REVIEW

Anti-Hyperglycemic Agents in the Adjuvant Treatment of Sepsis: Improving Intestinal Barrier Function

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Abstract: Intestinal barrier injury and hyperglycemia are common in patients with sepsis. Bacteria translocation and systemic inflammatory response caused by intestinal barrier injury play a significant role in sepsis occurrence and deterioration, while hyperglycemia is linked to adverse outcomes in sepsis. Previous studies have shown that hyperglycemia is an independent risk factor for intestinal barrier injury. Concurrently, increasing evidence has indicated that some anti-hyperglycemic agents not only improve intestinal barrier function but are also beneficial in managing sepsis-induced organ dysfunction. Therefore, we assume that these agents can block or reduce the severity of sepsis by improving intestinal barrier function. Accordingly, we explicated the connection between sepsis, intestinal barrier, and hyperglycemia, overviewed the evidence on improving intestinal barrier function and alleviating sepsis-induced organ dysfunction by anti-hyperglycemic agents (eg, metformin, peroxisome proliferators activated receptor-γ agonists, berberine, and curcumin), and summarized some common characteristics of these agents to provide a new perspective in the adjuvant treatment of sepsis.

Keywords: sepsis, sepsis-induced organ dysfunction, intestinal barrier, anti-hyperglycemic agents

Summary

Previous study has confirmed that hyperglycemia can independently drive intestinal barrier dysfunction. Since hyperglycemia and intestinal barrier dysfunction commonly exist and are associated with poor prognosis in sepsis, they might be the targets in the management of sepsis. Interestingly, some anti-hyperglycemic agents (eg, metformin, peroxisome proliferators activated receptor-γ agonists, berberine, and curcumin) have shown positive effects beyond controlling hyperglycemia, such as improving intestinal barrier function and resisting sepsis-induced organ dysfunction. With the ability to inhibit systemic inflammatory response and prevent enterogenous infection, agents capable of controlling hyperglycemia and improving intestinal barrier function might be beneficial in the management of sepsis.

Introduction

Sepsis is a series of pathophysiological events caused by uncontrolled reactions to various infections that result in multiple organ dysfunction syndrome (MODS) and even death.[1,2] Nowadays, sepsis has become a huge burden on global health. In 2017, nearly 50 million incident cases of sepsis were recorded, and 11 million sepsis-related deaths were reported, representing about 20% of all global deaths.[3] Noteworthy, sepsis is not a single disease but a syndrome comprising many pathophysiological changes caused by aggravated infectious diseases, and available treatment options beside antibiotics and supportive care are limited because of the heterogeneity of pathogenic factors in sepsis.[4] Therefore, feasible therapy is vital for sepsis management.[5]

Intestinal barrier injury is a common phenomenon in sepsis patients and plays an essential role in sepsis occurrence and deterioration. The intestinal barrier includes a mucosal barrier composed of the intestinal epithelium and secreted mucus, a biological barrier composed of intestinal microbiota, and an immune barrier composed of intestinal immune

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tissues. Normally, the intestinal barrier participates in absorbing nutrients and, meanwhile, prevents bacteria and toxins from crossing the barrier from the intestinal tract to the circulation. However, when the intestinal barrier is impaired, the intestinal permeability of the intestinal contents, such as intestinal bacteria and their metabolites, increases, and some adverse consequences occur.[6] In sepsis, lipopolysaccharide (LPS) generated from intestinal gram-negative bacteria crosses the impaired intestinal barrier and enters the circulation, aggravating the systemic inflammatory response and exacerbating the severity of sepsis.[7–9] Nevertheless, intestinal barrier injury is not only the accelerator but also the initiator of sepsis; therefore, intestinal barrier injury caused by reasons besides sepsis can initiate enterogenous infection and increase the risk of sepsis.[10–12] Consequently, blocking the vicious cycle between intestinal barrier injury and sepsis is a promising strategy for the adjuvant treatment of sepsis.

Another common symptom of sepsis is hyperglycemia. On the one hand, type 2 diabetes mellitus (T2DM) is a cause of pre-existing hyperglycemia, acting as a frequent complication during sepsis. On the other hand, stress-induced hyperglycemia occurs under the severe pathophysiological events of sepsis.[13] Notably, the occurrence of hyperglycemia is closely related to worse outcomes in sepsis.[14] Interestingly, intestinal barrier injury is independently driven by hyperglycemia,[15] and our previous study has further confirmed the relationship between intestinal barrier injury and hyperglycemia in humans.[16] In addition to the negative effects of hyperglycemia on the intestinal barrier and sepsis, some anti-hyperglycemic agents have been proven to protect against intestinal barrier injury[17] and alleviate sepsis-induced organ dysfunction in numerous animal experiments.[18]

Therefore, we assumed that by improving the intestinal barrier function, some anti-hyperglycemic agents could block or reduce the severity of sepsis. Accordingly, we explicated the connection between sepsis, intestinal barrier, and hyperglycemia, overviewed the evidence on improving intestinal barrier function and alleviating sepsis-induced organ dysfunction by anti-hyperglycemic agents (eg, metformin, peroxisome proliferators activated receptor-γ agonists, berberine, and curcumin), and summarized some common characteristics of these agents to provide new a perspective in the adjuvant treatment of sepsis.

Metformin

Metformin is a widely used anti-hyperglycemic agent in the treatment of T2DM. Recently, the intestine has been recognized as a major site of metformin pharmacodynamics.[19] Sum et al have found that peripheral glucose disposal by intravenous metformin infusion was not better than that by normal saline infusion as control, indicating that the anti-hyperglycemic effect of metformin has barely depended on its substance in the circulation.[20] Vancomycin is a broad-spectrum antibiotic, and orally administered vancomycin cannot be absorbed from the intestinal tract[21] but induces drastic and consistent changes in the intestinal microbiota.[22] Kim et al have found that after receiving oral vancomycin, the anti-hyperglycemic effect of metformin was weakened without pharmacokinetics change, while the relative abundance of intestinal microbiota was changed and associated with the anti-hyperglycemic effect. Taken together, the effect of metformin is more likely to depend on the improvement of intestinal microbiota but not on the concentration of metformin in circulation.[23] Given the close relationship between intestinal microbiota and intestinal barrier,[24,25] metformin can provide benefits by improving intestinal barrier function. Moreover, metformin can prevent sepsis-induced organ dysfunction with the effects of reducing reactive oxygen species and pro-inflammatory cytokines, inhibiting the activation of transcription factors related to inflammation, decreasing neutrophil accumulation and infiltration, and maintaining mitochondrial membrane potential.[26]

The main pharmacological effect of metformin is the activation of adenosine monophosphate-activated protein kinase (AMPK), and previous studies have demonstrated that AMPK is vital for intestinal barrier function.[27] Wu et al have found that LPS decreased the expression of tight junction (TJ) proteins, causing the pro-inflammatory response, oxidative stress, and intestinal barrier damage in mice, and those effects were attenuated by metformin through the activation of AMPK.[28] Since C-Jun N-terminal kinase (JNK) is involved in the disruption of the intestinal barrier, Deng et al have found that metformin prevents intestinal barrier dysfunction by inhibiting the activation of JNK through an AMPK-dependent signaling pathway in Caco-2 cell monolayers, colitis mice models, and ulcerative colitis patients.[29]

Besides AMPK, metformin improves the intestinal barrier function through other mechanisms. Mucin 2 is the main glycoprotein constituting the intestinal mucosal layer. Ke et al have found that metformin restored intestinal barrier

function by increasing the expression of mucin 2 in mice with ulcerative colitis induced by dextran sulfate sodium (DSS).[30] Myosin light-chain kinase (MLCK) is an enzyme activating the myosin light chain (MLC) and participating in cytoskeleton contraction and TJ regulation. Zhu et al have demonstrated that metformin stabilizes TJ proteins and improves intestinal barrier function by inhibiting the MLCK-MLC signaling pathway in Caco-2 cell monolayers.[31] Li et al have found that metformin protects the intestinal barrier function by normalizing the interaction between claudin-4 and zonula occludens (ZO) −1 and preventing the distribution of claudin-4 in rats with irritable bowel syndrome.[32] Recently, an increasing number of studies have focused on the relationship between metformin and intestinal microbiota, and Zhang et al have summarized that metformin was capable of improving intestinal barrier function by maintaining intestinal microbiota homeostasis.[33]

Given the advantages of intestinal barrier improvement, metformin can theoretically contribute to the management of sepsis. Clinical research has shown that metformin exposure is associated with decreased morbidity and mortality in patients with sepsis and pre-existing hyperglycemia.[34–36] Studies on sepsis models have also shown that metformin could prevent sepsis-induced organ dysfunction, and the specific efficacy and associated mechanisms are summarized in Table 1.[37–51] Surprisingly, Malik et al have found that metformin provides antimicrobial benefits in various infections in vitro and in vivo,[52] fundamentally preventing the occurrence and deterioration of sepsis. In conclusion, metformin might provide benefits in the adjuvant treatment of sepsis by improving intestinal barrier function. And the application of metformin in sepsis needs further clinical investigation.

Peroxisome Proliferators Activated Receptor-γ (PPAR-γ) Agonists

PPAR-γ agonists are another class of anti-hyperglycemic agents. As the name implies, PPAR-γ agonists act by increasing the activity of PPAR-γ.[53] PPAR-γ is abundantly expressed in intestinal epithelial cells,[54] and its activation can alleviate intestinal barrier injury.[55,56] Zhao et al have found that rosiglitazone effectively promoted the intestinal mucus integrity and prevented the intestinal barrier injury via an MLCK-dependent mechanism in chronic colitis mice.[57]

Considering the relationship between intestinal barrier injury and sepsis, PPAR-γ agonists with positive effects on the intestinal barrier can make a difference in the management of sepsis. Shih et al have found in a nested case–control study that PPAR-γ agonist exposure was associated with a decreased risk of sepsis in patients with pre-existing hyperglycemia.[58] Hsieh et al have shown in a propensity score matching observational study that over 4-week use of pioglitazone within three months was associated with decreased mortality in patients with sepsis and T2DM.[59] As early as 2004, Fink et al proposed that PPAR-γ agonists could be useful for adjuvant treatment of sepsis and MODS.[60] Li et al have described the role of PPAR-γ in the regulation of inflammatory response and emphasized the potential efficacy of PPAR-γ agonists as a novel therapeutic option in sepsis.[61] Many studies on sepsis models have also shown the positive effects of PPAR-γ agonists (rosiglitazone and pioglitazone) on sepsis-induced organ dysfunction, and the specific efficacy and associated mechanisms are summarized in Table 2.[62–74] Given the protective effects of PPAR-γ agonists on the intestinal barrier and sepsis, the corresponding clinical research is in progress,[75] and whether PPAR-γ agonists improve the prognosis of sepsis will be answered in the future.

Berberine

Berberine, isolated from traditional Chinese medicine, has been used to treat intestinal inflammation for decades. Recent studies have shown the therapeutic ability of berberine in many parenteral diseases.[76] Zhang et al have found in a randomized, double-blind, placebo-controlled trial that berberine significantly reduced glycosylated hemoglobin C and improved hyperglycemia in newly diagnosed T2DM patients.[77] Additionally, meta-analyses have indicated that berberine could be used as an anti-hyperglycemic agent in the treatment of T2DM.[78,79]

Until now, berberine has been proved to improve intestinal barrier function in many intestinal diseases. Xiong et al have overviewed previous studies and concluded that berberine repairs intestinal barrier injury by promoting differentiation of intestinal stem cells through identifying bitter taste receptors on Tuft cells in ulcerative colitis.[80] Li et al have demonstrated that berberine restores the intestinal barrier homeostasis, maintains the residence of enteric glial cells, suppresses inflammatory cell infiltrations, and attenuates the overactivation of immune cells in mice with DSS-induced ulcerative colitis.[81] Jing et al have found that berberine improves intestinal barrier function by regulating intestinal

Table 1 Beneficial Effects of Metformin on Sepsis-Induced Organ Dysfunction

Organs	Models; Methods	Results	Associated Mechanisms	References
Heart	Rats; LPS	Metformin inhibited the local innate immune responses in the isolated heart.	Activating AMPK and suppressing TLR 4-related pathway.	[48]
	Mice; LPS	Metformin reversed the histological abnormalities of the heart and the elevation of myeloperoxidase, CK-MB, and BNP.	Activating AMPK-dependent anti-inflammatory mechanism.	[44]
	Mice; LPS	Metformin rescued myocardial function.	Supporting metabolic activity and allowing efficient energy utilization.	[47]
	Zebrafish; *E. coli*	Metformin reduced heart congestion and swelling, increased heart rate, and decreased mortality.	Inhibiting inflammatory response.	[50]
	Mice; *E. coli*	Metformin prolonged life span.	Promoting the combination of PKCε with IRF4 at mitochondrial microdomain.	[43]
Lung	Rats; LPS	Metformin reduced BALF protein and lung wet/dry ratio and inhibited the infiltration of neutrophils and macrophages.	Alleviating capillary injury and promoting AMPK-α1 expression.	[51]
	Rats; LPS	Metformin attenuated congestion and inflammatory cell infiltration of the alveolar walls.	Resisting TLR4 activation and upregulating AMPK.	[49]
	Mice; CLP	Metformin assisted in the clearance of damaged mitochondria and the killing of bacteria.	Activating Parkin-independent autophagy by AMPK.	[39]
	Mice; LP/hemorrhage and resuscitation	Metformin alleviated lung injury and prevented immunosuppression.	Improving the cross-talk between the AMPK and GSK3β pathways.	[45]
Liver	Rats; LPS/Partial hepatectomy	Metformin blunted hepatic damage and improved coagulation function.	Decreasing proinflammatory and controlling hemostatic responses.	[38]
	Rats; LPS/D-GalN	Metformin protected liver function.	Regulating ADMA metabolism.	[37]
Kidney	Mice; CLP	Metformin protected against kidney tubule epithelial cells injury and improved survival.	Restoring mitochondrial function and metabolic fitness via Sirt3 signaling.	[42]
Brain	Rats; CLP	Metformin improved BBB function and attenuated brain injury.	Inhibiting inflammation and increasing expression of TJ proteins.	[40]
	Mice; CLP	Metformin improved survival, cognitive function, and BBB and decreased brain edema and neuronal apoptosis.	Activating PI3K/Akt pathway.	[46]
Intestine	Mice; Temporary occlusion of superior mesenteric artery	Metformin protected barrier function and reduced oxidative stress and inflammatory response.	Preserving cell pyroptosis via the TXNIP-NLRP3-GSDMD pathway.	[41]

Abbreviations: LPS, lipopolysaccharides; AMPK, adenosine monophosphate-activated protein kinase; TLR, toll-like receptor; CK-MB, creatinine kinase-myocardial band; BNP, brain natriuretic peptide; *E. coli, Escherichia coli*; PKCε, protein kinase C epsilon; IRF4, interferon regulatory factor 4; BALF, bronchoalveolar lavage fluid; CLP, cecal ligation and puncture; GSK3β, glycogen synthase kinase 3β; D-GalN, D-galactosamine; ADMA, asymmetric dimethylarginine; TJ, tight junction; BBB, blood-brain barrier; PI3K, phosphatidylinositol 3-kinases; AKT, also known as PKB, protein kinase B; TXNIP, thioredoxin-interacting protein; NLRP3, Nod-like receptor thermoprotein domain 3; GSDMD, gasdermin D.

microbiota-associated tryptophan metabolite and activating the aryl hydrocarbon receptor in rats with DSS-induced colitis.[82] Zhang et al have shown that berberine improves intestinal barrier function by promoting anti-inflammatory and antioxidative stress responses in mice with DSS-induced colitis.[83] Considering that A20, a ubiquitin-modifying enzyme, can protect cells from necroptosis,[84] Hou et al have found that berberine protected intestinal epithelial TJ and repaired

Table 2 Beneficial Effects of PPAR-γ Agonists on Sepsis-Induced Organ Dysfunction

Organs	Models; Methods	Results	Associated Mechanisms	References
Heart	Mice; LPS	Rosiglitazone protected cardiac function and improved survival.	Increasing fatty acid oxidation and preventing mitochondria reduction.	[66]
	Rats; CLP	Rosiglitazone improved myocardial tissue morphology.	Inhibiting cell apoptosis and TNF-α expression by NF-κB pathway.	[74]
	Rats; CLP	Rosiglitazone protected against cardiac dysfunction and improved survival.	Reducing pro-inflammatory cytokines, apoptosis, and necroptosis.	[72]
Lung	Mice; LPS	Rosiglitazone attenuated acute lung injury.	Downregulating HMGB1-RAGE pathway.	[73]
	Mice; CLP	Pioglitazone reduced inflammatory response.	Inhibiting the NF-κB pathway.	[68]
	Mice; CLP	Pioglitazone prevented lung injury.	Retaining anti-inflammatory status of visceral adipose tissue.	[69]
Liver	Rats; CLP	Rosiglitazone protected against acute liver injury.	Reducing inflammatory response.	[64]
Kidney	Rats; CLP	Rosiglitazone reduced kidney injury.	Reducing inflammatory response and decreasing apoptosis.	[65]
	Mice; LPS	Rosiglitazone decreased the elevated levels of blood urea nitrogen and creatinine.	Inhibiting NF-κB pathway and reducing the expression of ICAM-1 and VCAM-1 in renal tubular epithelial cells.	[70]
Brain	Rats; CLP	Rosiglitazone alleviated long-term cognitive impairment.	Ameliorating mitochondrial function.	[71]
	Mice; CLP	Rosiglitazone protected against microvascular dysfunction.	Increasing functional capillary density and decreasing leukocyte rolling and adhesion.	[63]
Intestine	Rats; CLP	Pioglitazone minimized indicators of intestinal injury and improved survival.	Maintaining intestinal barrier integrity.	[67]
Immunity	Mice; CLP	Rosiglitazone regulated inflammatory response, increased bacteria clearance, and improved clinical status and mortality.	Activating PPAR-γ and promoting the formation of NET.	[62]

Abbreviations: PPAR-γ, peroxisome proliferators activated receptor-γ; LPS, lipopolysaccharides; CLP, cecal ligation and puncture; TNF-α, tumor necrosis factor-α; NF-κB, nuclear factor-κB; HMGB1, high mobility group box 1; RAGE, advanced glycation end-product receptor; ICAM-1, intercellular adhesion molecule-1; VCAM-1, vascular cell adhesion molecule-1; NET, neutrophil extracellular trap.

intestinal barrier injury by increasing the expression of A20 in mice with diarrhea-predominant irritable bowel syndrome.[85]

Moreover, the protective effects of berberine on the intestinal barrier have also been confirmed in other diseases. Gong et al have found in T2DM rats that the anti-hyperglycemic effect of berberine might be attributed to the improvement of intestinal barrier function.[86] Shan et al have shown in T2DM rats that berberine effectively repairs the damaged intestinal mucosa, restores intestinal permeability, and improves endotoxemia.[87] Zhang et al have demonstrated in mice with renal failure and long-term peritoneal dialysis that berberine alleviates intestinal barrier dysfunction by increasing TJ and adhesion junction proteins, improving the morphology of microvilli, and promoting cell migration.[88] Yu et al have found in rats with uremia induced by the 5/6 kidney resection that berberine prevents intestinal barrier injury through antioxidant effect.[89] Li et al have demonstrated in mice with nonalcoholic fatty liver disease that berberine restores liver function by ameliorating intestinal barrier function.[90] Liang et al have found in rats with severe acute pancreatitis that berberine improves the intestinal barrier function and maintains the intestinal membrane permeability by inhibiting MLC phosphorylation.[91] Yu et al have shown in blunt snout bream that berberine alleviates intestinal barrier injury by inhibiting pro-inflammatory response and modulating intestinal microbiota.[92]

Despite the positive effects of berberine in different diseases, the bioavailability of berberine is unexpectedly low; in other words, berberine either plays biological roles through its metabolites[93] or through the positive effects on intestinal microbiota and intestinal barrier.[94,95] Furthermore, all those benefits generated from the improvement of intestinal barrier function suggest that berberine could be a candidate for the adjuvant treatment of sepsis. Additionally, increasing evidence has indicated that berberine could resist sepsis-induced organ dysfunction, and the specific efficacy and associated mechanisms are shown in Table 3.[96–111] However, the effects of berberine in patients with sepsis need to be investigated in the future.

Curcumin

Curcumin, an active component in turmeric, is used as spice, seasoning, and pigment in daily life. Due to its anti-inflammatory effect, curcumin has displayed treatment potential in various pro-inflammatory chronic diseases.[112] Recent studies have found that curcumin shows an anti-hyperglycemic effect by decreasing insulin resistance, preventing β-cell

Table 3 Beneficial Effects of Berberine on Sepsis-Induced Organ Dysfunction

Organs	Models; Methods	Results	Associated Mechanisms	References
Heart	Rats; LPS	Berberine attenuated heart injury and cardiomyocyte swelling.	Inhibiting TLR4/NF-κB signaling.	[109]
	Mice; LPS	Berberine protected against myocardial dysfunction.	Inhibiting cardiac I-κBα phosphorylation and apoptosis.	[110]
Lung	Mice; LPS/ D-GalN	Berberine attenuated lung injury and improved survival.	Inhibiting NF-κB and IL-6 mediated STAT3 activation.	[108]
	Mice; LPS	Berberine reduced lung edema, neutrophil infiltration, and histopathological alterations.	Inhibiting TNF-α production and cytosolic phospholipase A2 expression.	[111]
Liver	Rats; CLP	Berberine ameliorated liver function.	Rectifying glycolysis and nucleic acid metabolism.	[104]
Kidney	Mice; CLP	Berberine improved renal function and rescued histological injury.	Regulating metabolism via different signaling pathways.	[102]
Brain	Mice; CLP	Berberine alleviated cognitive impairment.	Blocking HMGB1/RAGE Signaling.	[100]
Intestine	Rats; CLP	Berberine improved compromised GVB.	Modulating the ApoM/S1P pathway.	[106]
	Rats; CLP	Berberine protected against GVB dysfunction.	Regulating the Wnt/beta-catenin signaling pathway.	[97]
	Rats; CLP	Berberine attenuated tissue injury and intestinal barrier dysfunction.	Modulating the TLRs pathway.	[105]
	Rats; LPS	Berberine alleviated intestinal injury and mucosal hypoplasia.	Normalizing glutamine transport and glutaminase activity.	[99]
	Rats; LPS	Berberine improved the expression of TJ proteins.	Activating IGF-1/IGFBP-3 signaling.	[98]
	LPS Rats;	Berberine inhibited inducible COX-2 overexpression.	Activating PPAR-γ.	[101]
	Mice; LPS	Berberine attenuated TJ disruption.	Downregulating the NF-κB and MLCK pathway.	[103]
	Mice; LPS	Berberine protected against intestinal injury.	Reducing enterocyte apoptosis and neutrophil infiltration and inhibiting the TLR4/NF-κB/MIP-2 pathway.	[96]
Immunity	Mice; *E. coli*	Berberine enhanced the efficacy of antibiotics and improved survival.	Inducing immunological alterations.	[107]

Abbreviations: LPS, lipopolysaccharides; TLR, toll-like receptor; NF-κB, nuclear factor-κB; D-GalN, D-galactosamine; IL, interleukin; STAT3, signal transducer and activator of transcription 3; TNF-α, tumor necrosis factor-α; CLP, cecal ligation and puncture; HMGB1, high mobility group box 1; RAGE, advanced glycation end-product receptor; GVB, gut-vascular barrier; ApoM, apolipoprotein M; S1P, sphingosine-1-phosphate; TJ, tight junction; IGF-1, insulin-like growth factor I; IGFBP-3, insulin-like growth factor binding protein 3; COX-2, cyclooxygenase-2; PPAR-γ, peroxisome proliferators activated receptor-γ; MLCK, myosin light chain kinase; MIP-2, macrophage inflammatory protein-2; *E. coli, Escherichia coli.*

death, and improving β-cell functions.[113] Huang et al have found in T2DM rats that curcumin could ameliorate hyperglycemia and alleviate metabolic endotoxemia, intestinal microbiota imbalance, and intestinal barrier injury.[114]

The protective effects of curcumin on the intestinal barrier have also been confirmed in many other studies. Burge et al have summarized how curcumin alleviated intestinal barrier injury by inhibiting bacteria, modulating immunity, and regulating intestinal microbiota.[115] In the studies on Caco-2 cell monolayers, Wang et al have found that curcumin prevents epithelial barrier damage and TJ disruption via upregulating the expression of heme oxygenase-1.[116] Zhou et al have shown that curcumin improves intestinal barrier integrity by controlling endoplasmic reticulum stress and subsequent apoptosis.[117] Tian et al have found that curcumin maintains the intestinal permeability and restores epithelial structure by enhancing ZO-1 protein expression through tumor necrosis factor (TNF)-α-related pathway in rats with intestinal ischemia-reperfusion injury.[118] Cao et al have unveiled that curcumin enhanced intestinal barrier and mitochondrial function by Parkin-dependent mitophagy through AMPK activation and subsequent nuclear translocation of transcription factor EB in vitro and in pigs with oxidative stress.[119]

Similar to berberine with low bioavailability, orally administered curcumin cannot be detected in the circulation; as a result, any biological effects of curcumin beyond the intestine are the subsequent results from the intestine.[120,121] In other words, all those beneficial effects of curcumin under such a low bioavailability are partly attributed to the improvement of intestinal barrier function.[122,123] Considering sepsis, curcumin has shown its therapeutic potential with the ability to inhibit inflammation, reduce oxidative coagulation factors, and regulate the immune response.[124] Many studies have proven that curcumin could prevent sepsis-induced organ dysfunction, and the specific efficacy and associated mechanisms are shown in Table 4.[125–139] Besides, Siddiqui et al have found that the anti-inflammatory effect of curcumin is mediated by the upregulation of PPAR-γ in sepsis rats, while PPAR-γ was the target of another class of anti-hyperglycemic agents.[140] Generally, curcumin might assist the management of sepsis by improving intestinal barrier function and a series of positive effects generated by the improvement of the intestinal barrier. Whether curcumin can improve the prognosis of sepsis patients will be answered in the future.

Other Anti-Hyperglycemic Agents

Besides these four above-mentioned agents, some other anti-hyperglycemic agents have displayed positive effects on sepsis. Insulin is the most commonly used anti-hyperglycemic agent in sepsis. In animals with sepsis, insulin treatment improves organ dysfunction through different mechanisms (Table 5).[141–144] However, whether insulin improves the intestinal barrier function needs further investigation. Glucagon-like peptide-1 (GLP-1) receptor agonists are another

Table 4 Beneficial Effects of Curcumin on Sepsis-Induced Organ Dysfunction

Organs	Models; Methods	Results	Associated Mechanisms	References
Heart	Rats; CLP	Curcumin enhanced myocardial contractility and restored ejection fraction and fractional shortening.	Alleviating inflammation and structural damage of myocardial cells.	[135]
Aorta	Rats; LPS	Curcumin restored vasoconstrictive function and alleviated the damage in the intima and media of the aorta.	Inhibiting TSP-1 and TGF-β1 expression.	[130]
Lung	Rats; CLP Rats; CLP Rats; CLP Mice; CLP Mice; LPS	Curcumin protected against acute lung injury. Curcumin presented antioxidant and anti-inflammatory effects. Curcumin protected against acute lung injury and improved survival. Curcumin alleviated inflammatory injury. Curcumin protected against acute lung injury.	Inhibiting the TGF-β1/Smad3 pathway. Enhancing antioxidant enzymes, reducing free radicals and iNOS. Inhibiting the infiltration of inflammatory cells and the generation of ROS and regulating cytokines. Enhancing the suppressive function of Tregs. Enhancing antioxidant effect.	[134] [126] [133] [125] [129]

(*Continued*)

Table 4 (Continued).

Organs	Models; Methods	Results	Associated Mechanisms	References
Liver	Rats; CLP Mice; LPS	Curcumin protected liver function. Curcumin attenuated liver injury.	Inhibiting inflammatory response and apoptosis. Suppressing oxidative stress-related inflammation through the PI3K/AKT and NF-κB signaling pathways.	[136] [138]
Kidney	Rats; CLP Mice; CLP Mice; CLP Mice; LPS	Curcumin protected against acute kidney injury. Curcumin alleviated inflammatory injury to the kidney. Curcumin protected kidney function. Curcumin decreased serum levels of blood urea nitrogen, creatinine, and cystatin C and reduced kidney injury.	Improving renal microcirculatory perfusion and reducing the inflammatory response. Enhancing the suppressive function of Tregs. Attenuating inflammation and apoptosis via the NF-κB and JAK2/STAT3 signaling pathways. Inhibiting the JNK/NF-κB pathway through suppression of lncRNA PVT1.	[132] [125] [139] [128]
Brain	Mice; CLP Mice; CLP	Curcumin ameliorated BBB and improved survival. Curcumin attenuated brain edema, enhanced BBB integrity, and improved survival.	Modulating leukocyte and platelet adhesion in cerebral microcirculation and attenuating P-selectin expression. Inhibiting apoptosis and attenuating mitochondrial dysfunction.	[131] [137]
Intestine	Rats; CLP	Curcumin protected the intestinal mucosal barrier.	Inhibiting apoptosis.	[127]

Abbreviations: CLP, cecal ligation and puncture; LPS, lipopolysaccharides; TSP-1, thrombospondin-1; TGF-β1, transforming growth factor-β1; iNOS, inducible nitric oxide synthase; ROS, reactive oxygen species; PI3K, phosphatidylinositol 3-kinases; AKT, also known as PKB, protein kinase B; NF-κB, nuclear factor-κB; JAK2, Janus kinase 2; STAT3, signal transducer and activator of transcription 3; JNK, C-Jun N-terminal kinase; lncRNA, long non-coding RNA; BBB, blood-brain barrier.

Table 5 Beneficial Effects of Insulin and SGLT2 Inhibitors on Sepsis-Induced Organ Dysfunction

Agents	Organs	Models; Methods	Results	Associated Mechanisms	References
Insulin	Heart	Rats; LPS	Insulin alleviated myocardial dysfunction and improved survival.	Attenuating cell apoptosis and stimulating UCP2 expression.	[142]
	Liver, Kidney	Rats; LPS/ *Staphylococcus aureus* peptidoglycan	Insulin normalized serum indicators of organ injury.	Inhibiting the activity of glycogen synthase kinase-3β.	[141]
	Muscle	Rabbits; Scald/LPS	Insulin alleviated hyperproteolysis of skeletal muscle.	Inhibiting the activity of the ubiquitin system.	[143]
	Intestine	Rats; CLP	Insulin improved intestinal microcirculatory.	Improving prostacyclin/thromboxane system and inhibiting the expression of platelet-activating factor.	[144]
SGLT2 inhibitors	Kidney	Mice; LPS	Empagliflozin reduced acute renal injury and improved survival.	Reducing systemic and renal inflammation.	[150]
	Lung	Mice; LPS	Canagliflozin alleviated lung inflammation.	Attenuating cytokine storm and reducing inflammation.	[151]
	Blood vessel	Mice; LPS	Canagliflozin protected against sepsis capillary leak syndrome.	Acting on the α1AMPK-dependent pathway.	[152]

Abbreviations: SGLT2, sodium-glucose cotransporter-2; LPS, lipopolysaccharides; UCP2, uncoupling protein 2; CLP, cecal ligation and puncture; AMPK, adenosine monophosphate-activated protein kinase.

class of anti-hyperglycemic agents. While the critical role of GLP-1 in the intestinal barrier has been gradually recognized,[145] the possible application of GLP-1 receptor agonists in sepsis has been well reviewed by Yang.[146] Sodium-glucose cotransporter-2 (SGLT2) inhibitors, a new class of anti-hyperglycemic agents, play the anti-hyperglycemic effect by increasing urinary glucose excretion. Some SGLT2 inhibitors have shown positive effects on the intestinal barrier. Zaghloul has found that empagliflozin ameliorated acetic acid-induced intestinal barrier injury in rats via modulation of the SIRT-1/PI3K/AKT pathway.[147] Nozu has demonstrated that ipragliflozin improves intestinal hyperpermeability in rats with irritable bowel syndrome.[148] Preventive effects of dapagliflozin on sepsis-induced organ damage have also been confirmed in rats.[149] The specific effects of SGLT2 inhibitors (empagliflozin and canagliflozin) on sepsis-induced organ dysfunction and the associated mechanisms are displayed in Table 5.[150–152] However, whether the positive effects of GLP-1 receptor agonists and SGLT2 inhibitors on sepsis are associated with intestinal barrier improvement requires further investigation, and the efficacy of these anti-hyperglycemic agents in sepsis patients will be evaluated in the future.

Discussion

Previous studies have proven a connection between sepsis, intestinal barrier, and hyperglycemia. Blocking the vicious cycle of this connection is expected to become a promising strategy for sepsis management.

Although hyperglycemia control can improve the prognosis of infectious diseases,[153–155] most clinical studies have not proven the advantages of intensive glycemic control in sepsis. Moreover, intensive glycemic control increases the risk of hypoglycemia, which is associated with worse outcomes in sepsis.[18] This contradiction forced us to make a compromise and set the goal of glycemic control at a relatively high level.[156] However, the optimal goal of glycemic control in sepsis is still a pending issue. Noteworthy, the deleterious consequences of hyperglycemia are not limited to themselves but also to a series of subsequent pathophysiological results; hence, hyperglycemia can induce intestinal barrier injury, increase intestinal permeability, cause intestinal microbiota imbalance, lead to intestinal mucosal immune disorder, and increase the susceptibility to infection and the risk of sepsis. Therefore, the benefits beyond the anti-hyperglycemic effect would bring advantages to sepsis management.[157]

The significance of intestinal barrier improvement among these benefits is highlighted by some characteristics of these anti-hyperglycemic agents. First, the effect of metformin does not depend on its concentration in the circulation, leaving the intestinal barrier the possible target to act on. Second, PPAR-γ is abundantly expressed in the intestinal epithelial cells, making the intestinal barrier the first target influenced by PPAR-γ agonists. Third, the bioavailability of berberine and curcumin is extremely low; thus, benefits generated by these agents are attributed to their effects on the intestinal barrier. Interestingly, both berberine and curcumin are isolated from a natural plant, and their positive effects on the intestinal barrier can partly explain how some traditional Chinese medicine work without finding a specific bioactive factor in the circulation.[158]

In this review, we overviewed the evidence that anti-hyperglycemic agents (eg, metformin, PPAR-γ agonists, berberine, and curcumin) protect against sepsis-induced organ dysfunction by alleviating intestinal barrier injury. However, clinical evidence is limited. In further studies, the efficacy, safety, and adverse effects of these agents need to be evaluated, and whether these agents improve the outcomes in patients with sepsis should be answered. Additionally, we suggested that other agents capable of controlling hyperglycemia and improving the intestinal barrier might be candidates for sepsis management.

Abbreviations

ADMA, asymmetric dimethylarginine; AKT, also known as PKB, protein kinase B; AMPK, adenosine monophosphate-activated protein kinase; ApoM, apolipoprotein M; BALF, bronchoalveolar lavage fluid; BBB, blood-brain barrier; BNP, brain natriuretic peptide; CK-MB, creatinine kinase-myocardial band; CLP, cecal ligation and puncture; COX-2, cyclooxygenase-2; D-GalN, D-galactosamine; DSS, dextran sulfate sodium; *E. coli, Escherichia coli;* GLP-1, gluca-gon-like peptide-1; GSDMD, gasdermin D; GSK3β, glycogen synthase kinase 3β; GVB, gut-vascular barrier; HMGB1, high mobility group box 1; ICAM-1, intercellular adhesion molecule-1; IGF-1, insulin-like growth factor I; IGFBP-3, insulin-like growth factor-binding protein 3; IL, interleukin; iNOS, inducible nitric oxide synthase; IRF4, interferon regulatory factor 4; JAK2, Janus kinase 2; JNK, C-Jun N-terminal kinase; lncRNA, long non-coding RNA; LPS,

lipopolysaccharide; MIP-2, macrophage inflammatory protein-2; MLC, myosin light chain; MLCK, myosin light-chain kinase; MODS, multiple organ dysfunction syndrome; NET, neutrophil extracellular trap; NF-κB, nuclear factor-κB; NLRP3, Nod-like receptor thermoprotein domain 3; PI3K, phosphatidylinositol 3-kinases; PKCε, protein kinase C epsilon; PPAR-γ, peroxisome proliferators activated receptor-γ; RAGE, advanced glycation end product receptor; ROS, reactive oxygen species; S1P, sphingosine-1-phosphate; SGLT2, sodium-glucose cotransporter-2; STAT3, signal transducer and activator of transcription 3; T2DM, type 2 diabetes mellitus; TGF-β1, transforming growth factor-β1; TJ, tight junction; TLR, toll-like receptor; TNF-α, tumor necrosis factor-α; TSP-1, thrombospondin-1; TXNIP, thioredoxin-interacting protein; UCP2, uncoupling protein 2; VCAM-1, vascular cell adhesion molecule-1; ZO, zonula occludens.

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Disclosure

The authors report no conflicts of interest in this work.

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