

## Therapeutic potential of butyrate supplementation in sepsis: a review of preclinical evidence and translational perspectives

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### ABSTRACT

Sepsis remains a major global health problem and is responsible for millions of deaths annually despite significant progress in antimicrobial therapy and organ support. Increasing evidence highlights the role of the gut-immune axis in shaping host responses during sepsis, with particular interest in microbiota-derived metabolites such as short-chain fatty acids (SCFAs). Among these, butyrate has emerged as a promising candidate due to its anti-inflammatory, immunomodulatory, and intestinal barrier-preserving properties. This narrative review summarizes current evidence regarding the biological activities of butyrate and its potential therapeutic relevance in sepsis and septic shock.

A comprehensive literature search of PubMed and additional sources up to April 2025 identified experimental and clinical studies evaluating butyrate supplementation in sepsis. Preclinical studies show that butyrate improves function across organ systems (neurologic, hepatic, intestinal, cardiac, pulmonary, and renal) mainly by reducing inflammation, oxidative stress, and epithelial barrier disruption. In models like cecal ligation and puncture (CLP) or endotoxemia, survival improved by 20–40 % with butyrate administration. Human data are limited: an observational study found higher circulating  $\beta$ -hydroxybutyrate levels in sepsis survivors, while a randomized trial reported fewer gastrointestinal complications and ventilator-associated pneumonia in patients with synbiotic-induced butyrate increases.

Overall, current evidence suggests that butyrate may modulate key pathophysiological pathways in sepsis and holds potential as an adjunctive therapy. Nonetheless, dedicated early-phase clinical trials are required to clarify safety, optimal dosing, pharmacodynamics, and clinical effectiveness.

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## 1. Introduction

### 1.1. Sepsis

#### 1.1.1. Sepsis definition

Sepsis is a critical global health concern, presenting significant challenges in clinical management and healthcare costs. Approximately 48.9 million cases of sepsis occurred in 2017, with 11 million sepsis-related deaths, accounting for 19.7 % of all global mortality (Rudd et al., 2020). The definition of sepsis has evolved over time. According to the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3), published in 2016, sepsis is defined as a life-threatening organ dysfunction resulting from a dysregulated host response to infection (Singer et al., 2016). This revised definition replaced the one established by the 2001 multi-society International Sepsis Definitions Conference, which characterized sepsis as a syndrome involving both infection and a systemic inflammatory response (Levy et al., 2003). Despite significant efforts made so far to understand the pathogenesis and to develop new antibiotic or supportive strategies, sepsis mortality rate remains high. Therefore, sepsis remains a major public health priority, necessitating continuous research efforts to develop more effective prevention strategies and new therapeutic approaches (Sepsis, WHO, 2023).

One of the most promising research areas related to this field is the role of gut microbiota, particularly its metabolites, short-chain fatty acids (SCFAs). These are increasingly recognized both as potential contributors to sepsis development and progression, and as targets for novel therapeutic interventions.

#### 1.1.2. Sepsis pathophysiology

The pathobiology of sepsis is shaped by the simultaneous presence of uncontrolled inflammation, immune suppression, and metabolic failure. Upon recognition of pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) through toll-like receptors (TLRs), innate immune cells initiate a potent inflammatory cascade involving activation of the transcription factor nuclear factor- $\kappa$ B (NF $\kappa$ B) and release of proinflammatory cytokines. Activated neutrophils also release neutrophil extracellular traps (NETs), webs of DNA and granule proteins that immobilize pathogens but contribute to endothelial injury and microvascular thrombosis. These processes drive endothelial damage, capillary leak, and impaired tissue perfusion (Jarczak et al., 2021; Meyer and Prescott, 2024).

In parallel, sepsis induces profound immunosuppression, characterized by reduced expression of the antigen-presenting molecule human leukocyte antigen DR (HLA-DR) on circulating monocytes, apoptosis-driven lymphopenia, and expansion of regulatory T cells, all of which weaken the host's ability to control infection. This combination of hyperinflammation and immunosuppression is a hallmark of sepsis and contributes to the heterogeneity of clinical presentation (Jarczak et al., 2021; Meyer and Prescott, 2024).

Increasing evidence highlights endoplasmic reticulum (ER) stress as a central and unifying component of this dysregulated host response. During infection-induced hypoxia, oxidative stress, and high metabolic demand, the ER accumulates misfolded proteins and activates the unfolded protein response. Although initially adaptive, persistent activation of the protein kinase R-like ER kinase (PERK)-activating transcription factor 4 (ATF4)-C/EBP homologous protein (CHOP) pathway shifts the unfolded protein response toward a pro-apoptotic program. CHOP, in particular, amplifies inflammatory responses and contributes to organ dysfunction. Its pathogenic role in sepsis has been demonstrated in murine cecal ligation and puncture (CLP) models, where CHOP deficiency markedly improved survival, reduced apoptosis and inflammatory cytokines, and enhanced bacterial clearance (Ferlito et al., 2014).

#### 1.1.3. Sepsis and gut microbiota

The human microbiota is a complex ecosystem consisting of trillions of diverse bacterial species (Giuffrè et al., 2020). Notably, the gastrointestinal tract contains the largest and most varied communities, which perform crucial physiological functions and enhance the host's health (Sender et al., 2016). The composition of the intestinal microbiome is significantly affected by sepsis, which may subsequently precipitate the emergence of organ failure (Haak and Wiersinga, 2017). Dynamic alterations in the gut microbiota of intensive care unit (ICU) patients have been reported by (Zaborin et al., 2014; Ojima et al., 2016), who observed a marked reduction in bacterial taxa responsible for SCFAs production, leading to significantly decreased levels of these metabolites within the gastrointestinal tract. Multiple factors contribute to microbiota modification in sepsis, including hypoxic damage, inflammatory responses, alterations in intestinal motility, and variations in intraluminal pH. Additionally, the use of vasopressors, proton-pump inhibitors, opioids, parenteral and enteral nutritional support, as well as compromised epithelial integrity, may further influence microbial composition (Dickson, 2016). Furthermore, the empirical administration of antibiotics targeting anaerobic bacteria has been correlated with an increased 30-day mortality rate among mechanically ventilated sepsis patients and those treated in emergency departments (Kullberg et al., 2025).

### 1.2. Butyrate

#### 1.2.1. SCFAs

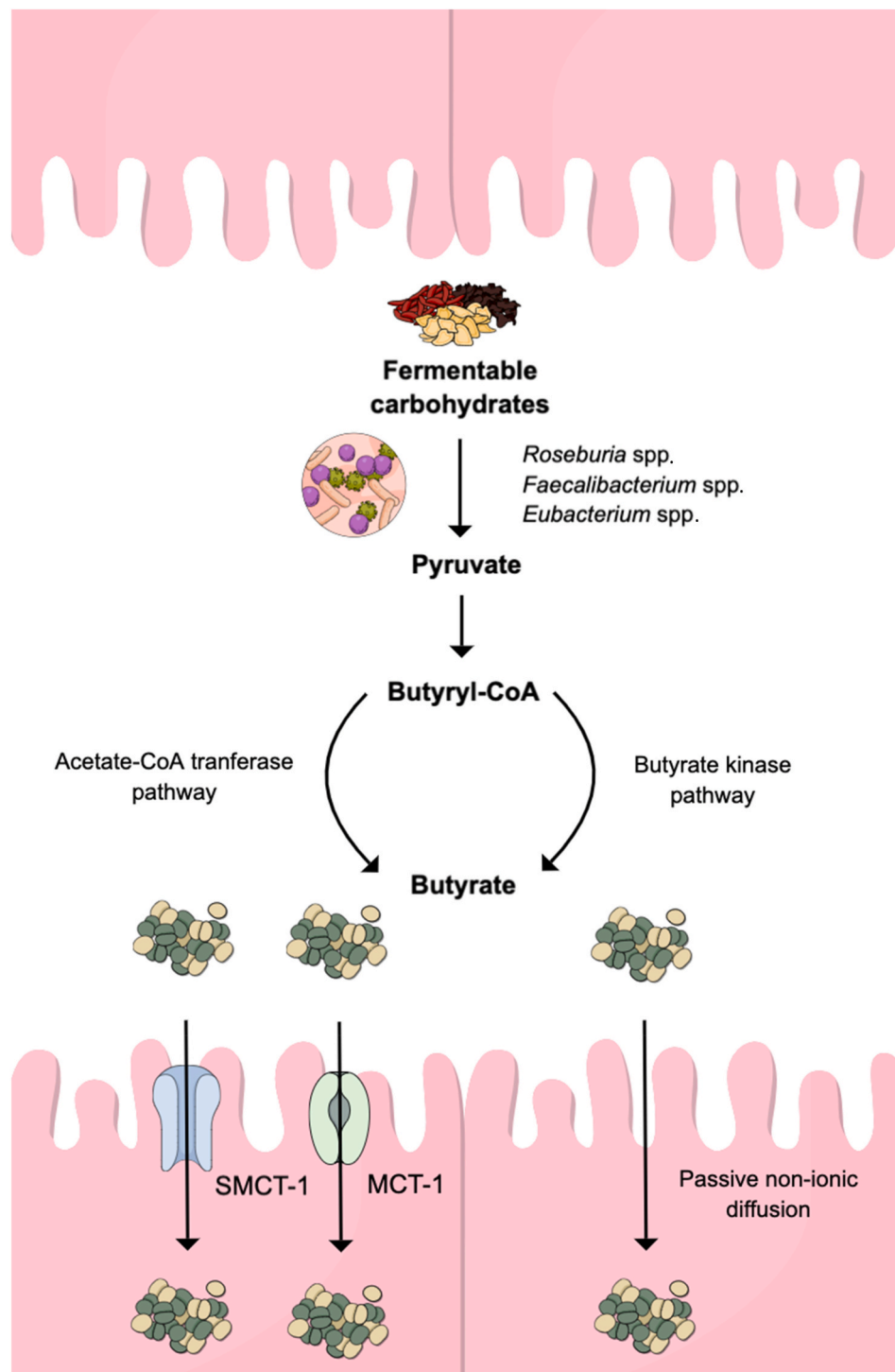
The gastrointestinal microbiota is responsible for the biosynthesis of a diverse range of metabolites, including SCFAs (Rooks and Garrett, 2016). SCFAs represent a major class of microbiota-derived molecules and consist of saturated carboxylic acids with fewer than six carbon atoms. Among them, acetic acid (which consists of a two-carbon chain), propionic acid (which consists of a three-carbon chain), and butyric acid (which consists of a four-carbon chain) are the most represented in the human colon, with acetic acid being the most abundant. These three SCFAs differ not only in chain length but also in the microbial substrates and metabolic routes that generate them, reflecting the close interplay between dietary composition, microbial ecology, and host physiology (Koh et al., 2016).

#### 1.2.2. Butyrate production

The production and absorption mechanisms of butyrate are shown in Fig. 1. Butyrate is predominantly synthesized by various bacterial species belonging to the *Firmicutes* phylum, with notable representatives including the *Faecalibacterium* spp., *Roseburia* spp., *Eubacterium* spp., and *Coprococcus* spp.. The synthesis of butyrate commences with the utilization of non-digestible carbohydrates, such as cellulose, pectine, and bran, which serve as the essential substrates for this metabolic process (Notting et al., 2023). Butyryl-CoA (produced from two acetyl-CoA molecules) can be converted to butyrate via two distinct pathways: the acetate CoA-transferase pathway and the butyrate kinase pathway, each with its own enzymatic mechanisms and regulatory factors. The butyrate kinase pathway employs the enzymes phosphotransbutyrylase and butyrate kinase; however, it is important to note that this particular pathway is relatively uncommon and is largely restricted to specific taxa within the *Coprococcus* genus. Conversely, the butyryl-CoA:acetate CoA-transferase pathway is the predominant route utilized by the majority of well-characterized butyrate-producing gut microbial strains, including but not limited to *Eubacterium* spp., *Roseburia* spp., *Faecalibacterium* spp., *Anaerostipes* spp., and certain species within the *Coprococcus* genus (Wang et al., 2019).

#### 1.2.3. Butyrate absorption

Butyrate is then absorbed with remarkable rapidity by colonocytes through a process that involves either passive nonionic diffusion or actively mediated transport via specific carrier proteins. Butyrate is



**Fig. 1.** Production and absorption mechanisms of butyrate.  
MCT-1: symporter H<sup>+</sup> monocarboxylate transporter-1; SMCT-1: sodium-coupled monocarboxylate transporter-1.

chiefly found in anionic form within the colon, due to the prevailing pH conditions, and its effective cellular uptake is largely facilitated through active transport methods, namely the symporter H<sup>+</sup> monocarboxylate transporter-1 and sodium-coupled monocarboxylate transporter-1 (Nedjadi et al., 2014). For butyrate metabolism, the colonocytes use elevated oxygen quantities, thus resulting in a hypoxic epithelial surface that promotes the development of obligate anaerobic SCFA producing bacteria (Notting et al., 2023).

#### 1.2.4. Butyrate biological functions

Once internalized by colonocytes, butyrate demonstrates its biological functions via various actions, as shown in Fig. 2. For example, butyrate facilitates the formation of tight junctions. This fortifies the epithelial barrier and diminishes paracellular permeability, thereby obstructing microbial translocation (Peng et al., 2009). Furthermore, butyrate promotes the secretion of mucin 2, reinforcing the mucus layer and restricting pathogen adherence (Burger-van Paassen et al., 2009). Additionally, it stimulates the biosynthesis of antimicrobial peptides, such as cathelicidin LL-37, which are instrumental in pathogen

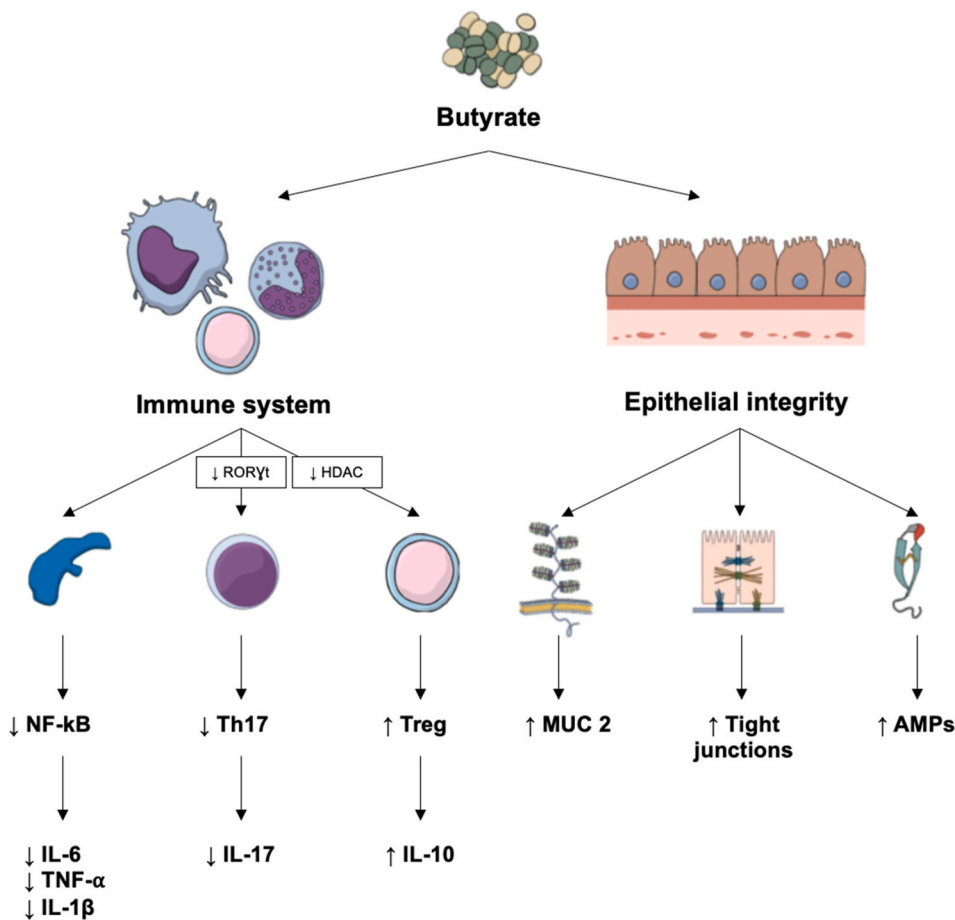


Fig. 2. Butyrate effects on immune system and gut epithelial integrity.

AMPs: antimicrobial peptides; HDAC: histone deacetylase; IL-1β: interleukin-1β; IL-6: interleukin-6; IL-10: interleukin-10; IL-17: interleukin-17; MUC 2: mucin 2; RORγt: retinoic acid-related orphan receptor gamma t; Th17: T helper 17 cells; T reg: T regulatory cells.

management and the maintenance of microbiota equilibrium (Du et al., 2021). In addition to its influence on epithelial integrity, butyrate serves as a vital modulator of intestinal immunity. It promotes the differentiation of regulatory T cells through the inhibition of histone deacetylases, resulting in epigenetic alterations that enhance Foxp3 expression, an essential transcription factor for regulatory T cells functionality. This mechanism amplifies the secretion of interleukin-10 (IL-10), an anti-inflammatory cytokine that is pivotal in sustaining immune tolerance and averting excessive immune activation. Concurrently, butyrate hampers T helper 17 cells differentiation by downregulating retinoic acid receptor-related orphan receptor gamma t, thereby diminishing the production of interleukin-17 (IL-17), a proinflammatory cytokine associated with autoimmune and inflammatory disorders (Chen et al., 2019; Recharla et al., 2023). Through the attenuation of NFκB, butyrate also curbs the synthesis of inflammatory cytokines, such as interleukin-6 (IL-6), tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ), and interleukin-1 $\beta$  (IL-1 $\beta$ ), thereby alleviating excessive immune responses and promoting intestinal immune homeostasis (Segain et al., 2000). Moreover, butyrate has been shown to attenuate ER stress by reducing CHOP expression and decreasing PERK activation. In addition, it reduced accumulation of p62, a marker of impaired autophagy, ultimately restoring cellular homeostasis (Kushwaha et al., 2022). It becomes increasingly evident that butyrate represents a fundamental biomolecule that plays a crucial role in the intricate coordination of gut integrity and its associated permeability, working synergistically with various other metabolites to ensure optimal functionality and homeostasis within the gastrointestinal system (McCarville et al., 2020; Recharla et al., 2023). Furthermore, it is widely acknowledged that the gut microbiota carries out a crucial

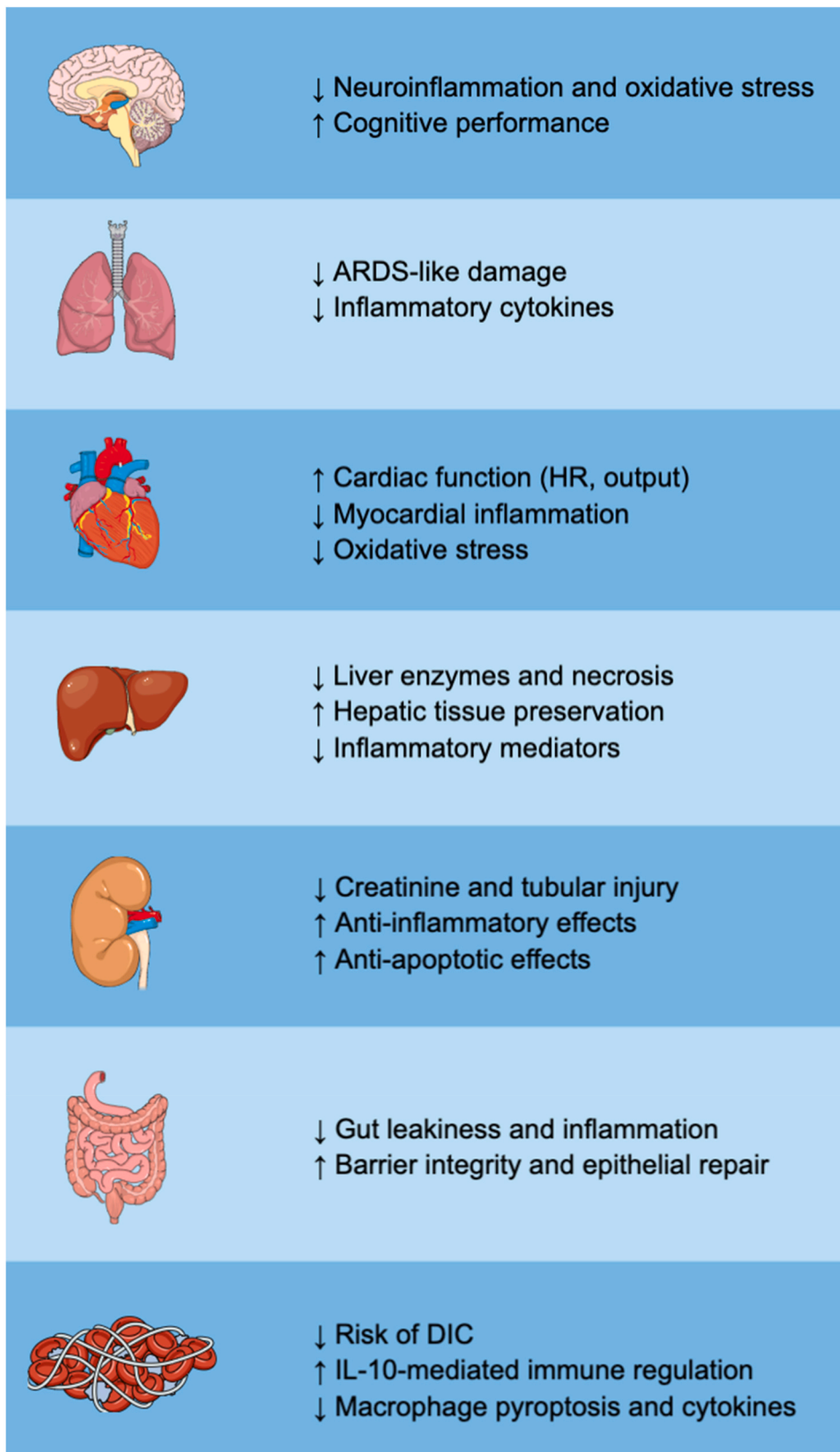
function in the preservation of homeostasis and the modulation of immune responses in remote organs, including the brain via the gut-brain axis (Aburto and Cryan, 2024), as well as the lungs through the gut-lung axis (Dang and Marsland, 2019). Maintaining a balanced gut microbiota in the context of a severe medical condition, such as sepsis, may significantly improve the prognosis of this disorder.

## 2. Objectives of the review

The main objective of this narrative review is to analyze and synthesize the current knowledge regarding the potential therapeutic effects, as well as the critical challenges and complications associated with the administration of butyrate, particularly within the context of sepsis. Currently, most studies are conducted on animal models or through *in vitro* methods, with limited human research available.

## 3. Research methods

This narrative review was conducted through a comprehensive selection of peer-reviewed publications, using PubMed and additional sources to identify relevant literature published up to April 2025. The search focused on the terms “butyrate”, “butyric acid”, “septic shock”, and “sepsis”. Both human and preclinical studies were considered for inclusion. Articles were evaluated based on their relevance, and key findings were extracted and critically discussed, with appropriate citations. Only manuscripts published in English were included. As a narrative review, this work does not follow a systematic methodology but rather aims to provide a broad, interpretive synthesis of current



**Fig. 3.** Effects of butyrate administration on various systems in the context of sepsis. ARDS: acute respiratory distress syndrome; DIC: disseminated intravascular coagulation; HR: heart rate; IL-10: interleukin-10.

**Table 1**

Summary of preclinical and clinical studies evaluating the effects of butyrate and its derivatives in sepsis.

INJURY	MODEL	COMPOUND, DOSE, TIMING	EVIDENCE	REFERENCES
<b>Encephalopathy</b>	Animal (mouse)	Sodium butyrate 500 mg/kg (oral) 7 d before CLP	↑ Cognitive function ↓ Oxidative stress and brain inflammation	Zhang et al. (2022)
<b>Liver injury</b>	Animal (rat)	Tributyryn 1 g/kg (oral) 1 h before LPS	↓ Liver injury and oxidative stress ↓ TNF- $\alpha$ and LTB4 levels ↓ NF- $\kappa$ B inhibition	Miyoshi et al. (2011) Miyoshi et al. (2020)
<b>Intestinal injury</b>	Animal (rat)	Sodium butyrate 200 mg/kg (intravenous) After CLP	↓ Intestinal permeability ↓ Pro-inflammatory cytokines - Restored tight junctions	Fu et al. (2019)
<b>GBS sepsis</b>	Animal (pregnant mouse) Human intestinal epithelial cells	Sodium butyrate 150 mM in drinking water During pregnancy ( <i>ad libitum</i> )	↓ Apoptosis and intestinal permeability ↑ Barrier integrity	Dominguez et al. (2024)
<b>Myocardial dysfunction</b>	Animal (mouse)	Sodium butyrate 200 mg/kg/day (oral) 3 d before LPS	↑ Cardiac function ↓ TNF- $\alpha$ , IL-6 and LTB4	Wang et al. (2017a)
<b>Myocardial dysfunction</b>	Animal (mouse)	$\beta$ -hydroxybutyrate 3 mg/kg/day For 3 d prior to LPS injection	↑ Cardiac function ↓ Myocardial oxidative stress	Ji et al. (2022)
<b>Lung injury</b>	Animal (mouse)	Sodium butyrate 300 mg/kg (oral) 1 and 6 h after CLP	↑ Lung function ↓ Cytokines and tissue damage - Restored barrier proteins	Wei et al. (2024)
<b>Kidney injury</b>	Animal (mouse)	$\beta$ -hydroxybutyrate 10 mmol/kg (intraperitoneal) 24 h before LPS	↑ Renal function ↓ Inflammation and tubular apoptosis	Kim et al. (2023)
<b>DIC</b>	Animal (mouse)	Butyrate n/a n/a	↓ Susceptibility to DIC by inhibiting macrophage pyroptosis	Li et al. (2024)
<b>Mortality and survival</b>	Animal (multiple models)	Varied Varied Varied	↑ Survival across multiple models with consistent anti-inflammatory and barrier-stabilizing effects	Zhang et al. (2007) Wang et al. (2017b) Fu et al. (2019) Zhang et al. (2022) Peters et al. (2022) Dominguez et al. (2024) Wei et al. (2024) Acar (2021)
<b>Metabolic profile in septic patients</b>	Human (observational)	Endogenous $\beta$ -hydroxybutyrate measured at hospital admission	↑ $\beta$ -hydroxybutyrate levels correlated with survival in septic patients	
<b>Clinical infections in ICU patients</b>	Human (RCT)	Synbiotics containing butyrate-producing bacteria, administered within 3 d of ICU admission	↓ Incidence of enteritis ↓ Incidence of VAP	Shimizu et al. (2018)

CLP: cecal ligation and puncture; DIC: disseminated intravascular coagulation; GBS: Group B Streptococcus; IL-6: interleukin-6; LPS: lipopolysaccharide; LTB4: leukotriene B4; TNF- $\alpha$ : tumor necrosis factor  $\alpha$

evidence.

#### 4. Results (Table 1)

##### 4.1. Evidence from animal and in vitro studies (Fig. 3)

###### 4.1.1. Neuroprotection and cognitive effects in sepsis-associated encephalopathy

One of the organs frequently impacted by sepsis is the central nervous system. Specifically, sepsis may result in neurological dysfunction, a phenomenon referred to as sepsis-associated encephalopathy (SAE). This condition can engender enduring complications, such as cognitive impairments and psychiatric disorders. The underlying mechanisms that contribute to this condition remain largely unidentified (Sonneville et al., 2023). In a work conducted by Zhang et al. (2022), researchers utilized a murine model to investigate SAE. They intragastrically administered sodium butyrate (500 mg/kg administered prophylactically 7 days prior to sepsis induction) to a subset of mice to evaluate its potential protective effects against oxidative stress and brain injury. Sodium butyrate improved survival and mitigated cognitive impairments in septic mice. Following CLP, sodium butyrate treatment significantly enhanced survival compared to untreated septic mice ( $p < 0.05$ ). Behavioral assessment via the spatial memory test Morris Water Maze (Wenk, 2004) demonstrated that, on day 3 post-CLP, sodium butyrate-treated mice swam significantly faster than CLP-only mice ( $p < 0.05$ ). Furthermore, CLP-only mice showed prolonged latency to locate the platform, an effect that sodium butyrate significantly reversed

from days 3–5 ( $p < 0.05$ ). The number of platform crossings, measured after training and after platform removal, was significantly reduced in the CLP-only group compared to the sham group, but sodium butyrate treatment restored crossing frequency to near-control levels ( $p < 0.05$ ). Additionally, mice in the CLP-only group followed longer search paths, whereas sodium butyrate treatment normalized trajectory patterns. Moreover, hippocampal concentrations of malondialdehyde ( $p < 0.05$ ) and prostaglandin E2 ( $p < 0.0001$ ) were markedly elevated in untreated mice on days 1 and 3 post-sepsis induction. Furthermore, levels of superoxide dismutase were significantly elevated on both day 1 and day 3 following sepsis induction in those mice that were treated with sodium butyrate ( $p < 0.05$ ). These findings suggested that butyrate may activate neurobiological pathways that mitigate inflammation and oxidative stress, both detrimental factors in sepsis.

###### 4.1.2. Hepatoprotective actions and inflammatory modulation in the liver

The liver is instrumental in eliminating toxins, such as lipopolysaccharide (LPS) from the bloodstream (Topchiy et al., 2016). Miyoshi and colleagues (2011) carried out a study to determine if oral administration of tributyrin (1.0 g/kg), a prodrug of butyric acid, might offer protective benefits for the liver against damage caused by LPS. The team of investigators sorted the rats into four sets: a control group, a group that received tributyrin, a group exposed to LPS, and a group that was treated with both tributyrin and LPS. Tributyrin exhibited effectiveness in mitigating hepatic injury induced by LPS, as indicated by enhanced preservation of hepatic tissue architecture. In the LPS + tributyrin group, the modified hepatic activity index score was  $2.3 \pm 0.3$ ,

significantly lower than the  $8.1 \pm 0.5$  observed in the LPS-only group ( $p < 0.01$ ). Furthermore, tributyrin reduced the incidence of confluent necrosis to  $1.3 \pm 0.7$  per 10 fields ( $100 \times$  magnification), compared to  $24.2 \pm 1.7$  in the LPS group ( $p < 0.01$ ). Additionally, tributyrin treatment led to a significant decrease in the concentrations of aspartate aminotransferase ( $p < 0.05$ ), alanine aminotransferase ( $p < 0.01$ ), and total bilirubin ( $p < 0.01$ ). Tributyrin also reduced TNF- $\alpha$  plasma levels ( $p = 0.09$ , not significant) and down-regulated the expression of NF $\kappa$ B p65. There was no statistically significant difference in 24 h survival rates between the LPS group and the LPS + tributyrin group, likely due to the small sample sizes (16 rats in the LPS group and 17 rats in the LPS + tributyrin group). The researchers postulated that tributyrin functioned by elevating butyrate levels, which subsequently aided in the suppression of NF $\kappa$ B, a pivotal regulator in the inflammatory process. Through this mechanism, tributyrin served to safeguard the liver from damage engendered by bacterial toxins. These findings are further substantiated by another work (Miyoshi et al., 2020), which examined the impact of oral tributyrin on hepatic lipid mediator profiles in a rat model of LPS-induced endotoxemia. Rats were pretreated with a single oral dose of tributyrin (1.0 g/kg) or vehicle 1 h prior to intraperitoneal injection of LPS, and liver tissues were collected at 0, 1.5, 6, and 24 h post-injection. The authors found that LPS increased hepatic leukotriene B4 (LTB4) levels, a potent pro-inflammatory eicosanoid, and that tributyrin significantly attenuated this increase at 24 h ( $p < 0.05$ ). This effect was not due to changes in expression of 5-lipoxygenase (5-LOX) or leukotriene A4 hydrolase (LTA4H), but rather to a reduction in the nuclear translocation of 5-LOX, a key step in LTB4 biosynthesis. Tributyrin also significantly reduced LPS-induced oxidative stress in the liver. The percentage of 8-hydroxy-2'-deoxyguanosine-positive hepatocytes, a marker of oxidative DNA damage, decreased from  $95.0 \pm 2.2\%$  in the LPS group to  $40.9 \pm 2.7\%$  at 6 h ( $p < 0.01$ ), and from  $86.2 \pm 4.4\%$  to  $62.6 \pm 4.5\%$  at 24 h ( $p < 0.05$ ) in the LPS + tributyrin group. These results suggested that tributyrin exerted hepatoprotective effects by modulating LTB4 production and reducing oxidative stress, potentially through the inhibition of 5-LOX nuclear translocation.

#### 4.1.3. Preservation of intestinal barrier integrity and permeability

As discussed previously, the gastrointestinal tract frequently emerges as the primary organ adversely impacted during sepsis, resulting in enhanced permeability and inflammation, which may exacerbate the clinical condition. In a study conducted by Fu et al. (2019), male rats received either sodium butyrate (200 mg/kg) intravenously or a vehicle control following the induction of sepsis. They evaluated the effects of sodium butyrate on survival, intestinal permeability, and inflammatory responses, using histological examinations and cytokine quantification. The rats administered sodium butyrate exhibited a markedly elevated survival rate at 72 h in comparison to those subjected to the vehicle treatment (50 % versus 22 % mortality,  $p < 0.05$ ). The use of sodium butyrate reduced the amounts of pro-inflammatory cytokines, like TNF- $\alpha$  and IL-6 ( $p < 0.05$ ) found in the intestinal tissues, which points to a decline in inflammatory activities. Regarding intestinal barrier disruption, rats treated with sodium butyrate had an approximately threefold reduction in serum fluorescein isothiocyanate-dextran 4 compared with untreated controls ( $p < 0.05$ ). The expression levels of claudin-1 ( $p < 0.05$ ) and zonula occludens-1 ( $p < 0.01$ ) were also restored in sodium butyrate-treated rats on Western blot analysis. Furthermore, sodium butyrate was able to inhibit NF $\kappa$ B activation. In fact, the nuclear/cytosolic ratios of p65 were  $0.51 \pm 0.23$ ,  $3.83 \pm 1.91$ , and  $0.53 \pm 0.37$  in the sham operation, CLP + vehicle, and CLP + sodium butyrate groups, respectively ( $p < 0.01$ ). These results suggested that sodium butyrate holds promise in countering the detrimental effects of sepsis on the intestinal barrier and in managing inflammation.

Another study conducted by Dominguez et al. (2024) aimed to investigate the potential of butyrate to alleviate the adverse impacts of Group B Streptococcus (GBS), a significant contributor to sepsis in neonates, on the integrity of the intestinal barrier, with a specific emphasis

on cellular apoptosis, invasion, and permeability. The research team utilized human intestinal epithelial cell lines alongside murine models to assess the influence of butyrate on the damage instigated by GBS. They systematically evaluated cellular viability, adhesion, invasion, and the permeability of the intestinal barrier. Furthermore, experimental procedures were conducted on pregnant mice to determine whether maternal oral administration of sodium butyrate *ad libitum* (at a final concentration of 150 mM in drinking water) could benefit their offspring by reducing GBS colonization. Butyrate markedly attenuated GBS-induced cellular apoptosis in human intestinal cells ( $p < 0.05$ ). It exhibited greater effectiveness in comparison to other SCFAs, such as propionate and acetate. Furthermore, butyrate significantly mitigated intracellular invasion in T-84 cell models ( $p < 0.05$ ). The disruption of epithelial monolayer integrity was assessed through transepithelial electrical resistance (TEER) and the transcytosis of GBS. In CACO-2 and human fetal tissue-derived enteroids (HFTEs) models, significantly elevated TEER values were recorded following pre-treatment with sodium butyrate ( $p < 0.05$ ). In relation to transcytosis, a significant reduction was observed solely in the HFTEs model upon administration of sodium butyrate. In murine models, maternal administration of butyrate did not significantly influence the gut microbiome composition of offspring. The results of this study indicated that butyrate enhanced the integrity of the intestinal barrier, leading to reduced permeability and preventing GBS from infiltrating the epithelial cells.

#### 4.1.4. Cardiovascular stabilization and attenuation of myocardial depression

Wang et al. (2017a) investigated the cardioprotective potential of butyrate in a murine model of LPS-induced sepsis. Mice were assigned to three groups: a saline-treated control group, an LPS-only group, and a group pretreated with sodium butyrate (200 mg/kg/day for 3 days prior to LPS). Cardiac function was assessed at 6 and 12 h post-LPS via invasive hemodynamic monitoring, histopathology, and biochemical analysis of oxidative stress and inflammatory mediators in myocardial tissue. Sodium butyrate pretreatment significantly attenuated sepsis-induced cardiac dysfunction. At 12 h after LPS challenge, the LPS-only group showed severe hemodynamic depression: heart rate dropped to  $229 \pm 5$  beats/min, left ventricular systolic pressure to  $60 \pm 1$  mmHg, maximal rate of left ventricular pressure rise during systole (+dp/dtmax) to  $1588 \pm 367$  mmHg/s, and maximal rate of left ventricular pressure fall during diastole (-dp/dtmax) to  $798 \pm 362$  mmHg/s, with left ventricular end-diastolic pressure elevated to  $10 \pm 2$  mmHg. In contrast, butyrate-pretreated mice exhibited significantly improved values: heart rate  $378 \pm 9$  beats/min, left ventricular systolic pressure  $80 \pm 2$  mmHg, +dp/dtmax  $3133 \pm 435$  mmHg/s, and -dp/dtmax  $2061 \pm 404$  mmHg/s ( $p < 0.01$ ). Histological evaluation revealed that sodium butyrate reduced myocardial edema, interstitial widening, inflammatory infiltration, and myofibril disintegration. Electron microscopy confirmed preservation of intercalated discs and mitochondrial structure in pretreated animals. Oxidative stress markers reflected similar protection: LPS significantly reduced superoxide dismutase and catalase activity and increased malondialdehyde levels in cardiac tissue ( $p < 0.01$ ), all of which were significantly reversed by butyrate ( $p < 0.05$ ). Moreover, myocardial concentrations of TNF- $\alpha$ , IL-6, and LTB4 peaked at 6 h post-LPS and remained elevated at 12 h. Butyrate pretreatment significantly decreased all three cytokines at both time points ( $p < 0.01$ ).

In a related LPS-induced septic cardiomyopathy model, Ji et al. (2022) further demonstrated that  $\beta$ -hydroxybutyrate provides myocardial protection. Male mice received a ketone ester delivering  $\beta$ -hydroxybutyrate (3 mg/g/day for 3 days) prior to LPS challenge (20 mg/kg i. p.). Echocardiography performed 6 h after LPS injection revealed marked reductions in left ventricular ejection fraction ( $\sim 35$ – $40\%$  vs.  $\sim 70\%$  in controls;  $p < 0.01$ ), fractional shortening ( $p < 0.01$ ), and cardiac output ( $p < 0.001$ ), all of which were significantly improved by  $\beta$ -hydroxybutyrate pretreatment ( $p < 0.05$ ). Circulating creatine

kinase-MB isoenzyme and lactate dehydrogenase levels were also significantly lower in treated mice ( $p < 0.001$ ). Moreover,  $\beta$ -hydroxybutyrate reduced myocardial oxidative stress (decreased DHE fluorescence, protein carbonyls, and malondialdehyde;  $p < 0.01$ – $0.05$ ), restored antioxidant enzyme activity ( $p < 0.01$ ), and improved mitochondrial respiration ( $p < 0.01$ ).

These results confirmed that butyrate exerted strong protective effects against sepsis-induced myocardial depression via anti-inflammatory and antioxidant mechanisms, preserving both systolic and diastolic cardiac function.

#### 4.1.5. Pulmonary protection via gut-lung axis modulation

The pulmonary system is the most predisposed organ system influenced by sepsis, making patients highly susceptible to acute lung injury (Sun et al., 2023). There is growing interest in the gut-lung axis, owing to the potential that these two systems may be interconnected and exert a crucial influence on inflammatory pulmonary pathologies (Chakradhar, 2017). In a study conducted by Wei et al. (2024), the authors investigated the effects of sodium butyrate on sepsis-associated lung injury. A murine model of sepsis was established via CLP, and mice were divided into four groups (sham, sham + sodium butyrate, CLP, and CLP + sodium butyrate). Sodium butyrate was orally administered at a dose of 300 mg/kg, 1 and 6 h after surgery. The researchers assessed survival rates, oxygenation index, lung histopathology, barrier protein expression, inflammatory mediators, and immune cell profiles. Sodium butyrate treatment significantly improved survival in septic mice, increasing the 5-day survival rate from 0 % in the CLP group to 40 % in the CLP + sodium butyrate group ( $p < 0.05$ ). The oxygenation index was also markedly improved in the sodium butyrate-treated septic mice compared to untreated mice ( $p < 0.05$ ). Histological analysis revealed that sodium butyrate reduced lung injury scores, indicating attenuated neutrophil infiltration, septal thickening, and proteinaceous debris ( $p < 0.05$ ). Sodium butyrate also enhanced alveolar-capillary barrier function, as evidenced by a decreased lung wet-to-dry weight ratio ( $p < 0.05$ ), reduced protein concentration in bronchoalveolar lavage fluid, and lower serum levels of surfactant protein D ( $p < 0.05$ ). Western blot analyses showed that sodium butyrate restored the expression of tight junction proteins (claudin-5, occludin, and VE-cadherin) in lung tissue ( $p < 0.05$ ). Furthermore, sodium butyrate reduced levels of proinflammatory cytokines TNF- $\alpha$ , IL-1 $\beta$ , and IL-17 ( $p < 0.05$ ), while increasing anti-inflammatory mediators such as IL-10 and transforming growth factor- $\beta$  ( $p < 0.05$ ). Notably, sodium butyrate elevated the proportion of CD4<sup>+</sup>Foxp3<sup>+</sup> regulatory T cells in lung tissue ( $p < 0.05$ ), which correlated with increased expression of amphiregulin, an effector molecule involved in epithelial repair. These findings suggested that sodium butyrate mitigated lung injury during sepsis by reinforcing the barrier functions of the gut and lungs and modulating immune responses, particularly through the enhancement of regulatory T cell-mediated anti-inflammatory pathways.

#### 4.1.6. Renal anti-inflammatory and anti-apoptotic mechanisms in sepsis-associated acute kidney injury

Sepsis-associated acute kidney injury (SA-AKI) is prevalent in critically ill individuals and correlates with negative outcomes, including chronic kidney disease, cardiovascular dysfunction, and mortality. Various mechanisms, including systemic and renal inflammation, complement activation, renin-angiotensin-aldosterone system (RAAS) dysregulation, mitochondrial dysfunction, metabolic reprogramming, microcirculatory dysfunction, and abnormalities contribute to SA-AKI. Additional factors, such as nephrotoxic drug exposure, hyperchloremia, and abdominal compartment syndrome, may also indirectly influence SA-AKI (Zarbock et al., 2023). Kim et al. (2023) investigated the effectiveness of  $\beta$ -hydroxybutyrate in mitigating SA-AKI in a murine model of LPS-induced sepsis. Mice were randomly assigned to four experimental groups ( $n = 6$  per group): sham,  $\beta$ -hydroxybutyrate, LPS, and  $\beta$ -hydroxybutyrate + LPS.  $\beta$ -hydroxybutyrate was intraperitoneally

administered at a dose of 10 mmol/kg, 24 h prior to intraperitoneal injection of LPS. Physiological and biochemical parameters were assessed 24 h post-LPS administration. Mice in the LPS group exhibited hypothermia ( $28.5 \pm 0.6$  °C vs.  $36.4 \pm 0.2$  °C in the Sham group,  $p < 0.05$ ), elevated serum creatinine levels ( $0.70 \pm 0.09$  mg/dL vs.  $0.30 \pm 0.05$  mg/dL,  $p < 0.05$ ), and significant renal injury on histopathology. Pre-treatment with  $\beta$ -hydroxybutyrate significantly ameliorated these changes: body temperature was higher ( $32.4 \pm 0.4$  °C,  $p < 0.05$  vs. LPS), and serum creatinine was lower ( $0.45 \pm 0.05$  mg/dL,  $p < 0.05$  vs. LPS). The urinary albumin-to-creatinine ratio was significantly increased in the LPS group and reduced in the  $\beta$ -hydroxybutyrate + LPS group ( $p < 0.05$ ), although exact numerical values were not specified. Histological evaluation revealed severe tubular damages in LPS-treated mice, with a mean injury score of  $3.83 \pm 0.17$ . This was significantly attenuated by  $\beta$ -hydroxybutyrate pre-treatment ( $2.33 \pm 0.33$ ,  $p < 0.05$ ). Furthermore,  $\beta$ -hydroxybutyrate reduced inflammatory responses, as evidenced by decreased mRNA expression of TNF- $\alpha$  and IL-6 ( $p < 0.05$ ), reduced macrophage infiltration (F4/80 staining), and lower expression of phosphorylated NF- $\kappa$ B p65.  $\beta$ -hydroxybutyrate also exhibited anti-apoptotic effects. TUNEL staining revealed fewer apoptotic tubular cells in the  $\beta$ -hydroxybutyrate + LPS group relative to LPS alone ( $p < 0.05$ ). Western blot analysis showed decreased levels of cleaved caspase-3 and a reduced Bax/Bcl-2 ratio in mice pre-treated with  $\beta$ -hydroxybutyrate ( $p < 0.05$  vs. LPS group). In conclusion,  $\beta$ -hydroxybutyrate pre-treatment conferred significant renal protection in a murine model of sepsis-induced AKI through both anti-inflammatory and anti-apoptotic mechanisms. These findings suggested that  $\beta$ -hydroxybutyrate might represent a promising prophylactic approach for the prevention of SA-AKI.

#### 4.1.7. Coagulation system

Li et al. (2024) investigated the role of butyrate in reducing susceptibility to septic disseminated intravascular coagulation (DIC) by inhibiting pyroptosis in macrophages. The research demonstrated that butyrate could alleviate the risk of septic DIC by suppressing caspase-11 and GSDMD-dependent macrophage pyroptosis, a highly inflammatory form of lytic programmed cell death.

#### 4.1.8. Mortality

Several of the preclinical studies previously discussed in this review also reported data on survival outcomes, which are summarized in this section. These findings reveal consistent, though model-dependent, effects of butyrate on mortality in sepsis. In a rat model of CLP-induced sepsis, intravenous sodium butyrate significantly improved survival from 22 % to 50 % at 24 h ( $p < 0.05$ ) compared to vehicle-treated animals (Fu et al., 2019). Similarly, Zhang et al. (2007) reported that sodium butyrate administration (25 mg/kg, 2 injections) conferred a statistically significant survival benefit in CLP rats between days 1 and 6 ( $p = 0.001$ – $0.003$ ), although no difference was observed at the 12 h mark. A significant difference emerged at 24 h ( $p = 0.034$ ), suggesting that butyrate's protective effect becomes more prominent in the early post-sepsis period. In LPS-induced endotoxemia models, butyrate pre-treatment (200 mg/kg) increased survival from 20 % to 60 % ( $p < 0.01$ ), while acetate and propionate had no statistically significant effect (Wang et al., 2017b). In the murine CLP model used by Wei et al. (2024), sodium butyrate treatment markedly improved survival in 7-day. Based on Kaplan–Meier curve analysis, survival in the CLP + sodium butyrate group was 40 % at day 5 versus 0 % in the untreated CLP group ( $p < 0.05$ ). In another CLP study of sepsis-associated encephalopathy, sodium butyrate-treated mice exhibited significantly higher 7-day survival compared to saline-treated controls ( $p < 0.05$ ) (Zhang et al., 2022). Conversely, Peters et al. (2022) found no survival benefit in a fecal peritonitis model despite observing hemodynamic deterioration following butyrate infusion. Finally, in a neonatal model of GBS-induced sepsis, maternal butyrate administration reduced offspring mortality from 7 % to 0 %, although this reduction did not reach statistical

significance (Dominguez et al., 2024).

#### 4.2. Evidence from human studies

In contrast to extensive animal studies, there is a notable lack of research investigating butyrate use in human sepsis. The primary emphasis of current research is on the use of probiotics or synbiotics, which frequently pertains to the administration of microorganisms that produce SCFAs, including butyrate.

Acar (2021) conducted a single-center, prospective study involving patients diagnosed with sepsis. He quantified the levels of  $\beta$ -hydroxybutyrate in the bloodstream upon hospital admission and monitored the patients for 28 days post-admission. His findings revealed that patients who did not survive exhibited significantly lower concentrations of  $\beta$ -hydroxybutyrate compared to those who survived ( $p = 0.013$ ). These findings indicated the potential utility of  $\beta$ -hydroxybutyrate in forecasting survival outcomes and informing treatment strategies in sepsis.

Shimizu et al. (2018) evaluated the impact of synbiotics on gastrointestinal outcomes and microbiota modulation in mechanically ventilated patients with sepsis in a randomized controlled trial. Seventy-two patients were enrolled and randomized to receive either daily synbiotics (comprising *Bifidobacterium breve* strain Yakult, *Lactobacillus casei* strain Shirota, and galactooligosaccharides) or no intervention, starting within three days of ICU admission. The incidence of enteritis was significantly lower in the synbiotics group (6.3 %) compared to controls (27.0 %,  $p < 0.05$ ), as was the rate of ventilator-associated pneumonia (14.3 % vs. 48.6 %,  $p < 0.05$ ). Fecal analysis revealed significantly higher counts of *Bifidobacterium* and *Lactobacillus* in the synbiotics group ( $p < 0.05$ ), indicating beneficial modulation of the gut microbiota. Total fecal organic acid concentrations, particularly acetate, increased significantly at one week ( $p < 0.05$ ), whereas the rise in butyric acid, though elevated (from 4.8 to 17.1  $\mu\text{mol/g}$ ), did not reach statistical significance ( $p = 0.722$ ). Nonetheless, the trend toward increased butyrate is clinically relevant, as butyrate plays a critical role in maintaining epithelial barrier integrity and regulating inflammation. These findings suggest that synbiotic supplementation may enhance host defenses and reduce complications such as enteritis and ventilator-associated pneumonia in septic patients, potentially through SCFAs-mediated mechanisms.

Recent pharmacokinetic investigations have provided further insight into the clinical applicability of different butyrate formulations. In a randomized crossover study on healthy volunteers, three orally administered compounds (sodium butyrate, lysine butyrate, and tributyrin), were compared in terms of systemic absorption and tolerability. Both sodium butyrate and lysine butyrate achieved significantly higher peak plasma concentrations ( $C_{\text{max}}$ :  $2.51 \pm 4.13 \mu\text{g/mL}$  and  $4.53 \pm 7.56 \mu\text{g/mL}$ , respectively) and greater overall exposure ( $AUC_{0-210}$ :  $144 \pm 214$  and  $189 \pm 306 \mu\text{g/mL}\cdot\text{min}$ ) compared to tributyrin ( $C_{\text{max}}$ :  $0.91 \pm 1.65 \mu\text{g/mL}$ ;  $AUC_{0-210}$ :  $108 \pm 190 \mu\text{g/mL}\cdot\text{min}$ ). Furthermore, sodium butyrate and lysine butyrate reached maximum plasma levels more rapidly ( $T_{\text{max}} \sim 20\text{--}22 \text{ min}$ ) than tributyrin ( $T_{\text{max}} \sim 51.5 \text{ min}$ ), supporting their use in settings requiring prompt systemic availability. These findings suggested that sodium butyrate and lysine butyrate may be more suitable for acute inflammatory conditions such as sepsis, where rapid immunomodulatory and barrier-preserving effects are desirable. Notably, lysine butyrate also demonstrated improved palatability and a reduced sodium burden, potentially offering better tolerability in critically ill patients (La Monica et al., 2025).

#### 4.3. Potential negative effects of butyrate administration in sepsis

As previously discussed, butyrate can modulate immune responses and exhibits anti-inflammatory properties and effects on cellular metabolism. Although it may enhance cellular energy production, certain studies suggest that it may concurrently attenuate ATP synthesis under specific conditions (Gallis et al., 2007). Peters et al. (2022) investigated

the immunometabolic effects of butyrate using both *ex vivo* human and *in vivo* rodent models of sepsis. In peripheral blood mononuclear cells from healthy human donors, butyrate (1.8 mM) significantly reduced LPS-induced secretion of TNF- $\alpha$  ( $p = 0.019$ ) and IL-10 ( $p = 0.001$ ), without affecting cell viability. To evaluate its *in vivo* effects, a fluid-resuscitated rat model of fecal peritonitis-induced sepsis was employed. Butyrate was intravenously administered (0.6 g/kg/h) starting 6 h after sepsis induction. At 24 h, all animals survived, but notable physiological alterations were observed. Compared to septic controls, butyrate-treated rats exhibited significantly reduced stroke volume ( $p = 0.010$ ) and cardiac output ( $p = 0.001$ ), along with increased lactate levels ( $p = 0.031$ ) and metabolic alkalosis (elevated pH,  $p = 0.010$ ; bicarbonate,  $p = 0.003$ ). A further decline in respiratory exchange ratio (from 0.84 to 0.78,  $p < 0.001$ ) suggested increased fatty acid metabolism. Splenocyte mitochondrial function was impaired in butyrate-treated septic rats, showing reduced proton leak ( $p = 0.022$ ) and increased mitochondrial membrane potential ( $p = 0.007$ ) and reactive oxygen species ( $p = 0.027$ ). Basal respiration trended to lower levels ( $p = 0.077$ ). Intracellular TNF- $\alpha$  and IL-10 levels remained unaffected, but IL-10 release after LPS stimulation was significantly diminished ( $p = 0.039$ ). These findings suggested that butyrate administration might worsen cardiac and mitochondrial function in early sepsis, indicating potential harm despite beneficial cytokine modulation.

Moreover, recent studies indicate that butyrate and other SCFAs may exert heterogeneous effects on cardiovascular regulation, particularly on blood pressure. In a randomized, placebo-controlled clinical trial involving hypertensive adults, oral sodium butyrate (3.9 g/day for 4 w) significantly increased daytime systolic blood pressure by +9.63 mmHg (95 % CI 2.02–17.20;  $p = 0.02$ ) and diastolic blood pressure by +5.08 mmHg (95 % CI 1.34–8.78;  $p = 0.02$ ), suggesting a potential pressor effect in susceptible individuals (Verhaar et al., 2024). Conversely, Poll et al. (2021) demonstrated that acetate exerts hypotensive effects *in vivo* using conscious, radiotelemetry-implanted mice. Intraperitoneal administration of acetate at 1.0 g/kg and 0.625 g/kg produced a significant reduction in mean arterial pressure ( $-52.2 \pm 12.1 \text{ mmHg}$  and  $-37.7 \pm 13.5 \text{ mmHg}$ , respectively;  $p < 0.0001$ ) and heart rate ( $-252.8 \pm 54.3 \text{ bpm}$  and  $-205.3 \pm 60.9 \text{ bpm}$ ;  $p < 0.0001$ ). Given the profound hemodynamic instability characteristic of sepsis, these observations underscore that blood pressure should be carefully monitored when administering butyrate or other SCFAs, and that the clinical implications of their diverging cardiovascular profiles warrant further investigation.

## 5. Future perspectives and challenges

Although preclinical findings consistently support the immunomodulatory, barrier-protective, and organ-specific benefits of butyrate in experimental models of sepsis, several critical challenges must be addressed before translation into clinical practice becomes feasible. First, there is an urgent need for early-phase clinical trials specifically designed to evaluate the safety, tolerability, pharmacokinetics, and preliminary effectiveness of butyrate or butyrate-derived compounds in septic patients. Such studies should clarify optimal dosing strategies, which remain uncertain due to the compound's rapid metabolism, short half-life, and variable systemic absorption across formulations. Another key question concerns timing: while most animal studies use prophylactic or early pre-treatment models, real-world sepsis interventions usually occur after diagnosis, necessitating trials that distinguish between prophylactic, early therapeutic, and late therapeutic administration.

Patient stratification represents an additional complexity. The profound heterogeneity of sepsis, driven by host factors, infection source, immune phenotype, and especially microbiome composition, suggests that butyrate supplementation may exert differential effects across patient subgroups. Future studies should incorporate microbiome profiling and stratification frameworks to identify individuals who may benefit most or, conversely, those at risk of adverse responses.

Finally, the development of improved drug delivery approaches represents a major translational priority. Strategies such as prodrug formulations (e.g., tributyrin), encapsulated delivery systems, or microbiome-targeted interventions may help achieve sustained therapeutic butyrate concentrations while minimizing systemic fluctuations. Together, these considerations highlight the complexity of translating butyrate from bench to bedside and emphasize the need for rigorous clinical research to define its true therapeutic potential in sepsis.

## 6. Conclusions

This review demonstrates that butyrate shows therapeutic potential in sepsis through its anti-inflammatory, immunomodulatory, and gut barrier-enhancing properties. Preclinical studies have demonstrated that butyrate can modulate immune responses, attenuate systemic inflammation, and reinforce intestinal integrity, all of which are critical in the pathophysiology of sepsis. The preclinical studies presented in this review have shown that butyrate and related metabolites can attenuate septic injury across multiple organ systems, including the neurological, hepatic, intestinal, renal, pulmonary, and the cardiovascular system.

Nevertheless, the immunomodulatory effects of butyrate should be interpreted with caution in the context of sepsis. Given the coexistence of hyperinflammation and immunosuppression, immune-regulatory mechanisms that are beneficial in limiting early inflammatory damage may, under certain conditions, exacerbate sepsis-associated immunoparalysis and impair host defense. The overall clinical impact of butyrate supplementation is therefore likely to depend on timing, dose, and the patient's underlying immune status.

Accordingly, the translation of butyrate's therapeutic benefits into human clinical practice remains unsubstantiated. A significant limitation in the current body of research is the complete lack of clinical trials evaluating the effectiveness and safety of butyrate supplementation in septic patients. Without robust human studies, it is challenging to determine the optimal dosing regimen, pharmacokinetics, and potential adverse effects, as well as its overall therapeutic impact in the context of sepsis. Its rapid metabolism and short half-life present obstacles to achieving sustained therapeutic concentrations in systemic circulation. Future research should explore innovative delivery mechanisms, such as prodrug formulations, targeted release systems, or gut microbiota modulation strategies, to enhance its clinical applicability.

## CRedit authorship contribution statement

**Nicola Benvenuto:** Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation. **Filippo Mearelli:** Writing – review & editing, Validation. **Gianni Biolo:** Writing – review & editing, Validation. **Filippo Giorgio Di Girolamo:** Writing – review & editing, Validation. **Erik Roman-Pognuz:** Writing – review & editing, Validation. **Abbas Yadegar:** Writing – review & editing, Validation. **Annalisa Serio:** Writing – review & editing, Validation. **Saveria Lory Crocè:** Writing – review & editing, Validation, Conceptualization. **Mauro Giuffrè:** Writing – review & editing, Validation. **Paolo De Cristofaro:** Writing – review & editing, Validation. **Nina Grasselli Kmet:** Writing – review & editing, Validation. **Maria Vittoria Micioni Di Bonaventura:** Writing – review & editing, Validation. **Verena Zerbato:** Writing – review & editing, Validation. **Stefano Di Bella:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ejphar.2026.178594>.

## Data availability

No data was used for the research described in the article.

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