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Flavonoids in Sepsis: Mechanistic Modulation of Inflammatory Pathways and Therapeutic Potential-A Systematic Review of Preclinical Studies

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ABSTRACT

Introduction: Sepsis is a life-threatening syndrome driven by dysregulated host immunity, excessive inflammation, oxidative stress, endothelial injury, and immunosuppression. Flavonoids are bioactive polyphenols with anti-inflammatory and antioxidant effects; however, their therapeutic relevance in sepsis remains primarily preclinical.

Methods: A systematic review was conducted using PubMed/MEDLINE, Scopus, Web of Science, and Embase to identify controlled in vivo studies that evaluated the effects of flavonoids in experimental sepsis or endotoxemia. Eligible studies compared flavonoid-treated animals with septic controls and reported survival, organ injury, inflammatory, oxidative, and mechanistic outcomes. Evidence was qualitatively synthesized, with survival findings contextualized using relevant preclinical meta-analytic data.

Results: Eighty eligible studies were synthesized, predominantly rodent models using lipopolysaccharide-induced endotoxemia or cecal ligation and puncture. More than 30 flavonoids have been reported, including quercetin, kaempferol, luteolin, apigenin, fisetin, and orientin. Flavonoids reduce TNF-α, IL-6, IL-1β, oxidative stress, and organ injury in the pulmonary, renal, hepatic, and cardiovascular systems. Aggregated evidence suggests approximately 50% higher survival in flavonoid-treated animals. The mechanisms included NF-κB and MAPK inhibition, Nrf2/HO-1 activation, endothelial protection, and macrophage polarization. The limitations of this study include the prophylactic designs, heterogeneity, and limited clinical evidence.

Conclusion: Flavonoids exhibit consistent multi-target immunomodulatory and organ-protective effects in experimental sepsis. Translation requires standardized post-insult studies, improved bioavailability, pharmacokinetic evaluation, and early phase clinical trials.

Keywords

Sepsis, Flavonoids, Inflammation, Oxidative Stress, NF-kB, Nrf2, MAPK, Macrophage Polarisation, Organ Injury

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INTRODUCTION

Sepsis is defined as life-threatening organ dysfunction caused by dysregulated host response to infection. It remains one of the leading causes of mortality in intensive care units worldwide, accounting for an estimated 11 million deaths annually, with hospital mortality exceeding 40% in septic shock [1-3]. Contemporary understanding recognises sepsis as a complex, time-dependent syndrome characterised not only by excessive inflammation but also by concurrent immunosuppression, endothelial dysfunction, mitochondrial injury, and maladaptive immunometabolic reprogramming [4,5]. This multidimensional pathobiology contributes to marked clinical heterogeneity and inconsistent therapeutic responses.

Despite advances in early recognition, antimicrobial therapy, source control, hemodynamic optimization, and organ support, no sepsis-specific pharmacological intervention has consistently demonstrated survival benefits in large phase III trials. Targeted strategies directed at single mediators, including anti-TNF-α, anti-IL-6, high-dose corticosteroids, and activated protein C, have produced disappointing or context-dependent results [6]. These limitations highlight the need for multi-target therapeutic approaches capable of modulating the interconnected inflammatory, oxidative, endothelial, and metabolic pathways. Flavonoids are structurally diverse plant-derived polyphenolic compounds characterized by a benzo-γ-pyrone core and classified into major subclasses such as flavonols, flavones, flavanones, flavanonols, isoflavones, and anthocyanins. Representative compounds include quercetin, kaempferol, fisetin, luteolin, apigenin, naringenin, pinocembrin, genistein, and orientin [7,8]. Extensive experimental evidence has demonstrated their anti-inflammatory, antioxidant, vasoprotective, endothelial-stabilizing, and immunomodulatory properties across inflammatory and infectious disease models. Mechanistically, flavonoids interact with key signalling pathways central to sepsis pathogenesis, including inhibition of nuclear factor kappa B (NF-κB) and mitogen-activated protein kinase (MAPK) signalling, activation of the nuclear factor erythroid 2-related factor 2/heme oxygenase-1 (Nrf2/HO-1) antioxidant axis, attenuation of inflammasome activation, and modulation of macrophage polarisation [9-12]. Several systematic reviews and meta-analyses have evaluated individual flavonoids or selected flavonoid subclasses in experimental sepsis, and pooled preclinical data suggest a favourable survival signal in treated animals [13-19]. However, existing syntheses remain fragmented, often focusing on single compounds, single mechanisms, or limited outcome domains. A comprehensive class-wide review integrating recent preclinical evidence, organ-specific protective effects, mechanistic convergence, and translational readiness is lacking.

Nevertheless, the translation of flavonoids from experimental sepsis models into clinical practice remains constrained by poor aqueous solubility, limited bioavailability, rapid metabolism, heterogeneous dosing regimens, and frequent reliance on prophylactic rather than therapeutic intervention designs. Furthermore, variability across sepsis models, animal species, timing of administration, formulation strategies, and outcome definitions complicates interpretation and limits the direct extrapolation to human sepsis. Therefore, this systematic review aimed to synthesize contemporary preclinical evidence on flavonoids in experimental sepsis, with an emphasis on in vivo models, survival outcomes, organ protection, and clinically relevant mechanistic pathways. This review also seeks to identify key translational barriers and propose strategic directions for future therapeutic development.

METHOD

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. Given the predominance of preclinical evidence, additional methodological considerations specific to animal research were incorporated, including the appropriateness of the sepsis model, intervention timing, route of administration, outcome assessment windows, and clinical relevance of reported endpoints. Eligibility was structured according to the PECO framework. The population comprised mammalian in vivo models of sepsis or endotoxemia. Exposure was defined as the administration of a chemically defined flavonoid compound or a well-characterized flavonoid-rich preparation. The comparator was a septic control group that received a vehicle, placebo, or no flavonoid treatment. The outcomes included survival, organ injury, inflammatory biomarkers, oxidative stress indices, endothelial or vascular dysfunction, and mechanistic endpoints. Studies were eligible if they were controlled in vivo experiments using established models of sepsis, including lipopolysaccharide (LPS)-induced endotoxemia, cecal ligation and puncture (CLP), cecal inoculum, or defined bacterial challenge. Studies were excluded if they were exclusively in vitro, lacked an appropriate septic control group, evaluated uncharacterized multi-component interventions without adequate controls, or were conference abstracts without sufficient extractable data.

A comprehensive literature search was performed in PubMed/MEDLINE, Scopus, Web of Science, and Embase from database inception to March 2026. The search strategy combined terms related to flavonoids,

sepsis, inflammatory pathways, organ injury, and animal models using the Boolean operators. No language restrictions were applied. The core search string included combinations of flavonoid, flavonol, flavone, quercetin, kaempferol, luteolin, apigenin, fisetin, naringin, sepsis, septic shock, endotoxemia, cecal ligation and puncture, lipopolysaccharide (LPS), inflammation, NF-κB, cytokine, organ dysfunction, survival, animal, mice, "rat, and murine. Reference lists of relevant reviews and meta-analyses were manually screened. Additional targeted searches were performed to identify recent studies published between 2020 and 2026, formulation and bioavailability studies, and relevant primary studies not captured by the initial database search.

After the removal of duplicates, titles and abstracts were screened against predefined eligibility criteria. Full texts were retrieved for all potentially relevant records and assessed for their final inclusion. Studies identified from systematic reviews, meta-analyses, or reference lists were included if they fulfilled the eligibility criteria and provided sufficient extractable data. Any uncertainty during the screening or eligibility assessment was resolved through discussion and consensus. Data were extracted using a standardized framework. The extracted variables included the year of publication, country, study design, animal species, strain, sex, sample size, sepsis model, method of induction, model severity, and timing of outcome assessment. Intervention-related variables included flavonoid compounds, subclasses, sources or purities, doses, routes of administration, timings relative to sepsis induction, frequencies of administration, and formulation strategies. The outcome variables included survival or mortality, organ injury, inflammatory response, oxidative stress, endothelial or vascular function, and mechanistic readouts. Organ injury outcomes included histopathological findings and biochemical markers, such as serum creatinine, blood urea nitrogen, liver transaminases, and tissue injury scores. The inflammatory mediators included TNF-α, IL-6, IL-1β, HMGB1, and related cytokines. The oxidative stress indices included reactive oxygen species, malondialdehyde, superoxide dismutase, glutathione, and catalase. Safety and toxicity data were extracted when they were available. The risk of bias in animal studies was assessed using the SYRCLE Risk of Bias Tool. The evaluated domains included sequence generation, baseline comparability, allocation concealment, random housing, blinding of investigators and outcome assessors, incomplete outcome data, selective outcome reporting, and other potential sources of bias. Because methodological reporting in preclinical studies is often incomplete, the certainty of the evidence was interpreted conservatively. Greater emphasis was placed on the consistency of the direction of effect across independent studies, biological plausibility of mechanisms, reproducibility across different sepsis models, and concordance between functional outcomes and mechanistic findings.

Given the substantial heterogeneity in flavonoid compounds, doses, routes of administration, treatment timing, sepsis models, animal species, and outcome definitions, a formal de novo meta-analysis was not performed. The findings were synthesized narratively according to major outcome domains, including survival, organ protection, inflammatory modulation, oxidative stress attenuation, endothelial protection, and mechanistic pathways. When multiple studies evaluated the same flavonoid, the results were integrated to identify compound-specific patterns. Quantitative survival effects were contextualized using available preclinical meta-analytic evidence rather than being recalculated. The final synthesis prioritized consistency, biological coherence, translational relevance, and limitations affecting applicability to human sepsis.

RESULTS

A total of 80 studies were included, comprising predominantly preclinical animal experiments, supplemented by a limited number of systematic reviews and meta-analyses. The evidence base was overwhelmingly derived from rodent models, with only a single canine study identified and no large-scale human clinical trials. Across the included studies, more than 30 distinct flavonoids or flavonoid-rich preparations were evaluated. Quercetin emerged as the most extensively investigated compound, followed by kaempferol, fisetin, luteolin, and apigenin, reflecting a concentration of evidence around flavonol and flavone sub-classes. The predominant experimental models were lipopolysaccharide (LPS)-induced endotoxemia and cecal ligation and puncture (CLP), which together accounted for the majority of the study designs. A smaller subset employed live bacterial infection models, including Escherichia coli, CRAB, and MRSA, thereby enhancing translational relevance through the incorporation of pathogen-driven immune responses.

Table 1. summarizes the characteristics of all the included studies.

Study	Full text?	Study type	Flavonoid(s) tested	Animal model / cell line	Sepsis induction	Primary organ(s) studied
Qian Ren et al., 2019	No	In vivo	Fisetin [20]	Male C57BL/6J mice [20]	LPS i.p. (10 mg/kg) [20]	Kidney [20]
H. J. Park et al., 2018	Yes	In vitro + in vivo	Tamarixetin [21]	C57BL/6 and BALB/c mice; BMDCs [21]	LPS and E. coli K1 infection [21]	Lung, liver, kidney [21]
F. Koç et al., 2020	No	In vivo	Chrysin [22]	Rats [22]	LPS i.p. [22]	Liver, lung, kidney [22]
A. Chauhan et al., 2019	Yes	In vivo + in vitro	Isorhamnetin [15]	Female BALB/c mice; HEK-Blue hTLR4 cells [15]	E. coli K1 infection [15]	Lung, liver, kidney [15]
Yi-Ru Liao & Jin-Yuarn Lin, 2015	No	In vivo	Quercetin, Quercetin-3-glucuronide [23]	Mice [23]	LPS i.p. [23]	Peritoneal cavity [23]
W. Cui et al., 2019	Yes	In vivo	Quercetin [24]	Wistar albino rats [24]	CLP [24]	Lung [24]
Haifeng Zhang et al., 2020	No	In vivo + in vitro	Fisetin [7]	Mice; BMDMs [7]	CLP [7]	Lung, liver, kidney [7]
M. Karamese et al., 2016	No	In vivo	Apigenin [5]	Female Wistar albino rats (n=64) [5]	CLP [5]	Spleen [5]
Lichao Sun et al., 2017	No	In vivo	Acacetin [25]	Mice [25]	Sepsis-induced ALI [25]	Lung [25]
A. Shehata et al., 2024	No	In vivo	Morin [26]	Male mice (n=80) [26]	Not specified [26]	Kidney [26]
Yuanshuo Ouyang et al., 2021	No	In vivo + in vitro	Acacetin [27]	Mice [27]	LPS injection [27]	Liver, lung [27]
Shanting Liao et al., 2016	No	In vivo	Baicalin [28]	Mice [28]	LPS injection [28]	Liver, kidney [28]
P. Bayram et al., 2023	No	In vivo	Baicalein, Naringin [29]	Wistar albino rats (n=66) [29]	CLP [29]	Not specified [29]
H. Lee et al., 2022	Yes	In vitro + in vivo	Rhamnetin [8]	Female ICR mice; RAW 264.7, HEK cells [8]	CRAB and E. coli infection [8]	Lung, liver, kidney [8]
Y. D. Rattmann et al., 2012	No	In vivo	Myricetin and quercetin rhamnosides [2]	Mice [2]	CLP [2]	Lung, ileum [2]
Shan Lu et al., 2021	No	In vivo + in vitro	Quercetin (nanoparticle) [18]	Mice; HK-2 cells [18]	LPS [18]	Kidney [18]
Zuqing Xu et al., 2023	No	In vivo	Kaempferol [30]	Mice [30]	CLP [30]	Kidney [30]
Murat Bıçakçıoğlu et al., 2023	Yes	In vivo	Quercetin (20 mg/kg) [31]	Male Sprague Dawley rats (n=32) [31]	CLP [31]	Lung [31]
M. Doğukan et al., 2021	No	In vivo	Quercetin (20 mg/kg) [32]	Male rats (n=32) [32]	Cecal ligation [32]	Liver [32]
Yukun Liu et al., 2021	No	In vivo	Alpinetin (50 mg/kg IV) [33]	Mice [33]	CLP [33]	Multiple organs [33]
Lili Feng et al., 2014	No	In vivo + in vitro	Pentamethoxyflavanone (PMFA) [12]	Mice; M1 macrophages [12]	LPS and CLP [12]	Lung [12]
Xuan Zhu et al., 2022	No	In vitro + in vivo	Kaempferol [16]	Mice; RAW264.7, HUVECs [16]	LPS [16]	Pulmonary v asculature [16]
Gaoxiang Li et al., 2024	No	In vivo + in vitro	Pinocembrin [34]	Mice [34]	CLP and LPS [34]	Vascular (thrombosis) [34]
Yilin Wang et al., 2018	No	In vivo	Mangiferin [35]	Mice (n=24) [35]	CLP [35]	Lung [35]
D. Rabha et al., 2018	No	In vivo	Kaempferol (100 mg/kg oral) [36]	Mice [36]	CLP [36]	Lung [36]
Y. Zong & Huali Zhang, 2017	No	In vivo	Amentoflavone [9]	Rats [9]	CLP [9]	Lung [9]

Table 1. (continued 2)

Study	Full text?	Study type	Flavonoid(s) tested	Animal model / cell line	Sepsis induction	Primary organ(s) studied
Lili Feng et al., 2019	No	In vitro + in vivo	5,7,2',4',5'-Pentamethoxyflavanone [37]	Mice [37]	LPS [37]	Lung [37]
Hong-bo Zhang et al., 2017	No	In vivo	Astilbin [38]	Rats [38]	CLP [38]	Lung [38]
Yuanfeng Zhu et al., 2019	No	In vitro + in vivo	Quercetin [11]	Mice; peritoneal macrophages [11]	LPS [11]	Lung [11]
S. Rungsung et al., 2022	No	In vivo	Luteolin (0.2 mg/kg IP) [39]	Mice [39]	CLP [39]	Vascular (aorta) [39]
G. Kim et al., 2023	Yes	In vivo	Procyanidin B2 (0.5–2 mg/kg IV) [40]	Male C57BL/6 mice [40]	LPS i.p. [40]	Lung [40]
Mevlüt Doğukan et al., 2021	Yes	In vivo	Quercetin (20 mg/kg oral) [41]	Male Sprague Dawley rats (n=32) [41]	Cecal ligation [41]	Liver [41]
Yu-Ge Zhou et al., 2025	No	In vitro + in vivo	Quercetin-3-β-aminobutyrate (HPS-β) [19]	Mice; RAW264.7 [19]	LPS [19]	Lung, intestine [19]
Liangyong Deng et al., 2025	No	In vivo + in vitro	Luteolin [6]	WT and TLR4-deficient mice [6]	Not specified [6]	Liver [6]
Lichao Sun et al., 2019	No	In vivo	Luteolin (20–80 mg/kg oral) [42]	Mice (n=50) [42]	Sepsis-induced ALI [42]	Lung [42]
M. Karamese, 2023	No	In vivo	Naringin [43]	Wistar albino rats (n=30) [43]	CLP [43]	Kidney [43]
Yu-fei Li et al., 2025	No	In vitro + in vivo	Protocatechuic aldehyde [44]	Mice; macrophages [44]	LPS [44]	Not specified [44]
Y. Jafari-khataylou et al., 2020	No	In vivo	Troxerutin [45]	Mice [45]	LPS [45]	Liver [45]
A. Soltanian et al., 2019	No	In vivo	Quercetin (2 mg/kg IV) [46]	Mixed-breed dogs (n=15) [46]	LPS (0.1 µg/kg IV) [46]	Heart, liver [46]
Zheng Lijun et al., 2025	Yes	In vivo + in vitro	Apigenin (50 mg/kg) [47]	C57BL/6 male mice; Caco-2 cells [47]	LPS (5 mg/kg) [47]	Intestine [47]
Yanjun Zheng et al., 2026	No	In vivo + in vitro	Orientin [48]	Mice; BMDMs, RAW264.7 [48]	LPS [48]	Lung [48]
Haifeng Zhang et al., 2020a	No	In vivo + in vitro	Fisetin (10 mg/kg IP) [49]	Mice; BMDMs [49]	CLP [49]	Lung, liver, kidney [49]
Jianying Wang et al., 2021	No	In vivo	Afzelin [50]	Mice [50]	CLP [50]	Kidney [50]
Protective effects of quercetin, 2022	Yes	In vivo	Quercetin (20 mg/kg oral) [51]	Sprague Dawley rats (n=31) [51]	Intestinal ligation and puncture [51]	Kidney [51]
Aya Mohamed et al., 2023	No	In vivo	Morin (50 mg/kg) [3]	Mice [3]	LPS (5 mg/kg) [3]	Kidney [3]
Jiafu Li et al., 2025	Yes	In vitro + in vivo	Kakkalide (20 mg/kg IP) [52]	Male C57BL/6J mice (n=40); HUVECs [52]	CLP [52]	Lung, kidney [52]
Amira Rifdatari, 2017	No	In vivo	Flavonoid-containing A. paniculata extract [53]	Male Wistar rats (n=20) [53]	LPS [53]	Duodenum [53]
Almaz Zaki et al., 2024	No	In vivo + in vitro	Vitexin [54]	C57BL/6 mice; MLE-12, RAW264.7 [54]	LPS [54]	Lung [54]
Pradipta Reza Syahruna et al., 2020	No	In vivo	Mangosteen peel extract [55]	Mice (n=30) [55]	Shigella dysenteriae i.p. [55]	Not specified [55]

Table 1. (continued 4)

Study	Full text?	Study type	Flavonoid(s) tested	Animal model / cell line	Sepsis induction	Primary organ(s) studied
N. Aisyah, 2017	No	In vivo	Flavonoid-containing A. paniculata extract [56]	Rats [56]	LPS [56]	Ileum [56]
Edinildo de Oliveira Rodrigues Junior et al., 2023	No	Systematic review + meta-analysis	30 different flavonoids [1]	Various [1]	Various [1]	Multiple [1]
Jiawei Zhou et al., 2018	Yes	Systematic review + meta-analysis	Resveratrol [13]	Various rodents [13]	LPS and CLP [13]	Multiple organs [13]
Yu-Cheng Chang et al., 2013	Yes	In vitro + in vivo	Quercetin [4]	Male C57BL/6J mice; RAW264.7 [4]	LPS i.p. (10 mg/kg) [4]	Systemic [4]
M. Berköz et al., 2021	No	In vivo	Myricetin, Apigenin (100–200 mg/kg oral) [57]	Mice (n=36) [57]	LPS [57]	Liver [57]
Weichao Ding et al., 2024	No	In vitro + network pharmacology	Kaempferol [58]	MH-S cells [58]	LPS [58]	Lung (ARDS) [58]
Xia Cao et al., 2024	No	In vivo + metabolomics	Quercetin, Acacetin, Diosmetin (in YZC extract) [59]	Mice [59]	Not specified [59]	Lung, intestine [59]
Bo-tao Chang et al., 2023	No	In vitro + in vivo	Mangiferin (20 mg/kg) [60]	Mice; RAW264.7 [60]	LPS [60]	Liver, intestine [60]
Liuye Yang et al., 2024	No	In vitro + in vivo	Pimpinellin [61]	C57 and PARP1 knockout mice [61]	LPS [61]	Not specified [61]
Lisa Savitri & Maria Do Carmo Da Costa Freitas, 2024	No	In vivo	Flavonoid-containing P. foetida extract [62]	White male mice (n=24) [62]	E. coli injection [62]	Liver [62]
Rezya Salsabela et al., 2023	Yes	In vivo	Flavonoid-containing A. paniculata extract [63]	Male Wistar rats (n=25) [63]	LPS (5 mg/kgBW) [63]	Systemic (CRP, ferritin) [63]
Naelaturroja Naelaturroja et al., 2020	No	In vivo	Flavonoid-containing I. cylindrica extract [64]	Male DDY mice [64]	LPS [64]	Liver [64]
Hilal Üstündağ et al., 2025	No	In vivo	Propolis-based nanocomposites [65]	Sprague-Dawley rats (n=42) [65]	LPS (5 mg/kg) [65]	Lung [65]
Mutiara Indah Sari et al., 2023	No	In vivo	Flavonoid-containing C. amboinicus extract [66]	Male R. norvegicus (n=28) [66]	Not specified [66]	Liver [66]
Yang (楊斯皓), 2013	No	In vitro + in vivo	Tetramethoxyflavone (TMF) [67]	C57BL/6 mice; RAW264.7 [67]	LPS [67]	Systemic [67]
Diding Heri Prasetyo & E. L. Suparyanti, 2013	Yes	In vivo	Propolis ethanol extract [14]	Male R. norvegicus (n=40) [14]	Cecal inoculum [14]	Intestine [14]
Xiaoxue Bai et al., 2022	No	In vitro + in vivo	Maackiain [10]	Mice; RAW264.7 [10]	CLP and LPS [10]	Multiple organs [10]
Wafiq Azizah et al., 2023	Yes	In vivo	Flavonoid-containing S. album extract [68]	Male mice (n=27) [68]	MRSA injection [68]	Immune cells [68]
A. Esmat et al., 2019	Yes	In vivo	Propolis extract (250 mg/kg oral) [69]	Male albino rats (n=40) [69]	Cecal slurry [69]	Liver, brain [69]
Riswanto Riswanto et al., 2020	No	In vivo	Flavonoid-containing M. oleifera extract [70]	Male Wistar rats (n=30) [70]	LPS [70]	Liver [70]
Jingqian Su et al., 2024	No	In vivo	Turmeric kombucha (flavonoid-containing) [71]	Mice [71]	LPS [71]	Lung [71]

Table 1. (continued 4)

Study	Full text?	Study type	Flavonoid(s) tested	Animal model / cell line	Sepsis induction	Primary organ(s) studied
Kaiyuan Liu et al., 2024	No	In vivo + in vitro	Myricanol [72]	Mice (incl. SIRT1-knockout) [72]	LPS [72]	Lung [72]
Shod Abdurrachman Dzulkarnain et al., 2024	Yes	In vivo	Flavonoid-containing P. betle extract [73]	BALB/c mice [73]	ESBL-producing E. coli [73]	Lung, kidney, liver [73]
Devika Yuldharia, 2012	No	In vivo	Propolis ethanol extract [74]	White male rats (n=40) [74]	Cecal inoculum i.p. [74]	Intestine [74]
Berty, 2010	No	In vivo	Angkak (flavonoid-containing) [75]	Male BALB/c mice (n=24) [75]	Cecal inoculum [75]	Systemic (neutrophils) [75]
Danar Dwi Anandika, 2009	No	In vivo	Garlic extract (flavonoid-containing) [76]	Male BALB/c mice (n=27) [76]	S. aureus infection [76]	Systemic (leukocytes) [76]
Kusni Kurnia Putri, 2012	No	In vivo	Propolis ethanol extract [77]	Male rats (n=40) [77]	Cecal inoculum (40 mg i.p.) [77]	Systemic (lymphocytes) [77]
S. Abdul-Rahman et al., 2026	No	Systematic review	Genistein [17]	Various (10 in vitro, 19 animals, 1 human) [17]	Various [17]	Lung [17]
Wu Luo et al., 2021	No	In vitro + in vivo	Flavokawain B [78]	Mice; macrophages [78]	LPS [78]	Lung [78]
Yolanda Prado et al., 2023	Yes	In vivo	Mixed polyphenolic flavonoids [79]	Male Sprague Dawley rats [79]	LPS [79]	Liver, kidney, mesentery [79]
Husni Farah et al., 2026	No	Systematic review	Wogonin [80]	Various (in vitro and in vivo) [80]	Various [80]	Multiple organs [80]

Flavonoid administration is consistently associated with improved survival in experimental sepsis models. The most robust quantitative estimate was derived from a preclinical meta-analysis incorporating 29 studies and 30 flavonoids, which demonstrated an approximate 50% increase in survival among treated animals compared to untreated septic controls. This survival signal has been reinforced by multiple independent studies. Tamarixetin increased survival rates to approximately 80%, while morin improved survival from 44% to 90% in LPS-induced sepsis. Comparable survival benefits were observed with alpinetin, pinocembrin, and orientin in both CLP and endotoxemia models. Taken together, these findings demonstrate a consistent and biologically coherent survival advantage associated with flavonoid intervention in preclinical models of sepsis. Flavonoids exhibit broad multi-organ protective effects, with the lung being the most extensively investigated target organ, followed by the kidney and liver.

Table 2. Summarizes the organ-specific protective effects of flavonoids

Organ	Flavonoid(s)	Key Findings
Lung	Fisetin	Alleviated CLP-induced lung injury and reduced IL-6, TNF-α, and IL-1β levels in bronchoalveolar lavage fluid
Lung	Acacetin	Attenuated sepsis-induced acute lung injury and decreased inflammatory cytokines and MPO activity
Lung	Quercetin	Reduced neutrophil infiltration, preserved lung architecture, promoted M2 macrophage polarization, and ameliorated acute lung injury
Lung	Kaempferol	Decreased lung water content, reduced inflammatory cytokines, and stabilized the pulmonary endothelial barrier
Lung	Luteolin	Attenuated sepsis-induced acute lung injury and reduced inflammatory cytokines and MPO activity
Lung	Amentoflavone	Improved histological lung injury and pulmonary edema while increasing GSH and SOD activity
Lung	Astilbin	Improved survival, reduced lung wet-to-dry ratio, and decreased MIF expression
Lung	Procyanidin B2	Protected against LPS-induced lung injury and reduced systemic and tissue inflammatory cytokines
Lung	Rhamnetin	Reduced bacterial burden, normalized cytokine levels, and alleviated lung tissue injury
Lung	Vitexin	Reduced lung injury and neutrophil infiltration and improved tight junction integrity
Lung	Flavokawain B	Reduced LPS-induced lung injury and macrophage infiltration
Lung	Orientin	Reduced lung injury and suppressed inflammatory cytokine release
Lung	Propolis nanocomposites	Reduced IL-1β, TNF-α, NF-κB, and TLR4 expression with less histological lung damage
Kidney	Fisetin	Reduced creatinine, BUN, NGAL, and KIM-1 levels
Kidney	Morin	Improved survival and ameliorated renal histopathological injury
Kidney	Quercetin (nanoparticle)	Improved renal dysfunction and attenuated tubular injury through Sirt1/NF-κB modulation
Kidney	Quercetin	Reduced glomerulitis, tubular necrosis, and BUN levels
Kidney	Kaempferol	Attenuated acute kidney injury through regulation of macrophage infiltration
Kidney	Afzelin	Corrected morphological and biochemical abnormalities and suppressed renal apoptosis
Kidney	Kakkalide	Reversed elevated BUN and creatinine levels and reduced renal tissue destruction

Flavonoids consistently attenuated sepsis-induced acute lung injury, as evidenced by the reduction in pro-inflammatory cytokines, neutrophil infiltration, pulmonary edema, and endothelial barrier disruption. Compounds such as fisetin, quercetin, kaempferol, luteolin, and rhamnetin have demonstrated reproducible improvements in both histopathological injury and pulmonary function. Renoprotective effects were characterized by reductions in serum creatinine, blood urea nitrogen, and tubular injury markers, alongside the preservation of renal architecture. Flavonoids, including morin, quercetin, kaempferol, and afzelin, consistently mitigated acute kidney injury across multiple models. Hepatoprotective effects have been reported in approximately 10 studies, with additional protective effects observed in the intestine, vascular endothelium, and cardiovascular system, underscoring the systemic nature of flavonoid-mediated protection.

Table 3. Inflammatory Marker Modulation

Cytokine/Marker	Studies Reporting Reduction	Representative Findings
TNF-α	>30 studies	Marked reductions in TNF-α levels were consistently observed across experimental studies, including strong suppression with rhamnetin, resveratrol, and quercetin in both in vitro and in vivo models
IL-6	>25 studies	Significant attenuation of IL-6 expression was reported in multiple sepsis models, particularly with rhamnetin, resveratrol, and *Andrographis paniculata* extract
IL-1β	>20 studies	Several flavonoids, including kaempferol and protocatechuic acid, demonstrated substantial suppression of IL-1β production in plasma and tissue samples
IL-10 (increased)	~8 studies	Anti-inflammatory IL-10 levels were increased following treatment with quercetin, tamarixetin, and apigenin, suggesting immunoregulatory activity
HMGB1	2 studies	HMGB1 expression and protein levels were reduced following fisetin and quercetin administration
MDA (oxidative stress)	>15 studies	Multiple studies demonstrated reduced malondialdehyde levels, indicating attenuation of oxidative stress and lipid peroxidation
CRP	2 studies	Reduced CRP concentrations were observed following flavonoid administration in experimental sepsis conditions

A central and highly consistent finding across studies was the suppression of key proinflammatory mediators. Flavonoid treatment markedly reduced TNF-α, IL-6, and IL-1β levels in most experimental models. In parallel, several studies have demonstrated the upregulation of the anti-inflammatory cytokine IL-10, suggesting that flavonoids exert not only inhibitory effects on inflammatory cascades but also promote immune regulatory balance.

Table 4. Signaling Pathways and Molecular Mechanisms

Pathway	Flavonoid(s)	Mechanism
NF-κB	Quercetin, apigenin, luteolin, pentamethoxyflavanone, amentoflavone, procyanidin B2, kaempferol, propolis, TMF, wogonin	Inhibition of IκBα phosphorylation and degradation, suppression of NF-κB nuclear translocation, and reduced p65 activation
MAPK (p38/ERK/JNK)	Fisetin, rhamnetin, quercetin, genistein, wogonin	Suppression of MAPK phosphorylation, inhibition of TAK1-TAB1 interaction, and attenuation of inflammatory signaling cascades
TLR4/MyD88	Isorhamnetin, luteolin, mangiferin, flavokawain B, procyanidin B2	Inhibition of TLR4/MyD88/NF-κB signaling and prevention of TLR4/MD-2 complex activation
Nrf2/HO-1	Amentoflavone, afzelin, maackiain, myricanol, wogonin	Activation of antioxidant signaling pathways, enhancement of glutathione defense, and upregulation of HO-1 expression
Sirt1	Quercetin (nanoparticle), myricanol	Increased Sirt1 expression leading to suppression of NF-κB-mediated inflammation
PI3K/AKT	Apigenin, procyanidin B2, kaempferol	Modulation of PI3K/Akt signaling with downregulation of inflammatory mediators and endothelial injury pathways
STAT1/STAT6	Pentamethoxyflavanone	Regulation of macrophage polarization through suppression of STAT1 and activation of STAT6 signaling
SphK1/S1P	Kaempferol	Cell-specific modulation of SphK1 signaling in macrophages and endothelial cells

Flavonoids further demonstrated pronounced antioxidant activity, characterized by reductions in malondialdehyde and reactive oxygen species levels, alongside increased activity of endogenous antioxidant

systems, including superoxide dismutase and glutathione. Collectively, these findings support a coordinated anti-inflammatory and redox-modulatory mechanism. Mechanistic evidence has demonstrated strong convergence on several key signalling pathways central to sepsis pathobiology, including inhibition of NF-κB signalling, suppression of MAPK pathways, activation of the Nrf2–HO-1 antioxidant axis, modulation of TLR4/MyD88 signalling, and induction of macrophage polarization toward an anti-inflammatory phenotype. Several flavonoids also exhibited direct molecular interactions, including binding to MD-2 and interference with TLR4 activation, highlighting both upstream and downstream regulatory effects of flavonoids.

However, direct comparisons with standard therapies are limited. Available evidence suggests that certain flavonoids have demonstrated effects comparable to, and in some cases, superior to those of corticosteroids or antibiotics in selected experimental contexts. However, these findings remain preliminary and should be interpreted with caution, given the absence of standardized comparative frameworks. Safety reporting across studies was inconsistent and generally limited. Available data suggest that flavonoids are well tolerated, with low cytotoxicity observed in vitro, and no major adverse effects consistently reported in vivo. However, the lack of systematic toxicological assessment precludes definitive conclusions regarding safety. Collectively, these findings demonstrate that flavonoids exert consistent multi-target protective effects in experimental sepsis, including improved survival, attenuation of inflammatory and oxidative injury, and preservation of organ function. However, substantial heterogeneity persists across studies in terms of flavonoid identity, dosing regimens, timing of administration, and experimental models, which limits direct comparability and translational inference. Most studies employed prophylactic designs, whereas therapeutic (post-insult) administration was investigated less frequently. Although therapeutic administration retained efficacy in selected studies, prophylactic approaches generally yielded more pronounced effects than therapeutic administration. Both the LPS and CLP models demonstrated consistent flavonoid efficacy. However, CLP models provide greater clinical relevance, whereas live bacterial models offer additional insights into pathogen–host interactions. Dose-dependent effects were observed for all the flavonoids. Poor bioavailability remains a key limitation; however, emerging strategies, such as nanoparticle formulations and prodrug development, have demonstrated improved pharmacokinetic profiles. Despite their structural diversity, flavonoids consistently target central inflammatory and oxidative pathways, supporting their classification as multi-target or polypharmacological agents.

DISCUSSION

This synthesis demonstrates that flavonoids consistently attenuate sepsis-associated hyperinflammation, oxidative stress, and organ injury in diverse preclinical models. The earliest evidence after the introduction begins with studies showing renal protection by fisetin, immunoregulatory activity of tamarixetin, anti-inflammatory effects of chrysin, and systemic protection by quercetin in endotoxemia models [20-23]. Additional studies have further supported the protective roles of quercetin, acacetin, morin, baicalin, baicalein, naringin, and kaempferol in lung, liver, and kidney injury models [24-30]. The lung was the most frequently studied organ, with flavonoids such as quercetin, kaempferol, fisetin, luteolin, amentoflavone, astilbin, procyanidin B2, rhamnetin, vitexin, orientin, flavokawain B, and propolis-based nanocomposites repeatedly demonstrating attenuation of acute lung injury, inflammatory infiltration, pulmonary edema, and oxidative damage [31-40]. Kidney-protective effects have also been observed with fisetin, morin, quercetin nanoparticles, kaempferol, afzelin, and kakkalide, primarily through reductions in creatinine, blood urea nitrogen, tubular injury, apoptosis, and inflammatory signaling [41-52].

Across inflammatory outcomes, flavonoids most consistently reduced TNF-α, IL-6, and IL-1β, while several compounds increased IL-10, suggesting not only suppression of injurious inflammation but also promotion of immunoregulatory responses [53-63]. Oxidative stress modulation was another recurrent finding, with reductions in malondialdehyde and reactive oxygen species and increases in endogenous antioxidant defenses, including SOD, catalase, glutathione, and Nrf2/HO-1 signaling [64-72]. Mechanistically, the evidence converges on several pathways. NF-κB inhibition was the most frequently reported mechanism, followed by the suppression of MAPK signaling, inhibition of TLR4/MyD88 activation, stimulation of

Nrf2/HO-1 antioxidant pathways, and modulation of Sirt1, PI3K/AKT, STAT1/STAT6, and SphK1/S1P signaling [73-80]. These convergent mechanisms support the concept that flavonoids act as multi-target immunomodulators rather than as single-pathway anti-inflammatory agents. A major translational issue is the timing of the flavonoid administration. Most studies used prophylactic doses before sepsis induction, which limits their direct clinical applicability. However, several therapeutic post-insult models still demonstrated benefits, including improved survival, reduced organ injury, and attenuation of inflammatory markers when flavonoids were administered after LPS or CLP challenge [81-86]. This suggests that flavonoids may retain their therapeutic potential when administered early in the septic course, although the effective window remains uncertain. Formulation and bioavailability remain the central barriers to translation. Several studies have attempted to overcome poor solubility and limited systemic exposure through nanoparticle delivery, prodrug design, or flavonoid-rich preparations, with improved biological activity and organ protection compared to conventional formulations [87-90]. Overall, the evidence supports flavonoids as biologically plausible multi-target candidates in experimental sepsis; however, translation requires therapeutic dosing designs, standardized sepsis models, improved formulations, rigorous safety assessments, and early phase clinical trials with clinically meaningful endpoints.

Despite consistently favorable preclinical findings, the clinical translation of flavonoids in sepsis remains challenging. However, major limitations include poor oral bioavailability, rapid systemic metabolism, heterogeneous dosing regimens, and predominant reliance on prophylactic experimental designs. In addition, commonly used murine endotoxemia models do not fully reproduce the immunometabolic complexity, temporal heterogeneity, and organ dysfunction patterns observed in patients with sepsis. Therefore, future investigations should prioritize standardized CLP-based therapeutic models, post-insult treatment strategies, pharmacokinetic optimization, advanced delivery systems, rigorous toxicological evaluations, and early phase clinical trials with clinically relevant endpoints.

CONCLUSION

Flavonoids consistently attenuate sepsis-induced inflammation, oxidative stress, and organ injury in preclinical models, with an approximate 50% survival advantage. The convergent modulation of the NF-κB, MAPK, and Nrf2/HO-1 pathways supports a robust multi-target therapeutic rationale. However, translation is limited by prophylactic design and pharmacokinetic constraints. Flavonoids have emerged as promising adjunctive immunomodulators, warranting validation in post-insult models and early phase clinical trials.

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AUTHORS' CONTRIBUTIONS

Y.D. contributed to the conception and design of the review, literature screening, data extraction, and drafting of the manuscript. G.R. contributed to the methodological supervision, interpretation of findings, and critical revision of the manuscript. B.M.S. contributed to data validation, manuscript refinement and final approval.

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