Targeting integrated cell death networks in sepsis-associated acute kidney injury: Shared regulatory nodes and diet-related small molecule modulation (Review)

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Abstract. Sepsis-associated acute kidney injury (SA-AKI) presents a significant challenge in critical care, largely due to the multifaceted nature of renal injury stemming from interconnected disturbances in inflammation, metabolism, microcirculation, mitochondrial function and programmed cell death, rather than arising from a singular dominant pathway. Increasing evidence indicates that apoptosis, pyroptosis, ferroptosis, necroptosis and autophagy-related responses function as an integrated yet heterogeneous cell death network, characterized by extensive crosstalk, compensatory signaling and disease stage-dependent regulation. The present review uses an integrated cell death network framework for SA-AKI, rather than simply summarizing individual cell death pathways or sequentially cataloguing diet-related small molecules. Current evidence was synthesized by organizing shared regulatory nodes according to their mechanistic roles, including upstream drivers, amplifiers or permissive states, context-dependent modifiers, and terminal execution mechanisms. Focus is placed on mitochondrial dysfunction, redox-iron imbalance, NF-κB-dependent inflammatory activation, inflammasome priming, failures in autophagy/mitophagy and immunometabolic stress. Furthermore, the present review explores how diet-related small molecules may influence these shared injury conditions, differentiating between food-derived phytochemicals, nutritional compounds, microbiota-derived metabolites and intensive care unit-based antioxidant or vitamin regimens. The potential efficacy of these compounds may derive less from their ability to selectively inhibit isolated death programs and more from their capacity to reshape common upstream environments that allow multiple death pathways to manifest. Finally, major translational barriers are discussed, including limited bioavailability, uncertainty surrounding active metabolites, altered pharmacokinetics during sepsis, disease-stage specificity, renal target exposure and inter-patient heterogeneity. An exposure-aware and endotype-guided framework is proposed for the future evaluation of diet-related small molecules in the context of SA-AKI.

Contents

1. Introduction

Sepsis-associated acute kidney injury (SA-AKI) remains one of the most frequent and lethal complications encountered among critically ill patients with sepsis in the intensive care unit (ICU) (1). Large cohort studies have indicated that AKI occurs in up to 40-70% of patients suffering from sepsis, with SA-AKI accounting for nearly half of all AKI diagnoses in the

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ICU (2,3). Beyond its association with short-term mortality, SA-AKI is associated with an increased need for prolonged mechanical ventilation, greater dependence on renal replacement therapy (RRT) and extended ICU stays (4). Survivors are also at a heightened risk of incomplete renal recovery and subsequent chronic kidney dysfunction. Sepsis research highlights the significance of systemic inflammatory dysregulation, immune-metabolic disturbances, endothelial injury and organ crosstalk as central determinants of sepsis progression and organ failure (5). For instance, the metabolic reprogramming of macrophages has been shown to exacerbate cytokine storm amplification through glycolysis-related inflammatory activation and stimulator of interferon genes (STING)-associated signaling, thereby reinforcing the perspective that sepsis is not merely an inflammatory disorder but also an immune-metabolic syndrome (6). Concurrently, studies focusing on nanomaterial-based delivery of bioactive therapeutics have shed light on the intricate pathophysiology of sepsis, characterized by excessive inflammation, oxidative stress, immune imbalances and multi-organ failure, as well as the necessity to address limitations regarding stability, bioavailability, tissue delivery and immune modulation (7,8). These findings provide a comprehensive context for understanding SA-AKI as a manifestation of systemic septic immune-metabolic and inflammatory injury, rather than as an isolated renal event.

Despite advancements in antimicrobial therapy, hemodynamic management and renal replacement support, effective interventions aimed at directly halting septic renal parenchymal injury remain elusive. The absence of effective kidney-targeted therapies in SA-AKI likely reflects the multifaceted nature of the injury, wherein inflammatory dysregulation, microvascular disturbances, metabolic stress and organelle dysfunction operate concurrently (9). Unlike conventional forms of AKI, SA-AKI is often characterized by endothelial activation, microvascular flow heterogeneity and mitochondrial structural damage accompanied by impaired bioenergetics, along with inflammatory signaling that persists even in the absence of significant tubular necrosis (10). These abnormalities are not restricted to a single compartment; rather, tubular epithelial stress, endothelial dysfunction, immune activation and metabolic failure frequently develop concurrently, which may elucidate why interventions targeting a singular pathway have exhibited only partial protective effects in complex sepsis injury models (11).

Programmed cell death (PCD) has emerged as a critical factor in renal injury associated with SA-AKI. Previous research has demonstrated that SA-AKI encompasses not only caspase-mediated apoptosis, but also pyroptosis linked to the NOD-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome, ferroptotic injury associated with lipid peroxidation and compromised antioxidant defense, and disturbances in autophagic flux (12-15). Historically, apoptosis, pyroptosis, ferroptosis, necroptosis and autophagy have been characterized as distinct pathways (16,17). However, emerging evidence from SA-AKI and sepsis models indicates that these responses frequently intersect rather than operate in isolation (18,19). Factors such as inflammatory cytokine signaling, mitochondrial dysfunction, accumulation of reactive oxygen species (ROS), iron dysregulation and inflammasome priming can lower the activation threshold for multiple death programs concurrently (20). Impaired autophagic control may further heighten susceptibility to apoptosis, pyroptosis, necroptosis or ferroptosis, contingent upon the stage of the disease and the cellular context (19,21). Investigations have suggested that mitochondrial injury may act as a pivotal convergence point between immune activation and cell death, while microvascular dysfunction, persistent hypoxia and dysregulated iron handling may promote lipid peroxidation and ferroptotic damage (22,23). This overlapping pathology may elucidate why the inhibition of a single death pathway typically yields only limited protective effects in preclinical sepsis models. Under conditions of severe inflammatory stress, apoptotic, pyroptotic and necroptotic signals may be activated simultaneously rather than through isolated mechanisms. The term 'PANoptosis' has been proposed to describe this coordinated response (24). Although the specific role of PANoptosis in SA-AKI remains to be elucidated, current evidence indicates extensive crosstalk among the regulated cell death pathways involved in SA-AKI (25).

The complexity and redundancy of PCD in SA-AKI have heightened interest in interventions capable of targeting multiple pathogenic processes concurrently. In this context, diet-related small molecules have garnered increasing attention, as a number of these compounds influence biological processes that are frequently implicated in SA-AKI (26-28). For the purposes of the present review, diet-related small molecules are defined as food-derived, naturally occurring or diet-associated bioactive small molecules that may have relevance to renal injury biology (29). This primary category primarily includes food-derived phytochemicals and related naturally occurring compounds. To enhance translational interpretation, a distinction is made between these molecules and other categories, including nutritional or essential small molecules, microbiota-derived metabolites, pharmacological derivatives or formulations, and ICU-based antioxidant or metabolic regimens (30). This differentiation is crucial, as evidence from one category should not be directly extrapolated to another. For instance, hydrocortisone, while relevant, is not classified as a diet-related small molecule and is discussed solely within the context of ICU combination regimens involving vitamin C and thiamine (31). Recent studies have indicated that food-derived or naturally occurring small molecules can modulate inflammatory signaling, oxidative stress, mitochondrial dysfunction, impaired antioxidant defenses and dysregulated cell death responses in SA-AKI (32,33). In experimental models of sepsis- or endotoxin-induced kidney injury, compounds such as resveratrol, morin and reduced glutathione have been shown to mitigate renal dysfunction and tubular injury while simultaneously decreasing the inflammatory burden, oxidative damage and signaling related to cell death (34-36). These protective effects often stem not from the selective inhibition of a single pathway, but rather from broader regulation of shared upstream injury mechanisms, including redox imbalance, stress signaling and organelle dysfunction (37). However, most existing evidence remains preclinical, accompanied by significant uncertainty regarding active species, bioavailability, timing of treatment, renal target exposure and clinical applicability (38).

Despite the growing interest in diet-related small molecules for addressing septic organ injury, current discussions

often remain descriptive and are commonly organized around individual compounds or isolated signaling pathways (39-41). Such an approach can obscure the interconnected nature of apoptosis, pyroptosis, ferroptosis, necroptosis and autophagy-related responses in SA-AKI, which are regularly regulated through shared upstream stress programs (20).

Consequently, the present review uses an integrated cell death network framework to analyze diet-related small molecules. Within this framework, these molecules are evaluated based on the shared regulatory nodes they influence, the strength and category of supporting evidence, the translational barriers that hinder development, and precision-oriented strategies that could enhance the biological and clinical coherence of future interventions.

2. PCD as an integrated network in SA-AKI

In the present review, 'integrated' refers to the dynamic interaction among multiple regulated cell death pathways through shared upstream drivers, overlapping signaling mechanisms and context-dependent crosstalk, rather than implying that these pathways function as a single unified mechanism. This section analyzes PCD in SA-AKI as a collection of interconnected injury responses rather than as distinct pathways. The focus shifts from reiterating the defining features of apoptosis, ferroptosis, pyroptosis, necroptosis and autophagy-related responses to the common stress conditions and overlapping signals that influence cell death patterns in SA-AKI. To facilitate mechanistic interpretation of the network concept, a distinction is made among upstream drivers, amplifiers or permissive states, context-dependent modifiers and terminal executors. This integrated regulated cell death network is summarized in Fig. 1 (19-21). At the receptor and proximal signaling levels, pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) activate pattern-recognition receptors, including toll like receptor 4 (TLR4), whereas TNF-tumor necrosis factor receptor (TNFR) signaling converges with these inputs on NF-κB- and receptor-interacting serine/threonine-protein kinase (RIPK)1-dependent pathways (42-48). Mitochondrial dysfunction, mitochondrial ROS and oxidized mitochondrial DNA (mtDNA), together with endoplasmic reticulum (ER) stress and STING-protein kinase R-like endoplasmic reticulum kinase (PERK) signaling, further promote inflammasome activation and lower the activation thresholds for apoptosis, pyroptosis, necroptosis and ferroptosis (48-53). Autophagy and mitophagy act as context-dependent modifiers: Early adaptive flux may limit the accumulation of damaged organelles, whereas defective or insufficient flux allows mitochondrial and inflammatory stress to accumulate and increases susceptibility to other cell death programs (19,54). The relative contributions of these pathways may vary across renal compartments, cell types and disease stages, resulting in spatiotemporal heterogeneity in the dominant cell death signatures (46,55-63).

In this hierarchy, mitochondrial dysfunction, microcirculatory-metabolic stress and inflammatory transcriptional activation function as upstream drivers that reduce the threshold for injury. Activation of NF-κB, inflammasome priming, iron dysregulation, oxidative stress and ER stress primarily serve as amplifiers or permissive states (64). Autophagy and mitophagy influence cell fate in a stage-dependent manner, either by limiting the accumulation of damaged organelles or, when insufficient, allowing mitochondrial and inflammatory stress to accumulate (65). Downstream execution mechanisms include caspase activation, gasdermin D (GSDMD) cleavage, lipid peroxidation-dependent ferroptotic execution and the machinery associated with necroptosis (42). This hierarchy is intended as a conceptual framework rather than a rigid classification. It emphasizes that the shared regulatory network is not a flat structure in which every node occupies the same mechanistic position or represents an equally suitable therapeutic target.

Pathophysiological drivers of cell death in SA-AKI. SA-AKI develops within a pathophysiological environment characterized by inflammatory dysregulation, microcirculatory disturbances, metabolic reprogramming and organelle stress (21). These processes interact continuously, shaping the susceptibility of renal cells to distinct but overlapping PCD pathways. Unlike forms of AKI primarily driven by ischemia-reperfusion or direct nephrotoxic injury, SA-AKI is marked by persistent exposure to signals from pathogens, endogenous danger molecules, endothelial dysfunction and maladaptive immune activation (21). Consequently, renal injury is influenced not only by the magnitude of the initial insult but also by the capacity to maintain immunometabolic homeostasis under septic stress.

Microcirculatory dysfunction emerges as one of the earliest determinants in this process. Sepsis disrupts intrarenal perfusion through mechanisms such as endothelial activation, capillary leakage, vasomotor dysregulation and regional blood flow redistribution. Even when global hemodynamic parameters appear normalized, the renal microenvironment may remain hypoxic and metabolically unstable (66). Tubular epithelial cells subsequently adapt by altering substrate utilization and compromising oxidative phosphorylation (49). However, this adaptive response is limited. Once the mitochondrial reserve is overwhelmed, energetic failure and redox imbalance act together to promote the activation of cell death signaling. Under these conditions, mitochondrial injury transcends being merely a downstream consequence of sepsis-induced stress; it acts as a central amplifier of renal vulnerability (43).

Inflammatory signaling exacerbates this vulnerability. PAMPs and DAMPs activate pattern recognition receptors and sustain the transcription of pro-inflammatory mediators through NF-κB signaling. Cytokines such as TNF-α and IL-6 not only recruit and activate immune cells but also directly alter the survival threshold of renal parenchymal cells (67). In parallel, inflammatory activation stimulates the production of reactive oxygen and nitrogen species, impairing mitochondrial integrity, and disrupting membrane lipid stability (21). Oxidative stress therefore serves as a critical junction linking inflammation, metabolic failure and cell death execution. Once the antioxidant buffering capacity is depleted, the renal epithelium becomes susceptible to apoptosis, ferroptosis, pyroptosis and other regulated death responses (68).

An additional layer of complexity arises from the significant biological heterogeneity of SA-AKI. Not all patients exhibit the same dominant pattern of injury; some present with pronounced inflammatory activation, whereas others

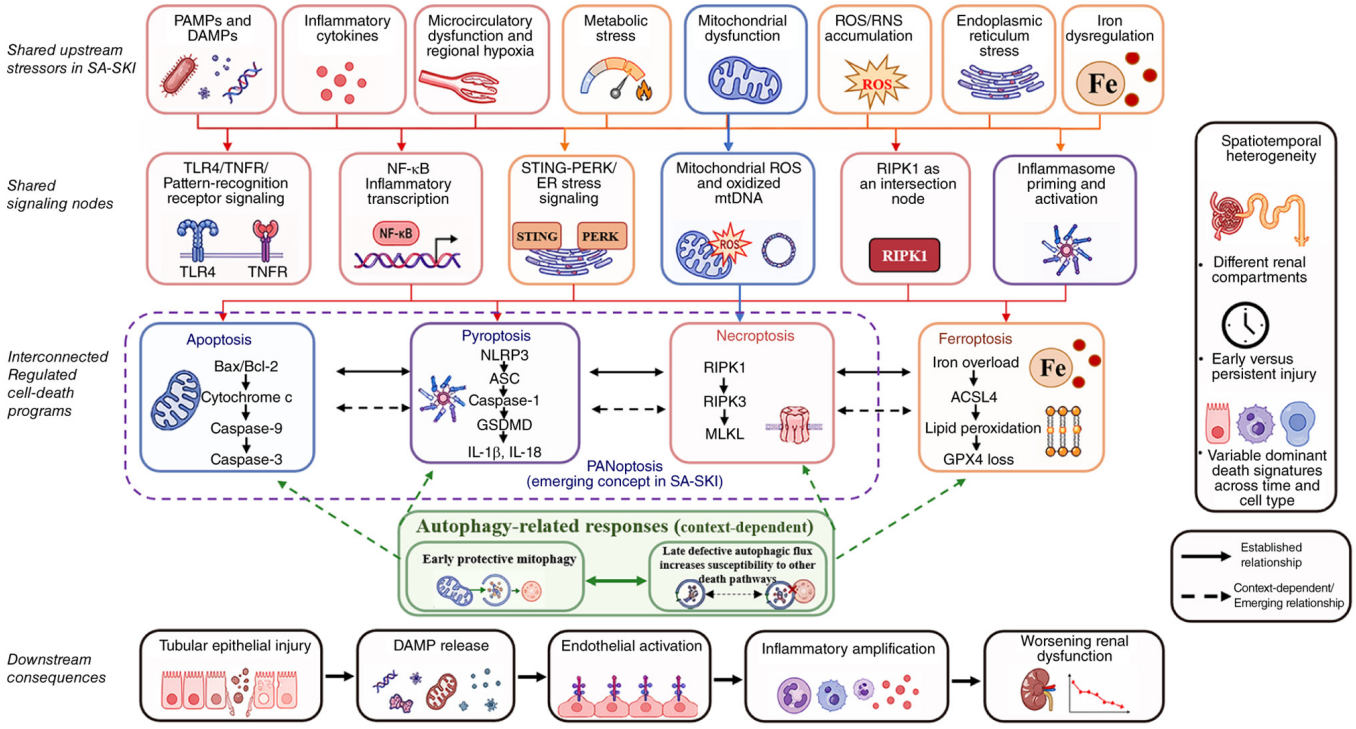

Figure 1. Hierarchical integrated regulated cell death network in SA-AKI. In SA-AKI, PAMPs and DAMPs, inflammatory cytokines, microcirculatory dysfunction and regional hypoxia, metabolic stress, mitochondrial dysfunction, ROS/RNS accumulation, ER stress, and iron dysregulation collectively lower the activation thresholds for multiple regulated cell death programs. These upstream stressors converge on shared signaling nodes, including pattern-recognition receptor signaling involving TLR4, TNFR signaling, NF-κB-dependent inflammatory transcription, STING-PERK/ER stress signaling, mitochondrial ROS and oxidized mtDNA, RIPK1-dependent signaling, and inflammasome priming and activation. Downstream apoptosis, pyroptosis, necroptosis and ferroptosis are interconnected rather than operating as entirely isolated pathways. PANoptosis is presented as an emerging concept restricted to the coordinated overlap among pyroptotic, apoptotic and necroptotic signaling. Autophagy and mitophagy are presented as context-dependent modifiers: Early adaptive responses may limit organelle damage, whereas defective autophagic flux may increase susceptibility to other cell death pathways. The relative contributions of these mechanisms may vary across renal compartments, cell types and disease stages. Collectively, this network promotes tubular epithelial injury, DAMP release, endothelial activation, inflammatory amplification and worsening renal dysfunction. ACSL4, acyl-CoA synthetase long-chain family member 4; ASC, apoptosis-associated speck-like protein containing a caspase recruitment domain; DAMP, damage-associated molecular pattern; ER, endoplasmic reticulum; GPX4, glutathione peroxidase 4; GSDMD, gasdermin D; MLKL, mixed lineage kinase domain-like pseudokinase; mtDNA, mitochondrial DNA; NLRP3, NOD-like receptor family pyrin domain-containing 3; PAMP, pathogen-associated molecular pattern; PERK, protein kinase R-like endoplasmic reticulum kinase; RIPK, receptor-interacting serine/threonine-protein kinase; RNS, reactive nitrogen species; ROS, reactive oxygen species; SA-AKI, sepsis-associated acute kidney injury; STING, stimulator of interferon genes; TLR4, toll-like receptor 4; TNFR, tumor necrosis factor receptor.

show stronger evidence of mitochondrial dysfunction, oxidative damage or tubular stress (55). Variability in biomarkers such as neutrophil gelatinase-associated lipocalin (NGAL) and kidney injury molecule-1 supports the view that SA-AKI involves heterogeneous tubular stress and injury patterns rather than a uniform disease process (69,70). This heterogeneity has major implications for the interpretation of PCD in sepsis. Different death programs are unlikely to contribute equally across all patients, disease stages or renal compartments. Any mechanistic framework attempting to explain SA-AKI must take into account the context, timing and biological diversity.

Crosstalk among major regulated cell death pathways in SA-AKI. In SA-AKI, apoptosis, pyroptosis, ferroptosis, necroptosis and autophagy-related responses are unlikely to function as entirely separate processes. Available evidence frequently indicates convergence at the level of shared upstream stressors rather than strict delineation into independent pathways. Factors such as inflammatory cytokine signaling, pattern recognition receptor activation, mitochondrial dysfunction, ROS accumulation, ER stress and disturbed iron handling can each lower the threshold for multiple forms of regulated cell death (20,44,50,51). This perspective is reinforced by a review of PCD in SA-AKI, which characterized these pathways as mechanistically interconnected rather than discrete. The authors noted that autophagic activity might transiently mitigate injury in early sepsis, while progressive stress is accompanied by the activation of alternative death programs (19).

Current renal studies also support the notion of crosstalk through shared signaling nodes. In sepsis, renal tubular epithelial cells have been shown to express acyl-CoA synthetase short chain family member 2, which promotes pyroptosis and inflammation through the KLF transcription factor 5/NF-κB axis, indicating that inflammatory transcriptional reprogramming can directly favor pyroptotic injury (44). Similarly, lipopolysaccharide (LPS)-induced AKI has been linked to ER stress, PERK activation and Bax/Bcl2 imbalance, linking stress-adaptive failure to apoptotic signaling (71). Additionally, another SA-AKI study demonstrated that STING-PERK activation was accompanied by inflammation, apoptosis and cellular senescence, again suggesting that upstream danger signaling does not engage only a single terminal pathway (51). These findings highlight NF-κB, ER stress, PERK and mitochondrial injury

as pivotal intersections where inflammatory and death-related signals converge rather than remain distinct.

The relationship between ferroptosis and other death programs in SA-AKI mirrors this complexity. In cecal ligation and puncture (CLP)- and/or LPS-based models, Guo *et al* (52) demonstrated that ginsenoside Rg1 restored ferroptosis suppressor protein 1 (FSP1)- and glutathione peroxidase 4 (GPX4)-associated ferroptosis defenses, and reduced iron accumulation and lipid peroxidation in renal tubular epithelial cells. Zhang *et al* (72) reported that andrographolide protected septic rats and LPS-treated HK-2 cells by activating the nuclear factor erythroid 2-related factor 2 (Nrf2)/FSP1 pathway, increasing solute carrier family 7 member 11 (SLC7A11) and GPX4 expression, and reducing iron accumulation and lipid peroxidation. Xiao *et al* (73) further demonstrated that NFIL3 knockdown attenuated acyl-CoA synthetase long chain family member 4 (ACSL4)-dependent ferroptosis and inflammation in models of SA-AKI. In addition, curcumin reduced renal iron overload, ACSL4 expression and 4-hydroxynonenal (4-HNE) accumulation while preserving GPX4 expression and attenuating inflammation and tubular injury in CLP- and LPS-based models (74). Because the anti-ferroptotic effects in these studies were accompanied by improvements in renal function, histological injury, oxidative stress and/or inflammation, these findings are consistent with modulation of shared upstream redox-inflammatory programs rather than an entirely isolated terminal death module (52,72-74). Evidence from non-septic AKI models further supports the context-dependence of cell death regulation. In ischemia-reperfusion- and folic acid-induced AKI, quercetin inhibited ferroptosis and ferroptosis-associated macrophage recruitment without inhibiting apoptosis, necrosis or autophagy (75). Collectively, these findings suggest that the predominant form of cell death and its downstream inflammatory consequences may vary according to the renal injury context.

Mechanistic overlap is particularly pronounced among apoptosis, pyroptosis and necroptosis. RIPK1 occupies a major signaling intersection downstream of TNF receptor pathways and can influence inflammatory activation as well as apoptosis, necroptosis and pyroptosis depending on its post-translational modifications and molecular partners (60). In addition, the caspase-3/gasdermin E axis provides a direct molecular pathway through which an apoptotic caspase can trigger pyroptotic membrane rupture (61). These observations elucidate why severe inflammatory injury may manifest as mixed death phenotypes rather than being confined to a single pathway. The term PANoptosis has been proposed to describe this coordinated activation of pyroptotic, apoptotic and necroptotic signaling (76). However, in the context of SA-AKI, direct evidence for a fully assembled PANoptotic process in renal cells remains limited. Therefore, PANoptosis should currently be regarded as a conceptual framework for interpreting coordinated cell death responses rather than as a firmly established mechanism in SA-AKI.

Autophagy should also be interpreted with care in this context. In SA-AKI, it is more appropriately considered to be a context-dependent modifier of cell fate rather than a uniformly terminal death program. Early autophagic activation can facilitate the removal of damaged mitochondria and mitigate inflammatory or oxidative injury, whereas defective or insufficient autophagic flux may allow the accumulation of mitochondrial damage, increased inflammasome activation and enhanced lipid peroxidation, ultimately heightening susceptibility to apoptosis, pyroptosis, necroptosis or ferroptosis (54,77). This may explain why studies concentrated on individual death pathways often converge on common upstream abnormalities and only partially elucidate the overall pattern of SA-AKI.

PANoptosis and integrated death signaling in SA-AKI. The concept of PANoptosis helps explain why inflammatory cell death in SA-AKI does not consistently follow a single canonical pathway. Rather than simply representing a coexistence of pyroptosis, apoptosis and necroptosis, PANoptosis signifies a coordinated form of inflammatory cell death in which components of these pathways are engaged in an integrated manner (78). For clarity, evidence related to PANoptosis in SA-AKI should be evaluated at three levels: The co-expression or parallel activation of death markers, functional crosstalk among pathways and the formation of a defined PANoptotic complex (62). This distinction is crucial because the co-activation of markers alone does not substantiate the existence of a fully assembled PANoptotic mechanism (79). Recent mechanistic studies have indicated that PANoptosis is driven by interactions among caspases, receptor-interacting protein kinases and innate immune sensors, reinforcing the notion that severe inflammatory injury may prompt mixed death phenotypes rather than strictly segregated programs (80,81).

In SA-AKI, direct evidence for PANoptosis is still limited but is beginning to surface. A recent study demonstrated that eukaryotic translation initiation factor 2 α kinase 2 promoted SA-AKI by upregulating absent in melanoma 2 and activating signaling associated with PANoptosis in both CLP mice and LPS-treated HK-2 cells, providing direct support for the involvement of integrated death signaling in the kidney during sepsis (18). This finding suggests that innate immune sensing may connect pyroptotic, apoptotic and necroptotic machinery under severe septic stress. However, most available evidence regarding SA-AKI currently supports marker co-activation and pathway crosstalk more robustly than the definitive formation of PANoptotic complexes (63). Consequently, PANoptosis in SA-AKI should be understood as a cautious mechanistic concept rather than a solid conclusion. Additional studies are necessary to define the responsible sensors, molecular complexes, cell-specific characteristics and temporal sequence of PANoptosis-related signaling during the progression of SA-AKI.

Accumulating evidence also supports the notion of integrated death signaling in SA-AKI. RIPK1, RIPK3 and mixed lineage kinase domain like pseudokinase have increasingly been implicated in SA-AKI and occupy a central role at the intersection of inflammatory signaling, apoptosis and necroptosis (45,46). Concurrently, mechanistic studies outside the kidney have demonstrated that caspase-8 and RIPK3 can cooperate in lytic inflammatory death responses with PANoptotic characteristics, further reinforcing the idea that traditional boundaries between apoptosis and inflammatory cell death may become destabilized under conditions of intense stress (82,83). Although these findings do not yet establish PANoptosis as a fully defined and uniformly validated mechanism in SA-AKI,

they suggest that the complex interactions among regulated cell death pathways cannot be fully explained by considering apoptosis, pyroptosis or necroptosis in isolation.

At present, PANoptosis should be interpreted as a cautious mechanistic concept rather than a definitive conclusion in SA-AKI. This perspective provides a useful framework for understanding how innate immune sensing, inflammatory cytokine signaling and stress-activated kinase pathways converge on shared cell death regulatory mechanisms in SA-AKI (76). At the same time, the current evidence base is still narrow. Additional studies are needed to define the responsible sensors, molecular complexes, cell-specific features and temporal sequence of PANoptosis-related signaling during the progression of SA-AKI.

Spatiotemporal heterogeneity of cell death programs. The activation of regulated cell death programs in SA-AKI is unlikely to be uniform in space or time. Clinical and biomarker-based research increasingly suggests that SA-AKI comprises biologically distinct subphenotypes, each exhibiting differing trajectories, pathophysiological features and outcomes (56,57). This heterogeneity is further observable at the bedside (84). In a large multicenter ICU cohort, SA-AKI was typically identified within the first day post-ICU admission; however, the severity, diagnostic patterns and subsequent courses varied among patients (85,86). These observations do not support the premise that a single dominant cell death pathway operates uniformly throughout AKI.

Spatial heterogeneity is also evident within the kidney itself. Spatial and single-cell transcriptomics analyses have revealed that AKI does not uniformly affect all renal regions and that epithelial immune interactions differ across local microenvironments (58,87). In murine models of CLP and ischemia reperfusion injury, regional expression differences were detectable even in areas with minimal histologic injury, and immune cell signatures localized preferentially to specific cortical and outer medullary regions (88). This spatial pattern is consistent with the microvascular abnormalities observed in SA-AKI, where glycocalyx disruption, endothelial dysfunction and disturbed microcirculatory homeostasis may lead to uneven exposure to hypoxia, inflammatory mediators and cell death triggers across renal compartments (89).

Temporal heterogeneity is similarly significant. The cellular response observed shortly after injury may differ from that during persistent injury or incomplete recovery (59). Single-nucleus profiling of AKI has identified a distinct failed-repair state in proximal tubular cells during recovery, and experimental work has further demonstrated that different forms of regulated necrosis may manifest sequentially rather than at a fixed stage (90). In this context, the dominant death signature in SA-AKI is unlikely to remain constant across time, cell type or renal region. Findings derived from a single-marker panel or a single sampling time point may therefore capture only a partial aspect of the overall injury pattern.

3. Diet-related small molecules as network modulators in SA-AKI

Functional classes and pharmacological characteristics. Current evidence suggests that diet-related small molecules in SA-AKI should not be treated as a chemically uniform group (91). Most compounds examined in preclinical sepsis and SA-AKI studies can be classified into several broad functional categories, including polyphenols (comprising flavonoids, stilbenes and phenolic acids), terpenoids, alkaloids and quinones (84). Microbiota-derived short-chain fatty acids (SCFAs) and related metabolites represent a distinct diet-associated category rather than food-derived phytochemicals. Among these metabolites, butyrate has been shown to attenuate SA-AKI by suppressing NLRP3-associated pyroptosis and STING/GSDMD signaling, while broader SCFA supplementation reduces systemic inflammation and organ injury in experimental sepsis (92,93). These categories and their convergence on shared regulatory modules are summarized in Fig. 2. For the purposes of translational interpretation, these compounds should be distinctly separated from pharmacological derivatives and ICU-based antioxidant or vitamin regimens such as vitamin C, thiamine or combination therapies involving hydrocortisone (94,95). Despite considerable structural diversity, these molecules frequently exhibit similar pharmacological patterns. They typically target upstream stress programs that recur across AKI rather than engaging solely with a single terminal death pathway (96). Consequently, factors such as redox imbalance, inflammatory transcriptional activation, mitochondrial dysfunction, disturbed iron handling and stress response signaling provide more informative bases for functional classification than the sources of the compounds (97).

Among these categories, polyphenolic compounds have received the most attention. This increased focus is attributable not only to their prevalence in plant-based foods, but also to their extensive metabolic and signaling effects following digestion and biotransformation (98). The biological activity of these compounds is influenced by their chemical forms; glycosides, aglycones and low-molecular-weight phenolic metabolites differ markedly in solubility, stability and intestinal absorption (32). Additionally, microbial transformations occurring during fermentation or within the gastrointestinal tract may produce metabolites with distinct bioactivity compared with their parent compounds (99). This consideration is directly relevant to SA-AKI. For instance, resveratrol has been reported to mitigate early polymicrobial SA-AKI by inhibiting ER stress-activated NF-κB signaling, while curcumin has been shown to alleviate SA-AKI with concomitant suppression of ferroptosis-related ACSL4/GPX4 signaling (74,100). These findings imply that representative diet-related small molecules often exert pleiotropic effects across inflammatory, oxidative, metabolic and death-related pathways rather than selectively blocking a single isolated target.

Nonetheless, the pharmacological potential of these compounds does not eliminate translational constraints. Numerous diet-related small molecules exhibit low oral bioavailability, extensive host and microbial metabolism, rapid elimination, and significant dependence on the food matrix, formulation and dose exposure (101). As a result, the species present in circulation or tissues may differ substantially from the parent compounds utilized in cell-based experiments, and compounds within the same chemical class may demonstrate markedly different pharmacokinetic behaviors. These characteristics help explain why seemingly similar

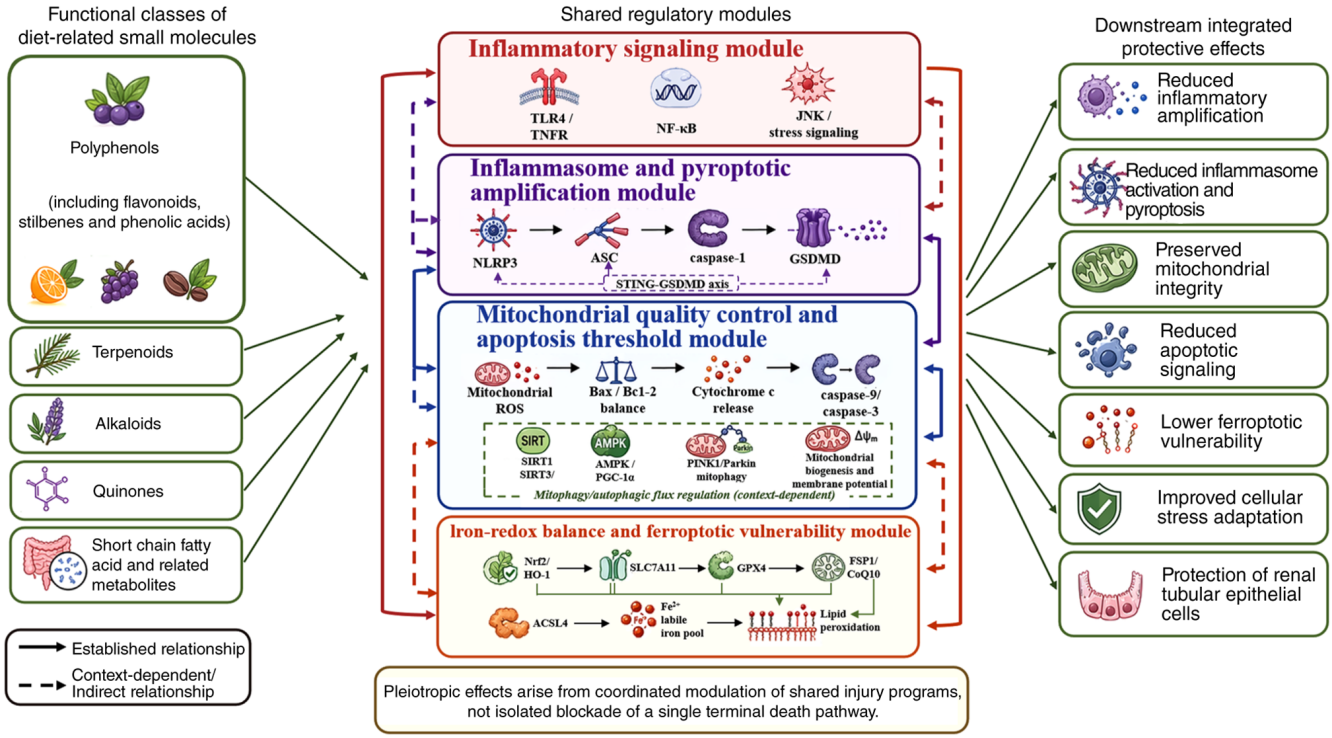

Figure 2. Diet-related small molecules as modulators of hierarchical shared regulatory nodes in SA-AKI. The functional classes shown include polyphenols (including flavonoids, stilbenes and phenolic acids), terpenoids, alkaloids and quinones, together with microbiota-derived short-chain fatty acids and related metabolites. Although chemically and pharmacologically diverse, these compounds and metabolites may converge on shared regulatory modules rather than selectively blocking a single terminal cell death pathway. The modules shown comprise inflammatory signaling involving TLR4/TNFR, NF-κB and JNK/stress signaling; NLRP3/caspase-1/GSDMD- and STING/GSDMD-associated inflammasome and pyroptotic signaling; SIRT1/SIRT3-, AMPK/PGC-1α- and PINK1/Parkin-related mitochondrial quality control, together with Bax/Bcl-2-, cytochrome *c*- and caspase-9/caspase-3-associated apoptotic signaling; and Nrf2/HO-1-, SLC7A11-, GPX4-, FSP1/CoQ10- and ACSL4-related regulation of iron-redox balance and ferroptotic vulnerability. Autophagy and mitophagy are presented as context-dependent modifiers. The resulting integrated protective effects include reduced inflammatory amplification and pyroptosis, preserved mitochondrial integrity, reduced apoptotic signaling and ferroptotic vulnerability, improved cellular stress adaptation, and protection of renal tubular epithelial cells. ACSL4, acyl-CoA synthetase long-chain family member 4; AMPK, AMP-activated protein kinase; ASC, apoptosis-associated speck-like protein containing a caspase recruitment domain; CoQ10, coenzyme Q10; FSP1, ferroptosis suppressor protein 1; GPX4, glutathione peroxidase 4; GSDMD, gasdermin D; HO-1, heme oxygenase 1; NLRP3, NOD-like receptor family pyrin domain-containing 3; Nrf2, nuclear factor erythroid 2-related factor 2; PGC-1α, peroxisome proliferator-activated receptor-γ coactivator 1α; PINK1, PTEN-induced kinase 1; ROS, reactive oxygen species; SA-AKI, sepsis-associated acute kidney injury; SIRT, sirtuin; SLC7A11, solute carrier family 7 member 11; STING, stimulator of interferon genes; TLR4, toll-like receptor 4; TNFR, tumor necrosis factor receptor.

molecules can exhibit inconsistent efficacy across models and why experimental benefits may not readily translate to clinically achievable exposures (102). Hence, the evaluation of diet-related small molecules in SA-AKI should incorporate both chemical class and metabolic fate, formulation properties, and achievable exposure rather than rely solely on nominal compound identity. The functional and pharmacological features of the primary diet-related small molecule groups relevant to SA-AKI are summarized in Table SI.

Shared regulatory nodes targeted by diet-related small molecules. Despite the chemical diversity of diet-related small molecules studied in SA-AKI, their reported protective effects converge on a limited number of shared regulatory nodes rather than targeting individual terminal cell death pathways (103).

As illustrated in Fig. 2, these nodes can be categorized by their mechanistic positions: Upstream inflammatory transcriptional activation focused on TLR4-, TNFR- and NF-κB-related signaling; amplifying or permissive states such as inflammasome priming, mitochondrial ROS generation, iron dysregulation and lipid peroxidation; context-dependent modifiers, including autophagy and mitophagy; and terminal execution mechanisms such as GSDMD cleavage, caspase activation, ferroptotic lipid membrane damage and necroptotic signaling (47,104). Puerarin has been shown to reduce systemic inflammation and organ injury in experimental sepsis by suppressing NF-κB/JNK signaling, while resveratrol mitigates early polymicrobial septic AKI through inhibition of ER stress-associated inositol-requiring enzyme 1-NF-κB activation (100,105). Similarly, luteolin exhibits a comparable effect in endotoxin-induced renal injury, as evidenced by reduced NF-κB activation, decreased inflammatory mediator levels, attenuated oxidative stress and reduced apoptosis (92). These findings suggest that certain diet-related small molecules act by initially lowering the inflammatory background, thereby limiting the activation of multiple downstream cell death programs (106).

A second recurring node is the Nrf2-centered antioxidant defense system (107). In the context of SA-AKI, allicin has been reported to promote Nrf2 nuclear translocation and heme oxygenase-1 (HO-1) expression, resulting in reduced ROS accumulation, inflammatory mediator release, mitochondrial dysfunction and apoptosis (108). More broadly, the literature on AKI positions Nrf2 at the intersection of

antioxidant enzyme induction, mitochondrial protection, lipid homeostasis and suppression of inflammatory signaling (109). In this regard, the activation of Nrf2/HO-1 is not merely an antioxidant response; it likely reflects regulation of a more extensive stress-adaptation program that impacts the redox balance, organelle integrity and vulnerability to regulated cell death (110).

Inflammasome-related pyroptotic signaling also emerges as a shared target. Recent research has indicated that butyrate mitigates SA-AKI by suppressing the STING/GSDMD axis, with parallel reductions in NLRP3-associated pyroptotic signaling and renal injury (53). This aligns with recent reviews that position NLRP3-caspase-1-GSDMD signaling at the core of inflammatory cell death in SA-AKI (48,111). These observations indicate that at least some diet-related small molecules, including resveratrol, curcumin and cichoric acid, may interrupt pyroptotic injury by modulating upstream innate immune sensors and inflammasome activation rather than solely targeting terminal membrane rupture (27,28,112-114).

Nodes associated with mitochondrial quality control and metabolic adaptation are also consistently targeted. Resveratrol improves SA-AKI in rats through activation of sirtuin (SIRT)1 and SIRT3, accompanied by attenuation of oxidative stress and restoration of autophagic activity (36). This pattern is significant because it situates certain dietary molecules upstream of organelle stress, rather than solely downstream of cytokine release. Studies focusing on ferroptosis further corroborate this view. Ginsenoside Rg1 ameliorates SA-AKI by regulating ferroptosis in tubular epithelial cells, andrographolide inhibits ferroptosis in renal tubular epithelial cells via Nrf2/FSP1-related signaling and curcumin reduces SA-AKI with concurrent regulation of the ACSL4/GPX4 axis (52,72,74). Together, these findings indicate that, in SA-AKI, diet-related small molecules repeatedly converge on a restricted set of shared regulatory nodes, particularly NF-κB, Nrf2, inflammasome-related pyroptotic signaling, SIRT-dependent autophagic or mitochondrial control, and ferroptosis-related lipid redox pathways. Thus, their apparent broad actions reflect the coordinated modulation of upstream injury programs rather than a selective blockade of a single terminal mode of cell death (41,115). The key shared regulatory nodes linking the actions of dietary small molecules with the integrated cell death network in SA-AKI are summarized in Table SII.

Bioavailability and variation in biological effects under septic conditions. The biological effects of diet-related small molecules in SA-AKI cannot be interpreted independently of bioavailability. For numerous compounds investigated in this domain, the parent molecule utilized in cell-based experiments may only be transiently present in circulation following oral administration or might not be detectable at all. For instance, while resveratrol is absorbed efficiently, it undergoes extensive first-pass conjugation, resulting in very low systemic exposure to the unconjugated parent compound (116). Similarly, curcumin exhibits limited systemic availability due to poor aqueous solubility and rapid metabolism, while quercetin absorption varies considerably based on its structural form and formulation (117,118). Intact ginsenosides also exhibit low plasma exposure after oral intake due to poor permeability and extensive presystemic transformation, and allicin is characterized by high instability, with rapid degradation limiting the persistence of the parent compound *in vivo* (119,120). These observations indicate that the biological effects observed in experimental settings may not directly translate to clinical settings, because *in vivo* efficacy depends more on metabolic fate and actual tissue exposure than on the administered parent compound alone.

This issue becomes increasingly critical under septic conditions. Sepsis alters the pharmacokinetic landscape through mechanisms such as splanchnic hypoperfusion, impaired intestinal absorption, reduced hepatic metabolic capacity, modified protein binding, capillary leak and disturbed microcirculatory delivery (121,122). Consequently, plasma concentrations may not accurately reflect renal tissue exposure, leading to an increasingly unstable relationship between the administered dose and biological effect during septic organ dysfunction (123). Furthermore, sepsis-related disruptions of the intestinal barrier and acute shifts in gut microbiota may further influence the generation, absorption and systemic persistence of secondary metabolites derived from dietary compounds (124). Under such conditions, the active species that reach the injured kidney may differ from the parent compounds typically examined in mechanistic *in vitro* studies (125).

Variation in biological effects across studies is therefore expected. For certain compounds, substantial protective effects observed in pretreatment scenarios may not be consistently replicated when administration is delayed until after the onset of sepsis (126,127). In other instances, intraperitoneal administration appears to provide more stable protection compared with oral dosing, particularly when prominent gut dysfunction is present. Furthermore, even when renal biomarkers demonstrate improvement, histological recovery and survival benefits do not always exhibit parallel changes (128). The apparent efficacy of the same compound may also fluctuate based on factors such as model severity, administration route and the underlying metabolic state (1,122). These discrepancies imply that inconsistent outcomes across studies do not necessarily indicate target irrelevance; rather, they may arise from unstable exposure, altered metabolism and marked context dependence under septic conditions.

Metabolic transformation provides an additional source of complexity. *In vivo*, the dominant circulating forms of numerous polyphenols are glucuronidated, sulfated, reduced or microbiota-derived metabolites rather than the parent compounds themselves (102,129). Some of these metabolites may exhibit biological activities that differ from, or even exceed, those of the original molecules. Inflammatory tissues may also locally deconjugate circulating metabolites, resulting in site-specific exposure to active aglycones (93,130). This phenomenon is particularly relevant in sepsis, where intestinal dysbiosis, altered fermentation and disrupted host-microbiota co-metabolism can alter the metabolite pool available to the kidney (131). Consequently, the *in vivo* protective species in SA-AKI may not align with the compounds directly applied in reductionist cell systems.

These pharmacokinetic and metabolic constraints have important translational implications. A number of promising diet-related small molecules are supported by preclinical

studies that utilize doses, formulations or administration routes not easily replicable through realistic nutritional exposure or routine clinical treatment (132). The gap between experimental dosing and clinically attainable exposure is further widened by the lack of dedicated pharmacokinetic data in sepsis and critical illness. Delivery strategies such as liposomal encapsulation, nanoparticle formulation or kidney-targeted carrier systems mitigate this issue by enhancing local exposure and limiting rapid systemic loss (133,134). Variability in biological effects under septic conditions arises not only from target selection but also from issues of absorption, metabolism, delivery and context-dependent exposure (135). Addressing these challenges is essential for the evaluation of diet-related small molecules as clinically meaningful interventions in SA-AKI.

4. Mechanistic basis for dietary small molecule intervention

The subsequent sections focus on three mechanistic axes that represent recurrent upstream convergence points in the current SA-AKI literature and are most directly linked to the reported actions of diet-related small molecules. Necroptosis, autophagy-related responses and PANoptosis-like signaling are discussed as interacting components of the integrated cell death network rather than as independent therapeutic targets, because direct evidence supporting diet-related small molecule modulation of these processes in SA-AKI remains limited.

Mitochondrial dysfunction and apoptotic signaling. Mitochondrial dysfunction serves as a critical determinant of apoptotic injury in SA-AKI. Experimental studies have indicated that SA-AKI frequently involves tubular epithelial apoptosis, along with caspase-3 activation and Bax upregulation even in the absence of extensive tubular necrosis (136,137). Ultrastructural analyses have revealed that mitochondrial swelling, cristae disruption and loss of membrane potential occur early in septic kidneys, subsequently leading to cytochrome *c* release and caspase-9-dependent apoptotic signaling (138,139). Concurrently, reductions in intracellular ATP levels are closely associated with tubular TUNEL positivity, suggesting that mitochondrial energetic failure and apoptotic execution occur in parallel rather than as distinct events (140).

The mitochondrial apoptotic response is driven by multiple upstream stressors that converge on organelle instability. Excessive ROS can induce pathological mitochondrial fission through dynamin-related protein 1 translocation, thereby exacerbating membrane damage and increasing apoptotic susceptibility. Prolonged ER stress may further propagate injury via the C/EBP homologous protein-Bax axis, linking calcium dysregulation to mitochondrial calcium overload and outer membrane permeabilization (141-143). Additionally, inflammatory cytokines such as TNF-α and IL-1β disturb mitochondrial homeostasis directly and may facilitate the opening of the mitochondrial permeability transition pore under septic conditions (144-146). Collectively, these processes drive the transition of renal tubular cells from adaptive stress responses to intrinsic apoptosis through Bax/Bcl-2 imbalance, cytochrome *c* release and downstream caspase activation (136).

An expanding body of evidence indicates that diet-related small molecules can modulate the mitochondria-mediated intrinsic apoptotic axis at multiple levels. In septic models, curcumin has been shown to preserve mitochondrial ultrastructure, reduce mitochondrial swelling and lower Bax expression in conjunction with decreased tubular apoptosis (74). Resveratrol effectively maintains the mitochondrial membrane potential and reduces both cleaved caspase-9 and caspase-3 levels (147). Furthermore, quercetin has been reported to attenuate mitochondrial apoptotic signaling involving Bax/Bcl-2 balance, cytochrome *c* and caspase activation in related renal injury models (148-150). Procyanidin B2 has also been shown to restore disturbed mitochondrial fusion-fission dynamics, reduce ROS accumulation and attenuate mitochondria-mediated apoptosis through Nrf2-related mechanisms (151). Although these compounds exhibit structural differences, their protective effects repeatedly converge on preservation of mitochondrial integrity rather than on blockade of apoptosis alone.

This pattern is further substantiated by studies focusing on mitochondrial quality control. In experimental sepsis, defective PTEN induced kinase 1/recombinant Parkinson disease protein 2-dependent mitophagy exacerbates apoptosis, reinforcing the notion that the clearance of damaged mitochondria represents an essential adaptive response rather than a secondary bystander event (152). Activation of AMP-activated protein kinase/SIRT1/peroxisome proliferator-activated receptor γ coactivator 1-α signaling promotes mitochondrial biogenesis and improves energy homeostasis, whereas SIRT3-dependent regulation of mitochondrial protein acetylation supports ATP production and limits apoptosis under septic stress (153). These findings imply that the anti-apoptotic effects of diet-related small molecules are frequently intertwined with broader impacts on mitochondrial turnover, metabolic adaptation and oxidative balance.

Mitochondrial protection should not be viewed solely as an anti-apoptotic mechanism. In SA-AKI, interventions aimed at reducing apoptosis often concurrently suppress inflammatory signaling, oxidative stress or inflammasome activation, and caspase inhibition alone does not fully restore renal function in severe sepsis models (154). Mitochondrial preservation may therefore exert broader protective effects by reducing both intrinsic apoptotic signaling and ROS-driven inflammatory amplification (155). In this context, the mechanistic value of diet-related small molecules lies not simply in lowering apoptotic readouts, but in stabilizing a central organelle system that links energy failure, oxidative injury, inflammatory stress and multiple downstream cell death responses.

Iron-redox disequilibrium and ferroptotic vulnerability. Iron-redox disequilibrium has emerged as a significant factor underlying ferroptotic vulnerability in SA-AKI. Experimental studies have demonstrated that tubular damage in SA-AKI is frequently characterized by classical ferroptotic features, including marked lipid peroxidation, glutathione depletion and loss of GPX4 expression (156,157). Concurrently, renal iron deposition, altered SLC7A11-associated cystine transport and accumulation of lipid peroxidation products, such as 4-HNE, malondialdehyde (MDA) and prostaglandin-endoperoxide synthase 2, are observed as renal injury progresses. These findings suggest that ferroptosis in SA-AKI is not solely defined by iron excess; rather, it signifies a broader collapse of

redox buffering capacity, phospholipid homeostasis and lipid peroxide detoxification in stressed tubular cells (73,158).

Several upstream processes appear to drive this state of vulnerability. Systemic inflammatory stress can increase the intracellular labile iron pool through mechanisms such as nuclear receptor coactivator 4-dependent ferritinophagy, thus enhancing the availability of redox-active iron for Fenton reactions (40). Simultaneously, excessive mitochondrial ROS generation rapidly depletes intracellular glutathione and weakens the GPX4-dependent repair system (159). This depletion is exacerbated by the upregulation of ACSL4, which causes membrane phospholipids to become increasingly enriched with polyunsaturated fatty acids that are highly susceptible to peroxidation (40). The role of HO-1 also appears to be context-dependent. Although HO-1 is often discussed as a protective antioxidant response, excessive heme degradation under severe septic stress may release additional free iron and thereby increase ferroptotic susceptibility rather than suppress it (160).

These observations clarify why ferroptosis is best understood as a state of increased vulnerability rather than as an isolated terminal event in SA-AKI. The septic kidney simultaneously endures oxidative stress, mitochondrial dysfunction, disturbed iron handling and impaired glutathione metabolism (10). Under such conditions, even modest increases in lipid peroxide generation may become challenging to neutralize. Nrf2 serves a particularly important role in this context by transcriptionally regulating key components of the anti-ferroptotic defense system, including SLC7A11, which maintains cystine uptake and glutathione synthesis, and GPX4, which detoxifies phospholipid hydroperoxides (161). Additionally, FSP1 provides a parallel glutathione-independent system for detoxifying lipid peroxides through coenzyme Q10 regeneration (162). Thus, ferroptotic susceptibility in SA-AKI hinges on the balance between ongoing oxidative and iron-driven injury, and the remaining capacity of Nrf2-, GPX4-, SLC7A11- and FSP1-related defense systems (14,163).

A growing number of diet-related small molecules appear to modulate this axis. In septic models, curcumin has been shown to reduce renal iron overload, suppress ACSL4 expression and limit 4-HNE accumulation, while preserving renal function (74). Quercetin alleviates AKI by inhibiting ferroptosis in renal tubular epithelial cells (75). Baicalein attenuates cisplatin- and folic acid-induced AKI by suppressing ALOX12-dependent ferroptosis, highlighting the broader relevance of flavonoid-mediated control of lipid peroxidation in renal tubular injury (164). In LPS-induced AKI, polydatin has been reported to reduce renal dysfunction, inflammatory cytokine production, MDA accumulation and NF-κB activation, while increasing Nrf2 and HO-1 expression (165). Resveratrol ameliorates sepsis-induced AKI through Nrf2-related antioxidant signaling (166). Collectively, these findings suggest that diet-related small molecules may stabilize the iron-redox environment through partially overlapping mechanisms, which include preservation of antioxidant defenses, attenuation of lipid peroxidation and reduction of inflammatory oxidative stress.

Ferroptosis should not be regarded as an isolated mechanism. Previous studies have indicated that lipid peroxidation products generated during ferroptotic stress can amplify inflammatory signaling and promote NLRP3-associated pyroptotic responses (167,168). Anti-ferroptotic interventions may also lead to a reduction in both apoptotic and pyroptotic markers, suggesting that protection extends beyond a single death program (169). Impaired autophagic clearance of damaged mitochondria further exacerbates intracellular iron overload, linking ferroptotic susceptibility to organelle quality control (170). In this context, the mechanistic value of diet-related small molecules lies not simply in reducing lipid peroxidation, but in stabilizing a broader iron-redox environment that influences inflammation, mitochondrial integrity and multiple downstream cell death responses in SA-AKI.

Inflammasome activation and pyroptotic amplification. Inflammasome activation has emerged as a significant mechanism of tissue injury amplification in SA-AKI (171). Experimental studies have demonstrated that renal dysfunction is associated with increased NLRP3 expression, apoptosis-associated speck-like protein containing a CARD assembly, caspase-1 activation, GSDMD cleavage, and IL-1β/IL-18 release in both renal tubular epithelial cells and kidney tissues from experimental models of SA-AKI (48,172). Beyond the canonical caspase-1-dependent pathway, non-canonical pyroptotic signaling mediated by caspase-11 has also been implicated in septic tubular injury, indicating that cytosolic endotoxin sensing can directly contribute to epithelial cell death in Gram-negative sepsis (173). These findings position pyroptosis at the intersection of innate immune sensing and structural renal injury rather than as a mere secondary inflammatory bystander.

The amplification of pyroptotic signaling in SA-AKI appears to be dependent on both priming and activation signals. Priming is facilitated by inflammatory pathways, such as the TLR4/NF-κB pathway, which increase transcription of inflammasome-related components and proinflammatory cytokines under septic stress (174). Activation is then reinforced by a second wave of danger signals, which includes mitochondrial ROS, oxidized mtDNA, thioredoxin interacting protein-dependent coupling and other damage-associated signals originating from stressed renal cells and infiltrating immune cells (48,175). This two-step process helps explain why inflammasome signaling in SA-AKI is often self-amplifying. Once GSDMD-mediated pore formation is initiated, inflammatory mediator release, ionic imbalance and cell lysis further intensify local tissue stress and propagate additional inflammasome activity in neighboring cells (176).

Increasing studies have indicated that diet-related small molecules can disrupt this amplification axis at multiple levels (177,178). In a recent study on SA-AKI, butyrate was shown to reduce renal injury by suppressing the STING/GSDMD pathway, with concurrent reductions in pyroptotic signaling and the overall inflammatory burden (53). This finding is crucial as it suggests that certain diet-related small molecules may not merely diminish downstream cytokine release but can act upstream of GSDMD cleavage by modulating inflammatory signal integration. More broadly, studies in related renal and inflammatory injury models suggest that natural compounds may restrain pyroptotic amplification through distinct upstream mechanisms. In experimental folic acid nephropathy, quercetin reduced macrophage

caspase-1 expression and the expression of proinflammatory cytokines, including IL-1β, IL-18, TNF-α and IL-6 (100). In LPS-induced acute lung injury, resveratrol reduced ROS accumulation and inhibited ROS-dependent thioredoxin interacting protein/NLRP3 inflammasome activation (101). In experimental hyperlipidemic acute pancreatitis, baicalein suppressed macrophage M1 polarization and high mobility group box 1/TLR4/NLRP3 signaling, thereby reducing caspase-1 activation, GSDMD cleavage and inflammatory cytokine release (102). Although these studies were conducted outside the specific context of SA-AKI, they illustrate how natural compounds may modulate upstream redox and inflammatory signals that amplify pyroptotic injury.

These findings suggest that the mechanistic importance of pyroptosis in SA-AKI lies not only in terminal membrane rupture, but also in its role as an inflammatory amplifier. GSDMD pore formation facilitates the release of IL-1β, IL-18 and other intracellular danger signals, thereby intensifying leukocyte recruitment, endothelial activation and further epithelial injury (179). In this context, inhibition of inflammasome signaling may reduce both direct tubular cell loss and the local inflammatory environment sustaining ongoing renal dysfunction. However, pyroptosis should not be interpreted as an isolated process. Available evidence indicates substantial overlap with oxidative stress, mitochondrial injury and other regulated cell death pathways, including apoptosis and ferroptosis (180,181). Mitochondrial protection, for example, may reduce pyroptotic signaling by limiting mitochondrial ROS and mtDNA release, while lipid peroxidation and iron-redox disequilibrium may further intensify inflammasome activation (19).

In summary, these observations support a model whereby inflammasome activation and pyroptotic amplification contribute to the progression of SA-AKI through the conversion of local danger sensing into sustained inflammatory tissue damage (182). The relevance of diet-related small molecules in this context lies not merely in the reduction of a single pyroptotic marker but in their capacity to weaken the broader upstream conditions that foster inflammasome overactivation, including NF-κB-dependent priming, mitochondrial damage, oxidative stress and impaired cellular stress control (183). Therefore, their apparent anti-pyroptotic effects should be interpreted as part of a wider network-level regulation of AKI rather than as selective suppression of a single terminal pathway.

5. Translational barriers to clinical application

Altered pharmacokinetics in SA-AKI. Pharmacokinetic behavior in SA-AKI exhibits significant instability, diverging considerably from that observed in healthy individuals or simplified preclinical models (184). Sepsis can impair enteral absorption due to gastrointestinal dysfunction and splanchnic hypoperfusion, while factors such as capillary leak, tissue edema and hypoalbuminemia alter the volume of distribution and protein binding (185). Simultaneously, hepatic metabolism may be diminished by inflammation, altered blood flow and downregulation of metabolic enzymes. These alterations are particularly critical for diet-related small molecules, a number of which already exhibit limited oral bioavailability and extensive presystemic metabolism under baseline conditions (186).

AKI introduces an additional layer of variability. In SA-AKI, changes in glomerular filtration rates are often accompanied by altered tubular secretion, reabsorption and transporter functionality, meaning that plasma concentrations may not accurately reflect intrarenal exposure (187,188). This discrepancy may be further amplified by septic microcirculatory dysfunction, which limits drug delivery to injured tubular regions despite measurable systemic levels. As a result, the biologically active concentration at the site of renal injury may differ markedly from what is predicted by circulating exposure alone (43).

Pharmacokinetic interpretation in SA-AKI is further complicated by intensive care interventions such as fluid resuscitation, vasopressor therapy and RRT (189). In certain patients, augmented renal clearance may lead to reduced exposure early in the disease process, whereas later organ dysfunction may favor accumulation (190). For orally delivered diet-related small molecules, sepsis-associated dysbiosis and intestinal barrier disruption may additionally alter microbial biotransformation and metabolite generation (32,191,192). These factors create a major translational barrier, as the experimental dosing regimens and exposure patterns are difficult to reproduce in patients with established SA-AKI (193).

In line with previous discussions regarding sepsis-targeted therapeutic delivery, the future development of diet-related small molecules for SA-AKI should not only focus on identifying biologically relevant targets, but also address formulation stability, bioavailability, renal tissue exposure and context-dependent delivery in the context of septic conditions (194,195).

Therapeutic timing and disease-stage specificity. Therapeutic timing is a critical determinant of efficacy in SA-AKI. Several interventions, including necrostatin-1 pretreatment, curcumin administered immediately after CLP, post-treatment with irisin and delayed administration of AP214, have shown renoprotective effects in experimental models of SA-AKI. However, these protective effects may be attenuated or lost when treatment initiation is delayed until after sepsis has been established (196-200). This pattern has been consistently observed in rescue-design studies, where early administration suppresses inflammatory escalation and preserves organ function, whereas delayed treatment results in only modest improvements in biomarkers or fails to enhance survival. For diet-related small molecules, this issue is especially important because numerous reported benefits have been generated under pretreatment or very early post-insult conditions that do not reflect the usual timing of clinical recognition (2,197-201).

The biological plausibility of this timing dependence arises from the fact that SA-AKI is not a static state. Early injury is frequently characterized by inflammatory amplification, oxidative stress, microvascular disturbances and rapid activation of regulated cell death pathways. As the disease progresses, the renal response transitions toward metabolic suppression, persistent organelle dysfunction, maladaptive repair and changing immune cell states (9). Available time-course studies have further indicated that the relative contributions of pyroptosis, apoptosis, ferroptosis and autophagy-related responses may change across disease stages rather than remain constant (2,202). A compound that is effective during early inflammatory priming may exhibit

diminished effects once tissue injury, metabolic failure or defective repair mechanisms have taken root.

Disease-stage specificity carries important translational implications as well. By the time SA-AKI is clinically recognized through indicators such as rising creatinine levels or reduced urine output, the underlying molecular injury may already be advanced (203,204). This scenario narrows the therapeutic window for compounds primarily aimed at suppressing early inflammatory or oxidative triggers. In addition, patients with SA-AKI do not adhere to a uniform trajectory (55). Some individuals experience rapid recovery, while others endure persistent injury, and biomarker-based studies have indicated that the inflammatory burden also varies across subphenotypes (205,206). These differences make it unlikely that one uniform timing strategy will be effective for all patients.

For diet-related small molecules, the primary implication is that apparent preclinical efficacy cannot be evaluated without consideration of treatment timing and disease stage. The protective effects observed in early or prophylactic models do not necessarily predict benefits after clinically manifest SA-AKI has developed. Future translational studies should therefore prioritize rescue designs, stage-specific intervention windows and patient stratification based on trajectory or inflammatory phenotype. Without this adjustment, promising mechanistic effects are likely to remain disconnected from clinically relevant treatment conditions.

Patient heterogeneity and mechanistic endotypes. SA-AKI is not a biologically uniform syndrome, and this heterogeneity presents a significant challenge for clinical translation. Patients with similar increases in serum creatinine may experience vastly different trajectories, including rapid reversal, persistent injury or recurrent deterioration (207,208). These patterns are not clinically trivial. They likely reflect differences in inflammatory burden, microvascular dysfunction, tubular stress and the extent of structural renal injury rather than variations in severity alone.

This variability is increasingly captured by biomarker-based and molecular subphenotypes. Research involving critically ill patients with AKI has identified distinct subgroups characterized by varying levels of inflammatory activation, endothelial injury and mortality risk (55,209). In this context, mechanistic endotypes are likely to have greater importance than the diagnostic label alone. For example, patients with predominant inflammasome activation, endothelial dysfunction and hyperinflammatory signaling may respond differently to treatment than those whose injury is primarily driven by metabolic shutdown, mitochondrial dysfunction or persistent redox imbalance (210).

This distinction holds particular relevance for diet-related small molecules. While a number of these compounds function through anti-inflammatory, antioxidant or organelle-protective mechanisms, their effects are unlikely to be uniformly beneficial across all endotypes (211). Agents that suppress NF-κB, NLRP3 or pyroptotic amplification may be more relevant in early hyperinflammatory states, whereas compounds that support mitochondrial quality control or limit ferroptotic vulnerability may be more rational in patients with persistent metabolic and redox stress (212,213). Thus, the therapeutic effects of the same intervention may appear inconsistent in unselected patient populations, not due to invalid mechanisms, but because the individuals treated do not share the same predominant biological profiles.

Patient heterogeneity is further amplified by age, chronic kidney disease, diabetes, cardiovascular comorbidity, pathogen burden, shock severity and exposure to organ support interventions such as vasopressors or RRT (207). These elements influence the trajectory of SA-AKI and shape the biological context in which an intervention is administered. Consequently, future clinical development of diet-related small molecules will likely require biomarker-guided or endotype-informed trial designs rather than one-size-fits-all treatment strategies. Without stratification, even mechanistically promising compounds are likely to show diluted or misleading effects in clinical studies.

Current clinical evidence and its limitations. Current clinical evidence for diet-related small molecules in sepsis and SA-AKI remains limited and uneven. Most human studies have focused on vitamins and antioxidant compounds, especially vitamin C, thiamine and combination regimens that include hydrocortisone, rather than exploring a diverse range of mechanistically defined diet-related small molecules (214,215). Among the data pertinent to kidney outcomes, secondary and post hoc analyses of randomized trials have suggested potential renal benefits of thiamine in septic shock, using the need for RRT and alive and RRT-free status as endpoints, while a recent pilot trial has indicated that vitamin C might enhance renal function in the short term for patients with SA-AKI (216-218).

Despite these findings, the overall clinical picture is inconclusive. Large sepsis trials assessing vitamin C strategies have produced conflicting results. For instance, in the ACTS trial, combined ascorbic acid, corticosteroids and thiamine did not lead to an improvement in the primary organ dysfunction outcome (219). Similarly, the CITRIS-ALI trial found that vitamin C did not significantly impact the prespecified biomarker or organ failure endpoints (220). However, in the LOVIT trial, high-dose intravenous vitamin C was associated with a higher rate of death or persistent organ dysfunction by day 28 (221). A recent meta-analysis has likewise shown substantial heterogeneity across trials, with inconsistent effects on mortality, vasopressor duration and organ failure scores (222).

The limitations of these studies extend beyond categorizing trials as positive or negative, which does not account for important differences in study design, patient heterogeneity, pharmacokinetics and endpoint selection. Kidney-specific data remain scarce, with numerous studies not designed to prioritize SA-AKI as a primary target. Sample sizes frequently remain small, patient populations are biologically heterogeneous and renal endpoints are often secondary, indirect or absent. Additionally, the rationale for dosing, treatment timing and formulation is often poorly aligned with the pharmacokinetic instability of sepsis. Even in cases where inflammatory biomarkers improve, this is not consistently associated with enhanced renal recovery, reduced need for RRT or improved survival outcomes (223,224). Future trials should aim to connect molecular target engagement with kidney-centered decision points. For interventions aimed at ferroptosis, linking

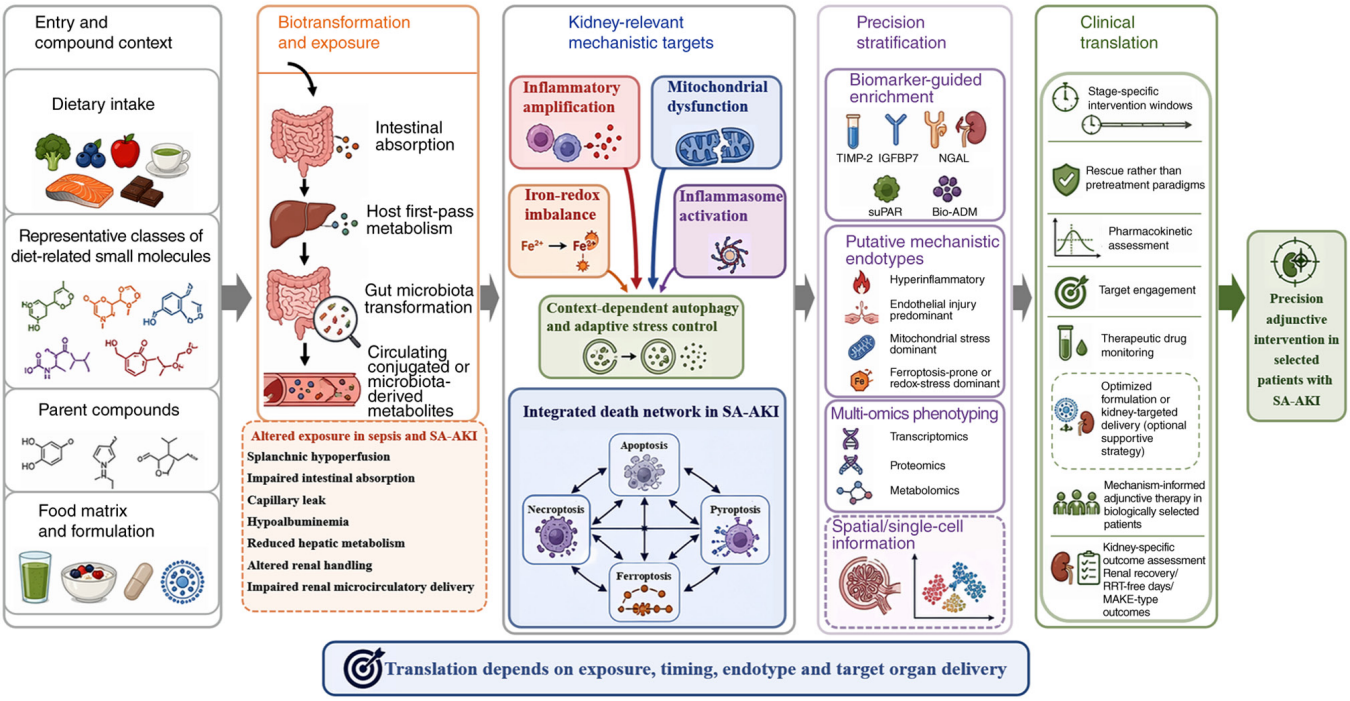

Figure 3. From metabolic fate to precision intervention: A translational framework for diet-related small molecules in SA-AKI. The framework links five sequential domains that determine the translational potential of diet-related small molecules and diet-associated metabolites. First, dietary intake, parent compound properties, representative compound classes, food matrix effects and formulation determine the context in which a compound enters the body. Second, intestinal absorption, host first-pass metabolism and gut microbiota-dependent transformation determine whether parent compounds, host-conjugated metabolites or microbiota-derived metabolites reach the systemic circulation. In sepsis and SA-AKI, exposure may be further altered by splanchnic hypoperfusion, impaired intestinal absorption, capillary leak, hypoalbuminemia, reduced hepatic metabolism, altered renal handling and impaired renal microcirculatory delivery. Third, kidney-relevant mechanistic targets include inflammatory amplification, mitochondrial dysfunction, iron-redox imbalance, inflammasome activation, and context-dependent autophagic and adaptive stress control, which converge on an integrated network involving apoptosis, necroptosis, pyroptosis and ferroptosis. Fourth, precision stratification may combine biomarker-guided enrichment using the urinary [TIMP-2] x [IGFBP7] product and circulating NGAL, suPAR and bio-ADM with putative mechanistic endotypes, transcriptomic, proteomic and metabolomic phenotyping, and spatial or single-cell information. Finally, clinical translation requires stage-specific intervention windows, rescue rather than exclusively pretreatment paradigms, pharmacokinetic and target-engagement assessment, exposure monitoring with therapeutic drug monitoring where applicable, optimized formulation or kidney-targeted delivery, mechanism-informed adjunctive therapy in biologically selected patients, and kidney-specific outcome assessment. Overall, successful translation depends on aligning achievable exposure, treatment timing, mechanistic endotype and target organ delivery to support precision adjunctive intervention in selected patients with SA-AKI. bio-ADM, bioactive adrenomedullin; IGFBP7, insulin like growth factor binding protein 7; NGAL, neutrophil gelatinase-associated lipocalin; SA-AKI, sepsis-associated acute kidney injury; suPAR, soluble urokinase plasminogen activator receptor; TIMP-2, TIMP metallopeptidase inhibitor 2.

preservation of GPX4 or SLC7A11, suppression of ACSL4, improvements in iron-redox indices, and reductions in lipid peroxidation products such as 4-HNE or MDA to patient selection, treatment windows, AKI progression, renal recovery and RRT-free days is essential (225). Similarly, for inflammasome- or pyroptosis-oriented treatments, assessments of NLRP3, caspase-1 activity, GSDMD cleavage, IL-1β and IL-18 should be contextualized with early hyperinflammatory endotypes and kidney-specific outcomes rather than viewed as isolated inflammatory metrics (226). Mitochondria-directed strategies should also align mitochondrial stress markers, mitophagy-related signals, oxidative injury markers and tubular stress biomarkers with clinically relevant endpoints such as renal recovery, avoidance or duration of RRT, RRT-free days, major adverse kidney events-type composite outcomes and survival (227). Establishing this connection is crucial because an improvement in a molecular biomarker does not necessarily signify renal recovery unless it is tied to relevant clinical decision points.

In conclusion, current clinical evidence does not yet support routine use of diet-related small molecules as an established therapy for SA-AKI. Nevertheless, it indicates that biological activity in humans is plausible, but highly context-dependent (228). Future trials will need clearer kidney-specific endpoints, improved control of treatment timing, direct assessments of pharmacokinetics and target engagement, and robust patient stratification. This emphasis on stratification may be particularly important in light of previous analyses suggesting that differential treatment responses in sepsis could be obscured when mechanistically distinct patients are grouped within the same trial (229,230). The available clinical evidence and major sources of translational failure are summarized in Table SIII. The complete translational framework is summarized in Fig. 3. Dietary intake, parent compound properties, food matrix effects and formulation determine compound entry, while intestinal absorption, host first-pass metabolism and gut microbiota-dependent biotransformation determine whether parent compounds, conjugated metabolites or microbiota-derived metabolites reach the systemic circulation (32,116-122,124,186,191,192). In sepsis and SA-AKI, splanchnic hypoperfusion, impaired intestinal absorption, capillary leak, hypoalbuminemia, reduced hepatic metabolism, altered tubular handling and disturbed renal microcirculatory delivery may further uncouple the administered dose and circulating concentration from the biologically

active exposure achieved within the kidney (185,187,188,190). These exposures may influence inflammatory amplification, mitochondrial dysfunction, iron-redox imbalance, inflammasome activation and context-dependent autophagic or adaptive stress responses, which converge on an integrated network of apoptotic, necroptotic, pyroptotic and ferroptotic injury (73,138,152,155,173,212,213). Accordingly, precision translation will require biomarker-guided enrichment using the urinary [TIMP metallopeptidase inhibitor 2 (TIMP-2)] x [insulin-like growth factor-binding protein 7] product and circulating markers such as NGAL, soluble urokinase plasminogen activator receptor (suPAR) and bioactive adrenomedullin (bio-ADM), together with mechanistic endotyping, transcriptomic, proteomic and metabolomic profiling, and spatial or single-cell analysis (84,231-237). These data should subsequently inform stage-specific rescue designs, pharmacokinetic and exposure assessment, target-engagement analysis, exposure monitoring, optimized formulation or kidney-targeted delivery, mechanism-informed adjunctive therapy in biologically selected patients, and kidney-specific outcome assessment (132-134,196,207-209).

6. Toward precision intervention in SA-AKI

Biomarker-guided stratification. Biomarker-guided stratification is likely essential for achieving precision intervention in SA-AKI. While serum creatinine and urine output remain critical for diagnosis, they are often too delayed and nonspecific to accurately define the dominant biology of injury (238). By contrast, urinary TIMP-2 and insulin like growth factor binding protein 7 reflect early tubular stress and cell cycle arrest, potentially identifying high-risk patients before overt functional decline becomes evident (231). In these biomarker-based stratification models, markers of inflammation and endothelial dysfunction often contribute more to subgroup assignment than serum creatinine alone.

The value of biomarkers becomes greater when they are used as panels rather than in isolation. In a multicenter cohort of 769 hospitalized adults with AKI, Bhatraju *et al* (84,239) applied latent class analysis and k-means clustering to 29 clinical, plasma and urinary biomarker variables and identified two molecularly distinct AKI subphenotypes with different long-term risks of major adverse kidney events. In both clustering analyses, plasma inflammatory markers and urinary epithelial injury markers were among the variables that most strongly differentiated the two subphenotypes, whereas serum creatinine ranked only 20th among the 29 discriminatory variables (240). These findings highlight the value of biomarker-guided stratification not only for risk assessment but also for distinguishing the biological context in which kidney injury occurs.

Recent investigations into SA-AKI have reinforced this approach. Transcriptomic endotypes combined with plasma biomarkers such as NGAL, suPAR and bio-ADM have identified clinically distinct groups characterized by different severity, mortality risk and underlying mechanisms of injury (233). Practically, this indicates that not all patients with SA-AKI are likely to benefit from the same intervention. A patient exhibiting a hyperinflammatory profile with predominant endothelial injury may be more appropriately treated with compounds targeting NF-κB, NLRP3 or pyroptotic amplification, whereas another patient demonstrating stronger metabolic stress or tubular injury signatures may be better suited for interventions directed at mitochondrial dysfunction or redox instability (241,242).

Stratification guided by biomarkers should therefore serve as both a prognostic and a mechanistic tool. The goal is not simply to detect AKI earlier, but to identify which patients are most likely to respond to a given class of diet-related small molecules and at what stage of disease. Future trials will likely require repeated biomarker assessment, panel-based rather than single-marker selection, and closer alignment between circulating readouts and the dominant injury mechanism. Candidate target engagement readouts should be paired with kidney-specific outcomes, encompassing AKI progression, renal recovery, duration or avoidance of RRT, RRT-free days and survival. Without this step, precision intervention in SA-AKI will remain largely theoretical.

Multi-omics approaches for mechanistic phenotyping. Multi-omics approaches offer a broader framework for mechanistic phenotyping in SA-AKI than clinical variables or single biomarkers alone (234). Transcriptomic, proteomic and metabolomic data capture different layers of the host response and facilitate the distinction of patients who share a diagnosis of SA-AKI but differ substantially in terms of the underlying biology (235). This differentiation is particularly important in sepsis, where inflammatory activation, endothelial dysfunction, metabolic disturbance and tubular stress often coexist but do not dominate to the same extent in every patient (243).

Previous studies support the value of this approach. An integrated analysis combining transcriptomic and protein-based data has identified AKI subphenotypes characterized by distinct molecular signatures, outcome risks and even differential responses to vasopressor therapy (84). In SA-AKI, the integration of transcriptomic endotyping with circulating protein biomarkers such as NGAL, suPAR and bio-ADM has further improved risk stratification beyond conventional clinical assessment by identifying mechanistically distinct patient subgroups (233). These findings suggest that mechanistic phenotyping is more informative when molecular layers are interpreted together rather than separately.

Multi-omics data also facilitate mapping back to specific injury mechanisms. Inflammatory endotypes may align with stronger inflammasome activity, endothelial injury and pyroptotic amplification, whereas other signatures may indicate metabolic shutdown, mitochondrial dysfunction or persistent tubular stress. Metabolomic studies similarly suggest that altered energy metabolism, amino acid handling and lipid remodeling could distinguish biologically different forms of septic organ injury (84,236). In this context, mechanistic phenotyping transcends mere descriptions and connects circulating signals with the dominant pathophysiology that diet-related small molecules are expected to modulate.

Single-cell and spatial transcriptomic approaches further extend this idea by elucidating the origins of these biological programs within specific cellular contexts. Studies integrating single-cell and spatial data have localized epithelial-immune crosstalk, injury-specific microenvironments and segment-specific tubular injury states in AKI (244,245).

Such approaches may eventually help explain why the same circulating biomarker profile can reflect different local tissue patterns (58,237). At present, the main challenge is translation. Multi-omics signatures remain difficult to standardize, validate and implement in routine care. Their immediate utility may therefore lie in identifying mechanistically defined patient populations for clinical trials and refining biomarker panels for bedside patient stratification (244).

Future directions for precision pharmaconutrition. Future progress in SA-AKI will likely depend on moving beyond the assumption that diet-related small molecules can be applied as broadly protective interventions. A more realistic direction is precision pharmaconutrition, in which compound selection, timing, formulation and target populations are aligned with the dominant biology of injury. In this context, the objective shifts from matching a single compound to a specific pathway to identifying which patients are most likely to benefit from interventions targeting inflammatory amplification, mitochondrial dysfunction, iron-redox imbalance or maladaptive stress responses at particular stages of the disease.

This transition necessitates closer integration of mechanistic endotyping, biomarker-guided patient stratification and pharmacological intervention. The utilization of biomarker panels, mechanistic endotypes and multi-omics profiling may aid in delineating patients exhibiting hyperinflammatory, endothelial injury predominant, mitochondrial stress dominant or ferroptosis-prone forms of SA-AKI. Concurrently, forthcoming research must adopt more clinically realistic dosing strategies, conduct direct pharmacokinetic assessments under septic conditions, and focus more on active metabolites, feasible routes of administration and target organ exposure. Without these translational measures, even mechanistically promising compounds will remain difficult to translate beyond preclinical proof-of-concept into clinical practice.

The subsequent phase of research should prioritize biomarker-enriched trial designs, in which biomarkers are used to identify patients most likely to benefit from a given intervention, together with rescue paradigms rather than pretreatment approaches and combination strategies that acknowledge the network nature of SA-AKI. Diet-related small molecules may be most effective as mechanism-informed adjuncts rather than as standalone universal therapies, and may be added to standard sepsis care for biologically selected patients. In this framework, precision pharmaconutrition should be understood as selecting diet-related small molecules according to disease stage, mechanistic endotype and expected pharmacokinetic exposure rather than assuming that nutrition-derived compounds are uniformly beneficial in SA-AKI. A proposed endotype-guided framework for precision pharmaconutrition in SA-AKI is shown in Table SIV.

7. Conclusions

SA-AKI represents a biologically complex syndrome featuring the concurrent development of inflammatory dysregulation, microvascular disturbance, metabolic failure, mitochondrial injury, iron-redox imbalance and multiple forms of regulated cell death. The processes of apoptosis, ferroptosis, pyroptosis, necroptosis and autophagy-related responses should not be viewed in isolation, as they are interconnected by shared upstream stress signals and notable mechanistic overlap. This complexity helps explain why single pathway interventions have shown limited and inconsistent benefits.

The primary value of diet-related small molecules in this context does not stem from their characterization as broadly protective natural products. Instead, it lies in the potential for certain compounds to modulate common regulatory nodes within the integrated death network associated with SA-AKI. However, the current literature is still dominated by preclinical studies, and the apparent protective effects of these compounds are strongly shaped by bioavailability, metabolic conversion, treatment timing and disease-stage specificity. Clinical translation is further complicated by the considerable heterogeneity of SA-AKI, which includes variations in inflammatory burden, endothelial injury, metabolic stress and injury trajectories across patients.

Future progress will hinge less on expanding compound catalogs and more on mechanism-based stratification. Essential developments will include biomarker-guided enrichment, in which biomarkers are used to identify patients most likely to benefit from a given intervention, together with multi-omics phenotyping, clinically realistic pharmacokinetic evaluations, and stage-specific intervention designs to determine when, in whom and under what exposure conditions these agents may prove beneficial. At present, diet-related small molecules should not be perceived as routine clinical treatments for SA-AKI. Instead, they are best understood as candidate adjuncts within a precision pharmaconutrition strategy that necessitates further validation through well-designed preclinical rescue studies and kidney-focused clinical trials.

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Authors' contributions

LS, AH, WJ, JY and RZ designed and conceived the review. KS, JW and LX generated the figures. Data authentication is

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Ethics approval and consent to participate

Not applicable.

Patient consent for publication

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Competing interests

The authors declare that they have no competing interests.

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