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Research progress of oxidative stress in sepsis-associated liver injury

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Highlights

- The approaches of antioxidant therapy to alleviate sepsis-associated liver injury are summarized from the perspective of oxidative stress in different cells of the liver.
- Reactive oxygen species, one of the main substances that induce oxidative stress, affects the molecular mechanism of the relevant signaling pathways.
- Antioxidant therapy is helpful for the recovery of various liver cells in sepsis-associated liver injury and is expected to advance basic and clinical research.

Abstract

Sepsis is a systemic inflammatory response that caused by infection or trauma, often resulting in multiple organ dysfunction. Its mortality rate is relatively high, ranging between 54% and 68%, and ineffective treatment and poor prognosis pose significant challenges to healthcare in recent years. One of the main pathogeneses of sepsis-induced liver injury is oxidative stress (OS), which refers to a state where the antioxidant system cannot balance oxidative products, leading to the accumulation of excessive oxidative products in the body. When sepsis occurs, the amount of reactive oxygen species produced by the body increases far beyond the levels that can be scavenged by the antioxidant system, thus damaging liver cells and aggravating liver damage. This article introduces the oxidative/antioxidant system, oxidative stress-related pathways, and the molecular mechanism of OS in various types of hepatocytes, with emphasis on the antioxidant treatment on different hepatocytes, in order to understand the mechanism of OS involved in the development and progression of sepsis-associated liver injury. As the research deepens, improving liver function through the treatment of different cells and facilitating related clinical research are expected to provide a new target pathway for the treatment of sepsis-associated liver injury.

Keywords: Sepsis-associated liver injury, liver injury, oxidative stress, reactive oxygen species

Introduction

Sepsis is a systemic inflammatory response caused by infection, trauma, and other factors, resulting in multi-organ dysfunction. In severe cases, it can progress to life-threatening septic shock and organ failure [1, 2]. Sepsis mainly induces liver injury, lung injury, cardiac dysfunction, gastrointestinal injury, and kidney injury. Among them, the liver is the most important detoxification and metabolic organ of the human body, and it is very susceptible to infection and damage. Previous studies have shown that the reasons for the pathogenesis of sepsis-associated liver injury include oxidative stress (OS), hepatic microcirculation disorders, energy metabolism disorders, inflammatory response, etc. [3-5]. When sepsis occurs, the main mechanism of liver injury is OS due to increased oxygen free radicals and peroxidation of lipids

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in the body [6]. Based on a review of recent literature, this paper summarizes the mechanism of OS-induced liver injury in sepsis, and the signaling pathways of reactive oxygen species (ROS) in sepsis-associated liver injury, as well as the effects of ROS on hepatocyte injury and antioxidant therapy.

Review progress

Oxidative stress

Oxidative damage

OS is a state of imbalance between oxidant and antioxidant in the body. When ROS and reactive nitrogen species such as nitric oxide (NO) increase in large quantities, the absence/shortage of antioxidants disrupts the balance in the body [7, 8]. ROS refers to oxygen free radicals and non-free radicals produced by the body, mainly containing the substrates of the respiratory chain of the inner mitochondrial membrane, such as O^{2-}, HO^{-} and H_2O_2, with oxidizing ability and toxic effects on most cells [9]. In a physiological state, as a by-product of the oxidation system, the production and clearance of ROS are in dynamic equilibrium in the body. Additionally, the level of ROS rises and exceeds the body's clearance ability, which can increase lipid peroxidation in related tissues, leading to abnormal expression of related proteins, DNA damage, and gene mutation [10]. Malondialdehyde (MDA), a lipid free radical, is the principal degradation product of lipid peroxides, which can damage mitochondrial and cell membranes, thereby inhibiting the function of membrane proteins, impairing the structural integrity of mitochondria, and leading to cell damage [10]. At the same time, NO synthase is greatly augmented, and NO can restrain the binding of mitochondrial cytochrome C to O_2, leading to mitochondrial dysfunction. Thus, damage to cellular mitochondria causes spillover of cytochrome C from mitochondria into the cytoplasm, contributing to apoptosis [11, 12]. Through a series of reactions, it eventually contributes to autophagy, necrosis, and apoptosis, etc.

Anti-oxidation system

The antioxidant system is composed of endogenous molecules, including both enzymes and non-enzymes. The main enzymes include superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), and catalase (CAT). To put it more precisely, SOD is an important antioxidant enzyme mainly involved in scavenging oxygen radicals. When ROS increases, SOD reacts with O^{2-} to produce H_2O_2, which is then converted into water by CAT and GSH-Px to remove ROS and protect cells from damage [13]. In contrast, when the contents of CAT, GSH-Px and SOD increase, the ROS and the MDA in the body reduce. The non-enzymes include vitamin C, vitamin E, uric acid, metal-binding protein, polyamines, bilirubin, carotenoids, etc. [14].

OS-related signaling pathways

Nuclear erythrocytes 2-related factor (Nrf2) signaling pathway

Nrf2 is a key factor in cellular oxidative stress and is negatively regulated by cytoplasmic Kelch-like ECH-associated protein 1 (Keap1) [15]. Under normal physiological conditions, Keap1 is a substrate linker protein of the Cullin3 (Cul3)-dependent E3 ubiquitin ligase complex. Keap1 contains three functional domains, a Broad-complex, Tramtrack, and Bric-à-brac (BTB) domain, an intervening region domain, and a Kelch or double-glycine repeat domain. Wherein, BTB domain binds to Cul3 to assemble into a functional E3 ubiquitin ligase complex (Keap1-Cul3-E3). Keap1-Cul3-E3 ubiquitin ligase targets the Neh2 domain located at the N-terminus of Nrf2 and promotes Nrf2 ubiquitination [16]. After that, ubiquitinated Nrf2 is delivered to the 26S proteasome for degradation.

When the body is in an OS state, ROS modifies specific cysteine residues in Keap1, causing conformational changes in Keap1-Cul3-E3 ubiquitin ligase and interfering with Nrf2 ubiquitination [17]. Alternatively, it facilitates the breakdown of Nrf2 with Keap1 by activating protein kinase C. Nrf2 is then transferred into the nucleus by oxidative stressors such as electrophiles and binds to the antioxidant response element (ARE) by heterodimerization with the small Maf transcription factors [18]. Subsequently, the Nrf2-ARE signaling pathway initiates and promotes the expression of antioxidant enzyme genes, such as CAT, SOD, GSH-Px, glutathione S-transferase, NADH quinone oxidoreductase 1, and heme oxygenase 1, which in turn provides antioxidant defense [19, 20]. Moreover, ROS activates glycogen synthase kinase 3, nucleating phosphorylated Nrf2 and Keap1 and affecting the degradation of Nrf2 (**Figure 1**) [21]. In general, ROS can promote Nrf2 into the nucleus through various ways, and then activate its downstream pathway.

Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling pathway

NF-κB is a transcription factor protein that con-

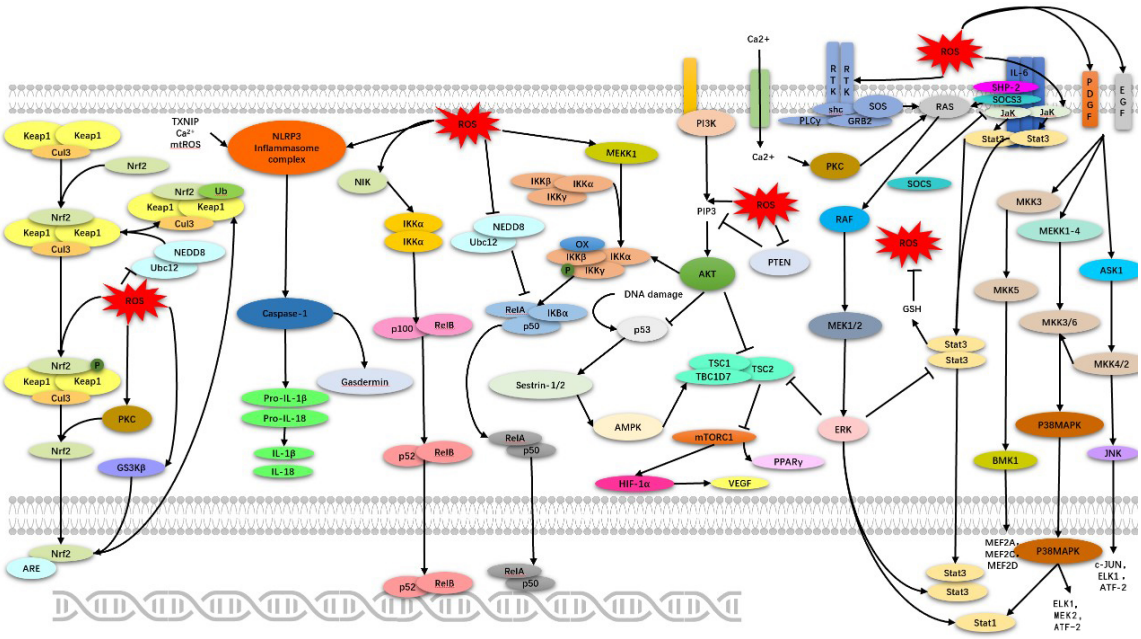

Figure 1. Effects of ROS on different signaling pathways. ROS, reactive oxygen species; Keap1, Kelch-like ECH-associated protein 1; Cul3, Cullin3; Nrf2, Nuclear erythrocytes 2-related factor; ARE, antioxidant response element; Ubc, E2-ubiquitin conjugating enzyme; NEDD8, neural precursor cell expressed developmentally downregulated 8; NLRP3, Nucleotide-binding oligomerization domain-like receptor protein 3; NIK, Nuclear factor kappa-light-chain-enhancer of activated B cells inducing kinase; IKK, IκB kinase; MEKK1, mitogen-activated protein kinase kinase kinase 1; AMPK, adenosine 5'-monophosphate-activated protein kinase; PI3K, Phosphatidylinositol 3-kinase; PIP3, phosphatidylinositol 3, 4, 5-triphosphate; AKT, activate protein kinase B; TSC, tuberous sclerosis complex (consisting ofTSC1, TSC2, TBC1D7); VEGF, vascular endothelial growth factor; PTEN, phosphatase and tensin homolog; RTK, receptor tyrosine kinase; shc, recombinant protein; GRB, growth factor receptor-bound protein; SOS, son of sevenless; PLCγ, specific phospholipase Cγ; STAT; Signal transducer and activator of transcription; SOCS, suppressor of cytokine signaling; SHP-2, Src homology 2 domain-containing protein tyrosine phosphatase; JAK, janus kinase; MAPK, Mitogen-activated protein kinase; MEF2, myocyte enhancer factor 2 (contain: MEF2A, MEF2C, MEF2D); ELK1, ETS transcription factor; ATF-2, activating transcription factor 2; ERK, extracellular signal-regulated kinase; ASK1, apoptosis signal-regulating kinase 1; PDGF, platelet-derived growth factor; JNK, c-Jun N-terminal kinase; PPAR, Peroxisome proliferator-activated receptor; HIF-1α, hypoxia-inducible factor-1 alpha; TXNIP, Thioredoxin-interacting protein; GSH, glutathione; PKC, protein kinase C; Raf, rapidly accelerated fibrosarcoma; OX, oxide. ⟶ : activation; —I: inhibition.

tains five different family proteins: Rel A (p65), Rel B, c-el, p105 (p50 precursor/NF-κB1), and p100 (p52 precursor/ NF-κB2), by forming homologous or heterologous dimers with the DNA-binding protein -Rel [22]. NF-κB is regulated by proteins of the IκBs family, including IκBα, IκBβ, IκBγ, IκBε, and B cell leukemia-3. In a physiological state, NF-κB is inactivated in the cytoplasm due to its binding with IκBα [23]. NF-κB activation occurs through two major signaling pathways: canonical and non-canonical NF-κB signaling pathways. The canonical pathway refers to the activation of IκB kinase (IKK) and subsequent phosphorylation of IκBα. IκBα in the complex dissociates from NF-κB1, activating NF-κB1 [24]. The non-canonical NF-κB pathway refers to NF-κB inducing kinase activation and subsequent phosphorylation of IKKα. IKKα phosphorylates p100 to degrade to p52 [25]. Following this, the combination of Rel B and p52 translocates to the nucleus to regulate gene transcription [26].

During OS, ROS mainly affects the activation of NF-κB by activating phosphorylation of IκBα and adjusting the mitogen-activated protein kinase kinase kinase 1 (MEKK1) upstream of IKK [27-29]. ROS can also interfere with ubiquitination and degradation of IκB by inactivating Ubc12, thereby impacting the activation of NF-κB [30]. In the non-canonical pathway, ROS could activate NF-κB2 by upregulating NF-κB inducing kinase (**Figure 1**) [31].

Nucleotide-binding oligomerization domain-like receptor protein 3 (NLRP3) signaling pathway

NLRP3 can form NLRP3 inflammasome bodies with precursors of apoptosis-associated spot-like protein in the caspase recruitment domain and cysteinyl aspartate specific proteinase 1 (Caspase-1). NLRP3 inflammasome is a

multi-protein macromolecular complex that processes Pro Caspase-1 into bioactive Caspase-1, cuts Gasdermin protein to cause cell perforation and mediates interleukin (IL) 1β- and IL-18-related responses.

With the invasion of pathogen-associated molecular patterns or damage associated molecular patterns, mitochondria are stimulated to produce ROS. ROS activates NLRP3 inflammasomes or reacts with thioredoxin interaction, which then releases thioededoxin and activates NLRP3 inflammasomes (**Figure 1**) [32].

Mitogen-activated protein kinase (MAPK) signaling pathway

The cascade of MAPK consists of four main components: extracellular signal-associated kinase (ERK1/2), c-Jun N-terminal kinase, p38 kinase (p38), and large mitogen-activated protein (MAP) kinase 1 (BMK1/ERK5) [33]. MAP kinase kinase kinase (MAPKKK/MEKK/MKK) is activated, which then phosphorylates and activates MAP kinase kinase (MAPKK/MEK/MKK). Phosphorylation of MAPKK activates MAP kinase (MAPK), which, in turn, phosphorylates various substrate proteins [34].

ROS can activate receptors of epidermal growth factor and platelet-derived growth factor, activating Ras on cell membranes. Ras then recruits rapidly accelerated fibrosarcoma (Raf) (MAPKKK) in cytoplasm into the cell membrane for activation [35]. Activated Raf phosphorylates MEK1/2(MAPKK), which then results in ERK activation [36]. ROS acts on thioededoxin and glutaraldehyde, dissociating them from MAPKKKs such as apoptosis signal-regulating kinase 1 and MEKK1-4 [37]. This activation of MAPKKKs leads to the activation of MAPKK, subsequently activating c-Jun N-terminal kinase, p38, and BMK1 (**Figure 1**).

Phosphatidylinositol 3-kinase (PI3K) signaling pathway

PI3K catalyzes the synthesis of phosphatidylinositol 3, 4, 5-triphosphate to recruit and activate protein kinase B (AKT). Furthermore, it promotes the activation and transcription of Sestrins, endothelial nitric oxide synthase, forkhead box protein O, mechanistic target of rapamycin 1, and p53.

ROS can not only activate PI3K and its downstream signaling pathways, but also inactivate phosphatase and tensin homolog (PTEN) and inhibit AKT activation by negatively regulating phosphatidylinositol 3, 4, 5-triphosphate. Its downstream pathway, Sestrins, comprises stress response proteins crucial for cellular adaptation to OS. Sestrins play a significant role in enhancing the body's tolerance to OS, preventing the accumulation of ROS and MDA through its inherent antioxidant activity and the regeneration of thiol peroxidase (peroxiredoxin) [38, 39]. Sestrin2 also inhibits sepsis-associated liver injury by activating the transcription factors p53, Nrf2, and hypoxia-inducible factor-1α [40]. The other downstream pathway, mTOR, is a class of serine/threonine kinases that affect the OS of the body by regulating hypoxia-inducible factor-1α, peroxisome proliferators-activated receptors-γ and other pathways (**Figure 1**).

Signal transducer and activator of transcription (STAT) signaling pathway

STAT, including STAT1-4, STAT5 (STAT5A and STAT5B), and STAT6, is also an important protein for OS. When IL-6 and other cytokines bind to the relevant receptors, they can change the molecular conformation of the receptor [41]. The coupled Janus kinase (JAK) kinases approach each other and phosphorylate tyrosine to activate the JAK kinases. The activated JAK kinases allow the corresponding STATs to form docking site with the receptor complex and bind to the receptor through its SH2 domain [42]. In response to JAK kinase, STATs are activated by phosphorylation and then form homo/heterodimers for incorporation into the nucleus. Dimeric STATs can bind to the promoters of target genes, and then the transcription of related genes can be activated [43].

During OS, ROS can inactivate tyrosine phosphatases and STAT phosphorylation. STAT3 also up-regulates glutathione to scavenge ROS (**Figure 1**) [44, 45].

Molecular mechanism of OS in sepsis-associated liver injury and antioxidant therapy

Hepatocytes

The roles of ROS production and accumulation in hepatocyte membrane and OS in sepsis-associated liver injury should not be underestimated. The main site of OS damage is the hepatocyte membrane. ROS can degrade unsaturated fatty acids on the hepatocyte membrane into lipid peroxides, which can aggravate the damage to mitochondria [46]. After mitochondria are damaged by ROS, they release cytochrome C into the cytoplasm and cause hepatocyte apoptosis. When sepsis occurs, the content of inducible nitric oxide synthase in the liver is significantly increased. Inducible nitric

Table 1. Signaling pathways and therapeutics of different cellular antioxidant therapies in liver

Types	Signaling pathway	Therapeutic agents
Hepatocyte	mTOR / p70S6K	Albiflorin [53], Anemoside B4 [54]
	Nrf2 / NF-κB	Wogonin [52]
	SIRT1 / STAT3	Melatonin [55]
	SIRT1 / AMPK	Ginsenoside R3 [51]
	Nrf2 / NLRP3	Malvidin [50]
	RAGE / p38	Idebenone [49]
Hepatic stellate cells	VEGF	Dihydroartemisinin [62]
	Nrf-2	Schisandrin B [60]
	ZEB-2 / PTEN	Orientin [59]
	CYP2E/Nrf2 / ROS and PI3K / AKT	Sophocarpine [63]
	ROS / NF-κB	Chlorogenic acid [64]
Hepatic sinusoidal endothelial cells	TLR4 / NFκB	Liquiritigenin and liquiritin [68]
	ROS / ERK	Curcumol [67]
Kupffer cells	CUL3	Pyrroloquinoline quinone [71]
	AMPK	Isoquercetin [72]
	TLR4 / NF-κB / NLRP3	Ginsenoside Rb1 [73]

Note: Nrf2, Nuclear erythrocytes 2-related factor; p70S6K, ribosomal protein S6 kinase; NF-κB, Nuclear factor kappa-light-chain-enhancer of activated B cells; SIRT1, silent information regulator 1; STAT; signal transducer and activator of transcription; AMPK, adenosine 5'-monophosphate-activated protein kinase; NLRP3, Nucleotide-binding oligomerization domain-like receptor protein 3; RAGE, receptor for advanced glycation end products; VEGF, vascular endothelial growth factor; ZEB-2, zinc finger E-box binding homeobox2; PTEN, phosphatase and tensin homolog; CYP2E1, cytochrome P450 family 2 subfamily E member 1; ROS, reactive oxygen species; ERK, extracellular signal-regulated kinase; PI3K, Phosphatidylinositol 3-kinase; AKT, activate protein kinase B; TLR4, toll-like receptor 4; Cul3, Cullin3.

oxide synthase can induce a large amount of NO, which in turn can react with mitochondrial cytochrome oxidase to inhibit the activity of cytochrome oxidase, and then bring about structural and functional damage on mitochondrial proteins. NO can also react with O^{2-} to generate strong oxidative nitrite peroxide ions, which can oxidize with various molecules, giving rise to apoptosis [47].

Celep et al. found that silymarin could alleviate sepsis-associated liver injury by reducing OS [48]. Gou et al. revealed that Idebenone could prevent sepsis-induced OS, apoptosis, and inflammation by inhibiting RAGE/p38 signaling [49]. Fan et al. discovered that Malvidin prevented the lipopolysaccharide (LPS)-induced decrease in antioxidant enzyme activity by upregulating the Nrf2 pathway, and at the same time inhibited the NLRP3 inflammasome, apoptosis, and autophagy, thereby alleviating sepsis-associated liver injury [50]. Wu et al. reported that ginsenoside Rg3 decreased ROS and stimulated the SIRT1/AMPK pathway, thereby enhancing autophagy to ameliorate sepsis-associated liver injury and mitochondrial dysfunction [51]. Dai et al. demonstrated that Wogonin improved both OS and inflammatory response by activating Nrf2, thus acting as a protective agent against sepsis-associated liver injury [52]. Liu et al. and Pei et al. found that both albiflorin and anemoside B4 inhibited LPS-induced apoptosis and OS of primary hepatocytes through the mTOR/p70S6K signaling pathway, and alleviated liver damage induced by sepsis [53, 54]. Chen et al. and Kleber et al. concluded that melatonin played a protective role in sepsis-induced liver injury by reducing ROS and activating SIRT1/STAT3 pathway [55, 56] (**Table 1**).

Hepatic stellate cells (HSCs)

HSCs are endothelial pericytes located in the hepatic sinusoid space. During liver injury, HSCs are activated into myofibroblasts and secrete extracellular matrix to participate in injury repair. At the same time, the activation of HSCs is also the central link in the development and progression of liver fibrosis [57]. HSCs also bring forth a large number of cytokines, chemokines, and growth mediators and express cell adhesion molecules in response to stimuli such as endotoxin (LPS). Hepatocyte injury results in the release of damage associated molecular patterns, which stimulates HSCs and Kupffer cells (KCs). Further, stimulation of HSCs and KCs recruit immune cells and secrete proinflammatory mediators. Interaction between HSCs and KCs produces a two-way environmen-

tal interaction, leading to the release of pro-inflammatory and anti-inflammatory cytokines. This continued release contributes to ongoing liver damage [58].

It has been found that orientin inhibited HSC activation and reduced LPS and CCl_4-induced liver injury by down-regulating ZEB-2/PTEN [59]. Yao et al. found that schisandrin B attenuated OS in LPS-induced HSC activation through the Nrf2 signaling pathway [60]. Rani et al. revealed that HSCs-sufficient mice treated with acetaminophen exhibited stronger OS compared to HSCs-depleted mice, suggesting that HSCs plays a major role in OS in hepatocytes [61]. Huan et al. found that dihydroartemisinin inhibited HSCs activation by regulating miR-29b-3p to affect vascular endothelial growth factor pathway [62]. Jiang et al. reported that sophocarpine alleviated LPS-induced liver injury, OS and inflammation by inhibiting CYP2E/Nrf2/ROS and PI3K/AKT pathways [63]. Shi et al. demonstrated that chlorogenic acid inhibited LPS-induced proinflammatory responses to HSCS through inhibition of the ROS/NF-κB signaling pathway (**Table 1**) [64].

Hepatic sinusoidal endothelial cells

Liver sinusoidal endothelial cells (LSECs) are highly sensitive to OS. ROS and reactive nitrogen species can reduce the activity of endothelial nitric oxide synthase messenger RNA, leading to dysfunction of LSECs. This dysfunction promotes vasoconstriction, increases intercellular block, raises vascular permeability, and accelerates thrombosis, and further aggravates liver injury [65].

Research indicated that artesunate enhanced the defense of LSECs and prevented the aggregation of inflammatory immune cells, mitigating the effects of sepsis-associated liver injury, inflammation, and dysfunction [66]. Gao et al. demonstrated that curcumin inhibited the angiogenesis of recombinant Kruppel like factor 5-mediated LSECs by inhibiting ROS/ERK signaling [67]. Chen et al. found that glycyrrhizin attenuated cyclophosphamide-induced LSEC injury and inflammatory injury in mice by reducing liver peroxidase activity (**Table 1**) [68]. Pioglitazone can suppress the activation of NF-κB, activator protein-1, MAPK and other inflammatory signaling pathways, and inhibit the release of ROS by KCs, the generation of cytokines and pro-inflammatory mediators, and the expression of adhesion molecule genes in LSECs. Tai et al. discovered that celecoxib reduced ROS through both cyclooxygenase-2 dependent and independent signaling pathways. This reduction in ROS is associated with a significant decrease in NO clearance, subsequently reducing LSEC capillaries and correcting endothelial dysfunction [69].

KCs

KCs are the most important resident macrophages in the liver with abilities of self-renewal, clearance of endotoxin by phagocytosis and release of inflammatory factors to maintain immune homeostasis in the liver. At the same time, during sepsis, KCs can facilitate the development of OS by releasing ROS. KCs further interact with hepatocytes to produce and release chemokines to recruit monocytes in the circulation and subsequently differentiate into monocyte-derived macrophages [70].

Wu et al. found that pyrroloquinoline quinone could inhibit Cul3 expression to alleviate OS and inflammation caused by KCs in sepsis-associated liver injury [71]. Qin et al. revealed that Isoquercetin alleviated inflammation and OS by activating AMPK pathway and inhibiting transforming growth factor β signaling [72]. Liu et al. found that ginsenoside Rb1 attenuated OS and inflammation through TLR4/NF-κB signaling pathway and NLRP3 inflammasome activation [73]. Zhou et al. demonstrated that ultralow doses of dextromethorphan reduced superoxide radicals and alleviated OS in KCs (**Table 1**) [74]. Zhai et al. reported that NADPH oxidase 4 activated the NLRP3 inflammasome through the generation of ROS. This activation promotes the inflammatory response of KC and the release of inflammatory factors, and inhibition of NADPH oxidase 4 ameliorated acute liver injury in mice [75]. Zhang et al. observed that stimulator of interferon genes signaling in KCs enhanced ROS production in response to LPS stimulation, which upgraded mitochondrial DNA release and hepatocyte death, contributing to LPS-induced liver injury [76].

Conclusion

In summary, OS plays an important role in the development and progression of sepsis-associated liver injury. Nrf2, NF-κB, PI3K, NLRP3, MAPK, STAT and other signaling pathways can regulate OS. This review provides the theoretical basis for the antioxidant therapy of sepsis-associated liver injury. Furthermore, liver circulatory and metabolic disorders, excessive inflammatory response, mitochondrial dysfunction, neutrophil and neutrophil extracellular trapping, and autophagy are all mechanisms leading to sepsis associated liver injury. At present, there are many studies on hepatic paren-

chymal cells and KCs in sepsis-associated liver injury. Most of the studies on hepatic stellate cells and hepatic sinusoidal endothelial cells are related to the treatment of liver fibrosis and cirrhosis, but few on sepsis-associated liver injury. This paper summarizes the OS status of different hepatocytes and the treatment of parenchymal and non-parenchymal cells, which can provide ideas for basic clinical research on sepsis related liver injury, so as to reduce the mortality of sepsis related liver injury.

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