Macrophage polarization reprogramming by resveratrol: A novel mechanism for protecting the intestinal mucosal barrier in sepsis (Review)

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Abstract. Sepsis is characterized by a life-threatening organ dysfunction caused by a dysregulated host response to infection. A key clinical feature of sepsis is disruption of the intestinal mucosal barrier, which not only increases intestinal permeability but also facilitates the translocation of bacteria and toxins, thereby exacerbating systemic inflammatory responses. M1/M2 macrophage polarization imbalance as an important contributor to sepsis-induced intestinal mucosal injury. M1 macrophages promote tissue damage primarily through proinflammatory mechanisms during sepsis, whereas M2 macrophages contribute to tissue repair and inflammation resolution through anti-inflammatory responses. However, dysregulated M1/M2 macrophage polarization during sepsis may aggravate intestinal inflammation and impair barrier function. Resveratrol, a natural plant compound, has demonstrated anti-inflammatory, antioxidant and immunomodulatory properties and has been reported to alleviate various pathological conditions, including sepsis-induced intestinal mucosal barrier dysfunction. Resveratrol may mitigate the inflammatory environment in sepsis and promote intestinal mucosal barrier repair through modulation of macrophage polarization. However, most current evidence is derived from experimental studies and further investigation is required to clarify its clinical applicability. The present review aimed to comprehensively examine the mechanisms underlying sepsis-induced intestinal mucosal barrier damage and its association with M1/M2 macrophage polarization and to explore the potential role of resveratrol in regulating macrophage polarization and alleviating sepsis-associated intestinal injury. By synthesizing current research, the present review identified critical gaps in knowledge and discusses future directions for understanding the role of resveratrol-mediated immunomodulation in sepsis-associated intestinal barrier dysfunction.

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Abbreviations: TLR4, toll-like receptor 4; HIF-1α, hypoxia-inducible factor-1 alpha; ROS, reactive oxygen species; LPS, lipopolysaccharide; ZO-1, zonula occludens-1; MAPK, mitogen-activated protein kinase; PKC, protein kinase C; iNOS, inducible nitric oxide synthase; Nrf2, nuclear factor erythroid 2-related factor 2; Arg1, arginase 1; IL, interleukin; TNF-α, tumor necrosis factor-alpha; PI3K, phosphoinositide 3-kinase; Akt, protein kinase B; GSH, glutathione; SphK1, sphingosine kinase 1; CLP, cecal ligation and puncture; PPARγ, proliferator-activated receptor gamma; AMPK, AMP-activated protein kinase; HK2, hexokinase 2; HO-1, heme oxygenase-1; TJ, tight junction; NF-κB, nuclear factor kappa B; TF, tissue factor.

Key words: sepsis, intestinal mucosal barrier, M1/M2 macrophage polarization, resveratrol, immunomodulation

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1. Introduction

Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection (1). As a vital immune organ, the gut plays a critical role in the pathophysiology of sepsis (2). Disruption of the intestinal mucosal barrier during sepsis represents an important contributor to systemic inflammation and organ dysfunction (Fig. 1) (3). Intestinal barrier damage not only facilitates the translocation of bacteria and toxins into the bloodstream (3) but also contributes to the development of multiple severe complications (Fig. S1). An imbalance in M1/M2 macrophage polarization has been identified as an important mechanism involved in intestinal injury during sepsis (Fig. 1) (4). Excessive activation of M1 macrophages promotes intestinal inflammation, whereas M2 macrophages are associated with inflammation resolution and tissue repair (5). Therefore, modulation of M1/M2 macrophage polarization has been proposed as a potential strategy for improving intestinal dysfunction associated with sepsis. Resveratrol, a natural polyphenolic compound found in grapes, red wine and other foods (6), has been recognized for its antioxidant, anti-inflammatory and immunomodulatory properties (6). Previous studies, summarized in Table SI, have demonstrated that resveratrol can attenuate excessive inflammatory responses and facilitate tissue repair by regulating M1/M2 macrophage polarization in experimental models. Therefore, investigating the potential role of resveratrol in ameliorating intestinal mucosal barrier dysfunction associated with sepsis is of considerable interest. The present review introduced and analyzed how resveratrol may exert protective effects against sepsis-induced intestinal mucosal barrier injury through the regulation of key signaling pathways involved in macrophage polarization, thereby influencing the balance between pro-inflammatory M1 and reparative M2 macrophage subsets. This regulatory activity may contribute to the suppression of excessive inflammatory responses, promotion of epithelial repair and alleviation of intestinal barrier dysfunction and bacterial translocation. The present review aimed to provide a theoretical framework for further understanding the potential application of resveratrol in sepsis management. The present review adhered to the TITAN 2025 Guidelines (7).

2. Search strategy

Literature searches were performed using Embase (https://www.embase.com/), PubMed (https://pubmed.ncbi.nlm.nih.gov/), Cochrane Library (https://www.cochranelibrary.com/) and Web of Science (https://www.webofscience.com/), with a focus on, but not limited to, publications between 2000 and 2026. The following keywords and various combinations were used to ensure broad coverage of the topic: 'Resveratrol' AND 'macrophage polarization' AND 'Sepsis' AND 'Intestinal Mucosa' AND 'Intestinal Barrier Function' ('resveratrol' OR 'RES' OR 'trans-resveratrol' OR 'macrophage' OR 'M1 macrophage' OR 'M2 macrophage' OR 'M1/M2' OR 'intestinal mucosa' OR 'tight junction' OR 'intestinal barrier' OR 'gut permeability' OR 'mucosal integrity' OR 'sepsis' OR 'cecal ligation and puncture' OR 'lipopolysaccharide' OR 'endotoxemia' OR 'septic shock'). Articles were included based on their relevance to the topic, with particular emphasis on studies investigating the potential effects of resveratrol on sepsis-induced intestinal mucosal injury. The inclusion and exclusion criteria are presented in Table SII. Additional screening of reference lists was conducted to identify further relevant studies.

3. Definition of sepsis and sepsis-induced gut dysfunction

Sepsis is life-threatening organ dysfunction caused by a dysregulated host response to infection typically caused by the invasion of pathogens, including bacteria, viruses and fungi, resulting in dysregulated immune responses and subsequent multiple organ dysfunction (Fig. S2) (8,9). Recent statistics from 44 intensive care units (ICUs) nationwide indicate that the incidence of sepsis is 20.6%, with a mortality rate of 35.5% (10). For severe sepsis, the mortality rate exceeds 50% (10). Up to 60% of critically ill patients develop gastrointestinal motility dysfunction, defined as acute gastrointestinal injury (AGI), which is associated with a 28-day mortality rate of 62.5% (11). Mortality rates vary according to the severity of sepsis-associated AGI. Furthermore, studies have indicated that dysfunction of the mechanical barrier is closely involved in the development and progression of sepsis-induced AGI and represents an important pathogenic mechanism underlying this condition (12).

The mechanical barrier, located at the apical region of the extracellular space, is primarily composed of intestinal mucosal epithelial cells and tight junctions (TJs) (13) (Fig. S3). These epithelial cells form a complex network through TJ proteins, adhesion junctions and desmosomes, establishing an essential physical barrier that limits the entry of potential pathogens into the intestinal tissue (13). Upon infection or injury, signals are rapidly transmitted to resident immune cells within the mucosa, allowing recognition of microbial 'nonself' components (13). TJs regulate the paracellular transport of solutes and macromolecules and restrict the penetration of antigens, bacterial toxins and pathogens across the intestinal barrier, thereby serving as critical structural components of intestinal defense (14). As a key component of the host defense system, the intestinal mucosal barrier prevents external pathogens and toxins from entering the bloodstream while playing an essential role in maintaining intestinal microecological homeostasis (Fig. S4) (15). During sepsis and septic shock, antibiotic administration and parenteral nutrition may disturb the intestinal microbiota, whereas intestinal microcirculatory dysfunction contributes to ischemia and hypoxia of intestinal epithelial cells (16). These pathological changes impair epithelial cell function, disrupt TJ protein activity and compromise intestinal barrier integrity (Fig. S4). Consequently, increased intestinal permeability facilitates the translocation of endotoxins and inflammatory mediators into the circulation, which may contribute to the development of multiple organ dysfunction (16) (Fig. S4). Sepsis-associated systemic inflammation affects intestinal microvascular perfusion, resulting in ischemic injury, mucosal damage and epithelial dysfunction (16) (Fig. S5). In addition, inflammatory responses may directly affect intestinal epithelial cells, promoting apoptosis and increasing intestinal permeability (Fig. S6) (17). The maintenance of intestinal barrier integrity depends on the normal

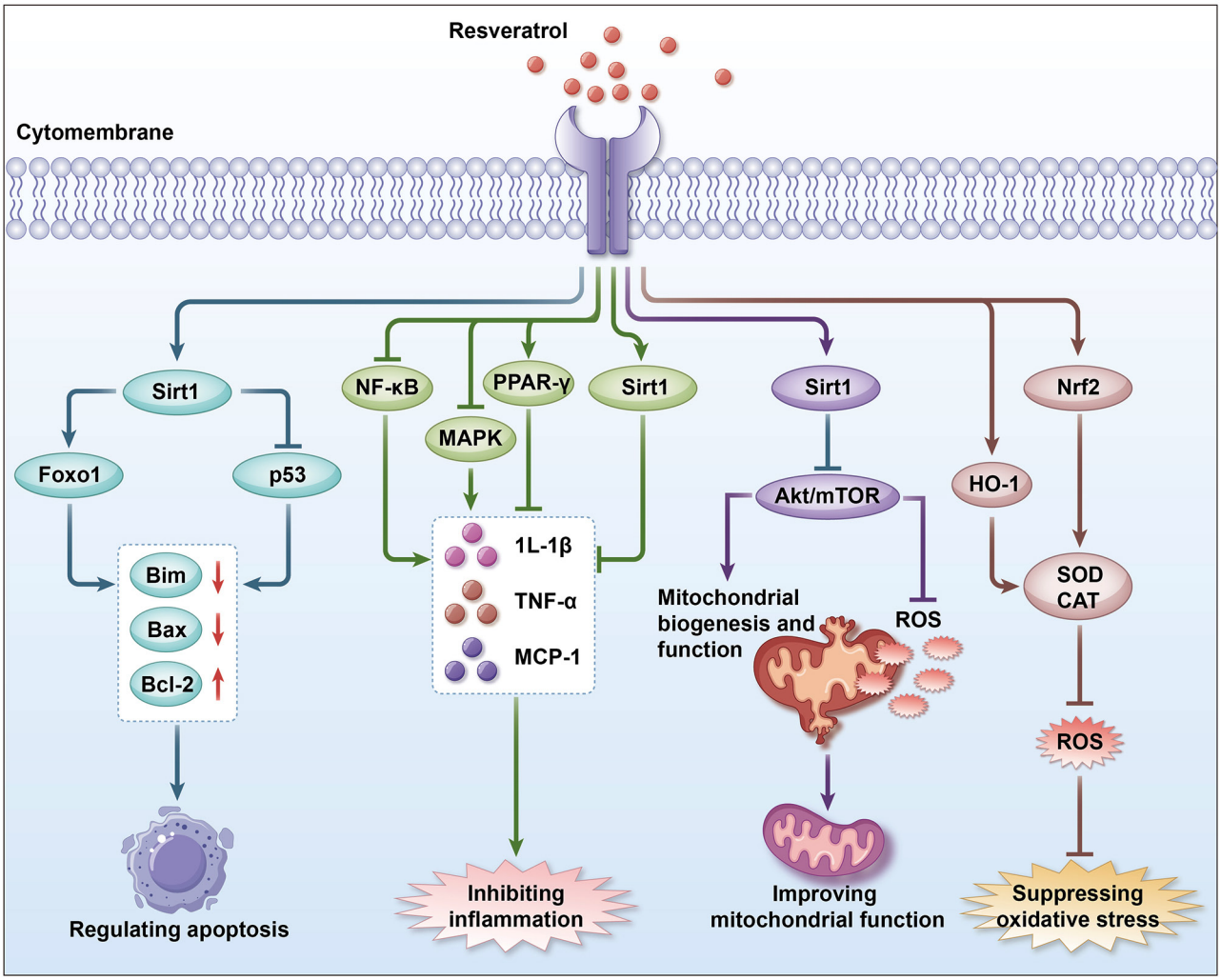


Figure 1. Anti-inflammatory and antioxidant mechanisms of resveratrol. Resveratrol removes free radicals from the body by modulating the Nrf2/HO-1, SIRT1 and SIRT1/FOXO1 signaling pathways, thereby alleviating oxidative stress and protecting cells from oxidative damage. Additionally, resveratrol exerts anti-inflammatory effects by regulating inflammation-related pathways, such as the NF-κB, SIRT1 and MAPK pathways. It also enhances mitochondrial function by modulating the SIRT/PI3K/Akt pathway, inhibiting ROS production and increasing the expression of antioxidant enzymes such as SOD1 and GSH. NRF2, NF-E2-related factor 2; HO-1, heme oxygenase-1; SIRT1, sirtuin 1; FOXO1, forkhead box protein O1; NF-κB, nuclear factor-kappa B; PPARγ, peroxisome proliferator-activated receptor gamma; MAPK, mitogen-activated protein kinase; mTOR, Mammalian target of rapamycin; TNF-α, Tumor necrosis factor alpha; SOD, superoxide dismutase; CAT, catalase; IL-1β, interleukin-1 beta; MCP-1, monocyte chemoattractant protein-1; p53, tumor protein p53; Bim, Bcl-2-interacting mediator of cell death; Bax, BCL2-associated X protein; Bcl-2, B-cell lymphoma 2; PI3K, phosphoinositide 3-kinase; Akt, protein kinase B; ROS, reactive oxygen species.

expression and function of TJ proteins, which can be altered by inflammatory factor activation during sepsis (Fig. S7). During sepsis, excessive immune activation and enhanced systemic inflammatory responses can disrupt TJ protein structures (Fig. S7). thereby contributing to impaired cellular integrity (18,19).

4. Role of M1/M2 macrophage polarization in sepsis

Macrophages are versatile immune cells involved in a wide range of biological functions, making them a critical focus in studies of phagocytosis, cellular immunity and molecular immunology (20). These cells originate from circulating monocytes, which are derived from hematopoietic stem cell precursors in the bone marrow (Fig. S8). After maturation and differentiation in the bone marrow, monocytes enter the bloodstream. Under specific stimuli, such as infection or inflammation, monocytes migrate across blood vessels into tissues, where they differentiate into macrophages (21). In response to disturbances in homeostasis, such as bacterial LPS exposure, macrophages contribute to restoring tissue balance by clearing pathogens and harmful microorganisms through phagocytosis, endocytosis and the release of inflammatory mediators (Fig. S8). This process is referred to as macrophage polarization (22). During polarization, cytokines and chemokines alter macrophage phenotypes and enhance their responsiveness to changes in the tissue microenvironment (Fig. S9) (22). Macrophage polarization is dynamic and plastic and occurs in specific spatial and temporal contexts, allowing transitions between M1 (proinflammatory) and M2 (anti-inflammatory) states (Fig. S9) (23). The balance between these polarized states is important in determining the body's response to inflammation and injury.

Characteristics of M1 macrophages and their proinflammatory effects in sepsis. M1 macrophages are primarily proinflammatory and secrete various proinflammatory factors to combat pathogen invasion (24). During the pathological progression of sepsis, M1 macrophage polarization plays an important role in promoting inflammation and amplifying inflammatory responses. When M1 macrophages are exposed to bacterial endotoxins such as lipopolysaccharide (LPS), they activate the nuclear factor kappa B (NF-κB) signaling pathway through Toll-like receptor (TLR) signaling, stimulating the production of proinflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1β and IL-6 (Fig. S10) (25,26). Additionally, M1 macrophages release substantial amounts of reactive oxygen species (ROS), which contribute to mitochondrial dysfunction and activation of the cyclic guanosine monophosphate-adenosine monophosphate synthase-stimulator of interferon genes pathway, thereby promoting intestinal inflammation (Fig. S10) (27). Meanwhile, M1 macrophages secrete tissue factor (TF), which activates the extrinsic coagulation pathway and may induce intestinal microvascular obstruction (Fig. S10) (28). Furthermore, glycolysis is enhanced through the hexokinase 2 (HK2)/pyruvate kinase isoform M2 (PKM2) pathway, resulting in increased lactate production, elevated hypoxia-inducible factor-1 alpha (HIF-1α) expression and enhanced intestinal inflammation (Fig. S10) (29). Further studies have shown that M1 macrophage polarization downregulates TJ proteins [zonula occludens-1 (ZO-1) and occludin] through TNF-α signaling, increases intestinal permeability and promotes bacterial translocation (with a 60% increase in blood culture positivity rate) (4). M1 macrophage infiltration in cecal ligation and puncture (CLP)-induced septic mouse colon tissue is negatively correlated with barrier function scores (30). However, excessive activation of M1 macrophages during sepsis may contribute to systemic inflammatory response syndrome, oxidative stress and coagulation abnormalities, thereby aggravating intestinal barrier injury.

Characteristics of M2 macrophages and their anti-inflammatory and repair effects in sepsis. Compared with M1 macrophages, M2 macrophages play important roles in anti-inflammatory responses and tissue repair (31). M2 macrophage polarization is typically induced by cytokines such as IL-4 and IL-13, which activate specific signaling pathways. During immune regulation in sepsis, M2 macrophages release anti-inflammatory cytokines, including IL-10 and transforming growth factor beta (TGF-β), which contribute to the attenuation of excessive inflammation and promotion of tissue repair (31). Furthermore, M2 macrophages participate in angiogenesis and tissue regeneration through the secretion of TGF-β and vascular endothelial growth factor (VEGF) (32) and facilitate apoptotic cell clearance through phagocytosis (33) (Fig. S10). The effects of M2 macrophages in sepsis are mainly associated with enhanced immune regulation and suppression of excessive inflammatory responses, which may help reduce systemic inflammation (34). M2 macrophage polarization is also closely associated with tissue repair during sepsis (34). Specifically, M2 macrophages regulate the intestinal microenvironment, supporting intestinal epithelial cell repair and regeneration and contributing to intestinal barrier reconstruction during immune responses (35). When exposed to low concentrations of LPS, M2 macrophages exert anti-inflammatory and immunomodulatory effects by regulating IL-10 secretion through the TLR4/TIR domain-containing adaptor inducing IFN-β (TRIF)/interferon regulatory factor 3 (IRF3) pathway (36). Additionally, LPS regulates IL-10 and TGF-β secretion through the TRIF/signal transducer and activator of transcription 3 (STAT3) pathway, further enhancing anti-inflammatory effects (37,38). Research has shown that M2 macrophage polarization can upregulate TJ proteins (ZO-1 and occludin) and in the CLP model, M2 overexpression reduces intestinal permeability by 40%; moreover, IL-10 levels are negatively correlated with mortality in patients with sepsis (39,40). However, the bacterial load in liver tissue increased by 32% in the M2 overexpression group compared with the control group, while the macrophage phagocytic index decreased by 40% (the proportion of Phrodo-positive cells decreased from 45-27%) (23).

Influence of M1/M2 macrophage polarization imbalance on sepsis. An imbalance in M1/M2 macrophage polarization plays an important role in the onset and progression of sepsis (41). Sepsis is characterized not only by systemic inflammation but also by immune dysregulation. When M1 and M2 macrophage polarization becomes imbalanced, the clinical manifestations of sepsis may be aggravated, resulting in poorer outcomes (42). During the early stages of sepsis, activation of M1 macrophages induces strong inflammatory responses and promotes the release of various proinflammatory factors (Table SIII), which contribute to host defense against infection (43). However, as sepsis progresses, insufficient regulation by M2 macrophages in counteracting inflammation and promoting tissue repair may result in persistent inflammatory responses and immune suppression (43). This imbalance may further aggravate sepsis progression, leading to sustained systemic inflammation and, in some cases, excessive immune suppression (44). Particularly during the later stages of sepsis, persistent M1 macrophage activation may exacerbate tissue injury and contribute to organ dysfunction, including gastrointestinal dysfunction (45).

5. Study of the regulation of M1/M2 macrophage polarization by resveratrol

Biological characteristics and efficacy of resveratrol. Resveratrol is a naturally occurring polyphenolic compound found in various plants, including grape skins, red wine and peanuts (6). In recent years, resveratrol has attracted considerable attention due to its biological properties and potential health benefits. Research indicates that resveratrol exhibits anti-inflammatory, antioxidant, antibacterial, anticancer and other biological activities (46-48) (Fig. S11). As a potent antioxidant, resveratrol alleviates oxidative stress by regulating key signaling pathways, including nuclear factor erythroid 2-related factor 2 (Nrf2)/heme oxygenase-1 (HO-1), Sirtuin 1 (SIRT1) and SIRT1/forkhead box protein O1 (FOXO1), thereby facilitating free radical elimination and protecting cells from oxidative damage (49-51) (Fig. 1). Additionally, resveratrol exerts anti-inflammatory effects through the modulation of inflammation-related pathways, including NF-κB, SIRT1 and mitogen-activated protein kinase (MAPK) pathways (52-54)

(Fig. 1). It also improves mitochondrial function by regulating the SIRT/phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt) pathway, reducing ROS production and increasing the expression of antioxidant enzymes such as superoxide dismutase (SOD)1 and glutathione (GSH) (55) (Fig. 1). As summarized in Table SIV, studies suggest that resveratrol may alleviate intestinal mucosal damage induced by inflammation, oxidative stress and ferroptosis (Fig. S12). Further studies have indicated that resveratrol, through core signaling pathways including SIRT1, AMP-activated protein kinase (AMPK), Nrf2 and NF-κB, may regulate macrophage polarization and influence the balance between proinflammatory M1 and anti-inflammatory M2 phenotypes. Meanwhile, resveratrol may contribute to intestinal barrier maintenance through multiple mechanisms, including protection of TJs, modulation of the microbiota and activation of autophagy (56). Research has shown that activation of SIRT1 by resveratrol promotes deacetylation of the NF-κB p65 subunit, thereby inhibiting its nuclear translocation and transcriptional activity and reducing M1-associated inflammatory responses [downregulation of TNF-α, IL-1β and inducible nitric oxide synthase (iNOS)] (57). Meanwhile, SIRT1-mediated deacetylation may activate transcription factors such as proliferator-activated receptor gamma (PPARγ) and STAT6, thereby promoting M2-associated polarization [upregulation of arginase 1 (Arg-1), CD206 and IL-10] (58,59). These effects may contribute to the attenuation of sepsis-associated intestinal inflammation and preservation of epithelial barrier integrity by reducing the disruption and internalization of TJ proteins, including ZO-1, occludin and claudin-1. Mechanistic target of rapamycin complex 1 (mTORC1) is considered an important regulator of M1 macrophage polarization through glycolysis-dependent mechanisms and resveratrol may inhibit mTORC1 activity via AMPK, thereby influencing macrophage metabolic reprogramming. Resveratrol modifies cysteine residues in Keap1, facilitating the nuclear translocation of Nrf2 and its binding to ARE elements, thereby promoting the expression of downstream antioxidant genes, including HO-1, quinone oxidoreductase 1 and glutamate-cysteine ligase catalytic subunit (60). HO-1 catalyzes heme degradation to generate CO, bilirubin and ferrous iron, which may promote M2-associated polarization and reduce M1-associated ROS production (61). Additionally, Nrf2 can interact with NF-κB p65 and inhibit proinflammatory transcriptional activity (62).

Regulatory effect of resveratrol on the polarization of M1/M2 macrophages

Promoting the polarization of M2 macrophages and inhibiting the polarization of M1 macrophages. Sepsis is a severe clinical syndrome commonly associated with dysregulated immune responses, in which macrophages, as key immune cells, play important roles (63). Macrophages can be classified into M1 and M2 types based on their polarization states (64). During the early stages of sepsis, M1 macrophages mainly exhibit proinflammatory functions, whereas M2 macrophages participate in anti-inflammatory responses, cell repair and tissue regeneration (65,66). Macrophage polarization is closely involved in sepsis-induced intestinal injury ((Fig. S13). Activated macrophages, particularly M1-polarized macrophages, release TNF-α, IL-1β, IL-6, IL-12 and high mobility group box-1 protein (a late inflammatory mediator) (67). These cytokines act through autocrine and paracrine mechanisms to recruit neutrophils, activate endothelial cells and stimulate other macrophages, contributing to cytokine amplification and oxidative stress (68). Cytokines, particularly TNF-α and IFN-γ, together with ROS, may reduce the expression and alter the localization of key TJ proteins, including claudin-1, claudin-4, occludin and ZO-1, through NF-κB/myosin light chain kinase (MLCK)-mediated cytoskeletal contraction, claudin endocytosis and matrix metallopeptidase (MMP)-mediated proteolytic cleavage. These alterations increase paracellular permeability ('leaky gut') and may further promote systemic inflammation and distant organ injury involving the lung, kidney and liver (69). ROS can also damage TJ proteins and oxidize membrane lipids, generating reactive aldehydes such as 4-hydroxynonenal and malondialdehyde (MDA), which further promote intestinal epithelial cell apoptosis (70). Furthermore, sepsis is associated with T-helper (Th)1/Th17 predominance, reduced regulatory T cells populations, impaired immunoglobulin A responses and microbiota alterations (dysbiosis) (71). Dendritic cells in the lamina propria may become activated and migrate to systemic sites, contributing to persistent inflammatory responses and multiple-organ dysfunction (72).

Resveratrol, a naturally occurring plant polyphenol, has attracted considerable attention in scientific research due to its antioxidant, anti-inflammatory and immunomodulatory properties. Numerous experimental studies have suggested that resveratrol can attenuate inflammation and oxidative stress by promoting M2 polarization and suppressing M1 polarization (Fig. 2) (73-75). Resveratrol inhibits NF-κB and MAPK (p38 and JNK) signaling by suppressing inhibitor of kappa light chain gene enhancer in B cells, alpha kinase activity and activator protein 1 activation, while promoting M2 polarization through SIRT1/PPARγ and STAT3/STAT6 signaling (Fig. 2) (65,76-78). These effects reduce the production of proinflammatory cytokines, including TNF-α, IL-1β and IL-6, activate PGC-1α, restore mitochondrial biogenesis, reduce ROS generation and decrease intestinal epithelial cell apoptosis. In the CLP sepsis mouse model, the proportion of M1 macrophages (CD11b+F4/80+CD86+) in the mesenteric lymph nodes of the resveratrol group (50 mg/kg) decreased from 45-18% and serum IL-6 levels decreased from 1,200 to 450 pg/ml (ELISA) (79). Immunohistochemical analysis showed that the number of positive cells decreased from 38±5 cells/high power field (HPF) in the sepsis control group to 15±3 cells/HPF in the treatment group (a 60% reduction, $P<0.001$). Electron microscopy analysis demonstrated that the TJ structural integrity score increased from 2.1±0.4 in the control group to 3.8±0.5 in the treatment group (normal group, 5.0±0.3; representing 75% recovery) and occludin protein expression increased by 80% based on western blot analysis (80). In a human intestinal organoid + THP-1 macrophage model, resveratrol (10 μM) reduced the expression of M1-related genes (IL-6 and IL-12b) by 50-65% (RNA-seq) and increased transepithelial electrical resistance (TEER) values by 2.3-fold (81).

Relevant experimental research results and data analysis. Substantial experimental evidence supports the regulatory effects of resveratrol on macrophage polarization (82-85).

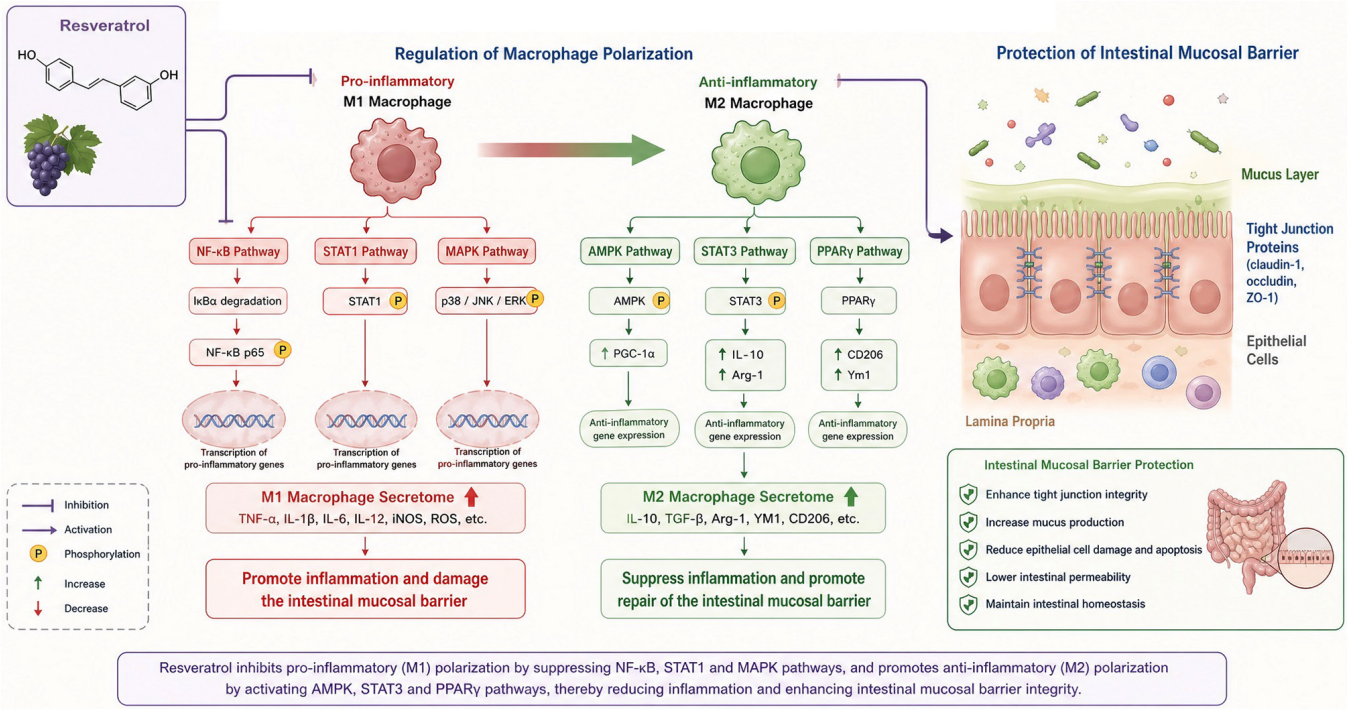


Figure 2. Protective mechanism of resveratrol against sepsis-induced intestinal barrier damage by regulating macrophage polarization-related pathways. Resveratrol blocks M1-type pro-inflammatory polarization by suppressing the MAPK, STAT1 and NF-κB pathways and promotes M2-type anti-inflammatory polarization by suppressing the AMPK, STAT3 and PPARγ pathways. Resveratrol decreases the secretion of pro-inflammatory cytokines TNF, IL-1β, IL-6, iNOS and IL-12, increases the production of anti-inflammatory factors IL-10 and TGF-β and improves intestinal mucosal damage induced by inflammation and oxidative stress. MAPK, mitogen-activated protein kinase; STAT, signal transducer and activator of transcription; NF-κB, nuclear factor kappa B; AMPK, AMP-activated protein kinase; STAT, signal transducer and activator of transcription; PPARγ, peroxisome proliferator-activated receptor gamma; TNF-α, tumor necrosis factor-α; IL, interleukin; iNOS, inducible nitric oxide synthase; LPS, lipopolysaccharide; IκBα, inhibitor of kappa light chain gene enhancer in B cells, alpha; p38, mitogen-activated protein kinase p38; JNK, c-Jun N-terminal kinase; ERK, extracellular regulated protein kinases; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; Arg1, arginase 1; Ym1, chitinase 3-like protein 3; TGF-β, transforming growth factor-beta; IL, interleukin.

Resveratrol can directly influence macrophage polarization states. *In vitro* studies using mouse primary macrophages have shown that resveratrol reduces the expression of M1-associated markers, including iNOS and TNF-α, while increasing the expression of M2-associated markers, such as CD206 and Arg-1 (55,86). Additionally, resveratrol treatment reduces the production of proinflammatory cytokines, including IL-6 and IL-1β, by M1 macrophages (87). Furthermore, resveratrol has been reported to regulate macrophage polarization in mouse models of sepsis (88). During acute sepsis, accumulation of M1 macrophages and increased secretion of proinflammatory factors contribute to intestinal mucosal barrier injury.

6. Improving the effects of resveratrol on intestinal mucosal barrier function damage in sepsis

Resveratrol can improve the intestinal inflammatory environment by regulating M1/M2 macrophage polarization. During sepsis, disruption of the intestinal mucosal barrier is often accompanied by enhanced inflammatory responses and immune dysfunction, which may disturb intestinal microbiota homeostasis and further impair intestinal barrier function (3). The regulatory effects of resveratrol on M1/M2 macrophage polarization may not only improve immune regulation but also alleviate the intestinal inflammatory environment (89). Resveratrol inhibits the secretion of proinflammatory factors from M1 macrophages, thereby reducing intestinal inflammation and potentially promoting tissue repair (90). M1 macrophages are considered important contributors to sepsis progression and intestinal inflammation (91). They secrete various proinflammatory cytokines, including TNF-α and IL-6, which affect intestinal epithelial cells and intestinal barrier integrity. In an *in vitro* macrophage model, resveratrol (20 μM) increased the M2/M1 ratio from 1:4 to 3:1 (flow cytometry analysis) (92). Intestinal tissue biopsy analysis in a mouse model of dextran sulfate sodium-induced colitis revealed that CD206-positive macrophage infiltration in the treatment group was significantly elevated, reaching 1.7-fold the level observed in the untreated control cohort (93). Following SIRT1 activation, the acetylation level of p65-K310 decreased by 60%, accompanied by a 50% reduction in the serum TNF-α/IL-6 ratio (94). NADPH oxidase (NOX)2 expression was downregulated, ROS generation was reduced (intestinal tissue MDA levels decreased by 40%) and SOD activity recovered to 85% of normal levels (95).

Resveratrol can promote the proliferation and differentiation of intestinal mucosal cells

Promotion of the proliferation and differentiation of intestinal mucosal cells. The repair and reconstruction of the intestinal mucosal barrier primarily depend on the proliferation and differentiation of intestinal epithelial cells (96). As summarized in Table SV, resveratrol has been reported to promote intestinal epithelial cell growth through multiple

signaling pathways, thereby contributing to the repair of intestinal injury associated with sepsis. Studies have indicated that resveratrol activates the PI3K/Akt signaling pathway and promotes intestinal epithelial cell proliferation (97). In a sepsis mouse model, resveratrol intervention markedly improved the proliferation rate and regenerative capacity of intestinal epithelial cells (98). This effect may facilitate intestinal barrier repair, restore epithelial integrity and reduce intestinal permeability, thereby limiting the translocation of pathogens and toxins. Moreover, resveratrol not only promotes cell proliferation but also enhances intestinal epithelial cell differentiation through regulation of the Wingless-related integration site/β-catenin pathway. Further studies using organoid models showed that resveratrol (10 μM) increased intestinal epithelial survival from 35±4 to 78±5% (99). In septic mice, resveratrol treatment restored goblet cell numbers to 70% of normal levels (Alcian blue staining) and restored intestinal mucus layer thickness to 65% of normal levels (measured in frozen sections) (100).

Resveratrol can enhance the close connection between intestinal mucosal cells. The integrity of the intestinal mucosal barrier depends not only on epithelial cell proliferation and differentiation but also on the maintenance of tight adhesion between intestinal epithelial cells (18). These cells form a cohesive physical barrier that limits the passage of harmful substances, including bacteria and toxins, across the intestinal lining (18). As summarized in Table SVI, resveratrol has been reported to improve intestinal barrier function by enhancing TJ integrity between intestinal epithelial cells. Its protective effects are primarily associated with the upregulation of TJ protein expression (101). Further studies revealed that resveratrol deacetylates NF-κB p65 through the SIRT1-dependent pathway, reduces MMP-9 expression and decreases occludin degradation by 40% (102). By maintaining TJ protein membrane localization through the protein kinase C zeta (PKCζ)/protein associated with lin seven 1 (PALS1) axis, resveratrol increased ZO-1 membrane localization from 30-80% in the sepsis group (immunofluorescence analysis), restored intestinal epithelial transmembrane resistance (TEER) values to 85% of normal levels and reduced bacterial translocation rates (positive blood culture) by 50% in the CLP mouse model (103). In sepsis model mice (CLP model), occludin expression in the resveratrol-treated group (50 mg/kg) increased from 30% in the sepsis control group to 97%, whereas ZO-1 and Claudin-3 levels recovered to 89 and 82% of normal levels, respectively (104). Serum LPS levels decreased by 52% (ELISA) and intestinal microbiota translocation rates (positive blood culture) decreased from 78% in the control group to 35% in the treatment group (105).

Resveratrol can regulate sepsis-induced dysbiosis of the microbiota. During sepsis, intestinal homeostasis is disrupted by endogenous and exogenous factors, including sepsis-associated M1 macrophage polarization, which contributes to inflammatory injury in the intestine. This disruption is characterized by decreased gut microbiota diversity, reduced abundance of Firmicutes and Bacteroidetes and increased colonization of potentially pathogenic bacteria, including *Clostridium difficile*, *Staphylococcus, Escherichia, Shigella, Salmonella* and *Enterococcus*, with relative abundances exceeding 50% (106). Fecal quantitative polymerase chain reaction analysis and microbial profiling further confirmed a reduction in dominant bacterial populations, particularly anaerobic species, during sepsis, accompanied by increased abundance of pathogenic bacteria such as *Escherichia coli*, *Pseudomonas aeruginosa*, *Enterococcus faecalis and Staphylococcus aureus* (107). Resveratrol markedly affects gut microbiota composition, including increasing the Bacteroidetes/Firmicutes ratio and promoting the growth of beneficial bacterial genera such as *Bacteroidetes, Lactobacillus* and *Bifidobacterium*, while reducing the abundance of Actinobacteria, thereby contributing to microbiota remodeling and immune regulation (108,109). Ding *et al* (110) further demonstrated that resveratrol alters microbiota composition by increasing beneficial bacteria, including lactobacilli and bifidobacteria, while decreasing fecal enterococci and *Escherichia coli*. Xu *et al* (111) reported that resveratrol reduces dysregulated metabolites, improves gut microbiota structure and diversity, reverses alterations in Bacteroidetes, Proteobacteria and Firmicutes, increases beneficial bacterial genera and decreases potentially pathogenic genera such as *Clostridium, Acinetobacter* and *Serratia*.

Recent studies have shown that resveratrol reduces the expression of virulence factors, such as flagellar proteins, in *Escherichia coli* by inhibiting quorum sensing and disrupting pathogenic bacterial biofilms, including a 40% reduction in *Staphylococcus aureus* biofilm thickness (112). Resveratrol also downregulates virulence-associated genes in enterohemorrhagic *Escherichia coli* (EHEC), with flagellar protein (fliC) expression reduced by 65% (reverse transcription-quantitative polymerase chain reaction), type III secretion system (T3SS) effector protein (EspB) secretion reduced by 55% and bacterial motility reduced by 60% in swimming assays (112). In a mouse sepsis model, the positive rate of blood culture in the treatment group decreased by 50% (112). In another mouse model of 2,4,6-trinitrobenzene sulfonic acid-induced colitis, resveratrol restored gut microbial alpha diversity (Shannon index, 16S rRNA sequencing) to 85% of normal levels, reversed colitis-associated dysbiosis, and increased short-chain fatty acid (notably butyric acid) production by 3.0-fold. This compound protected mice from colonic inflammation by inducing Tregs and suppressing inflammatory Th1/Th17 responses (113). In a sepsis pig model, nanoresveratrol (PLGA coating) increased intestinal Bacteroidetes abundance from 12±3 to 23±4% and reduced the 7-day mortality rate from 65 to 25% (114).

7. Challenges

As research on resveratrol has progressed, increasing attention has been directed toward its safety profile, particularly regarding toxicological evaluation, contraindications, special populations, precautions and potential drug interactions. The incidence and severity of resveratrol-related adverse effects appear to be largely dose-dependent. Hebbar *et al* (115) administered different doses of resveratrol (0.3, 1.0 and 3.0 g/kg) to rats for 28 days. The results showed that rats treated with 0.3 g/kg herbal water extract (HWE) exhibited no significant adverse effects, whereas rats receiving 1.0 and 3.0 g/kg HWE developed dehydration, respiratory distress, nephrotoxicity (indicated by elevated serum blood urea nitrogen and creatinine levels), kidney injury and anemia potentially associated

with suppressed erythropoietin synthesis. Another study reported that oral administration of resveratrol at doses ≤0.1 g/day did not result in observable adverse effects during either short-term or long-term administration (up to 1 year). However, occasional adverse effects, including gastrointestinal discomfort, diarrhea and heat rash, were observed at oral doses of 1.0 and 1.5 g/day. At doses exceeding 2.5 g/day, more severe reactions, including nausea, vomiting and abdominal pain, were reported (116), suggesting potential toxicity associated with high-dose resveratrol administration. Clinical studies have further indicated that oral administration of 0.15 g/kg resveratrol to healthy obese men for 30 days markedly reduced aspartate aminotransferase (AST) levels and liver fat accumulation (117). In patients with nonalcoholic fatty liver disease, administration of 0.05 g/kg resveratrol reduced total cholesterol and triglyceride levels and improved lipid metabolism, whereas higher doses (3.0 g/day for 8 weeks) increased AST and alanine aminotransferase levels (118). Overall, low-dose resveratrol appears to have a favorable safety profile with limited hepatic or renal toxicity. However, high-dose resveratrol administration, particularly in patients with nonalcoholic fatty liver disease, requires further evaluation and should be approached cautiously.

Low-dose resveratrol can reduce ROS levels in oocytes, increase glutathione levels, promote oocyte maturation and improve blastocyst formation rates *in vitro* (119-121). In addition, resveratrol supplementation may enhance antioxidant capacity in pregnant and lactating mice, increase uterine artery blood flow and reduce placental inflammation and hepatic triglyceride accumulation. However, some studies have suggested that resveratrol may induce fetal pancreatic enlargement or abnormalities (122), raising concerns regarding its safety during pregnancy. Furthermore, resveratrol, which exhibits phytoestrogen-like activity, may exert estrogenic effects. Long-term exposure may potentially influence the growth of hormone-sensitive cancer cells in breast, ovarian and uterine tissues (123,124). Therefore, caution is warranted when considering resveratrol use in individuals with cancer-related risks and during pregnancy. Although the pleiotropic effects of resveratrol, including anti-inflammatory, antioxidant, immunomodulatory and mitochondrial protective activities, may provide potential benefits, this complexity also makes it challenging to determine the primary mechanisms underlying clinical effects and to design targeted clinical trials.

Additionally, resveratrol may alter the pharmacokinetics of coadministered drugs, including absorption and metabolism, through inhibition of cytochrome P450 (CYP450) isoenzymes, potentially resulting in safety concerns. Resveratrol markedly inhibits CYP1A2 and CYP2C9 activity, affecting drug metabolism, potentially reducing therapeutic efficacy and increasing the risk of adverse effects (125). Therefore, when resveratrol is administered together with drugs metabolized by CYP1A2 and CYP2C9 in clinical settings, monitoring of blood drug concentrations may be necessary to optimize dosing strategies or consider alternative therapies.

Resveratrol has been extensively investigated as a multi-target candidate due to its anti-inflammatory, antioxidant, autophagy-modulating and microbiota-regulating properties (126). However, the transition from preclinical findings to clinical application remains challenging due to unresolved methodological, pharmacological and pathophysiological limitations (126). Most current formulation strategies primarily focus on improving bioavailability, while insufficient attention has been paid to the stage-specific pathophysiology of sepsis (127). Therefore, future delivery strategies may need to be phase-adapted, targeting early hyperinflammation, mid-phase intestinal barrier dysfunction, or late-stage immunoparalysis with distinct pharmacokinetic characteristics. The current delivery field also faces methodological limitations, as most efficacy data are generated from relatively healthy animal models (128). The pharmacokinetic characteristics of resveratrol under septic conditions remain insufficiently investigated, representing an important knowledge gap (126). Furthermore, safety assessments based on non-critical illness conditions may not fully reflect the complex physiological changes associated with sepsis. A sepsis-specific toxicological evaluation framework incorporating drug-drug interactions (DDIs), reversibility of immunomodulatory effects and metabolite profiling under organ dysfunction conditions is therefore needed. Current studies have generated substantial evidence regarding the preventive effects of resveratrol; however, data regarding clinically relevant treatment windows remain limited. Without rigorous evaluation of administration timing, clinical translation may be affected. The dose-exposure-response relationship of resveratrol remains incompletely established due to several limitations: i) Effective doses observed in animal models may not be safely achievable in humans; ii) effective concentrations observed *in vitro* may not be reached in target tissues; and iii) pre-treatment animal models do not fully represent clinical scenarios involving post-onset intervention. Addressing these translational gaps requires improved experimental strategies, including pathological models that improved reflect clinical conditions, pharmacokinetic/pharmacodynamic (PK/PD)-integrated trial designs, validation of molecular targets in human tissues and rational dose-finding approaches based on achievable human exposure. In addition, well-designed studies reporting both positive and negative findings are necessary to objectively evaluate the clinical potential of resveratrol. Furthermore, the biological effects of resveratrol may depend on the dynamic immune environment during sepsis.

Early proinflammatory (M1-type) macrophage overactivation contributes to cytokine release and inflammatory amplification, whereas later stages may involve immune suppression and M2-associated responses. Therefore, resveratrol may require precise temporal regulation of macrophage polarization, including early suppression of excessive M1 activation and avoidance of excessive M2 polarization during later stages. Inappropriate administration timing may potentially disturb immune balance, such as impairing tissue repair through excessive inhibition of M2-associated responses. The pathological environment of sepsis may also influence the efficacy of resveratrol. Reduced intestinal mucosal perfusion and oxidative stress may limit antioxidant activity and potentially alter its biological effects under highly oxidative conditions. Meanwhile, gut microbiota dysbiosis, including expansion of pathogenic bacteria, may continuously activate M1 macrophages through TLR/NF-κB signaling, potentially interfering with the immunomodulatory effects of resveratrol. Sepsis-associated capillary leakage and impaired liver

and kidney function may alter resveratrol pharmacokinetics, including distribution and clearance, thereby affecting local intestinal exposure (130). Intestinal mucosal edema and disruption of TJ integrity may further influence drug absorption, highlighting the potential need for advanced delivery systems, such as mucosal adhesive nanoparticles or exosome-based platforms. Additionally, liver dysfunction during sepsis may affect resveratrol metabolism through alterations in CYP450 enzyme activity, whereas bacterial translocation following intestinal barrier disruption may increase hepatic burden and contribute to a pathological feedback loop. Different pathogens (gram-negative bacteria, gram-positive bacteria and fungi) and infection sites may induce distinct macrophage responses, suggesting that individualized therapeutic strategies may be required for future clinical applications of resveratrol.

Resveratrol can exert comprehensive protective effects, including antioxidant, anti-inflammatory, barrier repair, inhibition of programmed cell death and microbiota regulation, in sepsis-induced intestinal mucosal injury through multi-target and multi-pathway synergistic mechanisms. However, limitations remain in *in vitro* studies, animal experiments, clinical studies and clinical trials, as summarized in Table SVII.

Current models for sepsis-induced intestinal injury exhibit significant inconsistencies in experimental conditions and outcomes, alongside notable limitations: as summarized in Table SVIII, LPS-induced models, varying in dosage, administration routes and animal strains, only activate the TLR4 pathway and fail to replicate the immune complexity of human sepsis (131), leading to divergent intestinal injury severities and time points across studies. The 'gold standard' CLP model suffers from poor inter-laboratory reproducibility due to variations in cecal ligation ratios, puncture techniques and post-operative care, with intestinal injury severity closely tied to sepsis grading but complicated by operational uncertainty (132). Intestinal ischemia/reperfusion models show marked individual differences in injury susceptibility due to factors such as ischemia duration and animal strains, making uniform evaluation challenging (133). Cell models, while useful for studying cellular-level damage, are limited by diverse preparation methods and an inability to recapitulate the *in vivo* intestinal structure and microenvironment (134). Collectively, these models have inherent shortcomings in simulating pathophysiological mechanisms, suffer from physiological differences between animals and humans, lack consistency and reproducibility and struggle to mimic clinical complexities, all of which severely restrict their translational value.

Limitations of the M1/M2 framework. The M1/M2 model describes macrophage activation as a binary classification between two relatively distinct functional states (135). However, macrophages exist along a continuum of activation states with extensive transcriptomic and functional diversity (136). Individual macrophages may simultaneously express M1- and M2-associated genes, resulting in hybrid or 'double-positive' populations that cannot be fully characterized by simple categorization (136). Therefore, the traditional binary framework may not completely reflect the functional plasticity and complexity of macrophages *in vivo* (137). The M1/M2 paradigm was primarily established based on bone marrow-derived macrophages (BMDMs) or cell lines stimulated with defined cytokines under *in vitro* conditions (138). These experimental systems may not fully represent the complex tissue microenvironments, cellular interactions and metabolic conditions present *in vivo*. Tissue-resident macrophages are influenced by multiple factors, including ontogeny (embryonic vs. monocyte-derived origin), local metabolic conditions (oxygen tension, pH and nutrient availability) and signals from surrounding cells (139). Therefore, applying *in vitro*-derived M1/M2 classifications to *in vivo* macrophage populations may not accurately reflect their functional states. Unlike relatively stable Th cell subsets (Th1, Th2 and Th17), macrophage polarization states are highly dynamic and reversible. Macrophages classified as M1 may acquire M2-associated features following environmental changes and vice versa (140). This plasticity challenges the concept of clearly separated macrophage subsets and suggests that macrophage activation should be considered a context-dependent process rather than a fixed differentiation program. Furthermore, there is currently no universal consensus regarding the defining markers of M1 and M2 macrophages across different studies. Although iNOS and CD86 are commonly used as M1 markers and Arg1 and CD206 as M2 markers, these molecules are not exclusively expressed in specific macrophage states and may be induced by different stimuli and vary among species and tissues. This inconsistency contributes to reproducibility issues and complicates comparisons among studies. The M1/M2 framework also does not fully account for macrophage developmental origin. Tissue-resident macrophages derived from embryonic yolk sac or fetal liver progenitors differ from monocyte-derived macrophages recruited during inflammation, even when they express similar activation markers. Moreover, tissue-specific transcriptional programs induced by local environmental signals further diversify macrophage phenotypes beyond the M1/M2 classification.

Furthermore, the half-life and plasma concentrations of resveratrol metabolites (RE) in the blood were reported to be ~10 times higher than those of the parent RE compound (141), suggesting that free RE may be locally released from these metabolites. Despite its relatively low bioavailability, rapid metabolism and elimination, RE exhibits significant biological activity. This may be attributed to its conversion into sulfate and glucuronide metabolites and/or its binding to plasma proteins, which may facilitate RE delivery to target organs (142).

Resveratrol has demonstrated anti-inflammatory, antioxidant and organ-protective potential in sepsis and existing small-scale clinical studies have preliminarily supported its safety and potential effects on biological activity indicators. However, clinical research investigating resveratrol in patients with sepsis faces several important limitations. First, large-scale, well-designed randomized controlled trials (RCTs) in humans remain limited (143). Most available evidence is derived from preclinical studies (animal models and *in vitro* experiments), small pilot studies, or trials with limited sample sizes, which may not provide sufficient statistical power for definitive conclusions (143-146). The optimal dose, formulation (such as micronized formulations or combination with piperine to improve bioavailability) and appropriate administration window during the dynamic course of sepsis remain unclear. Sepsis represents a highly heterogeneous clinical syndrome (147). Clinical trials often include patients with

different infection sources, comorbidities and disease severities (such as sepsis and septic shock), making it difficult to determine which patient subgroups may benefit most from resveratrol intervention. In addition, a number of studies rely on surrogate biomarkers, such as inflammatory cytokines, as primary outcomes. Future trials should focus more on clinically meaningful endpoints, including 28-day mortality, organ failure-free days and long-term functional outcomes (148). Although resveratrol is generally considered safe, comprehensive safety data regarding high-dose or prolonged intravenous administration in critically ill patients with sepsis remain insufficient, particularly concerning potential interactions with commonly used medications, including sedatives, anticoagulants and antibiotics. The beneficial effects consistently observed in controlled experimental models have not yet been fully translated into measurable clinical benefits in patients, highlighting the gap between preclinical findings and clinical application. In conclusion, although preclinical evidence regarding resveratrol in sepsis is encouraging, current clinical evidence remains preliminary and insufficient to support routine clinical use. Major limitations include the lack of large definitive RCTs, unresolved pharmacokinetic challenges, patient heterogeneity and the complexity of resveratrol-mediated biological effects. Future studies require well-designed multicenter clinical trials with standardized protocols and clinically relevant outcomes in clearly defined septic populations.

The immune regulation of resveratrol on sepsis is not the activation or inhibition of a single pathway, but through precise matching of macrophage plasticity, temporal changes and tissue microenvironment (Table SIX), achieving dynamic switching from 'anti-inflammatory' to 'immune promoting', providing a precise new approach for immunotherapy of sepsis.

Future progress in understanding the M1/M2 framework requires integration of scRNA-seq with additional approaches, including epigenomics (scATAC-seq), proteomics (CyTOF and CITE-seq), metabolomics and spatial transcriptomics. This multi-omics strategy may provide a more comprehensive understanding of macrophage states in health and disease. The field also requires standardized nomenclature and analytical frameworks to complement or refine the current M1/M2 classification. Recent approaches, including the 'macrophage activation continuum' model and ontology-based classifications, aim to provide more accurate descriptions of macrophage functional states. Applying these concepts to sepsis requires: large-scale longitudinal scRNA-seq studies using patient samples; integration with clinical metadata to identify clinically relevant endotypes; development of rapid and feasible methods for macrophage subset identification (such as flow cytometry panels and point-of-care transcriptomic approaches); and evaluation of subset-targeted therapies in preclinical models and clinical trials.

8. Problems that need to be solved in the future

In the future, gene editing technologies such as CRISPR may be applied to develop high-yield strains and address the challenges associated with low extraction rates (<1%) and high levels of impurities during chemical synthesis of plant-derived resveratrol (149). Current global efforts focus on optimizing metabolic pathways to increase fermentation yields to industrial production levels (150). Emerging technologies, including supercritical fluid extraction and enzymatic hydrolysis, may improve the utilization of resveratrol raw materials, reduce residual organic solvents and facilitate the production of pharmaceutical-grade resveratrol (>98% purity) (151). Carrier-based technologies, such as liposomes and polymer nanoparticles, may overcome the poor water solubility and rapid metabolism of resveratrol, thereby prolonging its biological activity (152). Experimental studies have shown that nanoencapsulation can increase oral bioavailability by 3-5-fold (153). Methylation and glycosylation modifications may also improve resveratrol stability, with tetramethyl resveratrol exhibiting an ~8-fold longer half-life than the natural form (154). Additionally, integration of single-cell sequencing and metabolomics may facilitate the identification of novel targets involved in resveratrol-mediated regulation of the SIRT1/AMPK pathway (155), while combined formulations containing resveratrol, nicotinamide nucleoside and quercetin may provide synergistic biological effects.

Furthermore, future studies may explore real-time adjustment of dosing regimens based on biomarkers such as IL-6 and M1/M2-associated surface markers CD86/CD206 (156). The development of intelligent responsive drug delivery systems, such as ROS-responsive nanoparticles, may enable targeted drug release at inflammatory sites (157). The combined effects of resveratrol with other organ-protective agents, including mitochondrial antioxidants, also warrant further investigation. In experimental studies, humanized mouse models and organoid systems may help improved simulate sepsis-induced intestinal injury and improve translational relevance.

9. Conclusion

Resveratrol, a natural plant polyphenol, has attracted increasing attention due to its diverse biological activities, including anti-inflammatory, antioxidant and immunoregulatory effects. It may regulate immune responses during sepsis by influencing M1/M2 macrophage polarization. Through modulation of macrophage functional states, resveratrol may contribute to the attenuation of intestinal inflammation, preservation of intestinal barrier integrity and reduction of intestinal permeability. These effects may limit bacterial and toxin translocation and alleviate systemic inflammatory responses associated with sepsis. However, current evidence remains insufficient to support routine clinical use of resveratrol in sepsis. Therefore, although resveratrol represents a promising experimental compound with potential immunomodulatory and barrier-protective properties, further mechanistic studies and well-designed clinical investigations are required before therapeutic conclusions can be established in patients with sepsis.

The M1/M2 framework, while historically valuable, has limitations in fully representing macrophage biology. Single-cell sequencing has revealed substantial complexity among macrophage states across different tissues, disease conditions and temporal stages. In sepsis research, considering this complexity rather than relying solely on binary classification may facilitate more precise diagnosis, patient stratification and targeted therapeutic strategies. Future macrophage research will likely require systems-level approaches to

characterize dynamic, context-dependent and ontogenically diverse macrophage populations, ultimately supporting the development of more effective immunomodulatory strategies for critical illness.

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Authors' contributions

YT, JX, MWL, CYQ and WZ conceived the research topic, conducted literature reviews for relevant articles and drafted the manuscript. YLZ performed language and grammar editing. MXS and XYY revised the manuscript drafts and restructured the content. SJG, YLZ and MWL provided access to the tools used for figure generation. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

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Competing interests

The authors declare that they have no competing interests.

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