Natural products as multi-target therapies for sepsis-induced myocardial dysfunction (Review)

FEI TANG[1], DONG LIU[2], SHI-CHAO ZHU[1], HUI-MIN ZHOU[1] and XUE-WEN QIU[1]

[1]Department of Pharmacy, Chongqing General Hospital, Chongqing University, Chongqing 400014, P.R. China; [2]State Key Laboratory of Southwestern Chinese Medicine Resources, Chengdu University of Traditional Chinese Medicine, Chengdu, Sichuan 611137, P.R. China

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Abstract. Sepsis, an infection-triggered systemic inflammatory response syndrome, ranks as the third leading cause of death worldwide due to its high incidence and mortality. Sepsis-induced myocardial dysfunction (SIMD) is a frequent and serious complication that notably increases patient morbidity and mortality. The underlying pathophysiology of SIMD involves a complex interplay of inflammation, oxidative stress, mitochondrial impairment and apoptosis, yet no effective therapies have been established. Thus, uncovering the molecular mechanisms of SIMD, identifying novel therapeutic targets and developing efficacious agents are key. For centuries, natural products have been used in traditional medical systems across China and Asia to manage cardiovascular disease. These compounds can confer cardioprotection by modulating inflammatory pathways, decreasing oxidative stress, inhibiting apoptotic cell death and improving mitochondrial function. The present review aimed to summarize the clinical manifestations and pathophysiology of SIMD and how natural products exert their protective effects. The present study aimed to explore structure-activity relationships and highlight key molecular targets and representative natural product binding affinities for SIMD-related proteins. In summary, the present study presents a comprehensive overview of the multi-targeted strategies employed by natural products against SIMD and provides guidance for the discovery of SIMD-focused dietary supplements and lead compounds, laying the groundwork for future translational research.

Correspondence to: Professor Xue-Wen Qiu, Department of Pharmacy, Chongqing General Hospital, Chongqing University, 118 Xingguang Avenue, Liangjiang New Area, Chongqing 400014, P.R. China
E-mail: qiuxuewen@cqu.edu.cn

Abbreviations: HO-1, heme oxygenase-1; PAMP, pathogen-associated molecular pattern; PI3K, phosphoinositide 3-kinase; PKC, protein kinase C; SIMD, sepsis-induced myocardial dysfunction; SIRT1, sirtuin 1

Key words: natural product, sepsis, myocardial dysfunction, mechanism, target

Contents

1. Introduction

Sepsis, an infection-driven systemic inflammatory response syndrome, poses a major global health challenge due to its high incidence and mortality (1,2). According to World Health Organization estimates, nearly 19 million people develop sepsis annually and 20-30% succumb to severe complications (2). In intensive care units, mortality is up to 56%, making sepsis the third leading cause of death worldwide (3,4). Among complications, sepsis-induced myocardial dysfunction (SIMD) is especially common and carries the worst prognosis. A total of ~70% of septic patients experience impaired myocardial contractility, decreased ejection fraction and arrhythmia. These cardiac impairments often coincide with hypotension and lactic acidosis, hastening circulatory collapse and multi-organ failure (5-7).

SIMD arises from a multifactorial network of inflammatory and oxidative processes. Pathogen-associated molecular patterns (PAMPs) engage toll-like receptor (TLR)4 signaling through MyD88 and TIR-domain-containing adaptor inducing interferon-β, thereby activating NF-κB and MAPKs (p38, JNK, ERK). This cascade triggers the release of proinflammatory cytokines such as TNF-α and IL-1β (8). The cytokine surge, in turn, stimulates NADPH oxidase to generate reactive oxygen species (ROS), which induce lipid peroxidation and protein damage (9). Oxidative stress further compromises mitochondrial integrity, leading to decreased ATP synthesis and the activation of caspase-3-mediated apoptosis. Collectively, these

events depress ejection fraction, promote ventricular dilation and drive circulatory failure (8).

Current clinical management of SIMD follows the Surviving Sepsis Campaign Guidelines, focusing on fluid resuscitation, broad-spectrum antibiotics and vasopressors. Inotropes or β-blockers may be used as adjunctive therapies, but they typically yield only transient hemodynamic benefits and can increase myocardial oxygen demand or provoke arrhythmia (5). Given the intertwined inflammation-oxidation-mitochondria-apoptosis network in SIMD, single-target drugs are unlikely to provide comprehensive cardioprotection. However, natural products offer promising multi-target interventions with low toxicity profiles (10). Traditional compounds such as flavonoids, glycosides, alkaloids and saponins exhibit anti-inflammatory, antioxidant, antiapoptotic and mitochondrial-restorative effects. Preclinical study demonstrates their capacity to attenuate key aspects of SIMD pathology (10); for example, curcumin has been found to have extensive cardiovascular protective effects by regulating endothelial function (10).

To the best of our knowledge, a systematic synthesis of how natural products counteract SIMD is lacking. The present review therefore summarizes the clinical features and pathophysiology of SIMD and the structure-activity-mechanism relationships of major natural product classes. Furthermore, the present study aimed to highlight the primary signaling pathways involved and evaluate advanced delivery strategies that improve bioavailability and representative compound binding to SIMD targets. By offering an integrated framework, the present study aimed to guide the development of novel multi-target therapeutic agents, including dietary supplements and lead compounds, for SIMD therapy.

2. Pathophysiology of SIMD

SIMD is a complex, dynamic process in which overwhelming infection and systemic inflammation disrupt normal cardiac function. Multiple interrelated mechanisms, including dysregulated cytokine release, oxidative stress, mitochondrial damage and impaired calcium handling, converge to depress myocardial performance (5). A comprehensive understanding of these pathways is key for accurate diagnosis and designing targeted therapies (Fig. 1).

Clinical characteristics of SIMD. SIMD describes a transient, sepsis-associated decline in myocardial function that can involve both the left and right ventricles and may affect systolic and/or diastolic performance (11). Many studies define SIMD by a reversible decrease in left ventricular ejection fraction (LVEF) accompanied by ventricular dilation and poor response to fluid resuscitation or catecholamines (3,5,7). However, because LVEF is load-dependent, it may not reliably reflect contractile reserve during sepsis (12). Consequently, SIMD is now recognized as a spectrum of load-independent myocardial depression manifesting as left ventricular systolic or diastolic dysfunction, right ventricular dysfunction or a combination of both, often with fluctuating hemodynamics (13).

Clinically, SIMD typically emerges within the first hours to days of septic illness and presents with a heterogeneous cardiac phenotype (14). Systolic abnormalities range from decreased contractility to ventricular dilation in certain patients (15), while diastolic dysfunction is identified by altered filling parameters. Right ventricular involvement is not uncommon and may exacerbate hemodynamic instability (16). SIMD is often reversible, although persistent dysfunction and worse outcomes occur depending on sepsis severity, underlying comorbidities and the level of hemodynamic support required (17). The clinical presentation may evolve over time, with an initial high-output state potentially progressing to a low-output phase, reflecting the interplay between preload, afterload, myocardial depression and microcirculatory redistribution (18). Thus, in clinical practice, the diagnosis of SIMD relies on a comprehensive, multi-faceted assessment. The typically involves confirming the presence of sepsis, identifying otherwise unexplained myocardial dysfunction, evidenced by new and often reversible echocardiographic abnormality and associating these findings with clinical signs of hemodynamic compromise, such as persistent vasopressor dependency or objective evidence of tissue hypoperfusion (14). While elevated biomarkers such as cardiac troponins and natriuretic peptides support the diagnosis by indicating myocardial injury or stress, they are not standalone diagnostic criteria due to their lack of specificity in the septic context (14).

Biomarkers of SIMD. Biomarkers of SIMD reflect diverse pathophysiological domains, including direct myocardial injury, ventricular wall stress, inflammatory remodeling and systemic perfusion. It is crucial to note that most currently used biomarkers are not specific to SIMD but indicate general myocardial injury, stress, inflammation, or dysfunction. High-sensitivity troponins I and T levels frequently rise in septic patients with cardiac involvement, signaling myocardial injury rather than an acute coronary syndrome. Troponin levels are associated with illness severity and adverse outcomes (12,19), but their release in sepsis is multifactorial, including demand ischemia, microvascular injury, cytokine-mediated toxicity and catecholamine effects, underscoring their lack of specificity for SIMD (19,20). B-type natriuretic peptides (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) increase with myocardial wall stress and diastolic dysfunction and also predict higher mortality (21,22). However, their variable association with LVEF reduces their value as standalone markers of intrinsic myocardial depression in SIMD (23).

Inflammatory and remodeling markers add prognostic information beyond troponin and NPs. Soluble ST2 and galectin-3 rise in septic patients with myocardial involvement and are associated with severity and adverse outcomes, reflecting ongoing inflammation and fibrosis (24). Similar to other markers, they are not specific to SIMD, and their interpretation requires integration with imaging and clinical context. Early injury markers such as heart-type fatty acid-binding protein (H-FABP) may increase before troponin in certain cases, offering potential for early risk stratification (25). Metabolic and perfusion markers, including lactate, indicate global tissue hypoperfusion and shock severity and thus complement cardiac-specific biomarkers in a comprehensive hemodynamic assessment (26). Specific circulating microRNAs (miRNAs or miRs) implicated in inflammatory and apoptotic pathways (such as miR-21, miR-155 and miR-146a) represent a promising class of biomarkers. They hold potential for more precise SIMD detection and risk

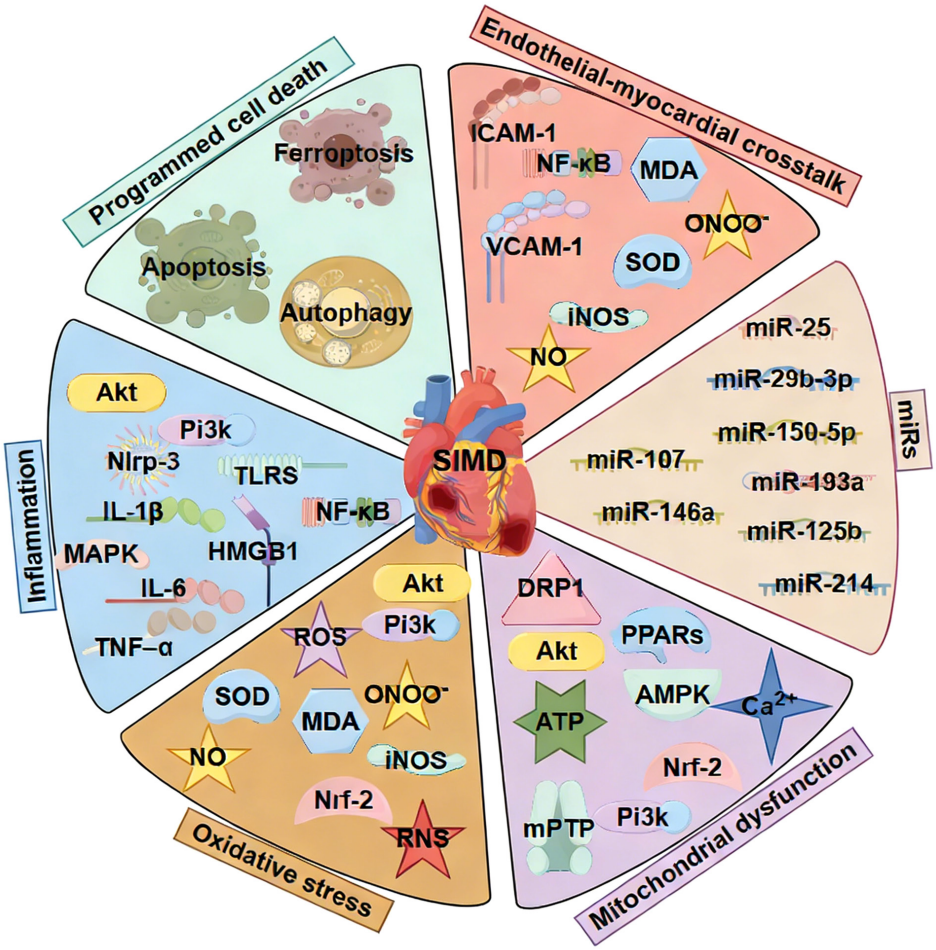

Figure 1. Pathophysiological mechanisms of SIMD. This schematic illustrates the key interrelated pathways (such as PI3K/Akt, NLRP3 and NF-κB) contributing to SIMD, including dysregulated cytokine release, oxidative stress, mitochondrial damage, impaired calcium handling and the regulatory roles of specific. miRs. SIMD, sepsis-induced myocardial dysfunction; miR, microRNA HMGB, high mobility group box; TLRS, Toll like receptors; ROS, reactive oxygen species; SOD, superoxide dismutase; MDA, malondialdehyde; iNOS, inducible nitric oxide synthase; RNS, reactive nitrogen species; DRP, dynamin-related protein; PPAR, peroxisome proliferator activated-receptors; mPTP, mitochondrial permeability transition pore.

stratification but require prospective validation before routine clinical use (27,28).

In summary, a multimodal strategy that integrates biomarkers with load-independent echocardiographic measures and detailed hemodynamic data is the most robust approach to defining myocardial involvement, monitoring progression and guiding management.

Pathology of SIMD

Programmed cell death. Cardiomyocyte loss in sepsis occurs through multiple interrelated programmed cell death pathways (29). Apoptosis proceeds through intrinsic mitochondrial pathways, where Bax and Bak mediate outer mitochondrial membrane permeabilization and caspase activation, and through endoplasmic reticulum stress pathways involving glucose-regulated protein 78 kDa, CHOP and caspase-12 (30-32). Death receptor signaling via TNF-R1 and FAS also contributes to caspase-8-mediated apoptosis. Pharmacological modulation of these signals modestly improves cardiac function in CLP (Cecum ligation and puncture (CLP)-induced rats (33). Necroptosis, driven by receptor interacting serine/threonine kinase RIPK1, RIPK3 and MLKL (Mixed lineage kinase domain-like) MLKL, amplifies inflammation and damages cardiomyocytes; inhibiting RIPK or MLKL attenuates myocardial injury in CLP-induced septic mice (34). Pyroptosis, a lytic form of cell death dependent on caspase-1-mediated gasdermin D (GSDMD) pore formation, releases IL-1β and IL-18 and amplifies systemic inflammation (35,36). Ferroptosis, an iron-dependent form of lipid peroxidation, also contributes to cardiomyocyte death; iron chelators and ferroptosis inhibitors lower ROS and lipid peroxidation to preserve cardiac function in endotoxemia (37,38). Autophagy plays a dual role in SIMD. Moderate autophagic flux supports cell homeostasis and cardiac resilience, but excessive or insufficient autophagy may worsen injury (39). Pharmacological induction of autophagy can restore homeostasis and improve cardiac outcomes in septic rats (40).

Inflammation. Sepsis releases PAMPs and damage-associated molecular patterns, which activate TLRs on cardiomyocytes, fibroblasts and endothelial cells (ECs) (41). Except for TLR3, most TLR signaling proceeds via the adaptor protein MyD88, activating downstream effectors such as the MAPKs JNK, ERK1/2 and p38, as well as the transcription factor NF-κB (42). This cascade drives production of proinflammatory cytokines (such as IL-1β, IL-6, TNF-α, IL-12, IL-17, IL-18) and chemokines such as CCL2/MCP-1 and CXCL8,

which recruit and activate immune cells (13,43-45). Activation of the NLRP3 inflammasome further amplifies IL-1β and IL-18 release, thereby creating an inflammatory milieu that impairs cardiomyocyte contractility by altering autophagy and lysosomal function (46). High mobility group box 1) HMGB1 and extracellular histones released during sepsis impair myocardial performance through TLR-dependent pathways, reinforcing the inflammatory cascade (47). Autonomic dysregulation also interacts with inflammation: Altered adrenergic signaling can modulate cytokine production and cardiomyocyte responsiveness, creating self-perpetuating feedback loops that influence disease progression (48).

Oxidative stress. Alongside inflammation, sepsis triggers a surge of ROS and nitrogen species (RNS) in cardiac tissue (49). ROS originate from electron leak in mitochondrial complexes I-III and from NO-derived species such as peroxynitrite ($ONOO^-$) (50). Oxidative and nitrosative stress damage lipids, protein and DNA, deplete antioxidants including superoxide dismutase, catalase and glutathione, and disrupt calcium handling and excitation-contraction coupling (51). NO produced by inducible nitric oxide synthase (iNOS) contributes to myocardial depression, while $ONOO^-$ nitrates tyrosine residues and further impairs mitochondrial and contractile protein (52). This redox imbalance shifts signaling toward proinflammatory pathways, creating a cycle that worsens contractile dysfunction (53).

Mitochondrial dysfunction. Mitochondria are key for energy supply and cell survival rate in SIMD (54). Sepsis induces structural changes, swelling and cristae disruption, alongside declines in oxidative phosphorylation and ATP synthesis (55). Excessive mitochondrial fission, driven by the GTPase dynamin-related protein 1 (DRP1), fragments the organelle and worsens energy deficits, whereas promoting fusion or mitophagy can maintain mitochondrial integrity in LPS-induced mice (56). The mitochondrial permeability transition pore (mPTP) opens under calcium overload, oxidative stress and ATP depletion, collapsing membrane potential and releasing cytochrome c (57). Agents that prevent mPTP opening or stimulate mitochondrial biogenesis improve mitochondrial function and cardiac performance in septic rats (58). In SIMD, energy metabolism shifts from fatty acid oxidation to glycolysis, decreasing ATP yield; downregulation of lipid-oxidation regulators such as PPARs and α subunit of peroxisome proliferators activated receptor-γ coactivator-1 (PGC-1α exacerbates energetic failure (58). Additional mitochondrial insults include mitochondrial DNA oxidation and impaired activity of electron transport chain complexes II and IV, limiting ATP production and contractile capacity (59). Restoring mitochondrial integrity with targeted antioxidants and NAD^+-boosting strategies offers a promising therapeutic approach in SIMD (60).

Endothelial-myocardial crosstalk. ECs coordinate vascular tone, perfusion and inflammation in the cardiovascular system (61). In sepsis, EC dysfunction transforms the vascular bed into a source of injurious signals that affect adjacent cardiomyocytes, fibroblasts and the microcirculation (62). Under inflammatory and oxidative stress, ECs activate TLRs, triggering NF-κB and MAPK pathways and increasing production of ROS and RNS (63). This pro-oxidant environment impairs myocardial relaxation and contraction and worsens microvascular perfusion. Upregulation of intercellular cell adhesion molecule-1 vascular cell adhesion molecule 1) promotes leukocyte trafficking into the myocardium, while degradation of the glycocalyx increases vascular permeability, edema and microvascular leakage, collectively decreasing oxygen delivery and substrate availability to the heart (64,65). Emerging evidence supports bidirectional communication between ECs and cardiomyocytes: Endothelial-derived signals modulate cardiomyocyte function and energy metabolism, while cardiomyocytes influence endothelial behavior via paracrine pathways and hemodynamic feedback (66). For example, endothelial-derived reactive species and altered NO signaling contribute to calcium handling abnormality and energetic stress in cardiomyocytes (67). Conversely, interventions that dampen endothelial inflammation or NO production yield downstream cardioprotective effects (68,69).

Role of miRNAs. Dysregulated miRNAs serve as key epigenetic regulators and downstream effectors in the pathogenesis of SIMD (70). These small non-coding (nc)RNAs fine-tune gene expression post-transcriptionally, predominantly by modulating central inflammatory and apoptotic pathways.

Numerous miRNAs critically regulate the inflammatory cascade in SIMD, primarily through targeting key components of the NF-κB signaling pathway. Certain miRNAs serve as endogenous negative feedback regulators to attenuate excessive inflammation. For example, miR-146a and miR-125b dampen NF-κB activation and subsequent pro-inflammatory cytokine production by targeting key adaptor proteins IL-1 receptor-associated kinase) and TNF receptor associated factor 6) (71,72). Similarly, miR-25 inhibits the TLR4/NF-κB pathway by directly targeting PTEN (73) and miR-29b-3p suppresses MAPK/NF-κB signaling by targeting FOXO3A (74). miR-335, although upregulated in SIMD, appears to exert a net beneficial effect on inflammation and injury when overexpressed, suggesting a complex, context-dependent regulatory role (75). Conversely, specific miRNAs exacerbate myocardial inflammation. miR-193a, expression of which is enhanced via METTL3-mediated m6A modification, promotes inflammation by targeting the anti-apoptotic gene BCL2L2 (76). The circROCK1/miR-96-5p/oxidative stress responsive kinase 1) pathway also promotes myocardial injury and NF-κB activation (77). Furthermore, hsa-miR-23a-3p, hsa-miR-3175 and hsa-miR-23b-3p are implicated in regulating NF-κB signaling via histone deacetylase 7)/ACTN4 (A-actinin-4), contributing to inflammatory damage (78).

Beyond inflammation, miRNAs determine cardiomyocyte fate by fine-tuning apoptotic and other cell death pathways. Multiple miRNAs confer cardioprotection by inhibiting pro-apoptotic signals or enhancing survival pathways. These include miR-214, which improves cardiac function and suppresses apoptosis (79). miR-21 inhibits apoptosis by targeting programmed cell death 4) to activate the PI3K/Akt pathway, as well as by directly regulating Bcl-2 and CDK6 (80). miR-150-5p alleviates apoptosis by modulating Akt2 expression (80). miR-107 promotes cardiomyocyte proliferation and inhibits apoptosis via the PTEN/PI3K/AKT pathway (81,82). Regulatory networks involving long (l)ncRNAs further augment this layer of control. For example, the lncRNA KCNQ1OT1 serves as a competitive endogenous RNA to

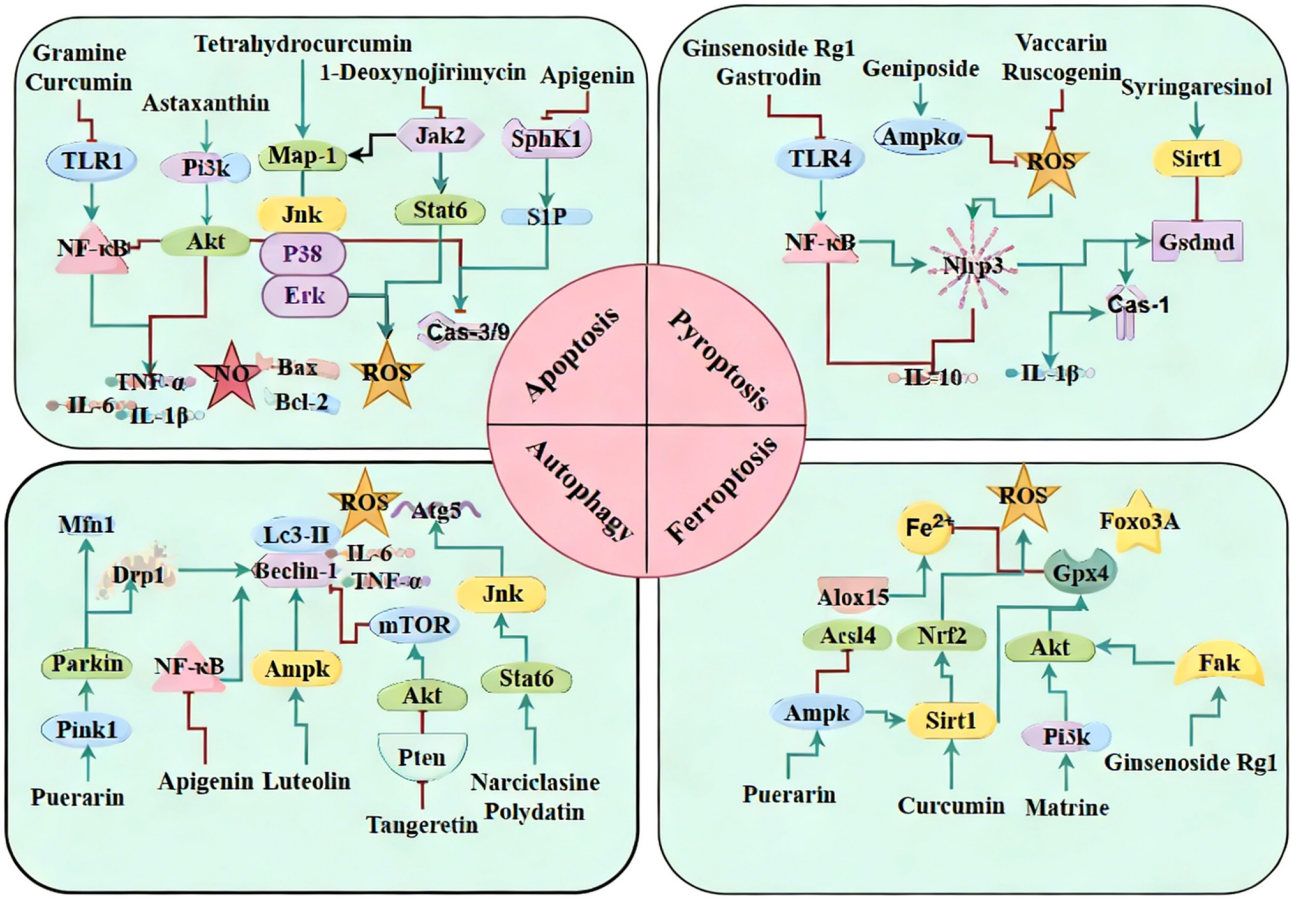

Figure 2. Regulation of programmed cell death by natural products in SIMD. Natural products attenuate SIMD through suppression of pro-oxidant NF-κB/TLR signaling, modulation of PI3K/Akt, AMPK/autophagy, TFEB, NLRP3/pyroptosis and mitophagy pathways and restoration of GPX4-associated antioxidant defenses. SIMD, sepsis-induced myocardial dysfunction; TLR, Toll like receptor; TFEB, T cell transcription factor EB; GPX, Glutathione peroxidase; SphK, Sphingosine kinases; S1P, Sphingosine Kinase 1; ROS, reactive oxygen species; MFN, mitofusin; SIRT, sirtuin 1; GSDMD, gasdermin D; ALOX, arachidonate 5-lipoxygenase.

sponge miR-192-5p, thereby upregulating the anti-apoptotic protein X-linked inhibitor of apoptosis (83), while the lncRNA ZFAS1 protects against apoptosis by sequestering miR-34b-5p to upregulate sirtuin (SIRT)1 (84). Conversely, detrimental miRNAs such as miR-208a-5p and miR-21-3p promote apoptosis (85).

Additionally, miRNAs participate in specialized cell death modalities and mitochondrial dysfunction associated with SIMD. miR-383-3p has been shown to alleviate SIMD by inhibiting ferroptosis via the activating transcription factor 4 (ATF)-CHOP-ChaC glutathione specific γ-glutamylcyclotransferase 1) (86), whereas miR-194-5p aggravates oxidative stress and apoptosis by targeting DUSP9 (87). The Xist/miR-7a-5p pathway serves a key role in sepsis-induced mitochondrial dysfunction. Inhibition of either Xist or miR-7a-5p upregulates the key mitochondrial biogenesis factor PGC-1α, increases ATP production, and decreases cardiomyocyte apoptosis, highlighting their key role in maintaining mitochondrial homeostasis (88,89).

3. Natural products against SIMD

The pathophysiology of SIMD is complex and multifactorial. Interplay of cytokine storm, excessive generation of ROS and RNS, mitochondrial dysfunction and dysregulated endothelial-myocardial crosstalk collectively drive cardiomyocyte apoptosis, ferroptosis and microcirculatory impairment.

Regulation of programmed cell death. Programmed cell death pathways implicated in SIMD include apoptosis, pyroptosis, autophagy and ferroptosis. Natural products can confer cardioprotection by either enhancing cell survival signals or inhibiting specific death pathways (Fig. 2).

Inhibition of apoptosis. Cardiomyocyte apoptosis is an early pathogenic event in SIMD, contributing to amplified inflammation and progressive cardiac dysfunction.

NF-κB, a master regulator of inflammation and apoptosis, is a common target for numerous natural compounds that also inhibit upstream TLR signaling. In CLP-induced septic mice, compounds such as gramine, curcumin, andrographolide and berberine suppress the TLR1/NF-κB axis, leading to lower TNF-α, IL-1β and NO levels, decreased caspase-3 activation and apoptosis and restored cardiac contractility, which translates into decreased mortality (90-94). Notoginsenoside R1 activates the PI3K/Akt pathway while concurrently inhibiting NF-κB, resulting in suppressed caspase-3 activation and downregulated TNF-α and IL-1β levels in both cardiomyocyte H9c2 and septic mice, thereby attenuating inflammation and apoptosis (95,96).

The MAPK family also influences stress-induced apoptosis. In LPS-challenged septic mice, tetrahydrocurcumin upregulates mitogen activated protein kinase phosphatase 1), suppresses ERK and JNK signaling and limits ROS production and caspase-3-mediated apoptosis, preserving cardiac function (97). Astaxanthin similarly inhibits ERK, JNK and p38 MAPK pathways while activating PI3K/Akt pathway, resulting in lower serum levels of TNF-α, IL-6 and BNP, and reduced myocardial injury and apoptosis in septic mice (98). Furthermore, 1-deoxynojirimycin decreases ROS generation by inhibiting JAK2/STAT6 signaling, thereby decreasing cardiomyocyte apoptosis and improving function in septic mice (99). Astragaloside IV protects against LPS-induced myocardial injury in rats by inhibiting the JNK/Bax pathway, reducing levels of caspase-3, CK-MB (Creatine kinase (CK-MB) and c-TnI (Cardiac troponin I c-TnI) and increasing the Bcl-2/Bax ratio to mitigate myocardial dysfunction (100).

In CLP-induced septic rats, apigenin inhibits the Sphingosine kinase 1/sphingosine 1-phosphate) pathway, leading to downregulation of cleaved caspase-3/-9 and Bax, upregulation of Bcl-2, decreased serum CK-MB and lactate dehydrogenase (LDH) levels, suppressed apoptosis and improved myocardial histology (101). Gastrodin, tested in CLP-induced septic mice and AC16 cardiomyocytes, modulates the denticleless E3 ubiquitin protein ligase-homolog histone acetyltransferase-driven ubiquitination-acetylation axis to promote degradation of pro-caspase-3/-9 and Bax, thereby attenuating apoptosis and alleviating myocardial damage (102).

Inhibition of pyroptosis. Pyroptosis is an inflammatory form of programmed cell death triggered by inflammasome activation, characterized by GSDMD-mediated pore formation and the release of IL-1β and IL-18 (103). In SIMD, pyroptosis not only accelerates cardiomyocyte loss but also perpetuates a local inflammatory cycle.

In CLP-induced septic mice, vaccarin and ruscogenin attenuate myocardial injury by suppressing the NLRP3 inflammasome, decreasing IL-1β and IL-18 release and limiting pyroptosis (103,104). Artemisinin decreases NLRP3 and caspase-1 expression in burned septic mice, lowers IL-1β and IL-18 mRNA in mouse monocytic macrophage leukemia RAW264.7 cells and decreases neutrophil infiltration, thereby mitigating myocardial damage (105). Similarly, thymoquinone inhibits the NLRP3/caspase-1/IL-1β/IL-18 pathway, downregulates p62 and c-TnT and upregulates IL-10, reducing inflammation and pyroptosis in septic mice (106). Additionally, in LPS-challenged septic mice, syringaresinol activates the endoplasmic reticulum (ER)/SIRT1 pathway and suppresses NLRP3/GSDMD signaling to block IL-1β and IL-18 release, significantly improving myocardial injury (107). Both ginsenoside Rg1 and gastrodin inhibit the TLR4/NF-κB/NLRP3 signaling cascade, downregulate Bax, upregulate Bcl-2 and restore cardiac function by reducing pyroptosis (108,109). Nifuroxazide similarly targets TLR4/NLRP3/IL-1β signaling to lower LDH and CK-MB levels, suppress pyroptosis and protect myocardial function (110).

ROS also regulate NLRP3 activation. In LPS-induced septic mice, carvacrol and emodin inhibit the ROS/NLRP3/GSDMD pathway, decreasing IL-1β and IL-18 levels, which enhances survival rate and restores cardiac function (111,112). Plumbagin also suppresses ROS-mediated NLRP3/GSDMD signaling, decreases HMGB1, caspase-3 and Bax expression and improves cardiac function through preventing pyroptosis (113). Geniposide downregulates neutrophil cytoplasmic factor 1 and suppresses the AMPKα/ROS/NLRP3 pathway, leading to reduced ROS levels and improved cardiac function and survival rate in septic mice (114). Finally, oxycodone markedly improves EF and fractional shortening (FS), decreases levels of ROS, c-TnI and CK-MB and activates the Nrf2/heme oxygenase (HO)-1 pathway to inhibit NLRP3-mediated pyroptosis, yielding notable cardioprotective effects (115).

Autophagy. Autophagy is a key homeostatic process that removes damaged organelles and proteins via lysosomal degradation. In cardiomyocytes, it maintains mitochondrial quality, balances energy metabolism and supports antioxidant defenses (39). In SIMD, autophagy exhibits a dual role: Moderate activation clears dysfunctional mitochondria and limits oxidative stress, whereas either excessive or insufficient autophagic flux can exacerbate cell death and impair cardiac function (116).

The AMP-activated protein kinase (AMPK) pathway induces autophagy. In CLP-induced septic mice, luteolin activates AMPK pathway signaling, which increases LC3-II and Beclin-1 expression, enhances autophagic flux, improves LVEF and FS, decreases levels of TNF-α, IL-6 and ROS, restores mitochondrial architecture and inhibits apoptosis (116). Conversely, in CLP-induced septic rats, tangeretin suppresses excessive autophagy by inhibiting PTEN and activating the Akt/mTOR pathway. This lowers serum levels of cardiac myosin light chain-1 (cMLC1), c-TnI, LDH and (CK), alleviates oxidative stress and inflammation and preserves myocardial function (117).

The NF-κB/TFEB (T cell transcription factor EBTFEB pathway also regulates autophagy. In LPS-challenged septic mice, apigenin inhibits NF-κB to decrease inflammation and oxidative stress while upregulating TFEB and its downstream target genes such as ATG5, lysosome-associated membrane protein 1), p62, microtubule-associated protein 1 light chain 3), vacuolar protein sorting 11), thereby boosting autophagic flux. These combined effects lower cardiac injury markers (CK, LDH, c-TnI, cMLC1), improve survival rate and maintain cardiac function (118,119).

Mitochondrial autophagy (mitophagy) is key for clearing damaged mitochondria. In LPS-stimulated H9c2 cardiomyocytes, puerarin upregulates Drp1 and mitofusin 1 to preserve mitochondrial dynamics and activates the PINK1/Parkin pathway, thereby reducing ROS, inhibiting apoptosis and restoring cell viability (120).

Other natural compounds modulate autophagy through alternative signaling nodes. In LPS-induced septic mice, narciclasine and polydatin activate SIRT6 and JNK signaling, which elevates LC3-II and Beclin-1 while lowering TNF-α and IL-6 levels, thereby suppressing inflammation and attenuating myocardial injury (121,122). Phlorizin modulates the Hif-1α/BCL2 interacting protein 3) axis to promote Beclin-1 release, autophagosome formation and lysosomal degradation, reducing oxidative stress and apoptosis, improving cardiac function and enhancing survival rate (123).

Inhibition of ferroptosis. Ferroptosis is an iron-dependent form of programmed cell death characterized by glutathione peroxidase 4 (GPX4) inactivation, accumulation of lipid peroxides and iron overload (37). In SIMD, inflammatory disruption of iron homeostasis coupled with mitochondrial dysfunction accelerates lipid peroxidation, triggering ferroptosis and exacerbating cardiomyocyte injury (124). Consequently, targeting antioxidant defenses, iron metabolism and lipid peroxidation represents a promising therapeutic strategy.

The AMPK signaling axis serves a central role in regulating ferroptosis. In LPS-induced septic mice, puerarin activates AMPK to upregulate GPX4 and ferritin and downregulate ACSL4 and the transferrin receptor (TFRC), reducing myocardial iron content, lipid peroxidation and ferroptosis (124). Curcumin engages the AMPK/SIRT1 pathway to increase expression of GPX4, ferritin and translocase of outer mitochondrial membrane 20 while decreasing levels of Fe^{2+}, MDA and prostaglandin-endoperoxide synthase 2, thereby preventing ferroptotic cell death (125). Similarly, matrine activates PI3K/Akt to enhance GPX4 and the Bcl-2/Bax ratio, reduce ACSL4 and ROS and inhibit ferroptosis, improving cardiac performance (126). Ginsenoside Rg1 stimulates FAK/Akt and upregulates FOXO3A, which decreases levels of TNF-α, IL-1β and Fe^{2+} and increases Bcl-2, collectively alleviating myocardial injury (127).

Direct inhibition of key lipid peroxidation enzymes provides another mechanism to block ferroptosis. In LPS-stimulated AC16 cardiomyocytes, resveratrol upregulates miR-149 and downregulates HMGB1, decreasing Fe^{2+} accumulation and lipid ROS to protect the myocardium (128). In CLP-induced septic mice, narciclasine restores glutathione, downregulates TFRC and upregulates GPX4 and HO-1, thereby inhibiting lipid peroxidation and preserving cardiac function (129). Furthermore, resveratrol activates the SIRT1/Nrf2 pathway to mitigate mitochondrial damage and lipid peroxidation (130). Arachidonic acid 15-lipoxygenase (ALOX15) is a key enzyme in lipid peroxidation. Wogonin directly inhibits ALOX15, mitigating lipid peroxidation and ferroptosis in the myocardium (131). Quercetin also activates PI3K/Akt to inhibit ALOX5-mediated lipid oxidation, restores GPX4 and glutathione (GSH) levels, lowers Fe^{2+} and ROS, and suppresses myocardial inflammation and ferroptosis (132).

Collectively, natural products, such as flavonoids, alkaloids and saponins, attenuate SIMD through diverse mechanisms. These include suppression of pro-oxidant NF-κB/TLR signaling, modulation of PI3K/Akt, AMPK/autophagy, TFEB, NLRP3/pyroptosis and mitophagy pathways and restoration of GPX4-related antioxidant defenses. For example, curcumin, resveratrol, and quercetin concurrently inhibit apoptosis and pyroptosis, promote adaptive autophagy and restrain ferroptosis. Similarly, astaxanthin, apigenin and puerarin protect the myocardium through combined activation of autophagy and inhibition of ferroptosis. This multimodal pharmacological profile highlights the potential of natural products to target the interconnected cell death networks that drive SIMD.

Regulation of inflammation. Sepsis provokes a systemic inflammatory response that contributes directly to myocardial injury. Endotoxins and other PAMPs activate key signaling cascades, most notably the TLR4/NF-κB, MAPK and NLRP3 inflammasome pathways, leading to the release of proinflammatory cytokines (TNF-α, IL-1β, IL-6, MCP-1) and recruitment of neutrophils and macrophages into cardiac tissue. The resulting inflammatory milieu impairs cardiomyocyte contractility and survival (Fig. 3).

Inhibition of the TLR4/NF-κB pathway. Numerous flavonoids and other phytochemicals suppress TLR4-driven NF-κB activation to decrease cytokine release and improve cardiac function. In LPS-challenged septic mice, isoquercitrin and quercetin inhibit NF-κB p65 phosphorylation, lower TNF-α, IL-6 and MCP-1 levels and significantly improve LVEF and FS (133,134). Ciprofol similarly blocks NF-κB activation in septic mice, decreasing levels of CK-MB, LDH, TNF-α and IL-6 and restoring LVEF and FS (135). In CLP-induced septic rats, astragaloside IV prevents NF-κB p65 phosphorylation, decreases levels of LDH, CK-MB, IL-6, IL-1β and HMGB1 and enhances both systolic and diastolic function as well as survival rate (136). Myricetin inhibits IκBα degradation and NF-κB/p65 nuclear translocation in septic rats, which lowers TNF-α, IL-6 and IL-1β and preserves cardiac function (137,138). Similarly, naringin blocks NF-κB nuclear translocation, decreases TNF-α, IL-1β and IL-6 levels and enhanced superoxide dismutase activity while lowering MDA levels and leads to improved cardiac performance in septic rats (139,140). Additionally, astilbin and esculin both target the TLR4/NF-κB pathway to downregulate TNF-α, IL-6 and MDA, correct QT prolongation and reduce the risk of ventricular arrhythmia (141,142). Puerarin also inhibits TLR4/NF-κB signaling in Langendorff-perfused hearts, decreasing LDH, CK and TNF-α release and improving LV end-diastolic pressure in septic rats (143). By contrast, oleuropein activates the glycogen synthase kinase (GSK)-3 beta)/NF-κB pathway, decreases c-TnI, CK-MB, IL-6 and HMGB1 levels and increases anti-inflammatory IL-10 levels, thereby protecting cardiac function in septic rats (144).

Inhibition of MAPK-associated pathways. The MAPK family intersects with NF-κB signaling to amplify inflammation. In LPS-stimulated H9C2 cells, zerumin A suppresses MAPK-mediated NF-κB activation, resulting in lower levels of iNOS, ROS, COX-2, NO, MCP-1, TNF-α, IFN-γ and IL-1β and higher IL-10 expression, which improves cell viability (145). In LPS-challenged septic mice, propofol and carvacrol both inhibit ERK1/2 phosphorylation, decrease IL-6 and TNF-α levels, alleviate myocardial injury and enhance survival rate (146,147). Pinocembrin blocks the p38/JNK MAPK pathway, decreasing myocarditis and arrhythmia risk in LPS-induced septic rats (148). Similarly, madecassoside inhibits ERK1/2 and p38 activation in septic mice, delays arterial pressure decline and lowers TNF-α levels, thereby mitigating tachycardia (149). Additionally, alisol B 23-acetate suppresses TLR4/NOX2 and p38/MAPK/ERK signaling, decreasing IL-6, IL-1β and TNF-α levels, which alleviates myocardial injury and improves survival rate (150). In LPS-treated septic rats, oxymatrine also inhibits the p38/MAPK/caspase-3 and JAK2/STAT3 pathways, decreases IL-1β and TNF-α levels and improves cardiac function (151,152).

Activation of the PI3K/AKT pathway. The PI3K/Akt pathway exerts anti-inflammatory and pro-survival effects in SIMD.

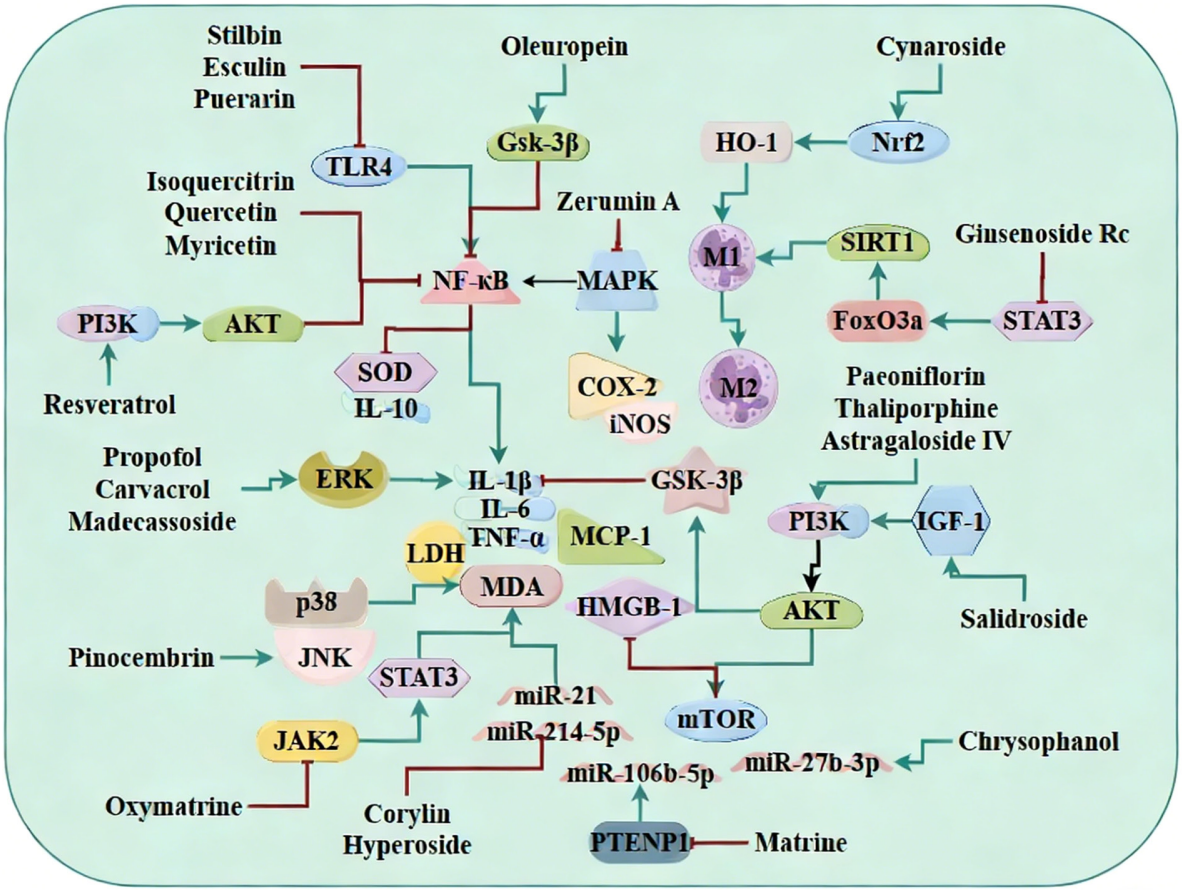

Figure 3. Anti-inflammatory mechanisms of natural products in sepsis-induced myocardial dysfunction). Natural products confer protection by inhibiting pro-inflammatory TLR4/NF-κB and MAPK signaling cascades, activating the PI3K/Akt survival pathway, modulating specific miR networks (miR-214-5p, miR-21) and promoting the polarization of macrophages towards the reparative M2 phenotype. TLR, toll-like receptor; miR, miRNA; GSK, glycogen synthase kinase; HO, heme oxygenase; SIRT, sirtuin 1; COX, cyclooxygenase; iNOS, inducible nitric oxide synthase; IGF, insulin like growth factor; LDH, lactate dehydrogenase; MCP, monocyte chemotactic protein; MDA, malondialdehyde; HMGB, high mobility group box.

In LPS-challenged septic mice, astragaloside IV activates PI3K/Akt signaling to reduce LDH and c-TnI levels, suppress myocardial inflammation and improve cardiac performance (153). Paeoniflorin and resveratrol also stimulate PI3K/Akt to decrease levels of TNF-α, IL-1β, IL-6, IL-12, MCP-1, IFN-γ and iNOS, thereby protecting against myocardial injury (154,155). In CLP-induced septic mice, thaliporphine activates the PI3K/Akt/mTOR pathway to decrease levels of TNF-α, c-TnI and LDH and enhance LV function (156). Salidroside modulates the IGF-1/PI3K/Akt/GSK-3β pathway to decrease levels of CK, LDH, TNF-α, IL-6 and IL-1β, thereby alleviating myocardial edema and dysfunction (157).

miRNA-dependent anti-inflammatory pathways. miRNAs have emerged as critical regulators of myocardial inflammation in sepsis. For example, corylin improves LPS-induced cardiac dysfunction in mice by downregulating myocardial miR-214-5p, which attenuates inflammatory signaling (158). In CLP-induced septic mice, hyperoside exerts protective effects by suppressing the sepsis-associated upregulation of miR-21, leading to decreased myocardial inflammation (159). Furthermore, matrine acts via the PTENP1/miR-106b-5p pathway to inhibit proinflammatory pathways and enhance cardiomyocyte viability, thereby improving cardiac function in CLP-induced mice (160). Chrysophanol downregulates miR-27b-3p and upregulates PPARγ, which suppresses inflammatory cytokines and apoptotic proteins to repair CLP-induced cardiac injury in mice (161).

Targeting macrophage polarization. Macrophage polarization strongly influences the inflammatory milieu in SIMD. Pinostrobin inhibits TLR4/myeloid differentiation protein-2 signaling in mouse monocytic macrophage leukemia RAW264.7cells, decreasing expression of NO, prostaglandin E2, TNF-α, IL-12, iNOS and COX-2, and improves heart rate and survival rate in LPS-treated zebrafish (162). Cynaroside activates the Nrf2/HO-1 pathway to lower IL-1β and TNF-α levels and promotes M2 macrophage polarization, thereby decreasing systemic inflammation and protecting the myocardium in septic mice (163). Similarly, ginsenoside Rc suppresses the STAT3/FoxO3a/Sirt1 pathway to limit M1 macrophage-mediated myocardial damage during sepsis (164).

Other anti-inflammatory agents. Several additional natural products exhibit potent anti-inflammatory and cardioprotective effects in SIMD. In LPS-induced septic mice, cyanidin lowers levels of LDH, CK, c-TnI, TNF-α, IL-1β, MIP-2, MCP-1 and cMLC1, inhibits caspase-3 and PARP cleavage and attenuates myocardial injury (165). Monotropein and baicalein suppress TNF-α, IL-6, HMGB1 and iNOS/NO production while

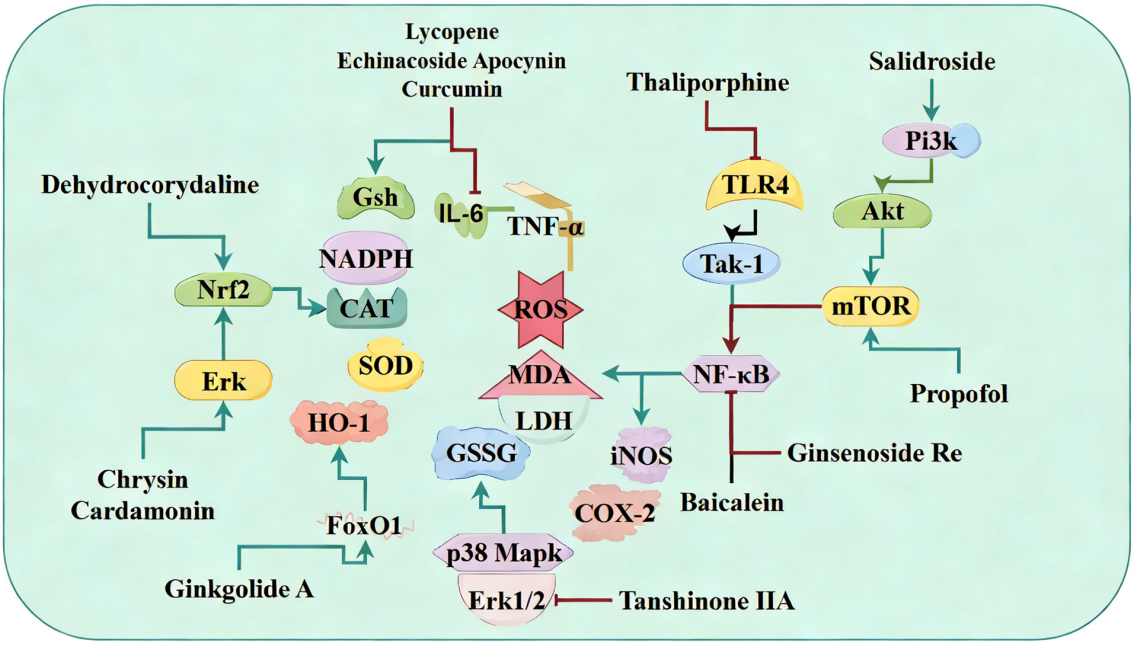

Figure 4. Modulation of oxidative stress by natural products in sepsis-induced myocardial dysfunction). Natural products primarily enhance antioxidant defenses by activating enzymes such as SOD, CAT and GSH-Px or by stimulating the Nrf2/HO-1 pathway. They also dampen proinflammatory signaling via NF-κB, TLR4 and ERK1/2-p38 MAPK signaling to reduce NOX2/iNOS-mediated ROS/RNS production. SOD, superoxide dismutase; CAT, catalase; GSH-Px, glutathione peroxidase; HO, heme oxygenase; TLR, Toll like receptor; NOX, nitrogen oxide; iNOS, inducible nitric oxide synthase; ROS, reactive oxygen species; RNS, reactive nitrogen species; GSSG, glutathione oxidized; MDA, malondialdehyde; LDH, lactate dehydrogenase; TAK, transforming growth factor-β-activated kinase 1.

decreasing MMP-2/9 and ROS levels to alleviate septic myocardial hypertrophy and dysfunction (166,167). Paeoniflorin and honokiol markedly decrease c-TnI, LDH, IL-6, TNF-α and IL-1β and raise IL-10 levels, improving cardiac contractility and enhancing survival rate in CLP-induced septic mice (168,169). Similarly, dobutamine increases serum levels of IL-10 and lowers c-TnI, NT-proBNP and H-FABP, thereby enhancing survival rate in CLP-induced rats (170).

In LPS-challenged septic rats, magnolol corrects hypotension and bradycardia by decreasing levels of iNOS, NO, TNF-α and alanine aminotransferase/aspartate aminotransferase) (171). Sodium tanshinone IIA sulfonate also improves LV function by inhibiting expression of TNF-α, IL-6, HMGB1, C-reactive protein, PCT (Procalcitonin (PCT), c-TnI/c-TnT and BNP (172). Additionally, micromeria congesta downregulates IL-2, caspase-3 and heat shock protein (HSP)-27 to attenuate septic myocardial pathology (173). Naringenin and tubeimoside I activate the SIRT3 or HIF-1α pathways to suppress IL-1β, IL-6 and TNF-α, improving myocardial injury (174,175). Yohimbine blocks α2A-adrenergic receptors at cardiac sympathetic terminals, promotes norepinephrine release and decreases NO and TNF-α levels to alleviate cardiac dysfunction in septic rats (176).

In summary, these natural products protect against SIMD by inhibiting TLR4/NF-κB and MAPK signaling, activating PI3K/Akt, modulating miRNA networks and promoting macrophage M2 polarization. They collectively reduce proinflammatory cytokine levels, limit inflammatory cell infiltration and improve cardiac function and survival rate.

Regulation of oxidative stress. Oxidative stress is a key driver of cardiac injury in SIMD. Inflammation, endotoxins and mitochondrial dysfunction increase ROS/RNS levels, leading to lipid peroxidation, protein carbonylation and DNA damage (49). These changes worsen contractile dysfunction and promote cardiomyocyte death (Fig. 4).

Activation of antioxidant enzymes. Natural products directly enhance the activity of endogenous antioxidant systems. In LPS-induced septic mice, lycopene, echinacoside and apocynin lower myocardial ROS and MDA levels while increasing NADPH oxidase and SOD activity (177-179). Similarly, rutin reduces CK, LDH, MDA, ROS, TNF-α and IL-6 and increases SOD and catalase (CAT) activity, thereby protecting cardiac structure and function (180). In CLP-induced rats, curcumin decreases plasma levels of ROS, c-TnI and MDA, restores the GSH/oxidized glutathione (GSSG) ratio and enhances SOD activity to improve LVEF and FS (181,182). Quercetin similarly upregulates endothelial (e)NOS and maintains the GSH/GSSG balance, alleviating hypotension and tachycardia in septic mice (183).

Activation of the Nrf2 pathway. The transcription factor Nrf2 orchestrates the cellular antioxidant response. In LPS-challenged septic mice, resveratrol activates Nrf2 to decrease myocardial ROS and increase the expression of antioxidant genes (184). Chrysin and cardamonin engage the ERK-Nrf2-HO-1 axis, upregulating HO-1 and SOD while lowering levels of ROS, MDA, TNF-α, IL-6 and IL-1β, which improves cardiac function (185,186). Dehydrocorydaline also triggers the Nrf2/HO-1 pathway, decreases levels of ROS, TNF-α and IL-1β and restores SOD and glutathione peroxidase (GSH-Px) activity, leading to improved survival rate (187).

Regulation of the PI3K/Akt/NF-κB pathway. NF-κB links inflammation with oxidative stress. In LPS-treated septic

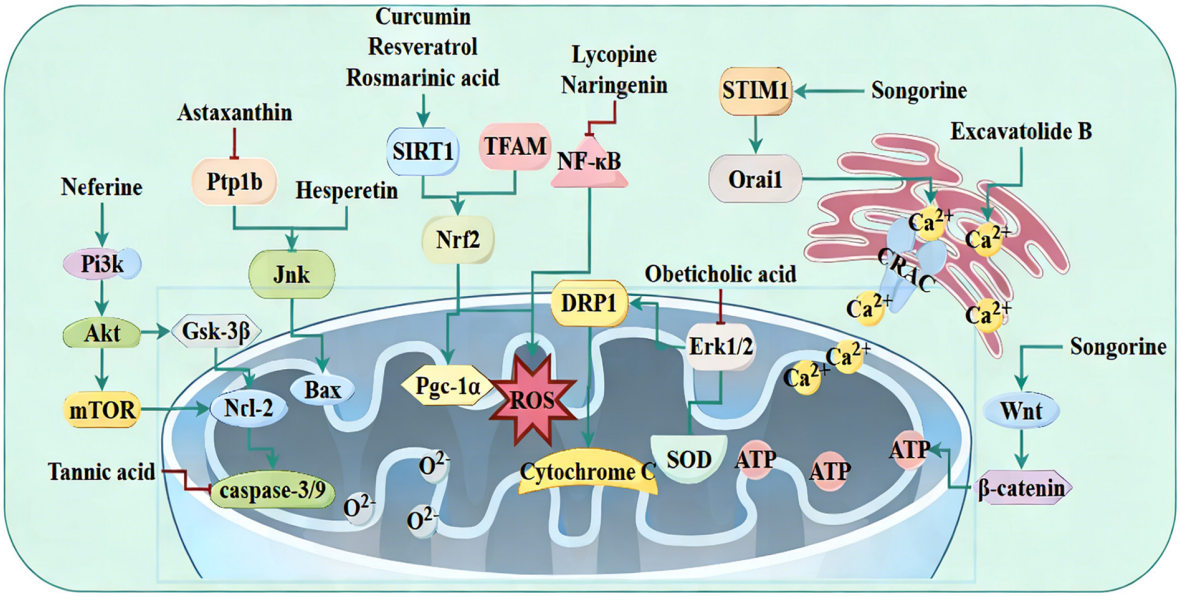

Figure 5. Targeting mitochondrial dysfunction with natural products in SIMD. Natural products counteract SIMD by engaging multiple mitochondrial-protective pathways, most notably SIRT1/Nrf2, PI3K/Akt/mTOR and AMPK, and by promoting mitochondrial biogenesis via PGC-1α/TFAM and UPRmt. SIMD, sepsis-induced myocardial dysfunction; SIRT, sirtuin 1; PGC, peroxisome proliferator-activated receptor γ coactivator; UPRmt, mitochondrial unfolded protein response; GSK, glycogen synthase kinase; PTP1B, protein tyrosine phosphatase 1B; ROS, reactive oxygen species; SOD, superoxide dismutase; DRP, dynamin-related protein 1; STIM, stromal interaction molecule 1; CRAC, calcium release-activated channels.

rats, baicalein inhibits the NF-κB pathway to decrease levels of iNOS, ROS and NO, improving blood pressure, heart rate and survival rate (188,189). Thaliporphine also suppresses the TLR4/transforming growth factor-β-activated kinase 1 (TAK1)/NF-κB pathway to lower myocardial NO, ROS, TNF-α and iNOS levels and improve LV pressure-volume indices (190). Ginsenoside Re corrects the iNOS/eNOS imbalance by inhibiting NF-κB signaling, thereby reversing myocardial injury (191). In LPS-treated rats, salidroside activates the PI3K/Akt/mTOR pathway while inhibiting NF-κB, which decreases levels of iNOS, COX-2 and ROS and improves cardiac function (192). Propofol also engages mTOR signaling to lower ROS and MDA levels and boosts SOD activity, thereby reverse myocardial damage (193).

Other antioxidant agents. Additional natural products modulate oxidative stress via unique pathways. In LPS-induced sepsis, ginkgolide A activates FoxO1 and downstream effectors such as Kruppel-like factor 15, thioredoxin 2), Notch1(Notch receptor 1), XBP1(X-box binding protein 1), which upregulates antioxidant enzymes and preserves mitochondrial function (194). Tanshinone IIA inhibits ERK1/2 and p38 MAPK phosphorylation, decreases NOX2 expression and lowers MDA and ROS levels to alleviate cardiac dysfunction (195).

In summary, natural products primarily enhance antioxidant defenses by activating enzymes such as SOD, CAT and GSH-Px or by stimulating the Nrf2/HO-1 pathway. They also dampen proinflammatory signaling via NF-κB, TLR4 and ERK1/2/p38 MAPK pathways to reduce NOX2/iNOS-mediated ROS/RNS production. Through simultaneous engagement of PI3K/Akt/mTOR and FoxO1 pathways, these compounds preserve mitochondrial integrity and myocardial contractility, thereby markedly improving SIMD outcomes and survival rate.

Regulation of mitochondrial dysfunction. Mitochondria serve not only as the energy source of cardiomyocytes but also as a key hub for ROS production and the regulation of programmed cell death (54). In SIMD, inflammatory mediators, oxidative stress and impaired mitochondrial quality control cause mitochondrial fragmentation, loss of membrane potential, respiratory defects, diminished ATP synthesis and ultimately cell death (55) (Fig. 5).

Activation of Nrf-associated pathways. Nrf pathways are key for maintaining mitochondrial redox homeostasis. In LPS-induced septic mice, curcumin and resveratrol upregulate PGC-1α and mitochondrial transcription factor A (TFAM), inhibit DRP1-mediated excessive mitochondrial fission and activate the SIRT1/Nrf2 pathway to normalize mitochondrial morphology and respiration, thereby markedly improving cardiac function (196,197). Rosmarinic acid similarly preserves mitochondrial membrane potential and ATP production by triggering the SIRT1/Nrf2 pathway, resulting in decreased ROS levels and enhanced survival rate (198). Songorine further boosts Nrf1/TFAM signaling and promotes PGC-1α-Nrf2 interactions, suppressing calcium release-activated channels) channel formation, lowering mitochondrial ROS levels, restoring calcium homeostasis and increasing contractile power (199).

Inhibition of AMPK-associated pathways. Although AMPK often supports mitochondrial homeostasis, certain stress contexts benefit from modulating its downstream effectors. In LPS-stimulated H9C2 cells, hesperetin upregulates Bcl-2, downregulates Bax and caspase-3/9 expression through inhibiting JNK phosphorylation, thus preserving mitochondrial membrane potential and decreasing apoptosis (200). In CLP-induced septic mice, tannic acid attenuates ER stress and decreases expression

of ROS, Bax, cytochrome c and caspase-3/-9/-12, thereby safeguarding mitochondrial function in cardiomyocytes (201). Additionally, astaxanthin inhibits the PTP1B/JNK pathway to maintain membrane potential and limit ROS generation, which decreases cardiomyocyte apoptosis (202). In LPS-challenged septic mice, lycorine and naringenin activate AMPK and suppress NF-κB signaling, together protecting cardiac function (203,204). Obeticholic acid blocks the ERK1/2-DRP1 axis to prevent cytochrome c release and upregulates GPX1 and SOD1/2, thereby restoring mitochondrial integrity (205).

Activation of PI3K/Akt signaling. The PI3K/Akt pathway also contributes to mitochondrial preservation. In LPS-induced septic rats, neferine activates PI3K/Akt/mTOR signaling to elevate the Bcl-2/caspase-3 ratio, decreases ROS levels and restores mitochondrial structure and function, leading to improved myocardial performance (206). Ginsenoside Rg1 also engages the recombinant purinergic receptor P2X to stimulate the Akt/GSK-3β pathway, suppressing mitochondrial superoxide generation and cytochrome c release, stabilizing calcium handling and enhancing survival rate (207).

Other pathways. In LPS-treated septic mice, verbascoside promotes mitochondrial biogenesis and morphological repair, thereby improving cardiac function (208). Silibinin also decreases CCR2 levels and activates LXRα (Liver X receptors) signaling to dampen inflammation and oxidative damage while improving mitochondrial function (209,210). Additionally, chicoric acid inhibits α-tubulin acetylation and NLRP3 inflammasome assembly, indirectly restoring mitochondrial architecture and alleviating myocardial injury (211). Songorine also activates Wnt/β-catenin signaling to boost mitochondrial biogenesis and suppress inflammation and apoptosis, thereby improving LVEF and FS (212). Furthermore, excavatolide B modulates intracellular and extracellular Ca^{2+} channels to reverse calcium dysregulation and repair mitochondrial structure in septic hearts (213). Salvianolic acid B induces an ATF5-mediated mitochondrial unfolded protein response (UPRmt), prevents excessive mitochondrial fission, preserves membrane potential and significantly enhances contractile function and mitochondrial ultrastructure (214).

In summary, natural products counteract SIMD by engaging multiple mitochondrial-protective pathways, most notably SIRT1/Nrf2, PI3K/Akt/mTOR and AMPK pathways, and by promoting mitochondrial biogenesis via PGC-1α/TFAM and UPRmt. These interventions preserve mitochondrial membrane potential, augment ATP production, decrease ROS accumulation and suppress apoptosis, collectively leading to substantial improvements in cardiac function and survival rate in SIMD.

Regulation of endothelial-myocardial crosstalk. ECs constitute the first line of defense in maintaining microcirculatory stability and myocardial function (61). In sepsis, endothelial barrier dysfunction increases vascular permeability, tissue edema and inflammatory cell infiltration, while endothelial-derived cytokines and exosomes propagate injurious signals to cardiomyocytes, exacerbating SIMD (63).

In LPS-induced septic mice, neohesperidin dihydrochalcone markedly suppresses vascular hyperpermeability and myocardial tissue damage. It decreases ROS production, preserves mitochondrial membrane potential and enhances antioxidant defenses (CAT, SOD, GSH) while lowering MDA levels (215). Mechanistically, it inhibits phosphorylation of TAK1, ERK1/2 and NF-κB, stabilizes endothelial junction protein and diminishes THP-1 monocyte adhesion and infiltration (215). These combined effects reinforce endothelial barrier function and mitigate myocardial injury (215). In LPS-induced septic shock rats, anisodamine restores hemodynamics and repairs the endothelial glycocalyx, thereby decreasing myocardial damage (8). It lowers levels of lactate, IL-1β, IL-6, TNF-α, CK, c-TnT, NT-proBNP, syndecan-1 and hyaluronic acid via inhibition of NF-κB and NLRP3 signaling and activation of the PI3K/Akt pathway (8). Moreover, exosomes released by LPS-stimulated human umbilical vein ECs transfer inflammatory and oxidative signals to the myocardium; anisodamine attenuates these exosome-mediated effects, indicating that it disrupts harmful endothelial-myocardial crosstalk to confer cardioprotection in SIMD (216).

4. Classification and structure-activity relationships

Natural products with efficacy against SIMD can be divided into five major chemical classes: Flavonoids, glycosides, phenolic acids, alkaloids and saponins (Fig. 6A). Notably, flavonoids and glycosides account for approximately half of the identified compounds. The prominent bioactivity of these classes is associated with their characteristic chemical scaffolds. Specifically, the presence of multiple hydroxyl (-OH) groups confers potent antioxidant capacity by serving as hydrogen donors to directly neutralize free radicals (217). Concurrently, conjugated double bond systems (extended π-electron networks) enable electron delocalization, which stabilizes antioxidant reaction intermediates and facilitates key interactions with cellular signaling proteins (kinases, transcription factors) (217). These combined physicochemical properties underpin their broad-spectrum antioxidant, anti-inflammatory and cytoprotective activities observed in SIMD models (Fig. 6B).

Flavonoids. Flavonoids share a characteristic C6-C3-C6 three-ring scaffold. Critical structural features include a C2-C3 double bond, hydroxyl groups at C3, C5 and/or C7 and a catechol-type dihydroxy arrangement on the B-ring (positions 3',4') (217). This configuration maximizes electron delocalization and hydrogen-donating capacity, explaining their strong radical scavenging activity and their direct, Structure-activity relationship (SAR)-driven inhibition of central pro-inflammatory signaling hubs such as NF-κB and MAPK (218). Mechanistically, flavonoids thereby modulate the TLR4/NF-κB pathway, NLRP3 inflammasome activation and MAPK pathways to lower proinflammatory cytokines (IL-1β, TNF-α) and attenuate cardiomyocyte apoptosis (219).

Glycosides. Glycosides consist of aglycone cores (flavonoid, sesquiterpene or other scaffolds) linked to sugar moieties via O- or C-glycosidic bonds. Glycosylation is a key SAR-modifying factor: It markedly enhances aqueous solubility and pharmacokinetic properties, improving tissue distribution and bioavailability (220). Notable glycosides in SIMD include isoquercitrin, paeoniflorin and salidroside. The sugar units

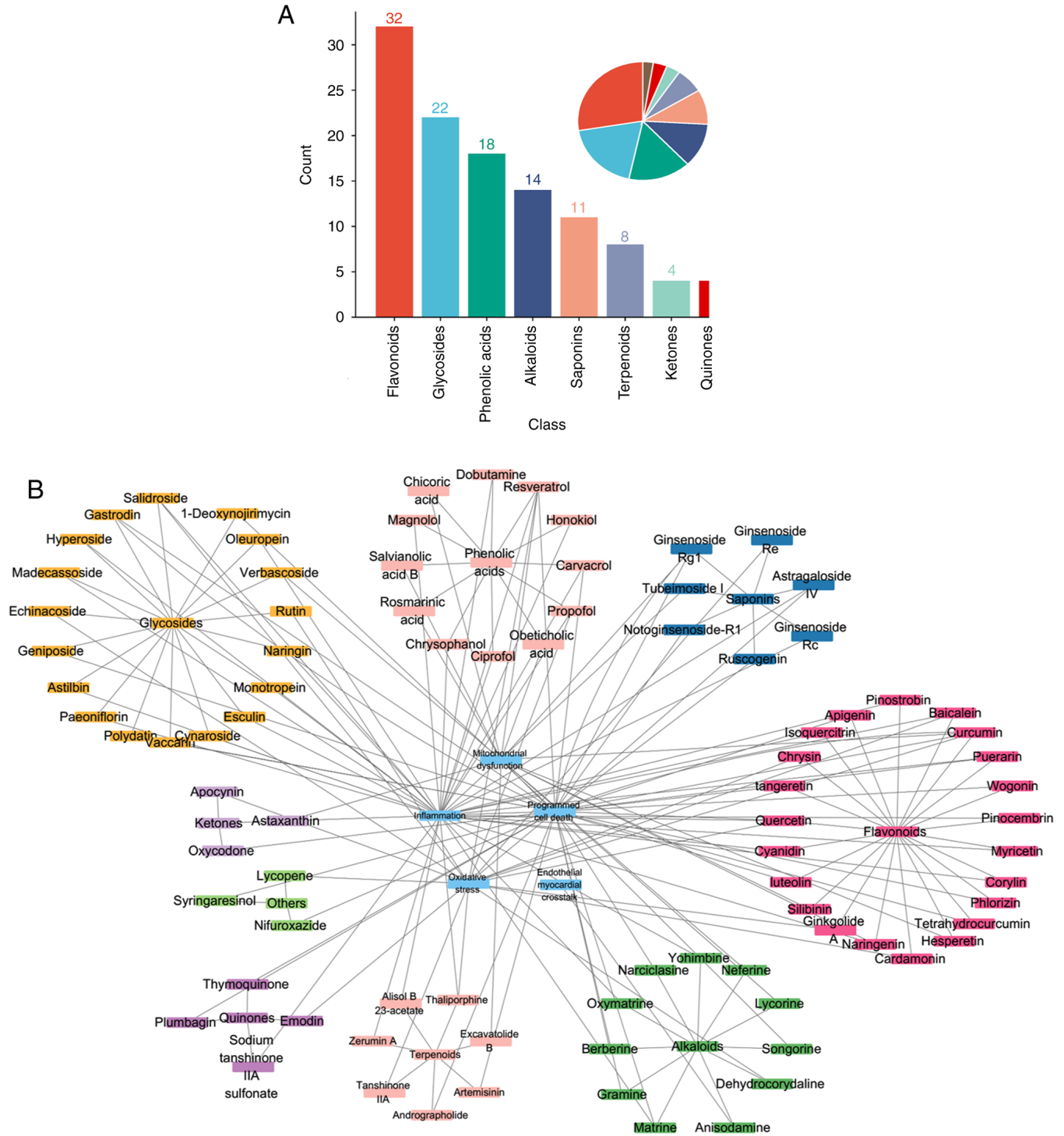

Figure 6. Classification and structure-activity analysis of natural products active against sepsis-induced myocardial dysfunction). (A) Active natural products are mainly divided into flavonoids, glycosides, phenolic acids, alkaloids and saponins, lignin and olefins. (B) Pharmacological activity analysis of natural products shows that functional groups are associated their antioxidant, anti-inflammatory and cell protective activities.

promote interactions with cell-surface receptors or transporters, facilitate macrophage M2 polarization and improve cardiomyocyte survival rate (220). Glycosides often retain and enhance the anti-inflammatory and anti-apoptotic properties of their parent aglycones, while also demonstrating distinct benefits such as stabilizing mitochondrial membrane potential (220).

Phenolic acids. Phenolic acids feature an aromatic ring substituted with ≥1 hydroxyl groups and a carboxyl group. The phenolic hydroxyls are primary sites for antioxidant activity via hydrogen atom transfer. The carboxyl group introduces an additional SAR dimension, allowing coordination with metal ions or formation of hydrogen bonds with target proteins (such as those involved in redox signaling), thereby stabilizing mitochondrial function and inhibiting NF-κB (221). In SIMD rats, phenolic acids efficiently scavenge ROS, preserve mitochondrial membrane potential, decrease intracellular Ca^{2+} overload and mitigate cardiomyocyte necrosis and apoptosis (128).

Alkaloids. Alkaloids contain ≥1 basic nitrogen atom within heterocyclic or polycyclic scaffolds. Examples relevant to SIMD include yohimbine and anisodamine. The basic nitrogen forms ionic interactions with acidic residues in receptors or enzymes, thereby modulating neurotransmitter release and inflammatory mediator levels (222). In sepsis, alkaloids often exhibit anti-inflammatory and anti-apoptotic effects by blocking α2-adrenergic receptors or inhibiting the NLRP3 inflammasome, helping to preserve cardiomyocyte function (199).

Saponins. Saponins are composed of triterpene or steroid aglycones linked to ≥1 sugar chains. This amphipathic structure defines their unique SAR: Aglycone enables interactions with and modulation of cell membrane properties and associated signaling pathways, while the sugar chains confer water solubility and influence pharmacokinetics (223). This structure allows saponins to modulate membrane fluidity and receptor clustering, leading to inhibition of caspase activation and decreased inflammatory mediator release, thereby mitigating apoptosis in cardiomyocytes (207).

Certain natural products display multi-target actions across SIMD-relevant pathways, combining anti-inflammatory and antioxidant effects with mitochondrial protection and anti-apoptotic signaling. Notable multi-target compounds include astragaloside IV, baicalein, carvacrol, curcumin, emodin, ginsenoside Re, matrine, propofol, quercetin and resveratrol (91,95,100,128,131). These agents exemplify the potential of pleiotropic natural products to regulate inflammation, oxidative stress, mitochondrial dysfunction and programmed cell death in SIMD (Table SI).

5. Notable therapeutic targets in SIMD

Key signaling pathways in SIMD. Natural products exert protective effects in SIMD by modulating multiple disease-associated pathways and molecular targets. Their primary actions are divided into four categories: Anti-inflammatory, antioxidant, anti-cell death and mitochondrial protection and repair (Fig. 7A). Notable signaling cascades include NF-κB, the MAPK family, the TLR4/MyD88 pathway, PI3K/Akt/mTOR, Nrf2/HO-1 and the NLRP3 inflammasome.

NF-κB serves as a key regulator of inflammation in SIMD (224). In cardiomyocytes and cardiac macrophages, LPS or endotoxin binding to TLR4/MyD88 activates the IKK complex, which phosphorylates and degrades IκBα. This frees NF-κB (p65/p50) to enter the nucleus and upregulate levels of IL-1β, IL-6, TNF-α and iNOS, thereby amplifying local inflammation and disturbing calcium homeostasis (225). As an upstream switch in early SIMD, TLR4 recruits TIR domain containing adaptor protein/MyD88 adaptors following LPS engagement, propagating both NF-κB and MAPK signaling and exacerbating myocardial injury (226,227).

The MAPK family, including p38, JNK, and ERK, also governs myocardial stress responses, inflammation and death in SIMD (228). p38 and JNK generally promote inflammation and apoptosis, while ERK supports survival or death depending on context (228). Overactivation of p38/JNK triggers c-Jun and ATF-2, leading to caspase-3-mediated apoptosis in SIMD (229). Nrf2/HO-1 provides the chief antioxidant defense. Under oxidative stress, Nrf2 dissociates from Keap1, translocates to the nucleus and binds antioxidant response elements to induce HO-1, NQO1 and other protective genes (230). Excess ROS in SIMD further damages membranes and amplifies NF-κB-driven inflammation (231).

PI3K/Akt/mTOR and SIRT1/AMPK form core networks that support cardiomyocyte survival and energy balance (232). PI3K activation leads to Akt phosphorylation and mTOR signaling, which promotes protein synthesis and restrains autophagy (233). SIRT1 deacetylates PGC-1α, p53 and NF-κB, coordinating mitochondrial biogenesis with anti-inflammatory effects (234). AMPK senses low ATP levels and works in concert with SIRT1 to maintain energy homeostasis (235). In SIMD, these pathways are typically downregulated, contributing to mitochondrial dysfunction and cell death (124).

Finally, the NLRP3 inflammasome and ferroptosis pathways drive inflammatory cell death in SIMD. NLRP3 assembly activates caspase-1, leading to IL-1β maturation and pyroptosis (236). Ferroptosis depends on iron-catalyzed lipid peroxidation, with key regulators including GPX4, acyl-CoA synthetase long chain family member 4 (ACSL4) and nuclear receptor coactivator 4) (237).

Rather than acting on a single target, natural products coordinate the aforementioned hubs to deliver combined anti-inflammatory, antioxidant, anti-death and mitochondrial-protective effects. Future studies should map the spatiotemporal dynamics and crosstalk between these pathways to guide the development of multitarget natural derivatives with improved precision and synergy.

Network pharmacology comparison of SIMD-associated targets. To evaluate how natural product targets align with known SIMD genes, 'sepsis', 'myocardial injury', and 'myocardial dysfunction' were in the Online Mendelian inheritance in Man and GeneCards databases (8,10). This search yielded over 350 unique disease-associated genes, with 41 common targets (Fig. 7B). High-frequency targets included iNOS (NOS2), NF-κB, MAPK family members (JNK, ERK1/2), PI3K/Akt/mTOR, NLRP3, SIRT1 and STAT3.

Notably, certain predicted targets, such as VEGF, cAMP, HSPs, Von Willebrand factor), MMP9 and PKC (Protein kinase C), lack thorough experimental validation in SIMD. Conversely, high-frequency targets such as NOX2, HO-1, GSK-3β, COX-2 and Nrf2 were not annotated as core SIMD targets in database queries. This discrepancy may reflect annotation lags, limited natural product-target interaction data and the inherent constraints of network pharmacology analyses. Integrating network pharmacology with systematic literature mining, multi-omics datasets and experimental validation is essential to build a comprehensive disease-drug-target network and inform the rational development of new SIMD therapies.

Docking of natural products to novel SIMD targets. To identify additional molecular targets for natural products in SIMD, molecular docking was performed for three proteins not yet validated *in vitro* or *in vivo*: cAMP-dependent protein kinase (cAMP), MMP9 and PKC). A total of five representative ligands (baicalein, quercetin, curcumin, matrine and resveratrol) were drawn in ChemDraw (14.0, revvitysignals.com/products/research/chemdraw), energy-minimized

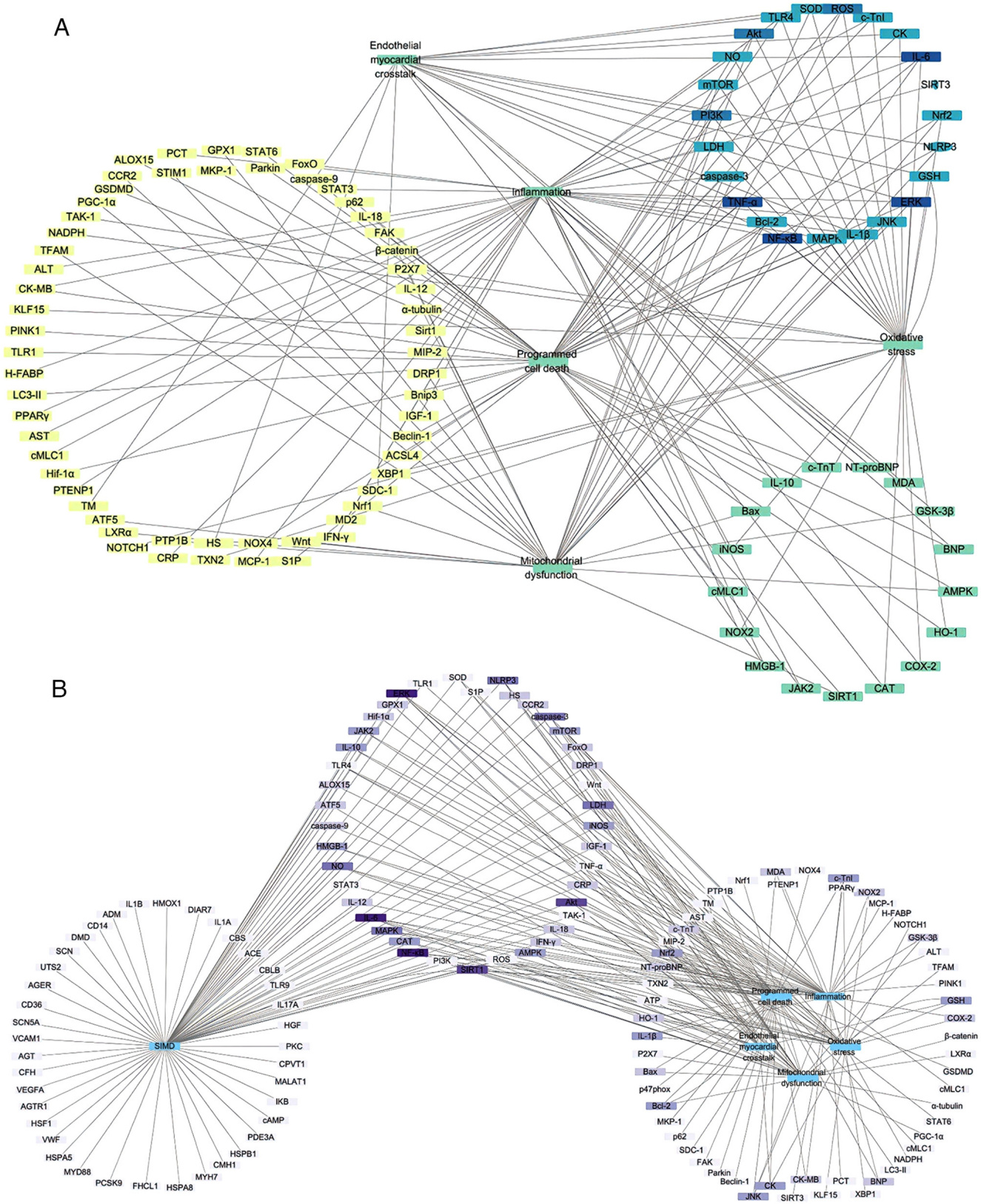

Figure 7. Notable therapeutic targets and network pharmacology analysis in SIMD. (A) Primary actions of natural products are categorized into anti-inflammatory, antioxidant, anti-cell death and mitochondrial protection. Major targeted signaling cascades include NF-κB, MAPK family, TLR4/MyD88, PI3K/Akt/mTOR, Nrf2/HO-1 and the NLRP3 inflammasome. (B) Network pharmacology comparison highlights high-frequency SIMD-associated targets, such as iNOS (NOS2), NF-κB, MAPK members (JNK, ERK1/2), PI3K/Akt/mTOR, NLRP3, SIRT1 and STAT3. SIMD, sepsis-induced myocardial dysfunction; TLR, Toll like receptor; HO, heme oxygenase; iNOS, inducible nitric oxide synthase ; SIRT, sirtuin 1.

using the Molecular mechanics 2 force field, and docked to each target with AutoDock Vina (1.1.2, github.com/ccsb-scripps/AutoDock-Vina). The lowest-energy poses exhibiting the most favorable orientations were selected for

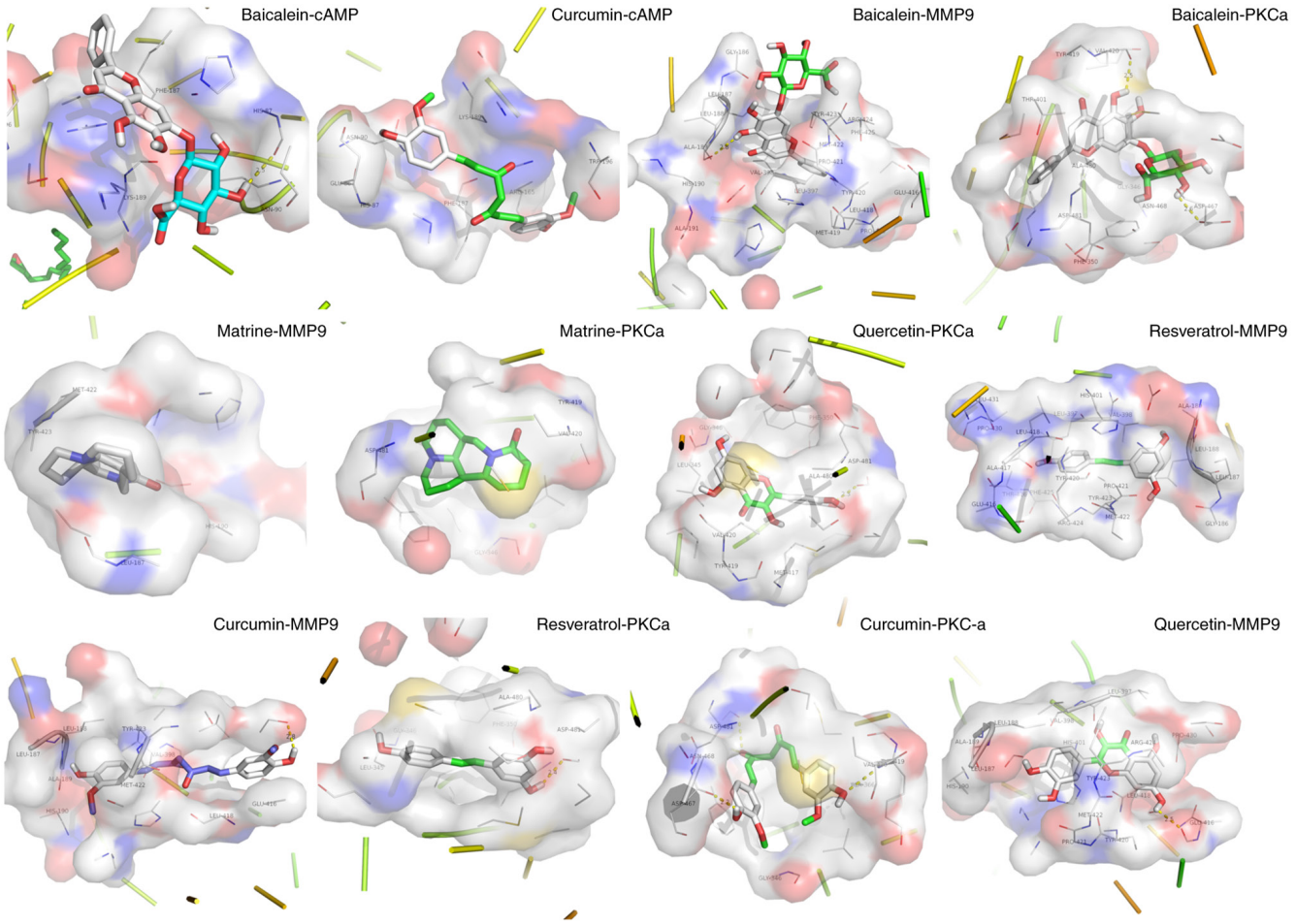

Figure 8. Docking of natural products to novel sepsis-induced myocardial dysfunction) targets. All five compounds bound tightly to both MMP9 and protein kinase C) (<-8.0 kcal/mol). Baicalein and curcumin also demonstrated appreciable affinity for cAMP (<-5.0 kcal/mol).

analysis (238). All five compounds bound tightly to both MMP9 and PKC, with calculated binding energies <-8.0 kcal/mol (Fig. 8). Baicalein and curcumin also demonstrated notable affinity for PKA, with binding energies <-5.0 kcal/mol, suggesting potential direct modulation of this kinase. Key interacting residues and hydrogen-bond contacts are detailed in Table SII. These findings indicate that multitarget natural products may exert cardioprotective effects not only through established anti-inflammatory and antioxidant pathways but also by directly engaging cAMP-dependent protein kinase, MMP9 and PKC. This *in silico* evidence lays the groundwork for experimental validation of these novel interactions.

6. Novel formulations for natural product therapeutics in SIMD

Although natural products offer multitarget synergy against SIMD, their clinical translation is hampered by poor solubility, low bioavailability and rapid clearance (239). Recent advances in formulation science, including nanotechnology, supramolecular chemistry and metal-organic coordination, provide new routes to improve delivery, targeting and efficacy (240).

Metal-organic nanozymes. Self-assembled nanozymes that incorporate metal-organic coordination combine drug delivery with enzyme-like catalysis (239,240). For example, ceria (CeO_2) or iron oxide (Fe_3O_4) nanoparticles mimic superoxide dismutase and catalase through reversible Ce^{3+}/Ce^{4+} or Fe^{2+}/Fe^{3+} redox cycling, efficiently scavenging O_2•- and H_2O_2 (241,242). By coordinating curcumin onto ceria, researchers have created ceria-curcumin hybrids (CeCHs) that exhibit dual SOD- and CAT-like activity *in vitro* (242). CeCHs neutralizes ROS, prevent glutathione peroxidase 4-induced ferroptosis in cardiomyocytes and shift macrophages toward an M2 phenotype (243). In LPS- and CLP-induced septic mice, CeCH decreases myocarditis and restores cardiac function (243). Similarly, Brazilin-Ce (IV) metal-organic nanoparticles inhibit IKKβ phosphorylation, suppress NF-κB signaling and deliver strong anti-inflammatory and cardioprotective effects in mice with myocardial infarction and sepsis (244).

Polymeric and lipid-based nanocarriers. Polymeric and lipid nanoparticles enhance the stability, circulation time and tissue distribution of natural products. Common polymers include poly(lactic-co-glycolic acid), PVA (Polyvinyl alcohol) and chitosan. Liposomal systems, solid lipid nanoparticles (SLNs) and mesoporous silica nanoparticles also serve as versatile carriers (245,246). In LPS-induced septic mice, curcumin-loaded SLNs decrease IL-6, TNF-α and IL-1β more effectively than free curcumin, while boosting IL-10 levels.

This improvement is associated with stronger suppression of the TLR2/TLR4/NF-κB pathway and decreased multi-organ injury (247). Nano-curcumin further enhances mTOR pathway regulation and offers superior protection against myocardial ultrastructural damage in SIMD mice compared with the unformulated compound (248).

Cyclodextrin (CD)-based inclusion complexes. CD hosts form non-covalent inclusion complexes with hydrophobic drugs, improving their solubility and stability (249,250). Hydroxypropyl-β-CD (HPβCD) and methyl-β-CD (MβCD) are used (249). In neonatal mice with LPS-induced sepsis, naringenin/HPβCD complexes more effective than naringin in decreasing inflammatory cell infiltration in the lung, heart, kidney and brain. They also lower TNF-α, IL-1β and IL-6, increase IL-10, catalase and SOD activity and decrease lipid peroxidation and protein carbonylation, leading to improved survival rate (251). Quercetin/β-CD complexes extend plasma half-life of quercetin and enhance myocardial accumulation in CLP-induced septic rats, strengthening TLR4/NF-κB inhibition and improving cardiac function (252). Chemical derivatization, such as converting steviol glycosides into isosteviol sodium salt, further boosts water solubility and, in LPS-induced septic mice, enhances survival rate, multi-organ function and reduces inflammation and macrophage infiltration (253).

However, systematic pharmacokinetics and pharmacodynamics analyses, long-term toxicity studies and validation in large-animal models remain outstanding needs. Standardization of manufacturing methods, drug-loading efficiency and *in vivo* kinetics is also required. Future efforts should integrate multi-omics, high-resolution imaging and large-animal models to optimize formulations, clarify dosing regimens, define safety margins and accelerate clinical translation of these advanced delivery systems.

7. Discussion

Sepsis ranks as the third leading cause of death worldwide, affecting nearly 20 million people each year. A total of 40-60% of these patients develop SIMD, and their 28-day mortality is ~3 times higher than that of patients without cardiac involvement (11). This underscores the urgent need for effective, low-toxicity treatments. Natural products modulate key signaling networks, including TLR4/MyD88/NF-κB, MAPKs (p38/JNK/ERK), the NLRP3 inflammasome, PI3K/Akt/mTOR, SIRT1/AMPK and Nrf2/HO-1, to restore mitochondrial membrane potential, maintain ATP production and decrease inflammation, oxidative stress and cell death (207,217,220-222).

Multi-center randomized controlled trials indicate that formulations such as Xuebijing injection can decrease 28-day mortality and lower cardiac injury biomarkers (cTnI, NT-proBNP) and inflammatory markers (PCT), indicating systemic and possible myocardial protective effects (254,255). Similarly, the JinHong Formula decreases mortality and improves organ function scores, potentially through inhibition of inflammatory pathways such as IL-17 and TNF (256). Other formulations, including Dachaihu Tang and Shenfu injection, improve organ dysfunction scores, microcirculation and inflammatory or coagulation parameters (257,258). The alkaloid anisodamine has decreases serum lactate and improves mortality in septic shock (259,260). However, challenges remain. Most trials did not specifically enroll patients with confirmed SIMD, limiting direct conclusions about cardiac-specific efficacy. Furthermore, notable heterogeneity exists in study designs, sample size and the compositions of natural product formulations. Additionally, pharmacokinetic challenges constrain the use of natural products. Poor water solubility, low oral bioavailability and rapid systemic clearance all decrease therapeutic impact. To overcome these issues, researchers are developing novel formulations, such as polymeric or lipid nanoparticles, metal-organic frameworks, CD inclusion complexes, supramolecular assemblies and chemical derivatives, to improve solubility, stability, half-life and tissue targeting (261). Well-designed clinical trials are essential to assess safety, pharmacokinetics, pharmacodynamics and real-world efficacy in patients with SIMD.

Furthermore, a deeper understanding of the pathogenic network of SIMD is also needed. Extracellular vesicles and their miRNA cargo mediate crosstalk between immune cells and cardiomyocytes, regulating inflammation and apoptosis (262). Specific miRNAs fine-tune gene networks that control survival, fibrosis and autophagy (263). Endothelial-myocardial interactions, governed by adhesion molecules, inflammatory mediators and the glycocalyx, critically influence microcirculatory perfusion and cardiac stress responses (63,264). Mitochondria-endoplasmic reticulum contacts sites serve as hubs for calcium homeostasis, lipid metabolism and cell fate decisions (265,266). Additionally, emerging evidence highlights the role of the gut-heart axis in SIMD (267). Sepsis-induced disruption of the intestinal barrier leads to microbial translocation, systemic dissemination of PAMPs and elevated levels of gut-derived metabolites (267). This fuels a persistent systemic inflammatory state and may contribute directly to remote organ injury, including myocardial dysfunction (267). Conversely, beneficial microbial metabolites, such as short-chain fatty acids, modulate host immune responses and exert anti-inflammatory effects. Interventions targeting the gut microbiota or its metabolites hold promise for attenuating systemic inflammation and improving cardiac outcomes in sepsis, presenting a novel therapeutic avenue for SIMD (268). Thus, future efforts should leverage single-cell sequencing, organoid models and multi-omics approaches to build a comprehensive molecular map of SIMD and natural product interventions. Such integrative studies may identify new precision targets and accelerate the development of optimized, multitarget natural therapies for clinical use.

In conclusion, the present study provides a systematic overview of the structure-activity-mechanism relationships between natural products and SIMD. The mechanisms involve inhibition of the TLR4/MyD88-NF-κB/MAPK pathway and the NLRP3 inflammasome and activation of antioxidant and anti-apoptotic pathways, including PI3K/Akt/mTOR, SIRT1/AMPK and Nrf2/HO-1. The present review also maps the association between natural product classes and pharmacological activities and validated potential compounds against new SIMD targets via network pharmacology and molecular docking. Collectively, the present study clarified how natural product structures are associated with SIMD pathology and

outlined a clear path from molecular design to clinical translation. The present study provides a systematic theoretical basis and practical avenues for multitarget natural product interventions in SIMD, with implications for drug discovery and clinical strategy advancement.

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Availability of data and materials

The data generated in the present study are included in the figures and/or tables of this article.

Authors' contributions

FT contributed to study design, performed the literature review and drafted the manuscript. DL, SCZ and HMZ performed the literature review. XWQ supervised the study. All authors contributed to manuscript revision. All authors have read and approved the final manuscript. FT and XWQ confirm the authenticity of all the raw data.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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