Table SI. Classification of diet-related small molecules and related intervention categories relevant to SA-AKI.

| Category | Representative examples | Relationship to diet-related small molecules | Main relevance to SA-AKI | Evidence status and translational caution | (Refs.) |
|---|---|---|---|---|---|
| Food-derived phytochemicals | Resveratrol, curcumin, quercetin, luteolin, puerarin, baicalein, polydatin | Core category | Modulate NF-κB signaling, Nrf2-related antioxidant defense, mitochondrial stress, ferroptosis, inflammasome activation and autophagy/mitophagy-related responses | Mainly preclinical. Low bioavailability, extensive metabolism, active-metabolite uncertainty and dose-exposure mismatch limit clinical translation. | (27,28,69,95-98, 101,102,111-113) |
| Nutritional or essential small molecules | Vitamin C, thiamine, reduced glutathione | Related but should be interpreted separately | Support redox buffering, mitochondrial metabolism, antioxidant defense and cellular stress adaptation | Some human sepsis evidence exists, but dosing is often pharmacological rather than nutritional. Findings should not be generalized to all phytochemicals. | (26,29,207-214) |
| Microbiota-derived or microbiota-modified metabolites | Butyrate, short-chain fatty acids, secondary phenolic metabolites | Diet-associated boundary category | Regulate gut-kidney crosstalk, STING-GSDMD signaling, inflammasome activation, immune metabolism and oxidative stress | Mostly preclinical. Effects depend on gut microbiota composition, intestinal barrier function, antibiotic exposure and sepsis-induced dysbiosis. | (48,119,124,126, 127) |
| Pharmacological derivatives or optimized formulations | Liposomal formulations, nanoparticle systems, kidney-targeted carriers, modified natural-compound derivatives | Not equivalent to dietary exposure | Improve solubility, stability, systemic persistence, renal delivery or target exposure | Mostly experimental. Evidence from optimized formulations cannot be directly used as evidence for parent dietary compounds or ordinary dietary intake. | (93,128,129) |
| ICU antioxidant or metabolic vitamin regimens | High-dose intravenous vitamin C, vitamin C plus thiamine, vitamin C plus thiamine plus hydrocortisone | Clinical comparator category, not the core category | Intended to reduce oxidative stress, support metabolism and improve organ dysfunction in sepsis or septic shock | Human evidence is inconsistent and often not kidney-specific. Hydrocortisone is not a diet-related small molecule and should only be discussed as part of ICU combination regimens. | (207-214) |
| Non-dietary pharmacological comparators | Hydrocortisone alone and other standard pharmacological comparators used in sepsis trials | Outside the core category | Used only as a clinical comparator or to provide translational context | Should not be presented as evidence supporting diet-related small molecules. | (88,89,207-213) |

GSDMD, gasdermin D; ICU, intensive care unit; NF-κB, nuclear factor kappa B; Nrf2, nuclear factor erythroid 2-related factor 2; SA-AKI, sepsis-associated acute kidney injury; STING, stimulator of interferon genes.

Table SII. Hierarchical organization of shared regulatory nodes connecting PCD pathways and diet-related small molecule actions in SA-AKI.

| Mechanistic position | Regulatory node shared across PCD pathways | Network role in SA-AKI | Main linked PCD programs | Potential diet-related small molecule actions | Representative examples | Evidence status | (Refs.) |
|---|---|---|---|---|---|---|---|
| Upstream driver/ amplifier | Inflammatory transcriptional activation | Initiates and amplifies septic renal inflammation and lowers the threshold for downstream death signaling | Pyroptosis, apoptosis, necroptosis-related inflammation, ferroptosis sensitization | Suppress TLR4-, TNFR-, NF-κB-, JNK- or ER stress-related inflammatory activation | Puerarin, resveratrol and luteolin | Mainly preclinical; direct SA-AKI evidence exists for selected compounds | (39,46,96, 101,102) |
| Upstream driver/ central amplifier | Mitochondrial dysfunction and metabolic stress | Links ATP depletion, mtROS generation, intrinsic apoptosis, inflammasome activation and ferroptotic vulnerability | Apoptosis, pyroptosis priming, ferroptosis sensitization, autophagy/mitophagy-related responses | Preserve mitochondrial integrity, reduce mtROS, support mitophagy or mitochondrial quality control and limit caspase activation | Resveratrol, curcumin, quercetin and procyanidin B2 | Mainly preclinical; clinical target-engagement data remain limited | (31,69, 133-135, 139-141, 143-148, 150) |
| Amplifier/ inflammatory executor | Inflammasome activation and pyroptotic amplification | Converts danger sensing into inflammatory tubular injury, and propagates local cytokine and DAMP release | Pyroptosis, apoptosis-pyroptosis crosstalk, PANoptosis-like signaling | Reduce NLRP3-, STING-, caspase-1-, caspase-11- or GSDMD-related pyroptotic signaling | Butyrate | Direct SA-AKI evidence exists for butyrate; broader pathway evidence remains mainly preclinical | (43,48, 168-170) |
| Permissive state/ ferroptotic amplifier | Redox-iron imbalance and lipid peroxidation | Creates a ferroptosis-prone state through iron accumulation, GSH depletion, impaired lipid peroxide detoxification and oxidative stress | Ferroptosis, apoptosis sensitization, pyroptotic amplification | Preserve Nrf2-, GPX4-, SLC7A11- or FSP1-related defenses and reduce lipid peroxidation or iron-driven oxidative injury | Curcumin, quercetin, baicalein, polydatin, ginsenoside Rg1 and andrographolide | Increasing preclinical evidence; human renal target-engagement data are lacking | (47,67-70, 153-155, 157-161, 165) |
| Context-dependent modifier | Autophagy and mitophagy dysfunction | Modifies cell fate according to disease stage; adequate flux may restrain injury, whereas defective flux permits mitochondrial and inflammatory stress accumulation | Apoptosis, pyroptosis, ferroptosis, necroptosis, autophagy-related stress responses | Support adaptive autophagy/mitophagy, mitochondrial turnover and metabolic stress adaptation | Resveratrol | Mainly preclinical; effects are stage-dependent and should not be interpreted as uniformly protective | (31,49,74, 147,148) |
| Terminal execution/ crosstalk hub | Downstream death-execution machinery and mixed death signaling | Executes structural renal injury after upstream thresholds are crossed; mixed phenotypes may occur under severe septic stress | Apoptosis, pyroptosis, necroptosis, ferroptosis, PANoptosis-like signaling | More likely to act indirectly by stabilizing upstream inflammatory, mitochondrial, redox-iron and inflammasome-related environments | Curcumin, butyrate, ginsenoside Rg1, andrographolide and other upstream node modulators | Mainly mechanistic and preclinical; PANoptosis-specific evidence in SA-AKI remains limited | (40,41, 47-49,67, 69,71-74, 76-80) |

DAMP, damage-associated molecular pattern; ER, endoplasmic reticulum; FSP1, ferroptosis suppressor protein 1; GPX4, glutathione peroxidase 4; GSDMD, gasdermin D; GSH, glutathione; JNK, c-Jun N-terminal kinase; mtROS, mitochondrial reactive oxygen species; NF-κB, nuclear factor kappa B; NLRP3, NOD-like receptor family pyrin domain-containing 3; Nrf2, nuclear factor erythroid 2-related factor 2; PCD, programmed cell death; SA-AKI, sepsis-associated acute kidney injury; SLC7A11, solute carrier family 7 member 11; STING, stimulator of interferon genes; TLR4, toll-like receptor 4; TNFR, tumor necrosis factor receptor.

Table SIII. Clinical evidence and translational limitations of diet-related small molecule strategies in sepsis and SA-AKI.

| Clinical evidence | Population or study context | Main intervention | Primary outcome | Kidney-related findings | Major translational limitation | Interpretation for SA-AKI | Recommended direction for future trials | (Refs.) |
|---|---|---|---|---|---|---|---|---|
| Vitamin- and antioxidant-focused human studies | Patients with sepsis or septic shock | Vitamin C, thiamine or vitamin C-based combination regimens | Human evidence remains limited and uneven, with most studies focused on vitamins and antioxidant compounds rather than mechanistically selected diet-related small molecules | Kidney-specific data are sparse and renal outcomes are often secondary, indirect or absent | Most studies were not designed around SA-AKI as the primary target | Biological activity in humans is plausible, but current evidence is not sufficient to support routine use for SA-AKI | Use SA-AKI-specific enrollment, predefined renal endpoints and target-engagement assessment | (207-214) |
| Thiamine-based intervention or subgroup analysis | Patients with septic shock | Intravenous thiamine | Post hoc analyses suggested potential clinical benefit in selected septic shock populations | Potential renal benefit was suggested, particularly for outcomes related to RRT or alive-and-RRT-free status | Evidence is mainly derived from post hoc or subgroup analyses, not SA-AKI-targeted trials | Benefit may depend on baseline metabolic state, thiamine deficiency and illness stage | Prospectively enroll patients with documented thiamine deficiency or elevated SA-AKI risk biomarkers; prespecify renal recovery, RRT requirement, and days alive and free of RRT as outcomes | (209) |
| Vitamin C in SA-AKI | Patients with SA-AKI | Vitamin C targeting oxidative stress | A prospective randomized pilot study suggested possible short-term improvement in renal function | Renal function improvement was reported over the short term | Pilot design, limited sample size and uncertain exposure-response relationship | Redox-directed treatment may be biologically relevant in selected patients with SA-AKI, but efficacy remains unconfirmed | Conduct adequately powered SA-AKI trials with PK-guided dosing, oxidative-stress biomarkers, and longer renal follow-up | (210) |
| Ascorbic acid, corticosteroids, and thiamine combination strategy | Patients with septic shock | Combined ascorbic acid, corticosteroids and thiamine | The combination of ascorbic acid, corticosteroids and thiamine did not significantly improve the change in SOFA score from enrollment to 72 h in the ACTS trial | No convincing kidney-specific therapeutic signal was established in an unselected septic shock population | Mixed population, broad organ dysfunction endpoint and lack of mechanistic enrichment | Combination antioxidant or metabolic therapy may be diluted when patients with different biological injury patterns are pooled | Enroll patients using prespecified biomarkers of oxidative or metabolic injury and evaluate AKI progression, renal recovery and RRT outcomes rather than using a global organ dysfunction score as the sole primary endpoint | (211) |
| Vitamin C in sepsis with severe acute respiratory failure | Patients with sepsis and severe acute respiratory failure | Intravenous vitamin C | Intravenous vitamin C did not significantly improve the prespecified primary outcomes of change in modified SOFA score from baseline to 96 h or plasma | Renal benefit was not established as a primary therapeutic effect | Trial was not designed specifically for SA-AKI and renal outcomes were not the | Improvement in inflammatory or vascular biomarkers does not necessarily translate into renal | Include renal target engagement, tubular stress markers and prespecified SA-AKI outcomes | (212) |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | CRP and thrombomodulin concentrations at 168 h in the CITRIS-ALI trial | | central endpoint | recovery | | |
| High-dose intravenous vitamin C | Adults with sepsis in the ICU | High-dose intravenous vitamin C | LOVIT trial reported a higher rate of death or persistent organ dysfunction at day 28 | No consistent renal benefit was shown in the overall population | Potential harm signal, unselected population and uncertain optimal therapeutic window | Redox modulation may be stage-sensitive and could be harmful or ineffective if timing, dose or patient selection is inappropriate | Prioritize safety monitoring, dose optimization, PK assessment and endotype-based selection | (213) |
| Evidence synthesis of intravenous vitamin C in severe sepsis | Severe sepsis populations across clinical studies | Intravenous vitamin C-based strategies | Evidence syntheses found substantial heterogeneity across trials | Effects on renal outcomes remain inconsistent and difficult to interpret | Differences in dosing, timing, illness severity, co-interventions and endpoints limit interpretation | Mechanism may not be invalid, but clinical effects are likely context-dependent | Standardize renal endpoints, treatment windows and exposure monitoring, and avoid pooling biologically distinct patients without stratification | (214) |
| Future diet-related small-molecule trials in SA-AKI | Mechanisticall y selected SA-AKI populations | Candidate small molecules targeting inflammation, mitochondrial dysfunction, redox-iron imbalance or inflammasome activation | Clinical efficacy of candidate diet-related small molecules for preventing or treating SA-AKI has not yet been established in adequately designed trials | Kidney protection remains a translational goal rather than a proven clinical benefit | Lack of SA-AKI-specific PK data, limited target exposure data and insufficient patient stratification | Future benefit is most plausible in biologically selected patients and stage-specific windows | Combine biomarker-guided enrollment, mechanistic endotyping, PK-informed dosing and predefined renal recovery outcomes | (190-193,200-206,213,214,216,219-230) |

CRP, C-reactive protein; ICU, intensive care unit; RRT, renal replacement therapy; PK, pharmacokinetic; SA-AKI, sepsis-associated acute kidney injury; SOFA, Sequential Organ Failure Assessment.

Table SIV. Endotype-guided framework linking mechanistic markers, target engagement and kidney-centered trial design in SA-AKI.

| Putative mechanistic endotype | Candidate patient-selection markers | Candidate target-engagement readouts | Proposed intervention window | Potential diet-related small molecule strategy | Kidney-centered trial endpoints | (Refs.) |
|---|---|---|---|---|---|---|
| Hyperinflammatory/ inflammasome-enriched pattern | IL-6, IL-1β, IL-18, CRP, ferritin, suPAR, bio-ADM, inflammatory transcriptomic signatures | Reduced NLRP3 activation, caspase-1 activity, GSDMD cleavage, IL-1β/IL-18 release, STING-GSDMD signaling | Early sepsis or early SA-AKI with active inflammatory amplification | Compounds or metabolites that limit NF-κB activation, NLRP3-related signaling, STING-GSDMD activation and pyroptotic amplification | AKI progression, SOFA score trajectory, RRT requirement, RRT-free days, renal recovery, survival | (43,48,79,92, 105,161,168-170, 222-224,232,233) |
| Mitochondrial stress/metabolic failure pattern | Lactate, oxidative stress markers, urinary tubular stress markers, metabolomic energy signatures, mitochondrial injury-related markers if available | Improved mitochondrial stress markers, reduced mtROS-related injury, preserved mitophagy or mitochondrial quality-control signals, reduced caspase-3/9 activation | Early-to-established SA-AKI with metabolic stress or tubular injury but before irreversible structural damage | Compounds that preserve mitochondrial integrity and support SIRT1/SIRT3-, AMPK-, PGC-1α- or mitophagy-related adaptation | Renal recovery, urine-output recovery, AKI duration, RRT-free days, MAKE-type composite outcomes, survival | (31,49,133-150, 216,221-225,230) |
| Iron-redox dysregulation/ferroptosis-prone pattern | 4-HNE, MDA, ferritin, transferrin saturation, lipidomic peroxidation signatures, GPX4/SLC7A11/ACSL4-related readouts when available | GPX4 or SLC7A11 preservation, ACSL4 suppression, reduced lipid peroxidation, improved GSH-related antioxidant capacity, reduced iron-driven oxidative injury | Early or persistent SA-AKI with dominant redox-iron imbalance or lipid peroxidation | Compounds that support Nrf2-, GPX4-, SLC7A11- or FSP1-related defenses and limit lipid peroxidation | AKI progression, creatinine trajectory, RRT requirement, RRT-free days, renal recovery, MAKE-type composite outcomes | (47,67-70,148, 150,153-165,205, 217,219,222-225, 230) |
| Endothelial injury/microcirculatory dysfunction pattern | bio-ADM, angiopoietin-2, syndecan-1, endothelial or glycocalyx injury markers, shock severity, vasopressor requirement | Improved endothelial injury markers, reduced inflammatory endothelial activation, improved perfusion-related or organ dysfunction readouts | Early septic shock or SA-AKI with microcirculatory instability and endothelial activation | Adjunctive compounds that reduce oxidative stress, inflammatory amplification and endothelial injury; use only with standard sepsis care | AKI progression, vasopressor-free days, organ failure trajectory, RRT requirement, renal recovery, survival | (196,222-224, 228-230,232-234) |
| Mixed or evolving endotype | Combined biomarker panels, repeated blood/urine biomarkers, transcriptomic, proteomic, metabolomic, single-cell or spatial signatures | Mechanism-specific target engagement selected according to the dominant evolving pattern | Dynamic reassessment during early, persistent or recovery phases of SA-AKI | Stage-specific or combination strategies matched to inflammatory, mitochondrial, redox-iron or endothelial dominance | AKI trajectory, renal recovery, RRT-free days, MAKE-28/90, long-term kidney function, survival | (53,63,81,197, 200-203,220-230, 235,236) |

4-HNE, 4-hydroxynonenal; ACSL4, acyl-CoA synthetase long chain family member 4; AKI, acute kidney injury; AMPK, AMP-activated protein kinase; bio-ADM, bioactive adrenomedullin; CRP, C-reactive protein; FSP1, ferroptosis suppressor protein 1; GPX4, glutathione peroxidase 4; GSDMD, gasdermin D; GSH, glutathione; MAKE, major adverse kidney events; MDA, malondialdehyde; mtROS, mitochondrial reactive oxygen species; 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 1-α; RRT, renal replacement therapy; SA-AKI, sepsis-associated acute kidney injury; SIRT, sirtuin; SLC7A11, solute carrier family 7 member 11; SOFA, Sequential Organ Failure Assessment; STING, stimulator of interferon genes; suPAR, soluble urokinase plasminogen activator receptor.