Table SI. Effect of resveratrol on the inflammatory response by regulating the polarization of M1/M2 macrophages.

Authors, year	Item	Models	Time	Resveratrol	Route of administration	Effect	Mechanism	Macrophage polarization markers	(Refs.)
Xu *et al*, 2023	*In vivo*	Corneal allograft rat models	30 days postoperatively	100 mg/kg/day	Injected intraperitoneally	Reduces the secretion of pro-inflammatory cytokines and recruitment of cornea inflammatory cells	Regulating macrophage recruitment and M1/M2 macrophage	CD11b↓, iNOS↓	(1)
Liu, *et al*, 2019		Mouse model of myocardial infarction	48 days	20 mg/kg/body weight	Gavage	Promotes anti-inflammatory M2-like polarization of macrophages after myocardial infarction	Regulating M1/M2 macrophage polarization	CD163 ↑ Arg-1↑	(3)
Shabani *et al,* 2020		Glucose-induced mice	26 weeks	4 g/kg	Diet	Alleviates obesity-induced skeletal muscle inflammation	Decreasing M2 macrophage polarization and increasing the regulatory T-cell population	Arg-1↑ ,CD206↑, iNOS↓, and CD11c↓	(5)
Jeong *et al*, 2015		High-fat diet-induced mice	12 weeks	25 mg/kg	Orally gavage	Decreases macrophage infiltration and pro-inflammatory cytokine production	Switching from M1 to M2 in high-fat diet mice	CD11c↓, CD163↑	(6)
Li *et al*, 2020		ISO-induced myocardial remodeling mice	1 week	100 mg/kg	Orally gavage	Decreases pro-inflammatory cytokine production and ISO-induced myocardial remodeling	Regulating M1/M2 macrophage polarization	CD68↓ CD206↑	(7)
Carreras *et al*, 2015		Hypoxia-induced mice	8 weeks	25 mg/kg	Diet	Attenuates intermittent hypoxia-induced macrophage migration to visceral white adipose tissue	Regulating M1/M2 macrophage polarization	CD11c↓ CD206↑	(8)
Ding *et al*, 2022		STZ-induced C57/B6 mice	0-15 days	20 mg/kg	Inject intradermally around the wound	Inhibits inflammatory mediators	Regulation of macrophage phenotypes and functions	Arg-1 ↑ CD206↑	(9)

Sav *et al*, 2016		Streptozotocin-induced rats with diabetes	3-8 weeks	5 mg/kg/day	Injected intraperitoneally	Improves pro-Inflammatory myocardial environment	Lead to a recovery of cardiomyocyte contractile efficiency	CD40 ↓ CD163 ↑	(10)
Qin *et al*, 2016		DSS-induced colitis model	1-14 days	100 mg/kg	Administer orally	Preemptively fortifies the gut against inflammation via microbiome-immune-metabolic crosstalk.	Orchestrates a protective network involving microbiota–epithelial crosstalk via promotion of anti-inflammatory M2 macrophage polarization.	iNOS ↓ CD206↑	(14)
Guo *et al*, 2023	*In vitro*	LPS and IFN-γ induced macrophage RAW264.7	12 h	1-10 *μmol/l*	Resveratrol added to macrophages for cultivation	Exerts a significant anti-inflammatory effect	Regulates M1 macrophage polarization and TLR4/NF-κB/HIF-1α pathway	CD206↓	(4)
Buttari *et al*, 2014		7-oxo-cholesterol-induced monocytes	20 h	30 μM	Resveratrol added to macrophages for cultivation	Counteracts the proinflammatory cytokines	Regulates M1 macrophage polarization in both subsets	CD14↑ CD16↑ CD163↑	(2)
Ryyti *et al*, 2022		LPS-induced Human U-937 monocytes	12 h	30 μM	Resveratrol added to Human U-937 monocytes for cultivation	Exerts a significant anti-inflammatory effect	Enhances macrophage polarization towards the anti-Inflammatory M2 Phenotype	CCL-17↑MRC-1↑ IL-4↑	(12)
Li *et al*, 2025		RAW264.7 cells were induced with CAL27-CM	24 h	0-40μM	Resveratrol added to RAW264.7 cells and TAMs for cultivation	Suppresses OSCC invasion, inflammation and migration	Regulates the polarization phenotype of TAMs via Syk signaling pathway	CD206↑ Arg1↑ IL-10↑	(11)
Conte *et al*, 2025		LPS or IL-4 induced human monocytic cell line THP-1	24-72 h	15 μM	RSV@CLgel added to THP-1 for cultivation	Suppresses pro-inflammatory cytokines (TNF-α, IL-1β, IL-6) while upregulating anti-inflammatory markers	Increases macrophage polarization towards the anti-Inflammatory M2 Phenotype	IL-10↑ TNF-β↑ Arg1↑	(13)

Manríquez-Núñez *et al*, 2023		LPS induced RAW 264.7 cells	24 h	2.5-20 μM	Resveratrol added to RAW264.7 cells for cultivation	Decreases pro-inflammatory interleukins	Enhances macrophage polarization towards the anti-Inflammatory M2 Phenotype	IL-10↑ TNF-β↑ Arg1↑	(15)

TLR4, Toll-like receptor 4; CD,Cluster of Differentiation; CCL-17, C-C motif chemokine ligand 17; NF-κB, nuclear factor kappa B; OSCC, oral squamous cell carcinoma; HIF-1α, hypoxia-inducible factor-1 alpha; iNOS, inducible nitric oxide synthase; LPS, lipopolysaccharide ;HIF-1α, hypoxia-inducible factor 1α; THP-1, Human Acute Monocytic Leukemia Cell Line; ROS, reactive oxygen species; MRC1, Mannose receptor C-type 1; RSV@CLgel, Resveratrol@Chitosan Lactate Gel; TAMs, tumor-associated macrophages; Arg1, arginase-1; TNF, tumour necrosis factor; IL, interleukin; IFN-γ, interferon-γ; Syk, spleen tyrosine kinase; STZ, streptozotocin; CAL27-CM, CAL27-Conditioned Medium; TLR4,Toll-like Receptor 4; ISO, isoproterenol.

Table SII. Inclusion and exclusion criteria.

Item	Criterion	Description
Inclusion Criteria	Design	Original research (RCT, cohort, case-control, animal experiment, in vitro) or systematic review.
	Intervention	RSV alone or in combination; any formulation.
	Population	Sepsis models (CLP, LPS, endotoxemia, bacterial infection) or human sepsis/septic shock.
	Outcome	≥1 macrophage polarization marker (iNOS, Arg1, CD86, CD206, TNF-α/IL-10 ratio) and/or ≥1 intestinal barrier endpoint.
	Language	English or Chinese with sufficient methodological detail.
Exclusion Criteria	Topic	Studies focused solely on non-sepsis inflammation (e.g., IBD alone) without sepsis model.
	Intervention	Studies using only RSV derivatives (pterostilbene, oxyresveratrol) without parent RSV data.
	Outcomes	Studies lacking both macrophage and intestinal barrier endpoints.
	Quality	Non-peer-reviewed publications, predatory journal articles, retracted papers.
	Duplicates	Same dataset published in multiple journals (use most comprehensive).

RCT, randomised controlled trial; CLP, cecal ligation and puncture; LPS, lipopolysaccharide; iNOS, inducible nitric oxide synthase;ARG1, arginase1; TNF-a, tumor necrosis factor-alpha; IL-10, interleukin-10; RSV, resveratrol.

Table SIII. Impact of macrophage polarization on target cell or organ inflammation.

Authors, year	Item	Model	Macrophage polarization	Effect	Mechanism	Macrophage polarization cell markers	(Refs.)
Jiao *et al*, 2021	*In vitro*	TNF-α-stimulated PMNs	Regulates M1 macrophage polarization	Increases sepsis-induced lung inflammation.	Increases M1 macrophage polarization by activating NF-κB signaling	CD11c↑ and CD206 ↓	(16)
Akbulut *et al*, 2026		LPS induced THP-1 macrophages	Regulates macrophage polarization from the M1 to the M2 subtype	Alleviates inflammatory conditions such as cytokine storm	Influences key molecular pathways, such as IRF3/IRF4 and PPAR-γ	CD80↓, CD86 ↓ , CD163↑, CD204↑, and, CD206↑	(17)
Liu *et al*, 2019		LPS-stimulated RAW264.7 cells/mouse peritoneal macrophages	LPS-stimulated macrophage polarization toward the M2-like phenotype	Reduces dinflammatory reactions and improve the phagocytic ability	Activates the Akt/FoxO1 pathway	CD206↑ and Arg-1↑	(20)
Ye *et al*, 2026		LPS-induced ALI mice and RAW264.7 cell models	Promotes macrophage polarization toward the M2 phenotye	Alleviates LPS-triggered lung inflammation and injury	Suppresses the JAK2/STAT3 signaling cascade	CD80↓, iNOS↓, CD163↑, and Arg1 ↑	(25)
Shu *et al*, 2026	*In vivo*	CLP-induced sepsis in weaned piglets	Inhibits M1 Macrophage polarization	Attenuates LPS-induced acute liver injury and inflammation	Regulates the mTOR–glycolysis pathway	iNOS↓, CD86↓, IL-10↑, and Arg-1↑	(18)
Luo *et al*, 2022		CLP-induced sepsis in mice	Inhibits M1 macrophage polarization	Improves sepsis-induced pulmonary injury and inflammation	Regulates NF-κB/PPARγ-mediated macrophage polarization	CD86↓ and CD206↑	(19)
Xu *et al,* 2023		Hypervirulent *Klebsiella pneumoniae* (hvKp) infection-induced sepsis-mice	Drives widespread macrophage M1 polarization	Drives widespread macrophage inflammation	Activates the MSK1/p38-MAPK Axis	iNOS↑, CD86+↑ and Arg1↓	(21)
Wang *et al,* 2025		LPS-induced macrophages and septic mice	Retrieves LPS-modulated M1/M2 polarization	Mitigates both hyperinflammation and multiorgan failure	Attenuates NF-κB p65 activation by S1PR3 knockdown	CD86↓, CD16/32↓, CD206↑, and Arg-1↑	(22)

Meng *et al*, 2023		RAW 264.7 cells stimulated by LPS and CLP induced mice	Suppresses M1 macrophage polarization	Decreases both inflammation and lung injury	Regulates HIF-1α by catalyzing H3K36me3 in sepsis	CD86↓ iNOS↓, and Arg-1↑	(23)
Yang *et al*, 2025		CLP induced mice	Promotes macrophage polarization toward the M2 phenotype	Mitigates sepsis-associated lung inflammation and injury	Upregulates the NCOR2/GR/STAB1 axis	CD206↑, CD163↑, and Arg-1↑	(24)

NF-κB, nuclear factor-kappa B; MAPK, mitogen-activated protein kinase; NLRP3, NLR family pyrin domain protein 3; CLP, cecal ligation and puncture; HIF-1α, hypoxia-inducible transcription factor-1 alpha; S1PR3, sphingosine-1-phosphate receptor 3;PPARγ, peroxisome proliferator-activated receptor gamma; PMNs, polymorphonuclear neutrophils; NF-κB, nuclear factor κB; THP-1, Human Acute Monocytic Leukemia Cell Line; TNF-a, Tumor necrosis factor alpha; IRF, Interferon Regulatory Factor; mTOR, mechanistic target of rapamycin; AKT, protein kinase B; JAK2, Janus kinase 2; STAT3, signal transducer and activator of transcription3; CD, Cluster of Differentiation; iNOS, inducible nitric oxide synthase; Arg1,Arginase-1; NCOR2, nuclear receptor corepressor 2; STAB1, scavenger receptor stabilin-1;GR, glucocorticoid receptor; MSK, mitogen- and stress-activated protein kinase; FOXO1, forkhead box protein O1;LPS, lipopolysaccharide.

Table SIV. Effects of resveratrol on intestinal mucosal damage induced by various factors, such as inflammation, oxidative stress and ferroptosis.

Authors, year	Item	Resveratrol	Time	Route of administration	Model	Effect	Mechanism	(Refs.)
Wang *et al*, 2023	*In vitro*	2.5-40μM	24-72 h	Resveratrol added to Caco-2 cells for cultivation	Caco-2 hypoxia-reoxygenation models	Ameliorates intestinal ischemia–reperfusion	Activates SIRT3 and reduced ferroptosis	(26)
Zhuang *et al*, 2019		25 -50μM	6 h	Resveratrol added to IPEC-J2 cells for cultivation	H_2O_2-induced IPEC-J2 cells	Attenuates oxidative stress-induced intestinal barrier injury	Regulates the PI3K/Akt-mediated Nrf2 signaling pathway	(27)
Yu *et al*, 2024		5-50 μM	24 h	Resveratrol added to Caco-2 cells for cultivation	DSS-induced Caco-2 cells	Ameliorates DSS-induced IEC barrier dysfunction	Increases Nrf2 and HO-1 protein levels, counteract oxidative stress, and pregulated TJ protein expression (ZO-1 and Occludin)	(35)
Qin *et al*, 2021		0.1–40.0 μM	24 h	Resveratrol added to IEC-6 cells for cultivation	IEC-6 were exposed to 10 Gy ionizing radiation	Protects intestinal epithelial cells against radiation-induced damage	Promotes autophagy and inhibited apoptosis through SIRT1 activation	(31)
Gan *et al*, 2019	*In vivo*	300 mg/kg	28 days	Resveratrol was fed	Piglets induced by weaning	Increases intestinal immune function	Regulates intestinal bacteria and alleviated intestinal inflammation	(28)
Wang *et al*, 2026		50-500 mg/kg	8 weeks	Oral gavage	Heat-stressed Siberian sturgeon	Alleviates heat-stress intestinal barrier dysfunction in Siberian sturgeon	Activates PPAR/NF-kB-mediated antioxidant capacity and microbiota homeostasis	(29)
Mohammadi *et al*, 2025		Resveratrol-loaded polymeric-based nanocapsules	7 days	Intravenous injection	X-ray radiation-induced mice	Mitigates radiation-induced intestine Injury	Decreases radiation-induced intestinal inflammation and oxidative stress	(30)

Yu *et al*, 2024		10–100 mg/kg	14 days	Administered intragastrically	DSS-induced male C57BL/6J mice	Decreases inflammatory responses and intestinal mucosal barrier damage in experimental UC mice	Upregulates Nrf2/HO-1 pathway activity	(32)
Yang *et al*, 2021		400 mg/kg	15 days	was fed the basal diet supplemented with resveratrol	Duck jejunum induced by heat stress	Sustains intestinal barrier integrity	Activates the SIRT1-NRF1/NRF2 signaling pathways, improve antioxidant capacity, and alleviate inflammation	(33)
Chen *et al*, 2021		150 and 300 mg/kg	42 days	was fed the basal diet supplemented with resveratrol	Piglets induced by weaning	Promotes the integrity of intestinal barrier	Increases the production of anti-inflammatory cytokines and antioxidant activity in weaning piglets.	(34)
Chen *et al*, 2026		400 mg/kg	4 weeks	Resveratrol was thoroughly mixed into the feed	Triclosan–induced intestinal injury in chickens.	Promotes the integrity of intestinal barrier	Increases antioxidant activity and the production of anti-inflammatory cytokines.	(36)

SIRT, sirtuin; PI3K, phosphatidylinositol 3-kinase; AKT, protein kinase B; NRF2, NF-E2-related factor 2; Caco-2, Human Colorectal Adenocarcinoma Cell Line; NRF1, nuclear factor-erythroid-2 related transcription factor-1; Res, resveratrol; H_2O_2, hydrogen peroxide; UC, ulcerative colitis; PPAR, peroxisome proliferator-activated receptor; IPEC-J2, intestinal porcine enterocyte cell line; IEC-6, intestinal epithelial cells; HO-1, heme oxygenase-1; DSS, dextran sulfate sodium; TJ, tight junction; ZO-1, zonula occludens-1; TLR-4, Toll-like receptor 4; NF-κB, nuclear factor-kappa B.

Table SV. Promotion of the proliferation and differentiation of intestinal mucosal cells.

Authors, year	Item	Model	Time	Route of administration	Resveratrol	Action mechanism	Correlated signal path	The resultant influence	(Refs.)
Zhou *et al*, 2023	*In vitro*	HCoEpiC was induced by LPS	24 h	Resveratrol added to HCoEpiC for cultivation	100 mg/kg/day	Promotes intestinal epithelial cell proliferation	ANRIL/miR-34a	Increases the proliferation rate and regeneration ability of intestinal epithelial cells and repaired the intestinal barrier.	(37)
Qin *et al*, 2021		Radiation-induced IEC-6 cell line	24 h	Resveratrol added to IEC-6 cells for cultivation	0.1-40.0 μM	Promotes intestinal epithelial cell proliferation by promoting autophagy and inhibiting apoptosis	SIRT1	Protects intestinal epithelial cells against radiation-induced damage	(31)
Wang *et al*, 2021		Intestinal ischemia-reperfusion induced caco-2 cells	24 h	Resveratrol added to IEC-6 cells for cultivation	2.5-40 μM	Ameliorates intestinal ischemia-reperfusion induced caco-2 cells injury.	SIRT3/FoxO3a and GSH/GPX4	Reduces caco-2 cells ferroptosis and oxidative stress	(26)
Xu *et al*, 2023	*In vivo*	Mice were treated with swimming exercise protocol	28 days	Oral gavage	15 mg/kg/day	Decreases intestinal permeability	Nrf2/FTH1/GPX4	Reduces intestinal permeability and enhanced barrier function.	(38)
Xie, *et al*, 2025		Salmonella Typhimurium-induced Wenchang chickens	12 days	was fed the basal diet supplemented with resveratrol	50, 100, and 200 mg/kg	Promotes intestinal epithelial cell differentiation by inhibiting inflammation.	COX-2	Improves intestinal epithelial cell differentiation.	(39)
Yu *et al*, 2022		Wheat gluten induced mice with celiac disease	5 days	Oral gavage	100 mg/kg	Improves intestinal barrier function by alleviating the intestinal inflammation and oxidative stress	PPAR, AMPK and FoxO	Repairs intestinal barrier and enhanced defense against foreign microorganisms.	(41)

Zhang *et al*, 2022		4HPP induced mice colitis	5 days	Oral gavage	100 mg/kg	Decreases intestinal permeability by inhibiting colonic inflammation	AMPK	Improves intestinal epithelial cell differentiation.	(40)
Yasmin *et al*, 2025		High-fat diet-fed rats	8 weeks	Oral gavage	100 mg/kg/days	Increases intestinal goblet cell differentiation by modulating antioxidant and anti-inflammatory pathways	PPARα, Nrf2, and HO-1	Preserves gut mucosal integrity	(42)
Zheng *et al*, 2021		Uremic toxin-induced mice with intestinal barrier dysfunction	4 weeks	Received an intraperitoneal injection	30 mg/kg/day	Ameliorates intestinal barrier dysfunction in chronic kidney disease.	IRF1-DRP1 and PI3K/Akt-HO-1	Restores autophagy, and inhibit apoptosis through the activation of the PI3K/Akt-HO-1 anti-oxidant pathway and mTOR regulated pathways.	(43)
Abulaiti *et al,*2025		Aspirin-induced rats with intestinal injury	3 weeks	Gavage	25- 100 mg/kg	Effectively mitigates intestinal injury induced by aspirin at high altitude in hypoxic environments	Ang II and ICAM-1	Downregulates the expression of Ang-II and ICAM-1, alleviating oxidative stress and the inflammatory response of the intestinal mucosa	(44)

4HPP, 3-(4-hydroxyphenyl)-propionic acid; IBD, inflammatory bowel diseases; HCoEpiC, Human colonic epithelial cells; Caco-2, Human Colorectal Adenocarcinoma Cell Line; IEC-6, intestinal epithelial cells; ICAM-1, Intercellular adhesion molecule 1; Ang II, angiotensin II; PI3K, phosphatidylinositol 3-kinase; AKT, protein kinase B; HO-1, heme oxygenase-1; mTOR,mechanistic target of rapamycin; DRP1, Dynamin-Related Protein 1; miR-34a, microRNAs-34a; IRF1, interferon regulatory factor 1; LPS,lipopolysaccharides; GSH, glutathione; ANRIL, antisense non-coding RNA in the INK4 locus; Nrf2, nuclear factor erythroid-2-related factor 2; FTH1, ferritin heavy chain 1; GPX4, glutathione peroxidase 4; COX-2, cyclooxygenase-2; PPAR, peroxisome proliferator-activated receptor; AMPK, AMP-activated protein kinase; FOXO, forkhead box O; PPARα, peroxisome proliferator-activated receptor-alpha; HO-1, heme oxygenase-1; SIRT, sirtuin .

Table SVI. Effect of resveratrol on intestinal barrier dysfunction by strengthening the tight connections between intestinal epithelial cells.

Authors, year	Items	Model	Time	Route of administration	Resveratrol	Effect	Mechanism	(Refs.)
Luo *et al*, 2022	*In vitro*	HT-29 cell model induced by LPS	24 h	Resveratrol added to HT-29 cells for cultivation	50-100 μmol/l	Upregulates the expression of the tight junction proteins occludin, ZO-1, and claudin-1	Reduces inflammatory response by attenuating the Notch1 pathway	(45)
Wang *et al,* 2016		Hydrogen peroxide -induced Caco-2 cells	1-6 h	Resveratrol added to Caco-2 for cultivation	10-40 μmol/l	Strengthens the integrity of the intestinal TJ barrier by increasing Claudin-1, Occludin, and ZO-1 expression	Inhibits oxidative stress by initiating HO-1-dependent signaling.	(47)
Yu *et al*, 2024		Fumonisin-induced the porcine intestinal epithelial cell line (IPEC-J2)	24 h	Resveratrol added to IPEC-J2 for cultivation	5-20 μM	Ameliorates intestinal barrier defects by increasing Claudin-1, Occludin, and ZO-1 expression	Inhibits inflammation by decreasing the activity of c-Jun N-terminal protein kinase/NF-κB pathway	(48)
Chen *et al*, 2020	*In vivo*	High-fat diet (HFD)-feeding induces mice	12 weeks	Oral gavage	100 mg/kg/day-body weight	Upregulates the expression of the tight junction proteins and ameliorate the intestinal barrier defect	Ameliorates endotoxemia, inflammation,and glucose intolerance in the HFD-fed mice.	(46)
Xu *et al*, 2023		Dextran sulfate sodium-induced BALB/c mice	10 days	Oral gavage	100 mg/kg/day	Repairs colon and spleen tissues and upregulate tight junction proteins Occludin and Claudin 1	Increases Arg1 and Slc6a8 and decrease iNOS and pro-inflammatory cytokines IL-1β, IL-6, and TNF-α	(49)
Yang *et al*, 2022		Duck ileitis caused by LPS	12 h	Basal diet	400 mg/kg/day	Alleviates LPS-induced ileitis by increasing Claudin-1, Occludin and ZO-1 expression	Inhibits inflammation and oxidative stress by regulating Nrf2 and NF-κB signaling pathways.	(50)
Pan *et al*, 2020		Dextran sulfate sodium-induced ulcerative colitis mice	7 days	Gavage	100 mg/kg/day	Alleviates UC intestinal mucosal barrier dysfunction by increasing the expression of tight junction proteins	Decreases the expression of inflammatory factors and enhances autophagy in intestinal epithelial cells	(51)

Liu *et al*, 2024		Chickens caused by high temperatures	12 days	Receive a basal diet	400 mg/kg/day	Improves the morphology and structure of jejunal mucosa by increasing the expression of tight junction proteins	Inhibits inflammation and apoptosis by blocking the TLR4/MAPK signaling pathway.	(52)
Song *et al*, 2022		Cyclophosphamide-induced immunosuppressed mice	24 h	Orally administrated	15-60 mg/kg	Improves intestinal barrier function by increasing the expression of tight junction proteins	Inhibits inflammation by regulating the TLR4/NF-κB signaling pathway	(53)

LPS, lipopolysaccharide; Caco-2, Human Colorectal Adenocarcinoma Cell Line; HT-29 cell, Human Colon Adenocarcinoma Cell Line; IEC-6, intestinal epithelial cells; IPEC-J2, intestinal porcine enterocyte cell line; NF-κB, nuclear factor κB; HFD, high-fat diet; c-Jun, cellular Jun; HO-1, Heme oxygenase-1; TLR4, Toll-like receptor 4; Notch1, Notch homolog protein 1; ZO-1, zonula occludens-1; MAPK, mitogen-activated protein kinase; PKC, protein kinase C; iNOS, inducible nitric oxide synthase; CDX-2, caudal-type homeobox protein 2; UC, ulcerative colitis; Nrf2, nuclear factor erythroid 2-related factor 2; Arg1, arginase 1; SLC6A8, X-linked creatine transporter; IL, interleukin; TNF-α, tumor necrosis factor-alpha.

Table SVII. Limitations of resveratrol studies in sepsis-induced *in vitro* models, animal experiments, clinical studies and clinical trials.

Authors, year	Research level	Limitation category	Specific issues	(Refs.)
Xu *et al*, 2023 Zabihi *et al*, 2019 Chen *et al*, 2019	*In vitro* studies	Cell model simplification	Use of single cell lines (Caco-2, IEC-6, HT-29) lacking crypt-villus axis architecture; absence of Paneth cells, goblet cells, enteroendocrine cells, and M cells; failure to reproduce dynamic tight junction assembly.	(54) (55) (56)
		Microenvironment defects	Inability to simulate immune-epithelial-microbiota tripartite interactions; neglect of mucus layer and microbial metabolites (SCFAs); lack of characteristic sepsis microenvironment (hypoxia, ischemia-reperfusion).	
		Concentration-metabolism disconnect	"Concentration paradox": in vitro doses (10–100 μM) far exceed human plasma levels (<1 μM); use of parent RSV ignoring sulfation/glucuronidation and microbial derivatives (e.g., dihydroresveratrol).	
		Oversimplified injury models	Single stimuli (LPS, H_2O_2, TNF-α) cannot recapitulate sepsis "cytokine storm + oxidative stress + microcirculatory dysfunction + immunoparalysis" composite pathology.	
Mohammadi *et al*, 2017 Gambini *et al*, 2015 Tariq *et al*, 2025	Animal studies	Model heterogeneity	Diverse sepsis models (CLP, LPS, bacterial infusion, zymosan) with divergent pathomechanisms; strong model-dependency of RSV outcomes	(57) (58) (59)
		Translational barriers	Species differences in microbiota, immunity, and drug-metabolizing enzymes (SULT/UGT); use of healthy young male mice vs. elderly comorbid septic patients; pharmacokinetic-pharmacodynamic mismatch.	
		Dose-exposure inaccuracy	Effective animal doses (20–100 mg/kg) translate to impractically high human doses; route-dependent bioavailability differences (i.p./oral gavage vs. clinical oral).	
		Endpoint limitations	Surrogate endpoints (histology scores, cytokines, tight junction expression) over functional assessments (gut barrier function, endotoxemia); lack of long-term survival and intestinal failure data; correlative rather than causal mechanistic evidence.	
		Confounding control	Unstandardized background dietary polyphenols; impact of anesthesia/surgical procedures on barrier function; non-standardized microbiota (SPF status, vendor variation).	
Springer *et al*, 2019 Riccio *et al*, 2020	Human observational studies	Evidence scarcity	Near-complete absence of dedicated studies on RSV and sepsis-related intestinal injury; existing data rely on indirect associations (wine/polyphenol intake vs. general inflammation)	(60) (61)

		Design weaknesses	Predominantly cross-sectional design preventing causal/temporal inference; small cohort sample sizes with short follow-up inadequate for acute events like sepsis.	
		Exposure assessment	Inaccurate dietary recall for polyphenol sources (wine, grapes, peanuts, herbs); lack of validated biomarkers (urinary RSV metabolites).	
		Confounding	Strong "healthy user bias" in wine consumers (higher SES, healthier lifestyles); difficulty isolating RSV from other polyphenols.	
Öztürk *et al*, 2017 Cho *et al*, 2017 Samuel *et al*, 2019	Clinical trials	Quantity and scale	No large RCTs specifically targeting sepsis-induced intestinal injury; existing trials focus on metabolic, cardiovascular, or neurological indications; predominantly small (n<100), single-center, underpowered studies.	(62) (63) (64)
		Population mismatch	Subjects are healthy volunteers or stable chronic disease patients—not critically ill septic patients; exclusion of those with hepatorenal dysfunction despite profound PK/PD alterations in sepsis.	
		Intervention heterogeneity	Wide dose range (5 mg–5 g/day) without dose-finding or exposure-response analyses; inconsistent routes, durations, and timing (prophylactic vs. therapeutic); diverse formulations (native RSV, nanocarriers, pterostilbene).	
		Endpoint disconnect	Lack of specific gut barrier endpoints (ZO-1, citrulline, I-FABP, D-lactate, endotoxemia); overreliance on surrogate inflammatory/oxidative markers; unvalidated link to hard clinical outcomes (28-day mortality, ICU stay, secondary infection).	
		Safety and PK gaps	Undefined safety profile in critical illness (platelet inhibition, enzyme induction, hormonal effects); extremely low oral bioavailability (<1%); unknown drug-drug interactions with vasopressors, antibiotics, sedatives, anticoagulants.	
		Sepsis heterogeneity	Failure to address sepsis syndrome heterogeneity; no precision medicine stratification by infection source or host-response endotype.	
Ren *et al*, 2021 Planas *et al*, 2012	Cross-cutting limitations	Translational valley of death	Effective in vitro/animal concentrations unachievable in humans; broken chain from molecular mechanism to bedside application.	(65) (66)
		Bioavailability bottleneck	Poor aqueous solubility, rapid metabolism, short half-life; limited pharmaceutical breakthroughs	
		Methodological heterogeneity	Wide protocol/model/endpoint/dose variation precluding robust meta-analysis.	
		Insufficient mechanistic depth	SIRT1, NF-κB, Nrf2 pathways supported mainly by correlative evidence; weak causal validation (genetic/pharmacological).	

		Publication bias	Underreporting of negative results risks efficacy overestimation.	
		Standardization deficit	Absence of SOPs and adherence to reporting guidelines (ARRIVE, STROBE, CONSORT).	

SCFAs, Short-chain fatty acids; ICU, Intensive care unit; RCTS, Randomized Clinical Trials; SPF, specific pathogen-free; Caco-2, Human Colorectal Adenocarcinoma Cell Line; IEC-6, Rat Small Intestinal Crypt Epithelial Cell Line; HT-29, Human Colon Adenocarcinoma Cell Line; LPS, lipopolysaccharides; H_2O_2, hydrogen peroxide; TNF-α, tumor necrosis factor-alpha; CLP, cecal-ligation and puncture; SULT, sulfotransferase; UGT, UDP-Glucuronosyltransferase; RSV, Resveratrol; RCTs, Randomized Controlled Trials; SPF, specific pathogen-free; ZO-1, zonula occludens 1; PK/PD, pharmacokinetic-pharmacodynamic; FABP2, fatty acid-binding protein 2; SIRT1, Sirtuin 1; NF-κB, nuclear factor-kappaB; Nrf2, Nuclear factor erythroid 2-related factor 2; SOPs, Standard Operating Procedures.

Table SVIII. Inconsistent findings and limitations of the sepsis induced models and experimental conditions where relevant.

Authors, year	Model type	Experimental condition inconsistencies	Inconsistent findings	Limitations	(Refs.)
Wang *et al*, 2025	Lipopolysaccharide (LPS)-Induced Model	- Dosage varies from 1 mg/kg to 20 mg/kg -Administration routes include intraperitoneal injection, intravenous injection. -Animal strains range from C57BL/6 mice, Balb/c mice to rats. -Different LPS source strains (e.g., E. coli O111:B4).	-Only activates TLR4 pathway, fails to mimic immune complexity of human sepsis. -Sensitivity to LPS differs among strains, leading to inconsistent intestinal injury severity. -Time points of intestinal injury induction vary from several hours to days.	- Cannot replicate the full spectrum of human sepsis pathophysiology. - Inconsistent results limit cross-study comparisons. - Ignores the role of gut microbiota in intestinal injury.	(67)
Alverdy *et al*, 2020	Cecal Ligation and Puncture (CLP) Model	- Cecum ligation ratio ranges from 25% to over 75%. - Puncture needle sizes (e.g., 18G) and amount of extruded intestinal content vary. - Animal strains and genders differ (males are more commonly used due to higher sepsis susceptibility). - Post - operative care measures like fluid resuscitation volume and antibiotic timing vary.	- High complexity of surgical operations leads to poor inter-laboratory consistency. - Different ligation ratios and puncture methods cause variations in infection severity and intestinal injury onset time. - Post - operative care significantly impacts model stability.	-Surgical variations make results difficult to reproduce. -Fails to fully simulate the chronic progression of human sepsis-induced intestinal injury. -Ethical concerns exist regarding animal suffering.	(68)
Gonzalez *et al*, 2015	Intestinal ischemia/reperfusion -induced model	- Ischemia duration ranges from 30 min to over 1 h. - Reperfusion methods differ. - Animal strains and ages vary. - Some studies combine I/R with other factors like bacterial infection.	-Significant differences in intestinal injury severity and susceptibility exist among animals. -Some mice show mild injury with high survival rates, while others have severe injury and high mortality. -Gut microbiota and genetic background contribute to susceptibility variations.	- Cannot fully represent the complex immune response in human sepsis. - Limited applicability to non -ischemic-related sepsis cases. -Difficulty in standardizing ischemia/reperfusion protocols.	(69)
Zhan *et al*, 2025	Cell culture models	- Diverse modeling methods, including co - incubation with pathogenic substances/inflammatory mediators, incubation with plasma from septic animals, and primary cell culture from septic animals. - Incubation time, cell types (e.g., intestinal epithelial cells, immune cells), and culture conditions (e.g., medium components, oxygen concentration) vary.	- Different preparation methods simulate different pathophysiological stages of intestinal injury. - Plasma from septic animals better mimics the in vivo environment but has high individual variability. - Co - incubation with inflammatory mediators only simulates the inflammatory response stage.	- Lack the three - dimensional structure and microenvironment of the intact intestinal tract. - Cannot fully replicate the crosstalk between different cell types in vivo. - Limited ability to study long -term intestinal injury and repair processes.	(70)

LPS, Lipopolysaccharide; Co, common; E. coli O111:B4, Escherichia coli O111:B4; CLP, Cecal ligation and puncture; I/R, Ischemia/Reperfusion; TLR4, toll-like receptor 4.

Table SIX. Effect of macrophage plasticity, temporal changes during sepsis, tissue-specific microenvironments and immune paralysis on resveratrol-mediated immunomodulation.

Authors, year	Key factors	Effect on resveratrol-mediated immunomodulation	Mechanistic details	(Refs.)
Zhu *et al*, 2025	Macrophage Plasticity	Determines the direction of resveratrol's immunoregulatory effect	Activates SIRT1 to inhibit NF-κB (reduces M1 pro-inflammatory cytokines); upregulates PPAR-γ to promote M2 polarization	(71)
Wang *et al*, 2017	Temporal Changes in Sepsis	Dictates the stage-specific therapeutic effect of resveratrol	Anti-inflammatory via NF-κB inhibition in the early (pro-inflammatory) phase; restores immune function via AMPK activation in the late (immune paralysis) phase	(72)
Üstündağ *et al*, 2024	Tissue-Specific Microenvironments	Shapes tissue-targeted immunomodulation of resveratrol	Inhibits TLR4 signaling to reduce lung injury; enhances Kupffer cell phagocytosis to clear endotoxin in the liver	(73)
Wang *et al*, 2017	Immune Paralysis	Requires resveratrol to switch from anti-inflammatory to immunostimulatory mode	Inhibits HDAC activity to upregulate MHC-II/CD86 expression; activates PI3K/Akt pathway to reduce lymphocyte apoptosis.	(74)

NF-κB, nuclear factor-kappa B;PPAR-γ, peroxisome proliferator-activated receptor gamma;SIRT1,Sirtuin 1;AMPK,AMP-activated protein kinase;TLR4,Toll-like receptor 4; HDAC, Histone deacetylase; CD86, Cluster of Differentiation 86; MHC- II, Major Histocompatibility Complex Class II; PI3K/Akt, Phosphatidlinositol 3-kinase/protein kinase B.

Supplementary References

1. Xu C, Guo R, Hou C, Ma M, Dong X, Ouyang C, Wu J and Huang T: Resveratrol regulates macrophage recruitment and M1 macrophage polarization and prevents corneal allograft rejection in rats. Front Med (Lausanne) 10: 1250914, 2023.
2. Buttari B, Profumo E, Segoni L, D'Arcangelo D, Rossi S, Facchiano F, Saso L, Businaro R, Iuliano L and Riganò R: Resveratrol counteracts inflammation in human M1 and M2 macrophages upon challenge with 7-oxo-cholesterol: Potential therapeutic implications in atherosclerosis. Oxid Med Cell Longev 2014: 257543, 2014.
3. Liu S, Du Y, Shi K, Yang Y and Yang Z: Resveratrol improves cardiac function by promoting M2-like polarization of macrophages in mice with myocardial infarction. Am J Transl Res 11: 5212-5226, 2019.
4. Guo L, Zhang X, Lv N, Wang L, Gan J, Jiang X and Wang Y: Therapeutic role and potential mechanism of resveratrol in atherosclerosis: TLR4/NF-κB/HIF-1α. Mediators Inflamm 2023: 1097706, 2023.
5. Shabani M, Sadeghi A, Hosseini H, Teimouri M, Babaei Khorzoughi R, Pasalar P and Meshkani R: Resveratrol alleviates obesity-induced skeletal muscle inflammation via decreasing M1 macrophage polarization and increasing the regulatory T cell population. Sci Rep 10: 3791, 2020.
6. Jeong JH, Lee YR, Park HG and Lee WL: The effects of either resveratrol or exercise on macrophage infiltration and switching from M1 to M2 in high fat diet mice. J Exerc Nutrition Biochem 19: 65-72, 2015.
7. Li Y, Feng L, Li G, An J, Zhang S, Li J, Liu J, Ren J, Yang L and Qi Z: Resveratrol prevents ISO-induced myocardial remodeling associated with regulating polarization of macrophages through VEGF-B/AMPK/NF-kB pathway. Int Immunopharmacol 84: 106508, 2020.
8. Carreras A, Zhang SXL, Almendros I, Wang Y, Peris E, Qiao Z and Gozal D: Resveratrol attenuates intermittent hypoxia-induced macrophage migration to visceral white adipose tissue and insulin resistance in male mice. Endocrinology 156: 437-443, 2015.
9. Ding Y, Yang P, Li S, Zhang H, Ding X and Tan Q: Resveratrol accelerates wound healing by inducing M2 macrophage polarisation in diabetic mice. Pharm Biol 60: 2328-2337, 2022.
10. Savi M, Bocchi L, Sala R, Frati C, Lagrasta C, Madeddu D, Falco A, Pollino S, Bresciani L, Miragoli M, *et al*: Parenchymal and stromal cells contribute to pro-inflammatory myocardial environment at early stages of diabetes: Protective role of resveratrol. Nutrients 8: 729, 2016.
11. Li W, Qi Y, Li Y, Liu L, Dong X and Li B: Resveratrol suppresses OSCC invasion and migration by regulating macrophage polarization via Syk signaling pathway. Front Immunol 16: 1660851, 2025.
12. Ryyti R, Hämäläinen M, Leppänen T, Peltola R and Moilanen E: Phenolic compounds known to be present in lingonberry (vaccinium vitis-idaea L.) enhance macrophage polarization towards the anti-inflammatory M2 phenotype. Biomedicines 10: 3045, 2022.
13. Conte R, Valentino A, Sepe F, Gianfreda F, Condò R, Cerroni L, Calarco A and Peluso G: Resveratrol-loaded solid lipid nanoparticles reinforced hyaluronic hydrogel: Multitarget strategy for the treatment of diabetes-related periodontitis. Biomedicines 13: 1059, 2025.
14. Qin S, Yang Z, Lei J, Xie Q, Jiang L, Fan Y, Luo Y, Wei K, Luo W and Yu B: Comparative efficacy of preventive vs therapeutic resveratrol in modulating gut microbiota and alleviating inflammation in DSS-induced colitis. BMC Immunol 26: 42, 2025.
15. Manríquez-Núñez J, Mora O, Villarroya F, Reynoso-Camacho R, Pérez-Ramírez IF and Ramos-Gómez M: Macrophage activity under hyperglycemia: A study of the effect of resveratrol and 3H-1,2-dithiole-3-thione on potential polarization. Molecules 28: 5998, 2023.
16. Jiao Y, Zhang T, Zhang C, Ji H, Tong X, Xia R, Wang W, Ma Z and Shi X: Exosomal miR-30d-5p of neutrophils induces M1 macrophage polarization and primes macrophage pyroptosis in sepsis-related acute lung injury. Crit Care 25: 356, 2021.
17. Akbulut I, Zhang Z, Hussell T, Derrick JP and Lu JR: Immunomodulatory effects of synthetic antimicrobial peptides on LPS-induced inflammatory responses in THP-1 macrophages. Front Immunol 17: 1829304, 2026.
18. Shu K, Xiong J, Xu X, Deng Y, Xiao K, Yang H, Liu Y and Chen S: Lysolecithin attenuates LPS-induced acute liver injury in weaned piglets by inhibiting M1 macrophage polarization via the mTOR-glycolysis pathway. Biology (Basel) 15: 333, 2026.

19. Luo J, Wang J, Zhang J, Sang A, Ye X, Cheng Z and Li X: Nrf2 deficiency exacerbated CLP-induced pulmonary injury and inflammation through autophagy- and NF-κB/PPARγ-mediated macrophage polarization. Cells 11: 3927, 2022.
20. Liu F, Qiu H, Xue M, Zhang S, Zhang X, Xu J, Chen J, Yang Y and Xie J: MSC-secreted TGF-β regulates lipopolysaccharide-stimulated macrophage M2-like polarization via the Akt/FoxO1 pathway. Stem Cell Res Ther 10: 345, 2019.
21. Xu Y, Zhang C, Cai D, Zhu R and Cao Y: Exosomal miR-155-5p drives widespread macrophage M1 polarization in hypervirulent Klebsiella pneumoniae-induced acute lung injury via the MSK1/p38-MAPK axis. Cell Mol Biol Lett 28: 92, 2023.
22. Wang D, Bi X, Zhao L, Xiang S, Xi W, Yang S, Wu W, Chen T, Zheng L, Chi X and Kang Y: Targeting SphK1/S1PR3 axis ameliorates sepsis-induced multiple organ injury via orchestration of macrophage polarization and glycolysis. Biochim Biophys Acta Mol Cell Res 1872: 119877, 2025.
23. Meng Y, Kong KW, Chang YQ, Deng XM and Yang T: Histone methyltransferase SETD2 inhibits M1 macrophage polarization and glycolysis by suppressing HIF-1α in sepsis-induced acute lung injury. Med Microbiol Immunol 212: 369-379, 2023.
24. Yang YH, Wen R, Huang XM, Zhang T, Yang N, Liu CF and Zhang TN: HNF4A mitigates sepsis-associated lung injury by upregulating NCOR2/GR/STAB1 axis and promoting macrophage polarization towards M2 phenotype. Cell Death Dis 16: 120, 2025.
25. Ye J, Pan Y, Jia C, Liu S, Li X, Zhao L, Zhang J, Chen X, Zheng B, Chen Z, *et al*: Selective JAK2 inhibition by TG101209 reprograms macrophage polarization and alleviates acute lung injury. Front Immunol 17: 1755208, 2026.
26. Wang X, Shen T, Lian J, Deng K, Qu C, Li E, Li G, Ren Y, Wang Z, Jiang Z, *et al*: Resveratrol reduces ROS-induced ferroptosis by activating SIRT3 and compensating the GSH/GPX4 pathway. Mol Med 29: 137, 2023.
27. Zhuang Y, Wu H, Wang X, He J, He S and Yin Y: Resveratrol attenuates oxidative stress-induced intestinal barrier injury through PI3K/Akt-mediated Nrf2 signaling pathway. Oxid Med Cell Longev 2019: 7591840, 2019.
28. Gan Z, Wei W, Li Y, Wu J, Zhao Y, Zhang L, Wang T and Zhong X: Curcumin and resveratrol regulate intestinal bacteria and alleviate intestinal inflammation in weaned piglets. Molecules 24: 1220, 2019.
29. Wang H, Zhang Y, Chen X, Zhang Z, Xu Z, Xu W, Chen X, Xiong Y, Jiang M, Wei Z, *et al*: Resveratrol alleviates heat-stress intestinal barrier dysfunction in Siberian sturgeon by activating PPAR/NF-kB-mediated antioxidant capacity and microbiota homeostasis. Comp Biochem Physiol Part D Genomics Proteomics 59: 101807, 2026.
30. Mohammadi M, Kiani A, Aghaz F, Arkan E, Rashidi K and Najafi M: Mitigation of radiation-induced acute hematopoietic system and intestine injury by resveratrol-loaded polymeric nanoparticles after whole body irradiation in mice. Curr Radiopharm 18: 182-200, 2025.
31. Qin H, Zhang H, Zhang X, Zhang S, Zhu S and Wang H: Resveratrol protects intestinal epithelial cells against radiation-induced damage by promoting autophagy and inhibiting apoptosis through SIRT1 activation. J Radiat Res 62: 574-581, 2021.
32. Yu X, Li X, Xu Y, Li Y, Zhou Y, Zhang J and Guo L: Resveratrol ameliorates ulcerative colitis by upregulating Nrf2/HO-1 pathway activity: Integrating animal experiments and network pharmacology. Mol Med Rep 29: 77, 2024.
33. Yang C, Luo P, Chen SJ, Deng ZC, Fu XL, Xu DN, Tian YB, Huang YM and Liu WJ: Resveratrol sustains intestinal barrier integrity, improves antioxidant capacity, and alleviates inflammation in the jejunum of ducks exposed to acute heat stress. Poult Sci 100: 101459, 2021.
34. Chen X, Zeng Z, Huang Z, Chen D, He J, Chen H, Yu B, Yu J, Luo J, Luo Y and Zheng P: Effects of dietary resveratrol supplementation on immunity, antioxidative capacity and intestinal barrier function in weaning piglets. Anim Biotechnol 32: 240-245, 2021.
35. Yu X, Wang Y, Xu Y, Li X, Zhang J, Su Y and Guo L: Resveratrol attenuates intestinal epithelial barrier dysfunction via Nrf2/HO-1 pathway in dextran sulfate sodium-induced Caco-2 cells. Immun Inflamm Dis 12: e1193, 2024.
36. Zhang Y, Zhang H, Li Q, Wang F, Luo T, Sun Q and Zhang W: Resveratrol protects against triclosan-induced impairment of colonic barrier function in chickens. Poult Sci 105: 106946, 2026.
37. Zhou X, Zhang Y, Hu M, Ge Z and Zhou G: Resveratrol enhances MUC2 synthesis via the ANRIL-miR-34a axis to mitigate IBD. Am J Transl Res 15: 363-372, 2023.

38. Xu Z, Sun X, Ding B, Zi M and Ma Y: Resveratrol attenuated high intensity exercise training-induced inflammation and ferroptosis via Nrf2/FTH1/GPX4 pathway in intestine of mice. Turk J Med Sci 53: 446-454, 2023.
39. Xie Y, Chen S, Guo D, Peng H, Ran X and Wen X: Resveratrol ameliorates Salmonella Typhimurium-induced intestinal inflammation and barrier dysfunction in chickens via COX-2 inhibition. Res Vet Sci 195: 105843, 2025.
40. Zhang B, Zhang Y, Liu X, Yin J, Li X, Zhang X, Xing X, Wang J and Wang S: Differential protective effect of resveratrol and its microbial metabolites on intestinal barrier dysfunction is mediated by the AMPK pathway. J Agric Food Chem 70: 11301-11313, 2022.
41. Yu T, Xie Y, Yuan J, Gao J, Xiao Z, Wu Y and Chen H: The nutritional intervention of resveratrol can effectively alleviate the intestinal inflammation associated with celiac disease induced by wheat gluten. Front Immunol 13: 878186, 2022.
42. Yasmin T, Menon SN, Pandey A, Siddiqua S, Kuddus SA, Rahman MM, Khan F, Hoque N, Rana MS, Subhan N, *et al*: Resveratrol attenuates hepatic oxidative stress and preserves gut mucosal integrity in high-fat diet-fed rats by modulating antioxidant and anti-inflammatory pathways. Sci Rep 15: 25162, 2025.
43. Zheng CM, Hou YC, Tsai KW, Hu WC, Yang HC, Liao MT and Lu KC: Resveratrol mitigates uremic toxin-induced intestinal barrier dysfunction in chronic kidney disease by promoting mitophagy and inhibiting apoptosis pathways. Int J Med Sci 21: 2437-2449, 2024.
44. Abulaiti P, Shi WH, Liu H, Tuerxuntayi A, Nuermaimaiti K, Liu ZS, Xing Y, Rehemutula N, Abdukelimu K, Liu W, *et al*: Resveratrol mitigates aspirin-induced intestinal injury in rats in a high-altitude hypoxic environment associated with reducing the expression levels of angiotensin II. BMC Gastroenterol 25: 623, 2025.
45. Luo Y, Yu X, Zhao P, Huang J and Huang X: Effects of resveratrol on tight junction proteins and the notch1 pathway in an HT-29 cell model of inflammation induced by lipopolysaccharide. Inflammation 45: 2449-2464, 2022.
46. Chen K, Zhao H, Shu L, Xing H, Wang C, Lu C and Song G: Effect of resveratrol on intestinal tight junction proteins and the gut microbiome in high-fat diet-fed insulin resistant mice. Int J Food Sci Nutr 71: 965-978, 2020.
47. Wang N, Han Q, Wang G, Ma WP, Wang J, Wu WX, Guo Y, Liu L, Jiang XY, Xie XL and Jiang HQ: Resveratrol protects oxidative stress-induced intestinal epithelial barrier dysfunction by upregulating heme oxygenase-1 expression. Dig Dis Sci 61: 2522-2534, 2016.
48. Yu S, Zou L, Zhao J and Zhu Y: Resveratrol alleviates fumonisin-induced intestinal cytotoxicity by modulating apoptosis, tight junction, and inflammation in IPEC-J2 porcine intestinal epithelial cells. Environ Toxicol 39: 905-914, 2024.
49. Xu X, Ocansey DKW, Pei B, Zhang Y, Wang N, Wang Z and Mao F: Resveratrol alleviates DSS-induced IBD in mice by regulating the intestinal microbiota-macrophage-arginine metabolism axis. Eur J Med Res 28: 319, 2023.
50. Yang H, Wang Y, Jin S, Pang Q, Shan A and Feng X: Dietary resveratrol alleviated lipopolysaccharide-induced ileitis through Nrf2 and NF-κB signalling pathways in ducks (Anas platyrhynchos). J Anim Physiol Anim Nutr (Berl) 106: 1306-1320, 2022.
51. Pan HH, Zhou XX, Ma YY, Pan WS, Zhao F, Yu MS and Liu JQ: Resveratrol alleviates intestinal mucosal barrier dysfunction in dextran sulfate sodium-induced colitis mice by enhancing autophagy. World J Gastroenterol 26: 4945-4959, 2020.
52. Liu L, Gong X, Zhang X, Zhang D, Tang Y, Liu J, Li Y and Pan D: Resveratrol alleviates heat-stress-induced impairment of the jejunal mucosa through TLR4/MAPK signaling pathway in black-boned chicken. Poult Sci 103: 103242, 2024.
53. Song X, Liu L, Peng S, Liu T, Chen Y, Jia R, Zou Y, Li L, Zhao X, Liang X, *et al*: Resveratrol regulates intestinal barrier function in cyclophosphamide-induced immunosuppressed mice. J Sci Food Agric 102: 1205-1215, 2022.
54. Xu X, Tian M, Deng L, Jiang H, Han J, Zhen C, Huang L and Liu W: Structural degradation and uptake of resveratrol-encapsulated liposomes using an in vitro digestion combined with Caco-2 cell absorption model. Food Chem 403: 133943, 2023.
55. Zabihi A, Shabankareh HK, Hajarian H and Foroutanifar S: Resveratrol addition to in vitro maturation and in vitro culture media enhances developmental competence of sheep embryos. Domest Anim Endocrinol 68: 25-31, 2019.
56. Chen LZ, Yao L, Jiao MM, Shi JB, Tan Y, Ruan BF and Liu XH: Novel resveratrol-based flavonol derivatives: Synthesis and anti-inflammatory activity in vitro and in vivo. Eur J Med Chem 175: 114-128, 2019.

57. Kolahdouz Mohammadi R and Arablou T: Resveratrol and endometriosis: In vitro and animal studies and underlying mechanisms (Review). Biomed Pharmacother 91: 220-228, 2017.
58. Gambini J, Inglés M, Olaso G, Lopez-Grueso R, Bonet-Costa V, Gimeno-Mallench L, Mas-Bargues C, Abdelaziz KM, Gomez-Cabrera MC, Vina J and Borras C: Properties of resveratrol: In vitro and in vivo studies about metabolism, bioavailability, and biological effects in animal models and humans. Oxid Med Cell Longev 2015: 837042, 2015.
59. Tariq M, Quddus A, Beshah KH and Mao D: Resveratrol's therapeutic role in heat stress-induced mitochondria and ER dysfunction in animal reproductive health: A review. Anim Reprod Sci 283: 108044, 2025.
60. Springer M and Moco S: Resveratrol and its human metabolites-effects on metabolic health and obesity. Nutrients 11: 143, 2019.
61. Riccio BVF, Spósito L, Carvalho GC, Ferrari PC and Chorilli M: Resveratrol isoforms and conjugates: A review from biosynthesis in plants to elimination from the human body. Arch Pharm (Weinheim) 353: e2000146, 2020.
62. Öztürk E, Arslan AKK, Yerer MB and Bishayee A: Resveratrol and diabetes: A critical review of clinical studies. Biomed Pharmacother 95: 230-234, 2017.
63. Cho S, Namkoong K, Shin M, Park J, Yang E, Ihm J, Thu VT, Kim HK and Han J: Cardiovascular protective effects and clinical applications of resveratrol. J Med Food 20: 323-334, 2017.
64. Samuel VP, Gupta G, Dahiya R, Jain DA, Mishra A and Dua K: Current update on preclinical and clinical studies of resveratrol, a naturally occurring phenolic compound. Crit Rev Eukaryot Gene Expr 29: 529-537, 2019.
65. Ren B, Kwah MX, Liu C, Ma Z, Shanmugam MK, Ding L, Xiang X, Ho PC, Wang L, Ong PS and Goh BC: Resveratrol for cancer therapy: Challenges and future perspectives. Cancer Lett 515: 63-72, 2021.
66. Planas JM, Alfaras I, Colom H and Juan ME: The bioavailability and distribution of trans-resveratrol are constrained by ABC transporters. Arch Biochem Biophys 527: 67-73, 2012.
67. Wang C, Ge F, Ge F, Xu Z and Jiang J: Harnessing stem cell therapeutics in LPS-induced animal models: Mechanisms, efficacies, and future directions. Stem Cell Res Ther 16: 176, 2025.
68. Alverdy JC, Keskey R and Thewissen R: Can the cecal ligation and puncture model be repurposed to better inform therapy in human sepsis? Infect Immun 88: e00942-19, 2020.
69. Gonzalez LM, Moeser AJ and Blikslager AT: Animal models of ischemia-reperfusion-induced intestinal injury: Progress and promise for translational research. Am J Physiol Gastrointest Liver Physiol 308: G63-G75, 2015.
70. Zhan JH, Wei J, Liu YJ, Wang PX and Zhu XY: Sepsis-associated endothelial glycocalyx damage: A review of animal models, clinical evidence, and molecular mechanisms. Int J Biol Macromol 295: 139548, 2025.
71. Zhu L, Yang M, Fan L, Yan Q, Zhang L, Mu P and Lu F: Interaction between resveratrol and SIRT1: Role in neurodegenerative diseases. Naunyn Schmiedebergs Arch Pharmacol 398: 89-101, 2025.
72. Wang N, Mao L, Yang L, Zou J, Liu K, Liu M, Zhang H, Xiao X and Wang K: Resveratrol protects against early polymicrobial sepsis-induced acute kidney injury through inhibiting endoplasmic reticulum stress-activated NF-κB pathway. Oncotarget 8: 36449-36461, 2017.
73. Üstündağ H, Kara A, Doğanay S, Kurt N, Erbaş E, Kalindemirtaş FD and Kariper İA: Molecular mechanisms of resveratrol and its silver nanoparticle conjugate in addressing sepsis-induced lung injury. Naunyn Schmiedebergs Arch Pharmacol 397: 6249-6261, 2024.
74. Wang Y, Wang X, Zhang L and Zhang R: Alleviation of acute lung injury in rats with sepsis by resveratrol via the phosphatidylinositol 3-kinase/nuclear factor-erythroid 2 related factor 2/heme oxygenase-1 (PI3K/Nrf2/HO-1) pathway. Med Sci Monit 24: 3604-3611, 2018.