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Artemisinin and its derivatives: a potential therapeutic approach for oral lichen planus

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Abstract

Background Oral lichen planus (OLP) is a common T-cell-mediated oral mucosal disease, whose pathogenesis mainly includes antigen-specific and non-specific mechanisms. As a refractory chronic inflammatory disease, there is still no curable management for OLP till now.

Findings Artemisinins are a family of compounds that are widely used as frontline treatment for malaria worldwide. In addition to its well-established antimalarial properties, emerging evidence hints that artemisinin family drugs also possess preferential immunoregulatory and anti-inflammation properties, such as modifying T lymphocytes' activation and cytokines release, modulating Th1/Th2 balance, activating regulatory T cells (Tregs), modulating inflammatory signaling pathways, as well as acting on non-specific mechanisms of OLP. However, there is still no report focused on the influence of artemisinins on OLP.

Conclusion This review outlined the data-based immunomodulatory effects of artemisinins on different immune cells in conjunction with their therapeutic prospective with regard to the pathogenesis of OLP, suggesting that artemisinin and its derivatives might be possible candidates for treatment of OLP.

Keywords Oral lichen planus · Artemisinins · Autoimmune disease · Pathogenesis · Treatment

Abbreviations

OLP	Oral lichen planus
SLE	Systemic lupus erythematosus
TGF-β	Transforming growth factorβ
AKT	Protein kinase B
MMP	Matrix metalloproteinase
CIA	Collagen-induced arthritis
NF-κB	Nuclear factor-kappa B
MAPK	Mitogen-activated protein kinase
m-TOR	Mammalian target of rapamycin
CCR	C–C chemokine receptor
CXCR	C–X–C chemokine receptor
ROS	Reactive oxygen species
COX-2	Cyclooxygenase-2

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Introduction

Oral lichen planus (OLP) is an immune-related chronic disease that affects 1–2% of the general adult population with female predilection and may decrease patients' quality of life [1]. World Health Organization (WHO) has labelled OLP as a potentially malignant disorder whose malignant transformation rate ranged between 0.07% and 5.8% [2, 3]. In OLP lesions, the most typical histopathological feature is large numbers of T lymphocytes accumulating in the superficial lamina propria of oral mucosa [4]. Etiology and pathogenesis of OLP is still unclear but it is generally

agreed that the main pathogenesis of OLP involves antigen-specific cell-mediated immune response and non-specific mechanisms [5]. Major antigen-specific mechanisms include T lymphocytes' activation, differentiation, and imbalance among T-cell subsets, insufficient regulatory T cells (Tregs) and dysregulation of inflammatory pathways. Meanwhile, non-specific mechanisms mainly comprise over-expression of MMP-9, insufficient TGF-β, chemokines, COX-2 and aberrant macrophage activation [5–7]. In addition, our previous study has suggested that dysfunction of autophagy and dysregulation of microRNAs are also involved in the progression of OLP [8–12]. Being one of the most common oral inflammatory disorders and recognized as early as in 1860s, there is still no radical therapy for OLP at present in spite of increased recognition of the pathogenesis and advances in therapeutic options. Current therapeutic approaches for OLP, topical or systemic corticosteroids, are associated with debilitating side effects and high recurrence rate, which highlights the requirement for new efficacious and safe therapeutic strategy [1].

Artemisinins (artemisinin and its related derivatives), a family of compounds with a sesquiterpene trioxane, are widely accepted as the most efficacious weapons fighting malaria with high efficiency and relatively low toxicity across the world [13]. Artemisinin was extracted for the first time from *Artemisia annua L* in 1972, whose impressive antimalarial activity led to the conferment of the Nobel Prize for Medicine or Physiology to its discoverer Youyou Tu, a Chinese scientist, in 2015 [14, 15]. Long before the discovery of artemisinin, several artemisinin derivatives were synthesized via versatile methods and proved to possess better bioactivity, solubility and longer half-life [16, 17]. Additionally, by inserting new chemical groups into the sesquiterpene trioxane skeleton of artemisinin, a series of new derivatives were manufactured, typical representatives of which are SM735, SM905, SM933, and SM934 [18–22]. In addition to the compound's well-described biological effects, artemisinin displayed strong anti-inflammatory activity [13]. Compelling evidence has shown that artemisinin family drugs exert anti-inflammation functions in various aspects [23–25]. In addition, considerable data have settled that artemisinin family drugs have therapeutic values for autoimmune diseases such as inflammatory bowel disease, rheumatoid arthritis, multiple sclerosis, and systemic lupus erythematosus (SLE) [26–28].

In recent years, there has been an increasing amount of literature established that artemisinin derivatives act upon multiple checkpoints in the inflammation and immune signaling cascades, particularly with the bias for activated pathogenic T cells, which could conceivably play a beneficial role in the pathogenesis of OLP [14, 28, 29]. Therefore, it can be assumed that the artemisinin and its derivatives may be developed into an alternative approach to the treatment of OLP due to their immunomodulatory and anti-inflammation effects. In this review, we will discuss the potential role that artemisinin and its derivatives may play in OLP management in multiple aspects.

Development of artemisinin and its derivatives

Artemisinin, a low-temperature ethyl ether extraction of a sweet wormwood herb called *Artemisia annua* L., was originally isolated in 1972 [30]. The unique chemical structure of Artemisinin is a endoperoxide linkage skeleton with a peroxy group, which was elucidated in 1975 [15]. However, poor aqueous or oil solubility and short half-life limit clinical usage of artemisinin [30]. Dihydroartemisinin, the first generation of naturally occurring artemisinin derivatives, was found to have more efficacy and significantly reduced side effect profile [31]. It was reported in 1982 that artemisinin and its water-soluble derivative possess remarkable immunosuppressive action in mitogen-stimulated human peripheral lymphocytes, when numerous new studies began to shed light on the potential immunosuppressive activity and clinical benefit of artemisinin [32–34]. Compounds with oil solubility like artemether and arteether were brought about [35]. Considering artemisinin with poor water solubility has disadvantages such as poor bioavailability, incomplete or erratic absorption, as well as slow onset of action, water-soluble derivatives of artemisinin were synthesized successively. By modifying the structure of dihydroartemisinin, artesunate, a water-soluble hemisuccinate ester came out [36]. With the research and development of synthetic biology, a series of artemisinin derivatives with higher bioavailability has been synthesized according to different purposes. Novel water-soluble artemisinin derivatives SM905 [1-(12β-Dihydroartemisinoxy)-2-hydroxy-3-tert-butylaminopropane maleate] and SM934 (β-aminoarteether maleate) that contain the unique peroxide bridge were synthesized with the demand of immunoregulatory agents, and they have shown curative benefits in SLE both experimentally and clinically [37, 38].

Collectively, the anti-inflammation and immunoregulatoy potential as well as efficacy and solubility of novel artemisinin derivatives have been improved greatly (Fig. 1). Artemisinin and its derivatives may be licensed as immunoregulatoy or immunosuppressive drugs in the coming future.

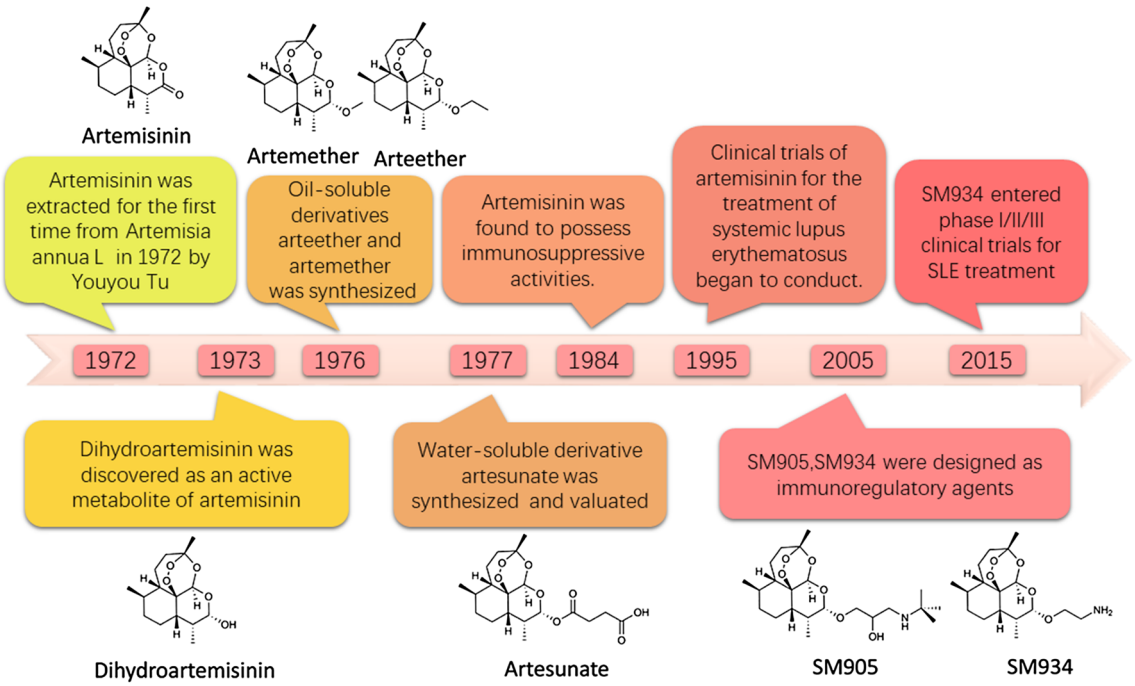

Fig. 1 Development of artemisinin and its derivatives. Artemisinin was originally isolated from *Artemisia annua* L. in 1972 with poor water or oil solubility and short half-life. In the next year, dihydroartemisinin was found as an active metabolite of artemisinin and was successfully isolated. In 1976, artemether and arteether were brought about with oil solubility. In 1977, artesunate was obtained with water solubility. Since 1972, artemisinin and its derivatives have been being used for treating malaria. With time goes on, they have become a family of thriving research hotspots against autoimmune disorders. In 2005, SM905 and SM934 were synthesized in the search for potential immunoregulatory agents with immunosuppressive activity and low toxicity

Potential effects of artemisinin and its derivatives on antigen-specific mechanisms

Potential effects of artemisinin and its derivatives on T cells

Affecting T cell activation, proliferation, and apoptosis

It is generally agreed that T cells the key players in the antigen-specific mechanisms of OLP [4]. In OLP lesions, both $CD4^+$ T cells and $CD8^+$ T cells are activated [39]. However, artemisinin and its derivatives have been involved in T cells and T cell-mediated immune inflammatory activities. To date, several groups have reported that artemether (50 μM), artesunate (8% purity), dihydroartemisinin (5 mg/ml), SM905 (0.5–1 mg/kg/day) as well as SM934 (10 μM) can profoundly suppress TCR cross-linking-induced $CD4^+$ T cell activation, proliferation, as well as IL-2 production both in vitro and in vivo [13, 14, 18, 37, 40, 41]. Li, T. et al. have demonstrated that artesunate can suppress T cell activation through regulating the function of antigen presenting cells (APCs) [40]. Unlike artesunate, artemether influenced the cell cycle regulatory molecules of G1 phase and blocked cell cycle progression through G1/S transition, leads to a inhibition of DNA synthesis and cell division [13]. Moreover, dihydroartemisinin at a dose of 20 mg/kg/day, can also diminish activated $CD8^+$ T cell proliferation as well as inhibit $CD4^+$ T cell differentiation in autoimmune thyroiditis mouse model [41]. It was also suggested that dihydroartemisinin and SM934 can bring about prompt apoptosis of $CD4^+$ T cells [41, 42].

Balancing Th1/Th2 subsets

Secondly, once stimulated by T-cell receptor (TCR) and other costimulatory molecules, naïve $CD4^+$ T cells can differentiate into diverse effector subsets, including Th1, Th2, Th17, regulatory T (Treg) cells, and T follicular helper (Tfh) cells and dysregulation of these subsets of $CD4^+$ T cells can determine the character, extent and duration of immune responses in the pathogenic processes of OLP [43]. Our previous data have evolved the imbalanced mRNA expression pattern of T-bet and GATA-3, two Th1/Th2-specific transcription factors, in the peripheral blood mononuclear cells of OLP are associated with different clinical features [44]. We also reviewed that lack of coordination between Th1/Th2 subsets and Th1/Th2 signature cytokines has been found in peripheral blood, local lesions, and saliva of patients with OLP indicating that they could influence the OLP considerably [45, 46]. Recent investigations showed that Th1

cytokines in OLP patients were lower than in healthy controls whereas Th2 cytokines especially IL-4 and IL-5 are higher [39]. Hence, targeting the Th1/Th2 cytokine networks is considered to be a therapeutic strategy for OLP. Liu, H. et al. established that dihydroartemisinin can regulate Th1/Th2 imbalance, coordinate the dysregulation of immune functions with alteration of the Th1/Th2 cytokines [47]. It was ascertained that dihydroartemisinin suppresses inflammatory cells and reduces IL-4 and IL-5 in mRNA level thus increasing the ratio in favor of Th1 cytokines [48] (Fig. 2).

Impeding maturation of Th17

Thirdly, except for Th1 and Th2 subsets, increasing data indicated that Th17 subset, with the ability of IL-17 secretion which is a pro-inflammatory cytokine that can activate different cells such as epithelial cells, may play a role in the formation and progress of the OLP [49, 50]. Overexpression of IL-17 has been observed in the reticular, erythematous, and erosive OLP group [45, 51]. The expression levels of IL-17 were markedly reduced in the 20 mg/kg/day artesunate-treated rats compared to vehicle group [52]. Likewise, Li group reported that artesunate acted to conduct and downregulate Th17 development, and provide a negative-feedback loop by suppressing IL-17-mediated immune activation. As a consequence, suppression of the Th17 pathway could abolish local tissue inflammation [53]. Additionally, dihydroartemisinin treatment virtually abrogated IL-17 production by limiting the differentiation of Th17 cells [41]. It is found that SM934 markedly impeded the polarization of naïve CD4 T cells to Th1 and Th17 cells in vitro [24]. While in autoimmune animal models, SM934 retarded the maturation of Th17 cells and significantly restricted the amounts of IL-17 [24, 54]. Other research suggested that SM905 could affect Th17 development through suppression of upstream signaling molecules [55].

Inhibiting Tfh differentiation

Finally, T follicular helper (Tfh) cells are recently highlighted for their essential roles in humoral immunity [56]. Our group has confirmed that there exists increased prevalence of circulating $CD4^+$Tfh-like cells in OLP indicating that Tfh cells may be involved in the pathogenesis of OLP [43]. Intriguingly, SM934 possesses striking capability to stamp out Tfh cells' differentiation both in vitro and in vivo [24].

In conclusion, artemisinin and its derivatives regulate biological functions of T cells and participate in the determination of T-cell survival and death, particularly in autoimmune diseases, implying they probably function as T-cell inhibitors in OLP and work in this fashion to ameliorate local inflammation and reduce associated symptoms.

Enhancing Treg generation

$CD4^+CD25^+FoxP3^+$ Tregs is a specialized subset of $CD4^+$ T cells that are important in the dynamic regulation of autoimmune responses and suppression of inflammation while TGF-β and IL-10 are critical for Treg cell function [57, 58]. Recent reports indicated that expanded proportions of $FoxP3^+$ Tregs and upregulated FoxP3 mRNA have been found in the local environment in OLP but relatively little amount of $Foxp3^+$ Treg cells in erosive OLP indicating its correlation with disease's severity and subtypes [59, 60]. In addition, though the proportions of $FoxP3^+$ Tregs in OLP are frequently increased, the expression of TGF-β and IL-10 declined in local peripheral blood of OLP patients,

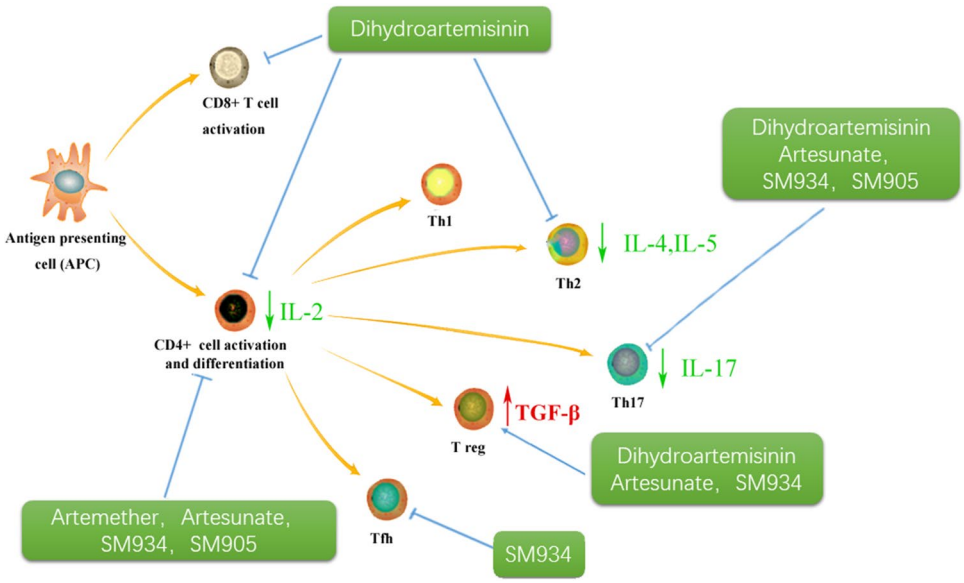

Fig. 2 Interactions of Artemisinin and its derivatives with T cells. Dihydroartemisinin, artesunate, SM905, and SM934 are capable of suppressing $CD4^+$ T cell activation and impede maturation of Th17. Dihydroartemisinin, artesunate, and SM934 have been found to enhance Treg generation. In addition, dihydroartemisinin, as an active metabolite of artemisinin, can also inhibit $CD8^+$ T-cell activation. SM934, which possesses potent immunosuppressive property, is able to depress Tfh differentiation. Moreover, $CD4^+$ T cell activation can be suppressed by Artemether

stimulating Treg cell dysfunction in OLP [61, 62]. It is worth noting that dihydroartemisinin treatment notably enhanced TGF-β-induced Treg cell generation [41]. Artesunate obviously increased the generation of Tregs and could favor the expression of Foxp3 via blocking the AKT signaling in cell culture experiments [53, 63]. In collagen-induced arthritis (CIA) rats, expression level of Foxp3 is markedly enlarged in the 20 mg/kg/day artesunate group [52]. SM934, a water-soluble artemisinin derivative synthesized from β-hydroxyarteether, is able to significantly magnify the proportion of $CD4^+FoxP3^+$ Treg subset, along with both intracellular FoxP3 protein, and FoxP3 mRNA levels in $CD4^+$ T cells elicited IL-10 production from macrophage, therefore balanced the pro-inflammatory and anti-inflammatory cytokines in vitro and in vivo [42]. Findings of another study emphasized that apart from specifically inducing regulatory T cells' expansion, SM934 treatment enhanced the functions of Treg cells and facilitated Treg differentiation as well [26].

Altogether, aforementioned data implied that acting on T cells is an important way that artemisinins exert immunoregulatory functions (Table 1).

Effects of artemisinin and its derivatives on inflammatory signaling pathways

It is generally accepted that perturbations of inflammatory pathways play an important role in the initiation, progression, and aggravation of OLP. Intriguingly, artemisinin and its derivatives have been found to possess potent ability of mediating certain signaling pathways involved in inflammatory responses (Fig. 3). Therefore, it is tempting to speculate that artemisinins can ease the situation of OLP patients by harmonizing these cell signaling pathways.

NF-κB canonical signaling pathway

The nuclear factor-kappa B (NF-κB) is a family of transcription factors, a major regulator of immune responses with distinct gene regulatory functions [64, 65]. Normally, NF-κB protein exists as an inactive form in the cytoplasm [65]. Once the antigen receptors, Toll-like receptors (TLRs), or cytokine receptors of the cells are stimulated, the NF-κB dimers translocate from the cytoplasm to the nucleus and promote transcription and expression of multiple pro-inflammatory genes, including TNF-α, MMP9, COX-2, IFN-γ, IL-6 etc., [65]. Our group has evolved that the nuclear expression of NF-κB is elevated in the basal epithelium and lamina propria of OLP patients while there also exists overexpression of TNF-α in basal epithelium of both erosive OLP and non-erosive OLP, indicating the NF-κB activation and its positive correlation with TNF-α may amplify and perpetuate inflammation in OLP [11]. What is more, TLR4, as an essential activator of NF-κB, is increased both in transcript levels and protein levels in OLP [66].

Published studies have confirmed that the inhibition of NF-κB activation may play an important role in anti-inflammatory effect. Consequently, inhibiting NF-kB activity can alleviate the degree of inflammatory diseases and could be an attractive therapeutic target for OLP [65]. Meanwhile, NF-κB is a crucial target of artemisinin and its derivatives. The level of NF-κB protein in the nucleus was decreased in artemisinin-treated group, which is a forthright proof of

Table 1 Interactions of artemisinin and its derivatives with T cells

Mechanisms	Drugs	Effective doses	References
Suppressing $CD4^+$ T-cell activation	Artemether	50 μM	[13]
	Artesunate	8% purity	[40]
	Dihydroartemisinin	0.4 μg/ml	[41]
	SM905	0.5–1 mg/kg/day	[37]
	SM934	10 μM	[18]
Suppressing $CD8^+$ T-cell activation	Dihydroartemisinin	20 mg/kg/day	[41]
Promoting apoptosis of $CD4^+$ T cells	Dihydroartemisinin	0.4 μg/ml	[41]
	SM934	1–10 mg/kg/day	[42]
Balancing Th1/Th2 subsets	Dihydroartemisinin	20 mg/kg/day	[47, 48]
	Artesunate	100 μmol/L	[52]
Impeding maturation of Th17	Artesunate	20 mg/kg/day	[52, 53]
	Dihydroartemisinin	20 mg/kg/day	[41]
	SM934	10 μM	[24, 54]
	SM905	0.25–0.5 mg/kg/day	[55]
Inhibiting Tfh differentiation	SM934	10 μM	[24]
Enhancing Treg generation	Dihydroartemisinin	0.4 μg/ml	[41]
	Artesunate	20 mg/kg/day	[52, 53, 63]
	SM934	1–10 mg/kg/day	[26, 42]

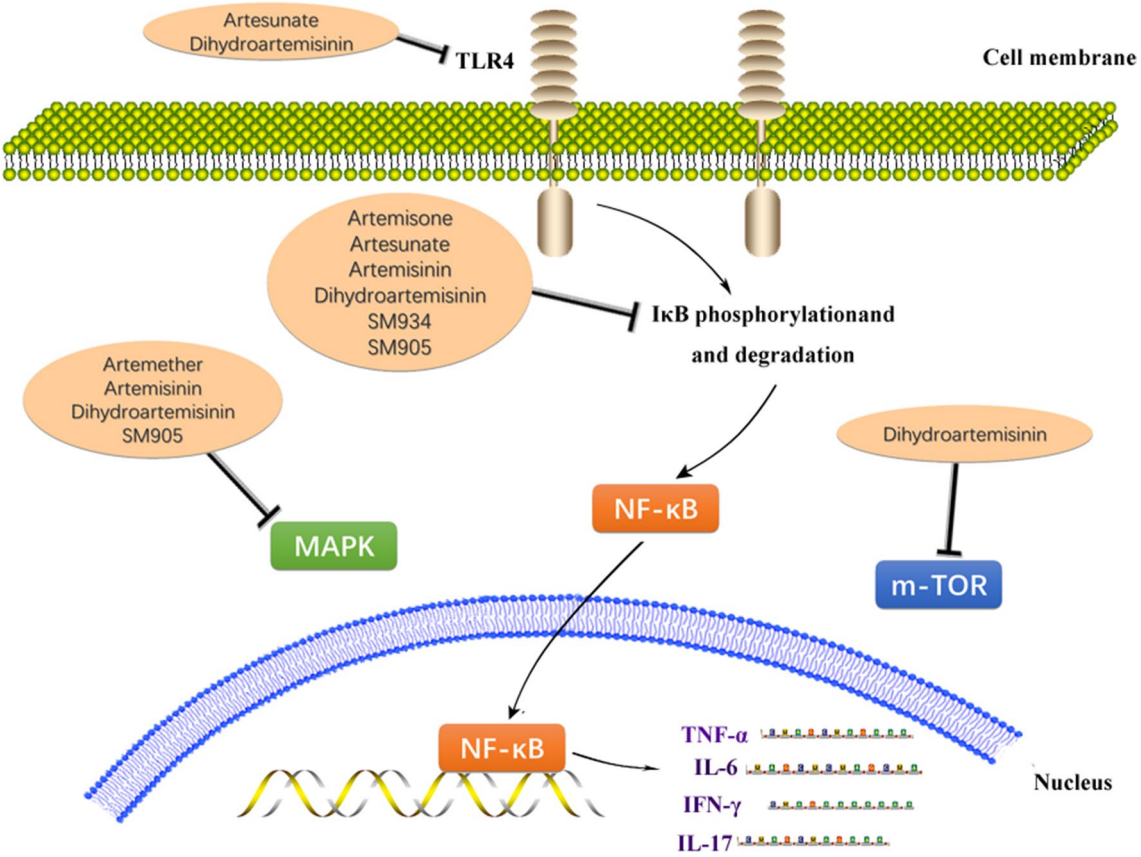

Fig. 3 Interactions of Artemisinin and its derivatives with inflammatory signaling pathways. Artemisinin, dihydroartemisinin, artesunate, artemisone, SM905 as well as SM934 are able to profoundly attenuate inflammation by disrupting NF-κB pathway. Additionally, both dihydroartemisinin and artesunate can also decrease the level of TLR4, which acts as an essential activator of NF-κB. Artemisinin, dihydroartemisinin, artemether, and SM905 have been observed to reduce pro-inflammatory cytokines via impairing the activation MAPK pathway. Phosphorylated-AKT has been found to be cut down by artesunate and m-TOR can be interrupted by dihydroartemisinin

the reduced translocation of NF-κB [67]. Artemisinin was shown to be capable of blocking TNF-α and LPS-induced activation of the NF-κB signaling pathways [68, 69]. Artemisinin also has distinct suppressive effect on NF-κB translocation by impeding the phosphorylation and degradation of IκB and inhibiting the translocation of the NF-κB, hereby retaining its cytosolic level [67, 70–72]. Consistent with previous studies, Wang et al. made the point that artemisinin (60 μg/ml) could decrease the mRNA levels and secretion of NF-κB-related inflammatory cytokines such as TNF-α, IFN-γ, TGF-β1, and IL-6 [70]. Moreover, artesunate, artemisone, and dihydroartemisinin can decrease TNF-α-induced NF-κB-driven transcription by 47–51% [25]. Specifically, artesunate administration weakened pre-inflammatory response by suppressing NF-κB-mediated gene transcription [73]. Along these lines, transcriptional activity of NF-κB can be inhibited by dihydroartemisinin in the same manner as artemisinin and artesunate [47, 48]. Congruent findings were also reported by Zhao et al. and Li et al. [40, 74]. Studies focused on dihydroartemisinin also revealed that NF-κB, and p-NF-κB, together with NF-κB-related markers PI3K, p-PI3K, AKT, and p-AKT, were significantly reduced after treatment by dihydroartemisinin [42]. Apart from acting on the upstream in NF-κB pathway by interfering with IκB phosphorylation and degradation, artesunate and dihydroartemisinin can also inhibit TLR4 expression [75, 76]. Another research affirmed a decreased LPS-induced TLR4 protein levels in dihydroartemisinin-treated MRL/lpr mice, an autoimmune disease mouse model [77]. Artesunate attenuates the production of TNF-α, IFN-γ, IL-17, and IL-6, and upregulates the IL-10 secretion through the inhibition of NF-κB activity in both cell culture and animal experiments [75, 76, 78, 79]. In a similar vein, SM934 dose-dependently reversed the rising production of pro-inflammatory cytokines (IL-6, IL-1β, TNF-α, IFN-γ, and IL-17) elicited by Concanavalin A [74]. In RAW 264.7 macrophages, SM905 inhibited LPS-induced NF-κB translocation into nucleus [19].

Taken together, these findings indicate that the effects of artemisinin family drugs may inhibit inflammation and

decrease inflammatory cytokines via the regulation on NFκB signaling pathway.

MAPK signaling pathway

Mitogen-activated protein kinase (MAPK) is a signaling cascade made up of a core tier of three kinases: extracellular signal-regulated kinase (ERK), p38 and c-jun N-terminal kinase (JNK) [80]. In conjunction with the activation of NF-κB, MAPK activation induces the expression of multiple genes that collectively regulate the inflammatory responses [81]. The p38 MAPK is generally recognized as a signaling event that plays a critical role in the regulation of T-cell proliferation and cytokine production. p38 MAPK expression was significantly higher in mucosal specimens, especially in the lamina propria from patients with OLP [82]. These discoveries suggested that p38 MAPK may function with unique regulatory role of in the pathogenesis of OLP. Accordingly, there exists conjectures that block MAPK pathway and p38 expression and phosphorylation may be a possible mechanism of therapy for OLP.

Several studies have shown that artemisinin significantly impaired the phosphorylation and activation of p38 MAPK signaling pathway [68, 83]. It can downregulate MMP-9 expression in PMA-induced macrophages via interrupting JNK and p38 pathway in a dose-dependent manner [84]. Ya He et al. revealed that dihydroartemisinin, the main active water-soluble metabolite of artemisinin derivatives, significantly inhibited p38 mitogen-activated protein kinase participated in reduction of pro-inflammatory cytokines [50]. As a semi-synthetic derivative of artemisinin, artesunate attenuates hypoxia-induced expression of TNF-α via inhibition of PI3K/Akt signaling pathway [85]. Experimental evidence suggests that by means of restraining the phosphorylation of JNK, ERK, and p38, the three main proteins in MAPK signaling pathway, artesunate administration is capable of lightening local inflammation probably via negative regulation of PI3K/Akt pathway, which may benefit Foxp3 expression [74, 86]. Artemether is an oil-soluble derivative of dihydroartemisinin with more hydrophobic properties and better stability. Artemether-growth-arrested T cells displayed a marked depletion of phosphor-MAPK. In addition, artemether caused a robust decline in secreted levels of IFN-γ and IL-2, which are known as markers of T-cell proliferation, suggesting that artemether may inhibit T-cell proliferation by this route [13]. In murine macrophage RAW 264.7 cells, SM905, a promising artemisinin derivative with potent immunosuppressive activity, inhibited LPS-induced phosphorylation of p38 [19]. Wang, J.X., et al. have found that SM905 can inhibit TCR/$CD3^+$ $CD28^+$-mediated activation of p38 and have provided compelling evidence implying that immunosuppressive effects of SM905 in T cells appear owing to the inhibition of MAPK activation [37]. On that account, SM905 profoundly, dose-dependently reduced IFN-γ production by T cells in this way [37].

Other signaling pathways

Mammalian target of rapamycin (m-TOR) has emerged as a major regulatory cascade of fundamental cell processes. The phosphorylation of mTOR is a substantial marker for the activation of this signaling pathway. Our group has demonstrated a substantial increase of p-AKT and p-mTOR in T cells of OLP tissues and in local OLP lesions [8]. AKT, and p-AKT were significantly reduced by dihydroartemisinin [47]. Zhao et al. illustrated that dihydroartemisinin treatment attenuated mTOR signaling in T cells. Interfering with the mTOR pathway is functionally critical for dihydroartemisinin-mediated effects on T cells in that cytokine IL-2 promoted mTOR activities curbed upon dihydroartemisinin treatment [41]. In addition, phosphorylated-AKT was cut down by artesunate significantly, and, artesunate may cause blockage of the AKT signaling [53].

Overall, it can be supposed that OLP may benefit from artemisinins for its inhibitory effect on canonical signaling pathways inclusive of NF-κB, MAPK, m-TOR, and Akt.

Potential effects of artemisinin and its derivatives on non-specific mechanisms in OLP

Inhibiting activation of macrophages

Macrophages can activate antigen-specific T cells and induce chemokine expression from T cells [87]. Macrophages can exacerbate OLP by means of activating T cells and producing pro-inflammatory agents IL-1β and TNF-α [1]. There is an increased macrophage density in the OLP lesions, and macrophages preferentially locate in the basal layer where they can contribute to the destruction of the basal membrane through TNF-α [87, 88]. In 2013, dihydroartemisinin has been shown to exert pronounced inhibitory effect of phagocytosis of macrophages and inhibiting TNF-α production from macrophages by suppression of nuclear translocation of NF-κB [89]. Occasionally, artesunate concentration dependently suppresses production of LPS-induced TNF-α in macrophages [79]. Artemisinin, together with its immunosuppressive derivatives SM905 and SM934 can reduce pro-inflammatory cytokines and promote anti-inflammatory cytokines' released from macrophages [19, 42, 90].

Effects of artemisinins on MMPs

Matrix metalloproteinases (MMPs) are a group of zinc-dependent endopeptidases that play an important role in the

degradation of extracellular matrix (ECM). MMP-9 activators secreted by OLP T cells are considered to be helpful in activating pro-MMP-9, hence leading to basement membrane disruption [1]. It has been suggested that the overexpression of MMP-9 may provoke T-cell migration and basement membrane disruption which further facilitate intraepithelial $CD8^+$ cytotoxic T-cell migration in OLP lesions [91]. Rubaci et al. showed an elevated expression of MMP-2 and MMP-7 in epithelium and connective tissues from OLP lesions [7]. Moreover, Chen et al. noted the importance of imbalance between MMPs and TIMPs in cancerization of oral lichen planus, notably is the upregulated expression of MMP-2 and MMP-9 [92]. It is possible, therefore, inactivating MMP-9 and MMP-2 can be salutary for OLP. Cao et al. put forward that treatment with 100 μM artemisinin for 2 h significantly reduced the mRNA expression levels of migration-related proteins MMP-2 and MMP-9 in human vascular smooth muscle cells [93]. These results corroborate the findings of Wang group, that is, Artemisinin (20–80 μg /mL) significantly blocked the induction of MMP-9 at both the transcriptional and translational levels dose-dependently in PMA-induced macrophages [84]. Recently, Wang et al. reported that pretreating cells with artemisinin have a downregulatory effect on the TNF-α-induced MMP-9 secretion, agreed with former study studies [83]. Results from another group showed that after artemisinin treatment, the MMP-9 activity was efficiently inhibited by artemisinin, but not the activity of MMP-2 [94]. But in contrast, Magenta et al. found that it is artemisinin derivatives dihydroartemisinin and artesunate, but not artemisinin itself, that depress MMP-9 mRNA level and downregulate MMP-9 secretion [25, 95, 96]. Hence, though artemisinin and its derivatives may alter pathologic MMP's secretion and activation, there are serious conflicting data about the impact of artemisinin and its derivatives on MMPs level in vivo and in vitro. Further investigation, on that account, needs to be conducted to confirm the effect artemisinins may have on MMPs.

Modulating TGF-β

It is commonly affirmed that transforming growth factor β (TGF-β) plays a meaningful role in down modulation of T cell-mediated immune responses and in controlling autoimmunity, especially inducing Treg differentiation [97]. Both in T cells and in serum, the level of TGF-β mRNA were significant diminished in reticular, erythematous, and erosive OLP groups compared with control groups [5]. Insufficient expression of TGF-β in OLP patients has been found to partly contribute to the chronic nature of OLP [61]. In addition, TGF-βI expression was significantly higher in OLP carcinogenesis patients than in OLP ones [92, 98]. Thus it is tempting to speculate upregulating TGF-β is a therapeutic target of OLP. It has been proved that artesunate can upregulate the production of TGF-β [40]. Data showed a significantly higher level of TGF-β in SM934-treated group in experimental autoimmune encephalomyelitis mouse model, which alleviated local inflammation [26].

Downregulation of chemokines

RANTES (regulated on activation, normal T cell expressed and secreted) by OLP pathogenic T cells plays a critical role in the recruitment of lymphocytes, monocytes, natural killer cells, eosinophils, basophils, as well as mast cells in OLP lesions [5]. CCR1, CCR3, CCR4, CCR9, and CCR10, which are cell-surface receptors for RANTES have been identified in lichen planus [99, 100]. Particularly, our previous study demonstrated that $CCR5^+CD4^+$ T cells and serum levels of CCL5 were significantly increased in OLP patients [101]. Thus hampering CCRs, or reducing RANTES are considered to be beneficial for OLP. The chemokines RANTES and its receptors CCR1, CCR3, CCR4, CCR5, CXCR3, which can promote different types of inflammatory cells infiltrating into inflammatory lesions, were found decreased after the treatment of SM934 [26]. Therefore, SM934 treatment can control RANTES-related inflammatory responses by suppressing RANTES and its receptors directly.

Influence of artemisinins on oxidative stress

The natural balance of oxidants and anti-oxidants was found to be disturbed in OLP and may associate with carcinogenesis of OLP [102]. According to Ergun and Lysitsa, there is an increased oxidative stress and imbalance in the antioxidant defense system in biological fluids of OLP patients [103, 104]. The proper reactive oxygen species (ROS) production mediates cell growth adaptation and survival, whereas excessive accumulation ROS can damage membrane, cellular lipids, proteins, and DNA and inhibit their normal function. Thus, abundant ROS is suspected to participate in the presence of keratinocytes apoptosis, one of the hallmarks in OLP. Recent study also hints an increased nitric oxide index in serum of patients with OLP, particularly with those erosive OLP [105, 106]. Nitric oxide (NO), a highly reactive free radical, is proved to be related to the chronic inflammatory process and erosive lesions in OLP, for higher level of NO in serum and saliva of erosive OLP patients have be discovered [107, 108]. It has been well established by various groups that artemisinin could downregulate the level of ROS and NO through NF-κB and MAPK pathway in mouse model [69, 70, 83]. Also, the NO production of murine macrophage cells, treated with 100 μg/ml of the artemisinin, was inhibited by 83.3% relative to vehicle groups [34]. Park et al. proved that artemisinin inhibits NO production and iNOS gene expression by inhibiting both IFN-β/STAT-1 and NF-κB signaling pathways in RAW 264.7 cell, consistent

with the previous literature [90]. As an active metabolite of artemisinin, dihydroartemisinin significantly reduced production of NO in rats in a similar way with artemisinin [109]. Furthermore, artesunate has been consistently shown, involving the mechanism of suppressing NF-κB cascade too, to decrease the NO level in a dose-dependent manner and alleviate oxidative stress [69, 73, 110, 111]. Besides, in RAW.247 cell line, SM905 has demonstrated to have strong curbing impact on LPS-induced mRNA expression of iNOS thence decrease the production of NO [19].

Inhibition of COX-2

Growing evidences have identified that elevated expression of cyclooxygenase-2 (COX-2) is found in OLP tissue specimens and enhanced COX-2 expression in OLP correlates well with the clinical severity [104, 112–114]. Danielsson et al. and Abdel Hay et al. suggested that the increased COX-2 proteins and transcripts in local lesions contribute to development of OLP [115, 116]. What is more, COX-2 overexpression was correlated with the histological grade of dysplasia, indicating that COX-2 could be positively correlated with the malignant transformation potential of OLP [104]. Thus inhibiting COX-2 expression might be a possible approach for preventing malignancies in OLP. Nowadays, it has been established that artemisinin downregulated expression of COX-2 in a great degree in a dose-dependent manner at concentrations 10–200 μM [70, 83]. Additionally, when macrophages were pre-treated with artesunate, dihydroartemisinin, or SM905, COX-2 resulted in compelling reduction in mRNA expression and protein production dependently [19, 75, 89]. It follows that artemisinins might act as potential agent impeding development and carcinogenic processes in OLP.

Antifungal activity of artemisinin and its derivatives

Facts have been revealed that *Candida albicans* infection was more prevalent in OLP patients implying *Candida albicans* may be a potential etiological factor of OLP [117]. Also, *Candida* spp. infection is one of the most frequent side effects of topical corticoid therapy, the main approach for treating OLP at present. Artemisinin derivatives showed in vitro activity against *Candida albicans* [118]. Acting synergistically with moconazole, artesunate and its structural homologues were proved to diminish *Candida albicans* biofilm's activity [119]. Pori Buragohain group have built up a novel series of derivatives of artemisinin with talented antifungal activities [120]. Considering these effects artemisinins have on *C. albicans*, this family of compounds could be a series of agents functioning alone or combined with other antifungal agents as a novel therapeutic strategy to improve OLP and against the side effects of topical corticosteroids (Fig. 4).

Cytotoxicity and side effect

Normally, it is believed that standard clinical application of artemisinin and its derivatives at effective concentration is safe. WHO guideline confirmed that, in individual parenteral artesunate doses between 1.75 and 4 mg/kg, no toxicity has been observed [121]. Rapid elimination of artemisinin after oral intake represents a comparatively safe route of administration compared to parenteral application [122]. However, artemisinin is reported to have embryo toxicity. The exposure to artemisinin at gestation time might result in post implantation embryo losses, in particular, among women who are in the first 3 months and last trimester of pregnancy [123]. On contrast, a study conducted by Mc Gready et al., containing 461 pregnant women, including 44 first-trimester episodes who were infected with acute falciparum malaria and treated with artesunate, indicated that artesunate, a hemisuccinate derivative of artemisinin, had no influence on rates for abortion, stillbirths, congenital abnormality, and mean gestation at delivery compared to general community [124]. So does artemether [125]. In addition, though with low cytotoxicity, improper concentrations of artemisinin and

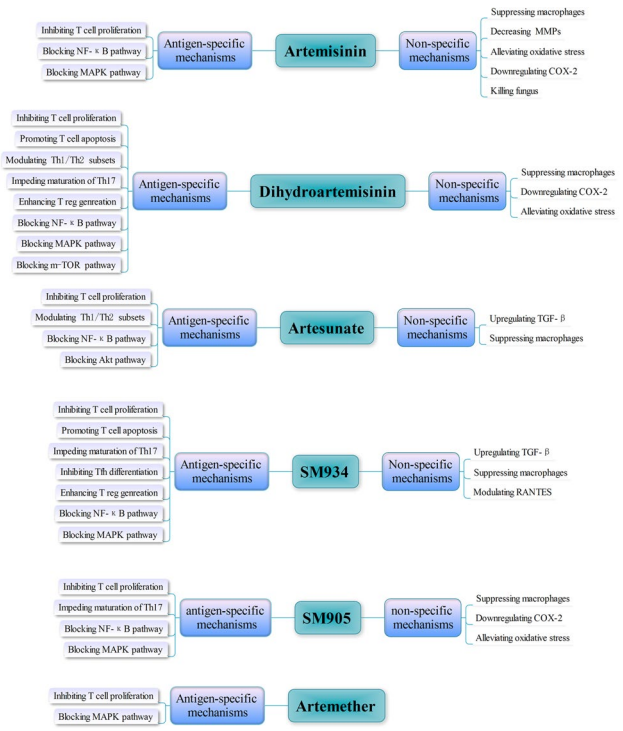

Fig. 4 Potential therapeutic effects of artemisinins and its derivatives on antigen-specific and non-specific mechanisms of the pathogenesis of OLP

its derivatives may cause different adverse reactions, most prevalence of which is the reduction of reticulocyte numbers [122]. Fortunately, Taylor and White have attested that mild-to-moderate reduction of reticulocyte numbers can drop to normal levels after discontinuation [126].

In general, artemisinins are a family of agents with low toxicity as long as correctly used. But the side effects artemisinins may have in treating autoimmune diseases are still unestablished, calling for further investigation.

Future perspectives of artemisinins

Artemisinin, an endoperoxide-containing sesquiterpene with multiple biological functions, is limited pharmacologically by poor bioavailability, short plasma half-life in the body, poor water solubility, thus suggesting that improvements were needed. With the research and development of synthetic biology, many derivatives with more efficiency but reduced side effects were obtained [20–22]. Several disadvantages of traditional artemisinin derivatives, especially low oral bioavailability, have limited their further application to treat autoimmune diseases, more study is needed to overcome these barriers.

In recent years, nanotechnology for fabricating nanoparticle-based delivery systems of artemisinins, can selectively convey drugs to inflamed tissues or specific cells and achieved targeted drug release [123]. The up-and-coming development of T-cell-targeting nanomedicines has provided another optional way to achieve targeted drug release [127]. So, the application of nanotechnology could result in excellent bioavailability, better stability, and reduced toxicity than traditional dosage forms and might lead to significant improvements in the use of the artemisinin family drugs and treatment of OLP as a cutting-edge strategy.

Nevertheless, research on the underlying molecular mechanisms of artemisinin and its derivatives in immunoregulation is still in early stage. Further studies, both animal experiments and clinical trials are urgently needed for better understanding and more widespread use of artemisinins for autoimmune-related diseases.

Conclusions

Artemisinin and its derivatives have been investigated as promising therapeutic candidates for multiple autoimmune disorders with potent regulatory effects on inflammation progress and immune system. Emerging evidence strongly suggests that artemisinins have the capacity to modify antigen-specific and non-specific mechanisms related with the pathogenesis of OLP. It is noteworthy that dihydroartemisinin, the active metabolite of artemisinin and its derivatives, is the first generation of artemisinin derivatives and possesses a preferential immunoregulation effect compared with artemisinin. Moreover, SM934, which has been approved to clinical trials for SLE, is a promising immunoregulatory agent for OLP.

We can conclude from the aforementioned findings that artemisinins, especially dihydroartemisinin, SM934, and SM905 may act as prospective agents for OLP with high therapeutic index. However, more targeted studies are needed to clarify the detailed immunoregulatory mechanism of artemisinins in OLP.

In summary, artemisinin and its derivatives might be a novel promising way of managing OLP.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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