved disease-fighting features at reduced toxicity.

Another word of caution is appropriate concerning the specific action of artemisinins toward immune cells. Whereas the vast majority of investigations reported on the immunosuppressive effects of artemisinin-type drugs, there are also some studies that observed an increase of immune function, for example, by the inhibitory activity against Treg cells, the recovery of the Th1/Th2 balance, and so on.\textsuperscript{243–247} This might be beneficial in cancer treatment, but counterproductive to treat inflammatory and autoimmune diseases. Here, immunosuppressive rather than immune-stimulating effects are required. It could be imagined that contrary effects might depend on divergent cellular or tissue-specific contexts in different diseases. This is a potential issue that has to be investigated and clarified in future experimentations.

To sum up in a nutshell, artemisinin-type drugs are a highly valuable class of drugs with high potentials for the treatment of inflammatory and autoimmune diseases. The available data in the literature justify to further investigations especially of randomized clinical trials to feed the drug development pipeline for the sake of patients suffering from inflammatory and autoimmune diseases.

ACKNOWLEDGEMENT
Open access funding enabled and organized by Projekt DEAL.

CONFLICT OF INTERESTS
The authors declare that there are no conflict of interests.

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**How to cite this article**: Efferth T, Oesch F. The immunosuppressive activity of artemisinin-type drugs towards inflammatory and autoimmune diseases. *Med Res Rev*. 2021;41:3023-3061. https://doi.org/10.1002/med.21842