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Potential Role of *Moringa oleifera* in Reducing Inflammation and Oxidative Stress in Sepsis-Related Reperfusion Injury

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ABSTRACT

Introduction: Sepsis-associated ischemia–reperfusion injury amplifies oxidative stress and inflammation, driving organ dysfunction. *Moringa oleifera* contains flavonoids, isothiocyanates (e.g., MIC-1) and other phytochemicals with reported antioxidant and anti-inflammatory activities that may mitigate these processes
Methods: This study was conducted as a narrative literature review. Relevant articles were searched in PubMed, Google Scholar, and Scopus using keywords related to sepsis, reperfusion injury, oxidative stress, inflammation, and *Moringa oleifera*. Articles published between 2016 and 2026, available as open-access full texts in English or Indonesian, were included. Selected studies were screened by title, abstract, and full text, and the findings were analyzed descriptively.
Results: *Moringa oleifera* contains a wide range of bioactive compounds, including phenolic acids, flavonoids, fatty acids, and isothiocyanates, which are widely recognized for their antioxidant and anti-inflammatory properties. These compounds may help reduce oxidative stress primarily by scavenging reactive oxygen species (ROS), lowering malondialdehyde (MDA) levels, and enhancing the activity of antioxidant enzymes such as superoxide dismutase and glutathione peroxidase
Conclusion: *moringa oleifera* shows reproducible antioxidant and anti-inflammatory effects in vitro and in animal models of sepsis-related reperfusion injury, supporting its potential as an adjunctive therapy to reduce reperfusion-mediated organ damage. Well-designed clinical trials and standardized extract/dose protocols are required to establish efficacy and safety in humans

Keywords: Antioxidant activity; Cytokines; Inflammation; *Moringa oleifera*; Oxidative stress

INTRODUCTION

Sepsis is a severe and potentially life-threatening condition that arises from an abnormal or dysregulated host response to infection. This response can trigger widespread inflammation, increased oxidative stress, and ultimately result in dysfunction across multiple organs[1,2]. Even with improvements in critical care and clinical management, sepsis continues to represent a major contributor to illness and death worldwide[3]. A key pathological feature of severe sepsis is the development of ischemia–

reperfusion injury, which occurs when impaired tissue perfusion during septic shock is followed by restoration of blood flow[4]. this process can paradoxically worsen cellular damage due to the excessive generation of reactive oxygen species (ROS) and the subsequent activation of inflammatory signaling pathways[5].

During reperfusion, sudden oxygen availability promotes mitochondrial generation of ROS, resulting in oxidative damage to lipids, proteins, and DNA. Biomarkers such as malondialdehyde (MDA) and hydrogen peroxide are commonly elevated during this process and reflect the degree of oxidative stress. At the same time, pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) are produced in substantial amounts, contributing to the cytokine storm that characterizes sepsis and further aggravates tissue damage[6,7]. The body's antioxidant defense mechanisms, including enzymes like superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase, normally function to neutralize reactive oxygen species. However, during intense inflammatory conditions, these protective systems are frequently overwhelmed[8].

Given the central role of inflammation and oxidative stress in sepsis-associated reperfusion injury, there is increasing interest in identifying therapeutic agents capable of modulating these pathways. Natural plant-derived compounds have attracted particular attention because of their antioxidant and immunomodulatory properties. Among these, *Moringa oleifera* has been widely studied for its rich content of bioactive phytochemicals, including flavonoids, phenolic acids, isothiocyanates, and fatty acid derivatives. These compounds have been reported to possess considerable antioxidant and anti-inflammatory properties. Their effects are mainly associated with mechanisms such as suppression of the NF-κB signaling pathway and activation of the Nrf2-mediated antioxidant response[9,10].

Several experimental studies have reported that *Moringa oleifera* extracts can reduce inflammatory cytokine production, enhance endogenous antioxidant defenses, and protect tissues from oxidative damage in various disease models[11–13]. These properties suggest that *Moringa oleifera* may have therapeutic potential in mitigating the pathological mechanisms underlying sepsis-related reperfusion injury.

Therefore, this review aims to explore the potential role of *Moringa oleifera* in reducing inflammation and oxidative stress associated with sepsis-related reperfusion injury, focusing on the molecular mechanisms, bioactive compounds, and experimental evidence supporting its protective effects.

METHOD

This study was carried out as a narrative literature review aimed at examining the potential role of *Moringa oleifera* in reducing inflammation and oxidative stress linked to sepsis-associated reperfusion injury. Relevant literature was identified through searches of electronic databases, including Google Scholar, PubMed, and Scopus. The search used combinations of keywords related to sepsis, reperfusion injury, inflammation, oxidative stress, and *Moringa oleifera*. Additional terms related to inflammatory cytokines and antioxidant systems, such as IL-6, TGF-β, and superoxide dismutase (SOD), were also included to identify studies discussing relevant inflammatory and oxidative stress pathways. Boolean operators (AND, OR) were used to refine the search.

Articles were included if they were published within the last 10 years (2016–2026), available as open-access full-text articles, written in English or Indonesian, and relevant to sepsis pathophysiology, reperfusion injury, inflammatory and oxidative stress mechanisms, or the pharmacological effects of *Moringa oleifera*. Experimental studies, clinical studies, and review articles were considered. Articles published before 2016, not available as open access, written in languages other than English or Indonesian, unrelated to the topic, or duplicate publications were excluded.

Relevant studies were initially screened based on title and abstract, followed by full-text review of eligible articles. The selected literature was analyzed descriptively and organized into thematic sections covering the pathophysiology of sepsis, mechanisms of reperfusion injury, inflammation and oxidative stress pathways, and the pharmacological properties and potential therapeutic role of *Moringa oleifera.*

RESULT

Pathophysiology of Sepsis

Sepsis is a complex clinical syndrome characterized by a dysregulated systemic inflammatory response to infection, which can ultimately lead to widespread tissue injury and organ dysfunction. The pathophysiology of sepsis involves an imbalanced immune response in which both pro-inflammatory and anti-inflammatory processes are activated simultaneously. In this process, pathogen-associated molecular patterns (PAMPs) are recognized by pattern recognition receptors, particularly Toll-like receptors, which then trigger a series of intracellular signaling events. One of the major pathways involved is the nuclear factor-kappa B (NF-κB) signaling pathway, which plays an important role in promoting the production of several pro-inflammatory cytokines, including tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6)[9,14].

Among these mediators, IL-6 has an important role in the progression of sepsis, as it contributes to systemic inflammatory response syndrome (SIRS), immune system dysregulation, and subsequent organ injury. Increased levels of IL-6 have also been linked with greater disease severity and complications observed in sepsis, including muscle wasting and various metabolic disturbances[7]. Similarly, TNF-α acts as an early inflammatory mediator that promotes endothelial activation, leukocyte recruitment, and vascular permeability, which collectively contribute to tissue injury[15].

In addition to inflammatory signaling, sepsis also disrupts microcirculatory function and tissue oxygen delivery[16]. Endothelial dysfunction and excessive nitric oxide production lead to impaired vascular tone and hypotension, while increased leukocyte adhesion and microvascular thrombosis further compromise tissue perfusion. These changes result in cellular hypoxia and metabolic disturbances, predisposing tissues to ischemic injury[17,18].

At the same time, oxidative stress is considered to play a significant role in the development of sepsis. During infection, excessive generation of reactive oxygen species (ROS) can overwhelm the body's natural antioxidant defenses, leading to lipid peroxidation, mitochondrial impairment, and damage to cellular structures. Increased levels of oxidative stress indicators, such as malondialdehyde (MDA) and hydrogen peroxide, have also been observed in experimental models of sepsis and reperfusion injury [6,12].

The imbalance between pro-inflammatory cytokines, oxidative stress, and impaired microcirculation ultimately leads to multi-organ dysfunction, affecting vital organs such as the kidneys, liver, lungs, and heart. For example, acute kidney injury is a common complication of sepsis and is often associated with inflammatory cytokine release, oxidative stress, and mitochondrial dysfunction[19]. These pathological processes set the stage for ischemia–reperfusion injury, which can further exacerbate organ damage when blood flow is restored.

Reperfusion Injury in Sepsis

Ischemia–reperfusion injury is a critical pathological process that contributes to organ dysfunction during sepsis[4,20]. In septic patients, impaired tissue perfusion caused by hypotension, microvascular dysfunction, and endothelial injury leads to periods of tissue ischemia, during which oxygen and nutrient delivery to cells are significantly reduced[21]. When circulation is subsequently

restored through resuscitation or recovery of vascular function, the sudden reintroduction of oxygen paradoxically triggers a cascade of damaging biochemical events known as reperfusion injury[5].

One of the key mechanisms involved in reperfusion injury is the excessive production of reactive oxygen species (ROS). During ischemia, mitochondrial electron transport chains become disrupted, leading to accumulation of partially reduced oxygen intermediates. Upon reperfusion, rapid oxygen availability results in a burst of ROS production. This process involves the formation of several reactive oxygen species, including superoxide radicals, hydrogen peroxide, and hydroxyl radicals. These reactive molecules can damage important cellular components such as lipids, proteins, and DNA, which ultimately disrupts normal cellular function and reduces cell viability [6,12].

Lipid peroxidation is a major consequence of oxidative stress during reperfusion injury, often reflected by increased levels of malondialdehyde (MDA), a widely used marker of oxidative damage. Experimental models of ischemia–reperfusion injury have consistently shown elevated MDA levels alongside reductions in antioxidant defense systems such as superoxide dismutase (SOD) and glutathione (GSH)[11,12]. The depletion of these antioxidant enzymes further exacerbates oxidative injury and promotes mitochondrial dysfunction.

Reperfusion injury also activates inflammatory pathways that amplify tissue damage. Oxidative stress stimulates the release of pro-inflammatory cytokines including IL-6 and TNF-α, which promote leukocyte infiltration, endothelial activation, and increased vascular permeability. Neutrophil accumulation in affected tissues further enhances oxidative damage through the release of proteolytic enzymes and additional reactive oxygen[13].

In addition to oxidative and inflammatory mechanisms, reperfusion injury can trigger programmed cell death pathways. Activation of apoptotic mediators such as caspase-3 and Bax has been observed in experimental models of ischemia–reperfusion injury, leading to cellular apoptosis and further organ damage[11,19]. These processes collectively contribute to the progression of multi-organ dysfunction in sepsis.

Given the interconnected roles of oxidative stress, inflammation, and apoptosis in reperfusion injury, therapeutic strategies that target these mechanisms may provide significant protective effects. Natural compounds with antioxidant and anti-inflammatory properties have therefore attracted increasing attention as potential adjunct therapies for reducing reperfusion-associated tissue damage.

Role of Inflammation and Oxidative Stress in Reperfusion Injury

Inflammation and oxidative stress are interconnected mechanisms that amplify tissue damage during sepsis-related reperfusion injury. Excessive reactive oxygen species (ROS) production promotes oxidative damage to cellular membranes, proteins, and nucleic acids, resulting in cellular dysfunction and tissue injury[22,23]. Elevated malondialdehyde (MDA) levels and impaired antioxidant defense systems, including superoxide dismutase (SOD) and glutathione peroxidase (GPx), have been consistently reported in experimental models of sepsis and ischemia–reperfusion injury, reflecting increased oxidative stress and disrupted cellular redox balance [6,11,12,13,,24].

Besides oxidative stress, reperfusion injury also induces a pronounced inflammatory response marked by increased production of pro-inflammatory cytokines. Among these mediators, interleukin-6 (IL-6) is widely recognized as an important biomarker of systemic inflammation in sepsis. Elevated IL-6 levels contribute to immune dysregulation, endothelial activation, and the amplification of cytokine signaling pathways, which can further exacerbate tissue damage[7]. Similarly, cytokines such as tumor necrosis factor-α (TNF-α) promote leukocyte recruitment and endothelial dysfunction, thereby enhancing inflammatory injury during reperfusion[9].

Regulatory cytokines also play important roles in the inflammatory response. Transforming growth factor-β (TGF-β) is involved in immune modulation and tissue remodeling processes that occur during inflammatory injury. While TGF-β can help regulate immune responses, excessive activation of

TGF-β signaling has been associated with fibrosis and tissue remodeling following severe inflammatory damage[6,25].

The interaction between oxidative stress and inflammatory signaling further amplifies tissue injury during reperfusion. are known to activate transcription factors such as NF-κB, which in turn promotes the increased production of pro-inflammatory cytokines[5,26]. In turn, inflammatory mediators stimulate immune cells such as neutrophils and macrophages to generate additional reactive oxygen species, creating a self-perpetuating cycle of oxidative and inflammatory damage[27].

The roles of key inflammatory and oxidative stress biomarkers involved in sepsis-related reperfusion injury are summarized in Table 1.

Table 1. Role of Key Biomarkers in SepsisReperfusion Injury

Biomarker	Type	Role in Sepsis and Reperfusion Injury	References
IL-6	Pro-inflammatory cytokine	Elevated during sepsis and ischemia-reperfusion injury; contributes to cytokine storm, immune dysregulation, and organ damage.	6,7,9,11,24,25
TNF-α	Pro-inflammatory cytokine	Key mediator of systemic inflammatory response syndrome (SIRS); promotes endothelial activation, leukocyte recruitment, and tissue injury.	6,9,11,24,25
TGF-β / TGF-β1	Regulatory cytokine	Involved in immune regulation and fibrosis; activation of TGF-β signaling contributes to tissue remodeling and inflammatory responses in sepsis.	6,25
Neutrophils	Innate immune cells	Increased neutrophil activation contributes to inflammatory damage and oxidative burst during sepsis.	13
ROS (Reactive Oxygen Species)	Oxidative stress markers	Excess ROS generated during reperfusion damages lipids, proteins, and DNA, leading to cellular injury.	9
MDA (Malondialdehyde)	Lipid peroxidation marker	Indicates oxidative damage to cellular membranes during sepsis-induced oxidative stress.	6,11–13,24
SOD / SOD-1	Antioxidant enzyme	Converts superoxide radicals to hydrogen peroxide; reduced activity contributes to oxidative stress during sepsis.	6,19,24
GPx / GST	Antioxidant enzymes	Detoxify peroxides and maintain cellular redox balance during oxidative stress.	12
GSH / Thiol compounds	Non-enzymatic antioxidants	Maintain intracellular redox balance and protect cells against oxidative damage.	12
NO (Nitric Oxide)	Reactive nitrogen species	Excess nitric oxide contributes to inflammatory tissue damage and vascular dysfunction.	12
H_2O_2	Reactive oxygen species	Elevated during oxidative stress and contributes to mitochondrial and cellular injury.	12
AOPP / Protein carbonyls	Protein oxidation markers	Indicators of oxidative damage to proteins during reperfusion injury.	12
Caspase-3	Apoptotic enzyme	Mediates programmed cell death following oxidative and inflammatory injury.	12

Ultimately, the combined effects of oxidative stress and inflammatory signaling contribute to endothelial dysfunction, mitochondrial injury, and activation of apoptotic pathways, resulting in progressive tissue damage and organ dysfunction during sepsis-related reperfusion injury[28]. Because these mechanisms are closely interconnected, therapeutic interventions that simultaneously target both

oxidative stress and inflammatory responses may provide promising strategies for mitigating reperfusion-associated organ damage[29].

Overview of *Moringa oleifera*

Moringa oleifera, commonly referred to as the drumstick tree or miracle tree, is a medicinal plant widely distributed across tropical and subtropical regions. The plant has long been utilized in traditional medicine, largely because of its rich nutritional composition and diverse pharmacological properties. Different parts of the plant, including the leaves, seeds, and pods, are known to contain a variety of bioactive compounds that exhibit antioxidant, anti-inflammatory, antimicrobial, and immunomodulatory activities[30,31].

Table 2. Bioactive compounds of Moringa oleifera and their biological activities

Specific Compound	Chemical Class	Plausible Biological Activity
Quercetin	Flavonoid	Scavenges ROS, inhibits lipid peroxidation, and enhances antioxidant enzymes (SOD, GPx).[12]
Kaempferol	Flavonoid	Reduces oxidative stress and suppresses inflammatory cytokines during reperfusion injury.[12]
Luteolin	Flavonoid	Suppresses NF-κB signaling and reduces pro-inflammatory cytokine production.[10]
Apigenin	Flavonoid	Exhibits antioxidant and anti-inflammatory activities through ROS scavenging. [10]
Caffeic acid	Phenolic acid	Inhibits oxidative stress and reduces inflammatory mediator production.[32]
Ferulic acid	Phenolic acid	Protects against lipid peroxidation and oxidative cellular injury. [32]
Oleic acid	Unsaturated fatty acid	Provides membrane-protective antioxidant effects and reduces inflammation.[11]
α-Linolenic acid	Unsaturated fatty acid	Modulates inflammatory responses and supports cellular antioxidant defense. [10]
3-Hydroxy-β-ionone	Terpenoid derivative	Suppresses inflammatory signaling in activated macrophages.[14]
γ-Diosphenol	Terpenoid derivative	Demonstrates antioxidant and anti-inflammatory activities. [14]
α-Tocopherol	Vitamin E compound	Prevents lipid peroxidation and protects cells against oxidative damage. [33]
Moringa isothiocyanate-1 (MIC-1)	Isothiocyanate	Activates Nrf2 signaling, inhibits NF-κB activation, reduces ROS, IL-6, and TNF-α. [9,33]
Oleamide	Fatty-acid amide	Inhibits TGF-β/SMAD signaling and reduces IL-6, IL-8, and MMP-9 expression. [34]
Moringinine A	Phenolic ester compound	Exhibits anti-inflammatory activity and modulates IL-6-associated signaling pathways. [32]
Hydrazine derivatives	Small organic compounds	Contribute to antioxidant and radical-scavenging activity. [11]

Among these plant components, Moringa leaves contain abundant bioactive compounds, including polyphenols, flavonoids, vitamins, and other phytochemicals. These compounds contribute to the plant's strong antioxidant capacity and its ability to modulate inflammatory responses.[31] Flavonoids such as quercetin, kaempferol, luteolin, and apigenin are among the most abundant bioactive compounds found in *Moringa oleifera* leaves and have been shown to possess potent free radical–scavenging activity. These flavonoids are reported to help alleviate oxidative stress by scavenging

reactive oxygen species and stimulating antioxidant signaling pathways, including activation of the Nrf2 pathway[10].

Besides flavonoids, *Moringa oleifera* leaves also contain several phenolic acids, such as caffeic acid, ferulic acid, and p-coumaric acid, which are known to contribute to their antioxidant and anti-inflammatory properties.. These compounds have been shown to inhibit lipid peroxidation and reduce oxidative damage in cellular and animal models[10,32]. Other bioactive molecules such as unsaturated fatty acids (e.g., oleic acid and α-linolenic acid) may provide membrane-protective and anti-inflammatory properties that support cellular stability during oxidative stress[19,33].

Furthermore, specialized phytochemicals such as moringa isothiocyanate-1 (MIC-1) have been identified as key bioactive compounds responsible for many of the plant's therapeutic effects. MIC-1 has been shown to suppress inflammatory signaling by inhibiting the NF-κB pathway while simultaneously activating antioxidant responses through the Nrf2 pathway, thereby helping to decrease the production of pro-inflammatory cytokines and reactive oxygen species[9]. Other compounds such as oleamide, a fatty acid derivative isolated from Moringa leaves, have demonstrated anti-inflammatory and anti-fibrotic effects through modulation of the TGF-β/SMAD signaling pathway[34].

The diverse phytochemical composition of *Moringa oleifera* provides a strong biochemical basis for its potential therapeutic effects in conditions characterized by excessive inflammation and oxidative stress. These properties are particularly relevant in the context of sepsis and reperfusion injury, where dysregulated immune responses and oxidative damage play central roles in disease progression[30].

The major bioactive compounds identified in *Moringa oleifera* and their reported biological activities are summarized in Table 2.

Anti-Inflammatory Effects of Moringa oleifera

An increasing amount of experimental research suggests that *Moringa oleifera* exhibits notable anti-inflammatory effects, mainly through its capacity to suppress the production of pro-inflammatory cytokines and regulate important inflammatory signaling pathways. These effects are largely associated with the plant's rich content of bioactive phytochemicals, including flavonoids, phenolic compounds, and isothiocyanates[30,35].

One of the important mechanisms underlying the anti-inflammatory activity of *Moringa oleifera* is its capacity to suppress the expression of several pro-inflammatory cytokines, such as interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and interleukin-1β (IL-1β). In experimental models of ischemia–reperfusion injury, pretreatment with methanolic *Moringa oleifera* leaf extract significantly reduced the levels of IL-6 and TNF-α, along with decreased myeloperoxidase activity, indicating reduced neutrophil infiltration and inflammatory damage[11]. Similarly, supplementation with *Moringa oleifera* in renal ischemia–reperfusion models was shown to suppress inflammatory mediators including TNF-α, IL-6, nitric oxide, and myeloperoxidase activity, accompanied by improved renal histology and function[19].

The anti-inflammatory effects of *Moringa oleifera* have also been demonstrated in models of systemic inflammation and sepsis. In lipopolysaccharide-induced inflammatory models, treatment with moringa isothiocyanate-1 (MIC-1) significantly reduced serum and tissue expression of pro-inflammatory cytokines such as TNF-α, IL-6, IL-1β, and interferon-[9]. These effects were associated with inhibition of the NF-κB signaling pathway, a major regulator of inflammatory gene transcription during infection and sepsis.

Consistent with these findings, in vitro studies using human macrophages have shown that *Moringa oleifera* extracts suppress the production of IL-6, TNF-α, and cyclooxygenase-2 (COX-2) following lipopolysaccharide stimulation. The inhibition of NF-κB activation in these immune cells

suggests that Moringa phytochemicals can directly modulate macrophage-mediated inflammatory responses[14].

In addition to suppressing pro-inflammatory mediators, *Moringa oleifera* has also been reported to enhance the production of anti-inflammatory cytokines. For example, administration of *Moringa oleifera* leaf powder significantly reduced IL-6 and TNF-α levels while increasing anti-inflammatory cytokines such as IL-10 and transforming growth factor-β (TGF-β) in experimental animal models[35]. This shift toward an anti-inflammatory cytokine profile suggests that Moringa may help restore immune balance during inflammatory conditions.

Further evidence indicates that certain bioactive compounds derived from *Moringa oleifera* can modulate inflammatory and fibrotic signaling pathways. Oleamide, a compound isolated from Moringa leaves, has been shown to inhibit TGF-β/SMAD signaling, resulting in reduced expression of inflammatory and fibrotic markers such as IL-6, IL-8, and matrix metalloproteinases in cellular models[34]. This suggests that Moringa compounds may not only suppress acute inflammatory responses but also mitigate long-term tissue remodeling processes following inflammatory injury.

Additional experimental studies further support the anti-inflammatory potential of *Moringa oleifera*. In sepsis models induced by lipopolysaccharide, treatment with Moringa extracts reduced neutrophil activation and inflammatory cell infiltration, indicating attenuation of systemic inflammatory responses[13]. Similarly, Moringa-derived nanomaterials have demonstrated the ability to suppress inflammatory mediators such as TNF-α, IL-2, and COX-2 in macrophage models while increasing TGF-β expression, further supporting the plant's immunomodulatory properties[36].

The experimental studies investigating the anti-inflammatory effects of *Moringa oleifera* are summarized in Table 3.

Table 3 Anti inflammatory studies of Moringa oleifera

Anti-inflammatory activity	Key inflammatory markers affected	Proposed mechanism	Ref.
Reduced pro-inflammatory cytokine production	↓ TNF-α, IL-6, IL-1β	NF-κB inhibition	9,14,32
Suppressed neutrophil activation and MPO activity	↓ MPO, ↓ neutrophil infiltration	Attenuation of inflammatory cell recruitment	11,13,19
Enhanced anti-inflammatory cytokine response	↑ IL-10, ↑ TGF-β	Immunomodulatory effect	32,35
Inhibited inflammatory mediators and enzymes	↓ COX-2, ↓ NO	Suppression of inflammatory signaling pathways	14,19,36
Reduced fibrotic and inflammatory signaling	↓ IL-8, ↓ MMP-9, ↓ TGF-β/SMAD signaling	Anti-fibrotic activity	34,37

Abbreviations: ↓ = decreased/reduced; ↑ = increased/enhanced.

Taken together, these findings suggest that *Moringa oleifera* exerts anti-inflammatory effects through several mechanisms. These include inhibition of NF-κB signaling, reduction of pro-inflammatory cytokine production, enhancement of anti-inflammatory mediators, and regulation of immune cell activity. Such mechanisms are particularly relevant in sepsis, where excessive cytokine release and dysregulated inflammatory responses play a major role in tissue damage.

Antioxidant Effects of Moringa oleifera

In addition to its anti-inflammatory activity, *Moringa oleifera* has been widely recognized for its strong antioxidant properties. Oxidative stress is a central pathological mechanism in ischemia–reperfusion injury and sepsis, where excessive production of reactive oxygen species (ROS)

overwhelms endogenous antioxidant defense systems and leads to cellular damage[10,30,31]. Several experimental studies have shown that extracts of *Moringa oleifera* can markedly reduce oxidative stress, mainly by increasing the activity of antioxidant enzymes and by scavenging free radicals.

One of the most commonly observed antioxidant effects of *Moringa oleifera* is the reduction of lipid peroxidation markers such as malondialdehyde (MDA). In intestinal ischemia–reperfusion models, pretreatment with methanolic Moringa oleifera leaf extract significantly decreased MDA levels while restoring antioxidant enzymes including superoxide dismutase (SOD), catalase, and glutathione peroxidase (GPx)[11]. Similar findings have been reported in renal ischemia–reperfusion injury, where Moringa supplementation reduced oxidative stress markers such as hydrogen peroxide, MDA, and advanced oxidation protein products while increasing antioxidant defenses including glutathione and SOD activity[19].

Experimental studies also suggest that *Moringa oleifera* enhances endogenous antioxidant systems that protect cells against oxidative injury. In renal ischemia–reperfusion models, treatment with methanolic Moringa leaf extract significantly reduced oxidative stress markers including protein carbonyls and lipid peroxidation products, while increasing antioxidant enzymes such as glutathione peroxidase and glutathione-S-transferase[12]. These findings indicate that Moringa phytochemicals may help maintain cellular redox balance during oxidative stress.

At the molecular level, activation of antioxidant signaling pathways has been proposed as a key mechanism underlying the protective effects of *Moringa oleifera*. Several studies have demonstrated that Moringa extracts can activate the Nrf2 signaling pathway, a major regulator of cellular antioxidant responses. Activation of Nrf2 promotes transcription of antioxidant genes including superoxide dismutase (SOD), catalase, glutathione peroxidase, and heme oxygenase-1, thereby enhancing the cellular capacity to neutralize reactive oxygen species[9,10].

In cellular models of oxidative stress, *Moringa oleifera* leaf extract has been shown to significantly reduce intracellular ROS levels while increasing the expression of antioxidant enzymes such as SOD-1, catalase, and GPx[33]. These findings suggest that Moringa not only scavenges reactive oxygen species directly but also stimulates endogenous antioxidant defense systems.

Table 4. Antioxidant studies of Moringa oleifera

Key antioxidant activity	Main oxidative stress parameters affected	Proposed mechanism	Ref.
Reduced oxidative stress and lipid peroxidation	↓ ROS, ↓ MDA, ↓ H_2O_2, ↓ AOPP	ROS scavenging and restoration of redox balance	10,12,13,19
Enhanced endogenous antioxidant enzymes	↑ SOD, ↑ CAT, ↑ GPx, ↑ GST, ↑ GSH	Activation of cellular antioxidant defense systems	10–12,19,33
Activated Nrf2-mediated antioxidant signaling	↑ Nrf2, ↑ HO-1, ↑ NQO1	Upregulation of antioxidant gene transcription	9,10
Improved mitochondrial oxidative status	↓ mitochondrial superoxide, restored mitochondrial membrane potential	Protection against mitochondrial oxidative injury	9
Demonstrated free radical scavenging activity	↑ DPPH radical scavenging activity	Direct antioxidant and radical-neutralizing effects	36
Reduced oxidative tissue injury and improved organ protection	↓ oxidative damage markers with improved renal/hepatic function	Attenuation of reperfusion-associated oxidative injury	13,19,38

Abbreviations: ↓ = decreased/reduced; ↑ = increased/enhanced.

Furthermore, studies investigating Moringa-derived bioactive compounds have demonstrated potent radical scavenging activity. For example, Moringa cellulose-derived nanomaterials have shown strong antioxidant activity in biochemical assays, with significant free radical scavenging capacity and reduction of oxidative stress markers in cellular models[36]. Similarly, reductions in serum MDA levels have been observed in experimental sepsis models treated with Moringa extracts, indicating attenuation of oxidative damage[13]. The experimental studies evaluating the antioxidant effects of *Moringa oleifera* are summarized in Table 4.

Overall, the antioxidant effects of *Moringa oleifera* seem to involve several complementary mechanisms. These include the direct scavenging of reactive oxygen species, stimulation of endogenous antioxidant enzymes, and activation of protective signaling pathways such as Nrf2. Such mechanisms are particularly important in conditions associated with high oxidative stress, including sepsis-related ischemia–reperfusion injury.

Potential Role of *Moringa oleifera* in Sepsis-Related Reperfusion Injury

Sepsis-related reperfusion injury is characterized by excessive oxidative stress and inflammatory responses that contribute to mitochondrial dysfunction, apoptosis, and progressive organ damage. Experimental evidence suggests that *Moringa oleifera* may attenuate these pathological processes through its antioxidant and anti-inflammatory properties. Bioactive compounds such as flavonoids, phenolic acids, and moringa isothiocyanate-1 (MIC-1) have been shown to reduce reactive oxygen species (ROS), decrease lipid peroxidation markers such as malondialdehyde (MDA), and enhance endogenous antioxidant enzymes including superoxide dismutase (SOD), catalase, and glutathione peroxidase [11,12,19].

In addition, *Moringa oleifera* suppresses inflammatory mediators including IL-6, TNF-α, and IL-1β, primarily through inhibition of NF-κB signaling and activation of the Nrf2 antioxidant pathway[9,14]. Several experimental studies further demonstrated reduced caspase-3 expression, improved histopathological outcomes, and protection against liver and kidney injury following Moringa treatment[11,13,19]. Although current evidence is mainly derived from experimental models, these findings indicate that *Moringa oleifera* may serve as a promising adjunctive therapy for reducing oxidative and inflammatory tissue damage in sepsis-related reperfusion injury.

CONCLUSION

Moringa oleifera demonstrates promising potential as an adjunctive therapy for sepsis-related reperfusion injury due to its antioxidant and anti-inflammatory properties. Experimental studies consistently show that Moringa bioactive compounds can reduce oxidative stress markers, suppress pro-inflammatory cytokines such as IL-6 and TNF-α, enhance endogenous antioxidant defenses, and modulate NF-κB and Nrf2 signaling pathways involved in tissue injury and organ dysfunction. However, current evidence is still largely limited to in vitro and animal studies. Future research should therefore focus on standardized extract preparation, identification of the most active bioactive compounds, and well-designed clinical trials to evaluate the efficacy and safety of Moringa oleifera in human sepsis patients.

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CONFLICT OF INTEREST

The authors confirm that there are no conflicts of interest to disclose in relation to the preparation and publication of this manuscript. All authors declare that the research was conducted in the absence of any financial or personal relationships that could potentially influence the work presented in this study.

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