

Preclinical Efficacy and Mechanistic Insights of Polyphenols Targeting the NLRP3 Inflammasome in Cardiometabolic Diseases: A Systematic Review

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History

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ABSTRACT

Background: The nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome is a central mediator of cardiometabolic inflammation. Its activation promotes the maturation and release of interleukin-1 β (IL-1 β) and interleukin-18 (IL-18), accelerating vascular endothelial dysfunction, metabolic dysregulation, and tissue injury. Although polyphenols have shown promising therapeutic potential as natural modulators of this pathway, preclinical evidence remains fragmented across diverse experimental models. This systematic review synthesized in vitro and in vivo preclinical evidence regarding the efficacy and molecular mechanisms of polyphenols targeting NLRP3 inflammasome activation in cardiometabolic diseases. **Methods:** This review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement and was prospectively registered in PROSPERO Animal (CRD420251232088). A comprehensive literature search was executed across PubMed, ScienceDirect, BioMed Central (BMC), and Google Scholar for studies published between 2020 and 2025. Original in vitro and in vivo preclinical studies evaluating polyphenol interventions on NLRP3 inflammasome-related outcomes in cardiometabolic disease models were included. Methodological risk of bias was assessed using the Systematic Review Centre for Laboratory Animal Experimentation (SYRCLE) tool for in vivo animal studies and the Quality Assessment Tool for In Vitro Studies (QUIN) for cell-based studies. **Results:** Six studies met the inclusion criteria. Polyphenolic compounds and formulations—including quercetin, salivianolic acid A, curcumin, 6-shogaol, Qiqilian capsule, and Qian Yang Yu Yin Granule—consistently attenuated NLRP3 inflammasome activation. These interventions suppressed the expression and assembly of NLRP3, apoptosis-associated speck-like protein containing a CARD (ASC), and cleaved caspase-1, thereby decreasing IL-1 β and IL-18 secretion. Mechanistically, polyphenols conferred cardioprotective and vasculoprotective benefits through the suppression of oxidative stress and mitochondrial reactive oxygen species (ROS), downregulation of Akt/nuclear factor-kappa B (NF- κ B) priming signaling, restoration of autophagic flux, and upregulation of nuclear factor erythroid 2-related factor 2 (Nrf2)-mediated antioxidant pathways. **Conclusion:** Preclinical evidence demonstrates that polyphenols act as multitarget modulators of the NLRP3 inflammasome pathway, offering promising therapeutic strategies for cardiometabolic disorders. However, substantial methodological heterogeneity across preclinical models and a lack of pharmacokinetic and clinical data highlight the need for standardized study designs and early-phase clinical trials to facilitate translational application. **Key words:** Polyphenols, NLRP3 inflammasome, cardiometabolic diseases, oxidative stress, inflammation, pyroptosis, cardiovascular disease

INTRODUCTION

Cardiometabolic diseases represent a major global health burden driven by chronic low-grade inflammation that disrupts cardiovascular and metabolic homeostasis¹. Metabolic stress and inflammatory signaling pathways are intricately interconnected, positioning systemic inflammation at the core of disease pathogenesis and progression². The nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome functions as a pivotal molecular sen-

sor linking metabolic perturbation to innate immune activation³. Pathological stressors, including nutrient excess, lipotoxicity, mitochondrial dysfunction, elevated oxidative stress, and gut dysbiosis, trigger NLRP3 inflammasome assembly³. Upon activation, NLRP3 recruits the adaptor protein apoptosis-associated speck-like protein containing a CARD (ASC) and pro-caspase-1, facilitating caspase-1 maturation and the subsequent cleavage and secretion of interleukin-1 β (IL-1 β) and interleukin-18 (IL-18)^{4,5}. These proinflammatory

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cytokines exacerbate vascular endothelial dysfunction, accelerate atherosclerotic plaque progression, promote adverse cardiac remodeling, and disrupt glycemic and lipid homeostasis^{4,5}. Although the NLRP3 inflammasome represents a compelling therapeutic target, the clinical development and translation of synthetic small-molecule NLRP3 inhibitors have been hindered by off-target toxicities, adverse pharmacokinetics, and poor oral bioavailability⁶⁻⁸. Consequently, polyphenols—a diverse class of secondary plant metabolites abundant in dietary sources—have gained significant attention as potential natural modulators of inflammasome-driven inflammation⁹. Preclinical investigations have indicated that polyphenolic agents, such as quercetin, curcumin, epigallocatechin-3-gallate (EGCG), salvianolic acids, 6-shogaol, and chlorogenic acid, mitigate NLRP3 inflammasome activation by suppressing nuclear factor-kappa B (NF-κB) transcriptional priming, quenching reactive oxygen species (ROS), and preserving mitochondrial integrity¹⁰. Nevertheless, current preclinical findings remain heterogeneous regarding experimental designs, disease models, dosing regimens, and evaluated signaling cascades. Therefore, this systematic review synthesizes recent *in vitro* and *in vivo* preclinical evidence evaluating the efficacy and molecular mechanisms of polyphenols targeting the NLRP3 inflammasome in cardiometabolic disease models to clarify their therapeutic relevance and identify critical knowledge gaps.

MATERIALS AND METHODS

Research Design

This systematic review synthesized preclinical evidence regarding the regulatory effects and underlying mechanisms of polyphenols on NLRP3 inflammasome activation in cardiometabolic disease models. The protocol was prospectively registered in the PROSPERO Animal register (CRD420251232088) and conducted in strict accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement. The primary research question was formulated using an adapted Population, Intervention, Comparison, Outcome (PICO) framework for preclinical research (Table 1).

Search Methods

A comprehensive literature search was conducted to identify mechanistic preclinical studies investigating polyphenol interventions targeting

NLRP3 inflammasome signaling in models of cardiometabolic disease. Electronic databases including PubMed, BioMed Central (BMC), ScienceDirect, and Google Scholar were systematically searched. The search strategy was tailored to capture contemporary mechanistic studies evaluating inflammasome-related molecular cascades in both *in vitro* cell culture systems and *in vivo* animal models.

The search was restricted to peer-reviewed articles published between January 1, 2020, and December 31, 2025, to capture the latest advances following the rapid expansion of NLRP3 inflammasome research in cardiometabolic pathophysiology. Studies published within this timeframe offer detailed molecular characterizations of inflammasome-associated signaling, including mitochondrial oxidative stress, pyroptosis, autophagy, and the NF-κB/Nrf2 axes, compared with earlier exploratory reports. Limiting the search window also ensured greater methodological consistency across experimental models, molecular assays, and phenotypic outcome assessments.

Medical Subject Headings (MeSH) and free-text keywords were combined using Boolean logic operators (AND, OR). Search terms encompassed polyphenols, flavonoids, NLRP3 inflammasome, caspase-1, ASC, interleukins, pyroptosis, oxidative stress, cardiometabolic disease, atherosclerosis, diabetes, obesity, metabolic syndrome, and preclinical experimental models. The representative search string was formulated as follows:

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("polyphenol" OR "polyphenols"
OR "flavonoid" OR "flavonoids")
AND ("NLRP3 inflammasome" OR
"NLRP3" OR "caspase-1" OR "ASC"
OR "interleukin-1 beta" OR "IL-1β"
OR "interleukin-18" OR "IL-18" OR
"pyroptosis" OR "oxidative stress")
AND ("cardiometabolic disease" OR
"atherosclerosis" OR "diabetes" OR
"obesity" OR "metabolic syndrome" OR
"vascular inflammation") AND ("in vitro"
OR "cell line" OR "in vivo" OR "animal
model")
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Inclusion and Exclusion Criteria

Study selection followed the PRISMA 2020 guidelines. Original *in vitro* and *in vivo* preclinical studies published between 2020 and 2025 were eligible if they evaluated polyphenol interventions—including

Table 1: Description of the adapted Population, Intervention, Comparison, and Outcome (PICO) framework for preclinical study eligibility.

Component	Study Description
Population	<i>In vitro</i> cell models (macrophages, endothelial cells, VSMCs, adipocytes, cardiomyocytes) and <i>in vivo</i> rodent models of cardiometabolic diseases (atherosclerosis, T2DM, obesity, hypertension-induced VED, cardiac remodeling, diabetic encephalopathy).
Intervention	Polyphenol-based interventions (quercetin, salvianolic acid A, curcumin, 6-shogaol), polyphenol-rich extracts, and polyphenol-standardized herbal formulations (Qiqilian capsule, QYYYG).
Comparison	Untreated controls, vehicle controls, sham controls, or pharmacological positive controls (atorvastatin, valsartan, MCC950, NAC).
Outcome	Primary: NLRP3 expression/activation, ASC, caspase-1, mature IL-1 β , IL-18. Secondary: ROS, MDA, SOD, pyroptosis, autophagic flux (LC3, p62), functional endpoints (endothelial dysfunction, plaque area, hypertrophy, fibrosis).

purified polyphenolic compounds, polyphenol-rich extracts, or polyphenol-standardized herbal formulations—in established models of cardiometabolic diseases (e.g., atherosclerosis, type 2 diabetes mellitus, obesity, hypertension-induced vascular dysfunction, hypertensive cardiac remodeling, and diabetic encephalopathy). Included studies were required to report mechanistic outcomes directly associated with NLRP3 inflammasome signaling, such as expression or activity levels of NLRP3, ASC, caspase-1, IL-1 β , IL-18, oxidative stress markers, or pyroptosis-related indicators. Only peer-reviewed, full-text original articles published in English were considered. Exclusion criteria comprised: (1) clinical trials or human observational studies; (2) review articles, meta-analyses, editorials, letters, and conference abstracts; (3) studies lacking mechanistic evaluation of the NLRP3 inflammasome axis; and (4) studies with primary outcomes unrelated to cardiometabolic inflammatory mechanisms. Following screening, six studies satisfied all criteria and were included in the qualitative synthesis.

Study Screening

Two reviewers independently screened all retrieved records through duplicate identification, title and abstract evaluation, and full-text eligibility assessment based on the predefined eligibility criteria. Any discrepancies or disagreements between the reviewers were resolved through discussion and consensus.

Data Extraction

Data extraction was performed independently by two reviewers using a standardized extraction form to minimize transcription errors and ensure consistency. Extracted parameters included: publication

details (first author, publication year), experimental models (animal species, strains, cell lines, disease induction protocols), polyphenol interventions (compound/extract name, dosage, route of administration, treatment duration, vehicle controls), comparator groups, targeted molecular pathways, and specific NLRP3 inflammasome-related biomarkers (NLRP3, ASC, pro- and cleaved caspase-1, IL-1 β , IL-18). Additional mechanistic endpoints—including oxidative stress markers (ROS, malondialdehyde [MDA], superoxide dismutase [SOD]), pyroptosis markers, autophagic indicators (LC3, p62, Beclin-1), and systemic metabolic/vascular parameters—were extracted when available. Discrepancies were resolved through mutual agreement.

Quality Appraisal

Methodological quality and risk of bias for *in vivo* animal studies were assessed using the Systematic Review Centre for Laboratory Animal Experimentation (SYRCLE) Risk of Bias tool, which covers 10 domains: sequence generation, baseline characteristics, allocation concealment, random housing, blinding of caregivers/investigators, random outcome assessment, blinding of outcome assessors, incomplete outcome data, selective outcome reporting, and other potential sources of bias¹¹. Methodological quality and transparency of *in vitro* cell culture studies were appraised using the Quality Assessment Tool for In Vitro Studies (QUIN) across 12 criteria^{12,13}.

Data Analysis

Due to substantial heterogeneity in experimental animal models, cell types, disease induction methods, compound formulations, dosing regimens, and analytical assays, quantitative meta-analysis was

not feasible¹⁴. A qualitative narrative synthesis was conducted. Findings were systematically categorized by experimental setting (in vivo vs. in vitro), disease models, specific polyphenol interventions, and molecular pathways involved.

RESULTS

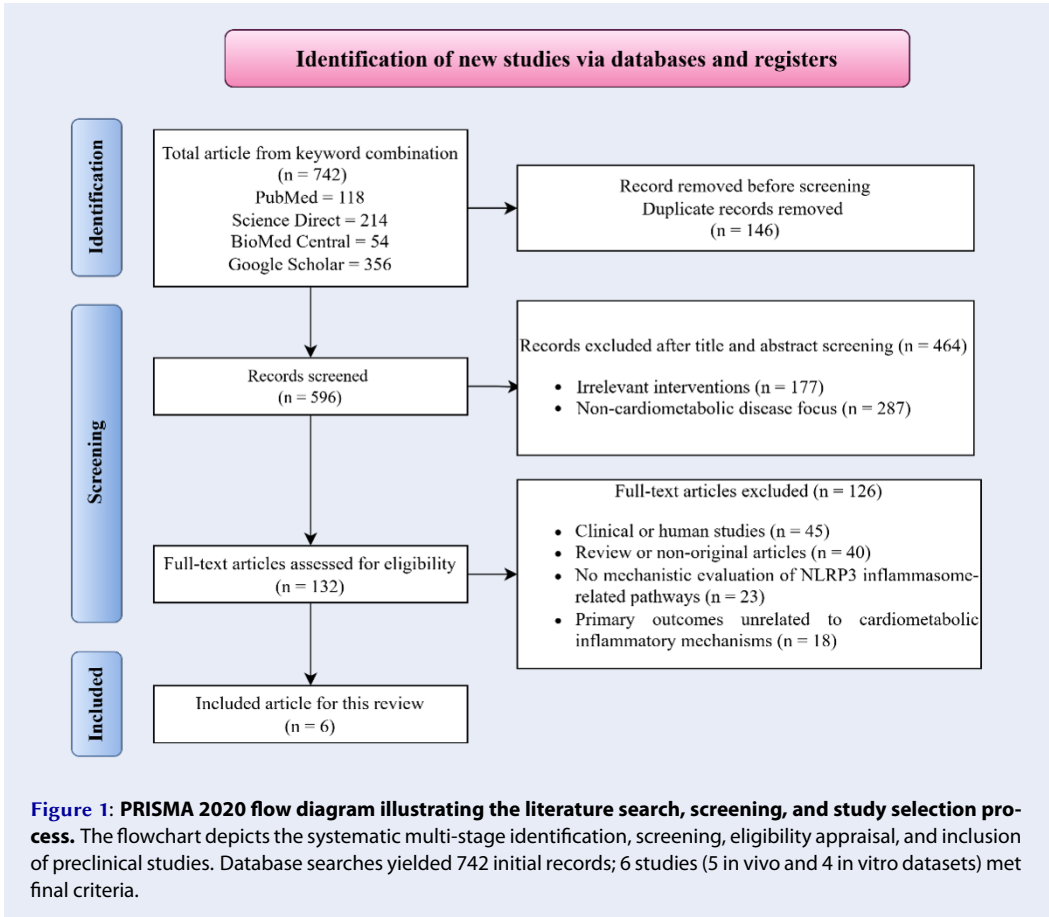
Study Selection

A total of 742 records were identified through database searches across PubMed (n = 118), ScienceDirect (n = 214), BioMed Central (n = 54), and Google Scholar (n = 356). Following the removal of 146 duplicate records, 596 titles and abstracts were screened. Of these, 464 records were excluded because they investigated irrelevant interventions (n = 177) or focused on non-cardiometabolic disease conditions (n = 287). The remaining 132 full-text articles were evaluated against the eligibility criteria, resulting in the exclusion of 126 studies due to: clinical/human study design (n = 45), review or non-original publication type (n = 40), absence of mechanistic evaluation of the NLRP3 inflammasome path-

way (n = 23), or primary endpoints unrelated to cardiometabolic inflammatory mechanisms (n = 18). Ultimately, six preclinical studies met all inclusion criteria and were included in the final qualitative synthesis (Figure 1).

Characteristics of Included Studies

The six included studies published between 2020 and 2025 evaluated the modulatory effects of polyphenols on NLRP3 inflammasome activation across diverse preclinical models of cardiometabolic disease. The majority of studies were conducted in Asia, with additional research originating from Europe. Experimental systems comprised rodent in vivo models—including db/db mice, ApoE^{-/-} mice, spontaneously hypertensive rats (SHRs), and Zucker diabetic fatty (ZDF) rats—and primary or established cell lines, such as human umbilical vein endothelial cells (HUVECs), human aortic endothelial cells (HAECs), human artery smooth muscle cells (HASMCs), and H9c2 rat cardiomyoblasts. Evaluated interventions encompassed isolated polyphenols (quercetin, salicylic acid A, curcumin, 6-shogaol) as well as



polyphenol-standardized traditional herbal formulations (Qiqilian capsule and Qian Yang Yu Yin Granule [QYYYG]). All studies examined core inflammasome components (NLRP3, ASC, caspase-1, IL-1 β , IL-18) along with upstream regulatory cascades, including NF- κ B priming, mitochondrial ROS generation, Akt signaling, autophagic degradation, and Nrf2 antioxidant defense^{10,15–17}. Study characteristics and key findings are summarized in Table 2 (in vivo studies) and Table 3 (in vitro studies).

Risk of Bias Assessment

Risk of bias assessment for the five in vivo animal studies using the SYRCLE tool revealed an overall unclear risk of bias, with no studies exhibiting a high risk of bias in any domain (Figure 2)¹¹. Sequence generation (Domain 1) was rated as low risk in all five studies (100%). Baseline characteristics (Domain 2) were judged as low risk in two studies (Luo et al.¹⁹ and Ma et al.²⁰) and unclear in the remaining

three studies due to incomplete reporting. Allocation concealment (Domain 3), random housing (Domain 4), caregiver/investigator blinding (Domain 5), random outcome assessment (Domain 6), and outcome assessor blinding (Domain 7) were rated as unclear across all studies owing to insufficient methodological details in the published reports. Completeness of outcome data (Domain 8) and selective outcome reporting (Domain 9) were rated as low risk across all included studies. Other potential sources of bias (Domain 10) were assessed as low risk in two studies^{19,20} and unclear in three^{18,21,22}. Quality appraisal of the four in vitro studies using the QUIN tool demonstrated an overall low risk of bias profile (Figure 3)^{12,23}. All four studies scored low risk for clearly stated aims/objectives (D1), sample size calculation details (D2), sampling technique explanation (D3), comparison group description (D4), methodological detail (D5), randomization (D7), outcome measurement methods (D8), statistical analysis (D11), and presentation of results

Table 2: Characteristics and mechanistic findings of included in vivo animal studies.

Study	Therapy	Animal Model	Dosage / Route	Induction	Targeted Pathways & Outcomes
Hu (2020) ¹⁸	Quercetin	db/db mice	35-70 mg/kg p.o.	Diabetic encephalopathy	Upregulated SIRT1; suppressed NLRP3; improved synapse/cognition.
Luo (2023) ¹⁹	Qiqilian (QQL)	SHRs	0.3-1.2 g/kg p.o.	Hypertension-VED	Inhibited NLRP3-ASC; reduced ROS; restored autophagic flux.
Ma (2020) ²⁰	SAA	ZDF rats	0.5-1 mg/kg i.v.	T2DM / Atherosclerosis	Inhibited NF- κ B/NLRP3; reduced lipids & systemic inflammation.
Ruan (2024) ²¹	Curcumin	ApoE ^{-/-} mice	100 mg/kg p.o.	Atherosclerosis	Suppressed NLRP3-ASC; reduced MDA/SOD; restored NO.
Xu (2025) ²²	QYYYG	SHRs	0.7-1.4 g/kg p.o.	Hypertensive remodeling	Activated Nrf2; inhibited ROS/NF- κ B; reduced fibrosis/pyroptosis.

Table 3: Characteristics and molecular targets of included in vitro studies.

Study	Compound	Cell Line	Model / Stimulus	Key Mechanistic Observations
Chen (2020) ¹⁶	6-Shogaol	HASMCs	Hyperglycemia	Suppressed Akt/ROS/NLRP3; prevented vascular calcification.
Luo (2023) ¹⁹	QQL Serum	HUVECs	Ang II	Inhibited NLRP3-ASC; p62-dependent NLRP3 degradation.
Ruan (2024) ²¹	Curcumin	HAECs	ox-LDL	Downregulated NLRP3/ASC; scavenged intracellular ROS.
Xu (2025) ²²	QYYYG Extract	H9c2	Isoproterenol	Nrf2 translocation; inhibited ROS/NLRP3-mediated pyroptosis.

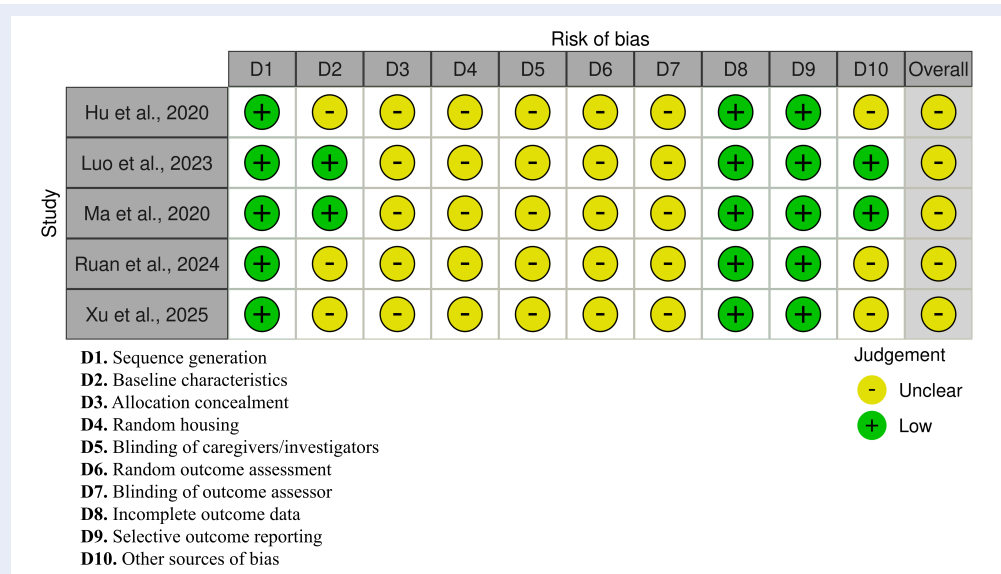


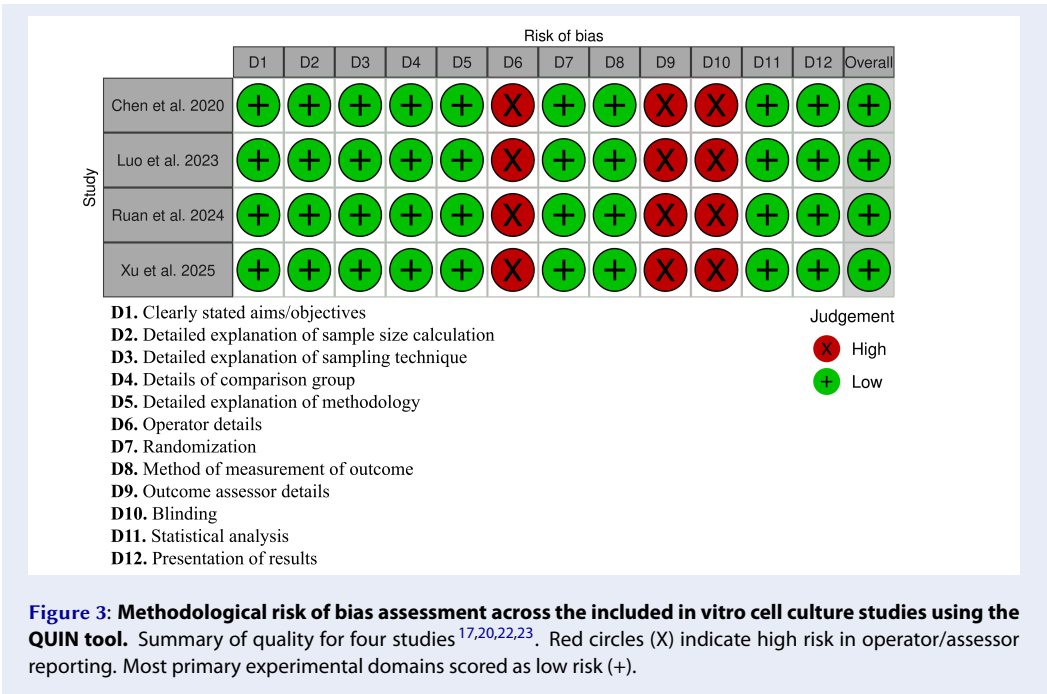
Figure 2: Methodological risk of bias assessment across the included in vivo animal studies using the SYR-CLE tool. Matrix displaying risk judgments for five studies^{19–23}. Green circles (+) indicate low risk; yellow (–) indicates unclear risk due to reporting gaps. No study showed high risk.

(D12). Conversely, operator details (D6), outcome assessor details (D9), and blinding (D10) were consistently assessed as high risk across all studies because of omission of reporting for these parameters. Despite these specific reporting gaps, the in vitro studies demonstrated robust methodological execution and data reporting.

Modulation of NLRP3 Inflammasome and Upstream Signaling Pathways by Polyphenols

Across both in vivo and in vitro models, polyphenol interventions consistently suppressed NLRP3 inflammasome assembly and downstream inflammatory cascades. In ApoE^{-/-} atherosclerotic mice, curcumin and salvianolic acid A (SAA) significantly downregulated protein expression of NLRP3, ASC, and cleaved caspase-1, leading to reduced maturation and release of IL-1β and IL-18 under proatherogenic stimuli such as oxidized low-density lipoprotein (ox-LDL) and vitamin D3^{20,21}. In db/db diabetic mice, quercetin upregulated SIRT1 expression and suppressed NLRP3 inflammasome components, attenuating neuroinflammation, synaptic dysfunction, and systemic insulin resistance¹⁸. In ZDF rats, SAA suppressed NLRP3 inflammasome activation via inhibition of NF-κB signaling, reducing circulating high-sensitivity C-reactive protein (hs-CRP), IL-1β, and IL-18 levels²⁰.

In vitro investigations substantiated these molecular mechanisms. In hyperglycemic HASMCs, 6-shogaol inhibited Akt phosphorylation, suppressed intracellular ROS generation, and downregulated NLRP3, ASC, and caspase-1 activation, thereby preventing osteogenic transdifferentiation and vascular calcification¹⁶. In HUVECs exposed to angiotensin II (Ang II), Qiqilian-mediated serum suppressed NLRP3-ASC assembly, reduced ROS accumulation, and restored autophagic flux via p62-mediated NLRP3 clearance¹⁹. In HAECs, curcumin attenuated ox-LDL-induced endothelial injury and pyroptosis by suppressing ROS production and blocking NLRP3 inflammasome activation²¹. Similarly, in H9c2 cardiomyoblasts challenged with isoproterenol (ISO), QYYYG activated the Nrf2 antioxidant axis and inhibited the ROS/NF-κB/NLRP3 signaling cascade, preventing oxidative injury and cardiomyocyte pyroptosis²². Upstream mechanistic targets across these studies included: (1) attenuation of intracellular and mitochondrial ROS generation^{16,19–22}; (2) suppression of Akt and NF-κB signaling pathways responsible for transcriptional priming of NLRP3 and pro-IL-1β^{16,20,22}; (3) enhancement of autophagic flux facilitating lysosomal degradation of inflammasome components^{19,21}; and (4) upregulation of Nrf2-mediated antioxidant defenses^{21,22}.



Effects on Cardiometabolic Outcomes

Suppression of the NLRP3 inflammasome by polyphenols translated into broad improvements in structural, functional, and biochemical cardiometabolic endpoints. In models of atherosclerosis, curcumin and SAA markedly reduced aortic plaque area, lipid deposition, and macrophage infiltration in ApoE^{-/-} and ZDF rodents, accompanied by significant reductions in serum hs-CRP, tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6), and total cholesterol^{20,21}. In hypertension-induced vascular and cardiac injury models, Qiqilian capsule improved endothelium-dependent vasodilation, preserved vascular structural integrity, and corrected pathological autophagy in SHR¹⁹, whereas QYYG attenuated left ventricular hypertrophy, reduced interstitial fibrosis, and suppressed cardiac expressions of collagen I, collagen III, and α -smooth muscle actin (α -SMA)²². At the cellular level, polyphenol treatments protected vascular endothelial cells from ox-LDL- and Ang II-induced pyroptotic cell death^{19,21}, suppressed osteogenic differentiation markers (osteopontin [OPN], osteocalcin [OCN], and alkaline phosphatase [ALP]) in vascular smooth muscle cells¹⁶, and preserved cardiomyocyte viability under hypertrophic stress²².

Summary of Evidence Patterns

In summary, preclinical evidence consistently demonstrates that polyphenols exert potent inhibitory effects against NLRP3 inflammasome signaling in cardiometabolic disease models. The primary molecular mechanisms involve a multi-pronged mode of action: suppressing transcriptional priming via NF- κ B/Akt inhibition, reducing trigger signals by scavenging mitochondrial ROS and activating Nrf2, and facilitating clearance of inflammasome components through autophagy restoration. These molecular actions collectively reduce caspase-1 activation and mature IL-1 β /IL-18 release, leading to significant protection against atherogenesis, endothelial dysfunction, hypertensive cardiac remodeling, and diabetic complications.

DISCUSSION

The NLRP3 inflammasome has emerged as a central orchestrator of cardiovascular and cardiometabolic diseases, serving as a critical molecular bridge between metabolic stress, oxidative damage, and innate immune activation^{4,5,24,25}. In response to pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs), canonical NLRP3 activation proceeds through a two-step process: (1) a priming step mediated by pattern recognition receptors (such as TLR2/4/6, IL-1R, and RAGE) that activates NF- κ B, driving the

transcriptional upregulation of NLRP3, pro-IL-1 β , and pro-IL-18; and (2) an activation step triggered by stimuli such as cholesterol crystals, oxidized LDL, advanced glycation end-products (AGEs), extracellular ATP (via P2X7R), and calcium influx, which promotes mitochondrial ROS production, NEK7 recruitment, and NLRP3 oligomerization with ASC and pro-caspase-1^{26–33}. The resulting catalytic cleavage of pro-caspase-1 into active caspase-1 facilitates the proteolytic maturation and release of IL-1 β and IL-18, while cleaving gasdermin D (GSDMD) to execute pyroptotic cell death^{4,5,24,25}. Extensive evidence from LDLR^{-/-} and ApoE^{-/-} rodent models demonstrates that genetic deletion or pharmacological inhibition of NLRP3 pathway constituents substantially diminishes atherosclerotic plaque burden, vascular inflammation, and adverse cardiac remodeling^{27,32,33}.

Polyphenolic compounds—including resveratrol, curcumin, quercetin, epigallocatechin-3-gallate (EGCG), salvianolic acid A, and 6-shogaol—exert cardioprotective and vasculoprotective effects by acting as multitarget modulators of the NLRP3 inflammasome network^{34–38}. For instance, resveratrol attenuates doxorubicin-induced cardiotoxicity and post-infarction myocardial remodeling through the inhibition of NLRP3 inflammasome assembly and downregulation of the TGF- β 1/SMAD2 pathway^{36,37}. Curcumin and quercetin reduce NF- κ B activation, lower systemic hs-CRP, and inhibit NLRP3-dependent cytokine maturation in diabetic

and pulmonary hypertensive vascular models^{38,39}, while EGCG prevents high glucose-induced inflammasome activation and improves glucose tolerance⁴⁰.

The synthesized findings in this review highlight that polyphenols operate predominantly upstream of the inflammasome complex rather than acting as narrow, single-target direct inhibitors (Figure 4)^{41,42}. Specifically, polyphenols: (1) attenuate transcriptional priming by inhibiting Akt, MAPK, and NF- κ B signaling; (2) diminish trigger-induced assembly by mitigating mitochondrial dysfunction, scavenging ROS, and activating the Keap1/Nrf2 antioxidant response pathway; and (3) enhance autophagic degradation of NLRP3 and ASC aggregates via p62/sequestosome-1 pathways^{16,19–22,39,40}. This multi-tiered regulatory mechanism attenuates vascular inflammation, prevents endothelial pyroptosis, suppresses vascular smooth muscle calcification, and mitigates myocardial fibrosis and hypertrophy^{41,42}.

Despite these promising preclinical findings, several translational limitations must be acknowledged. First, the included in vivo and in vitro studies exhibited notable methodological heterogeneity regarding disease models, compound dosing, and experimental duration. Second, risk of bias assessments revealed incomplete reporting of key methodological domains in animal studies, such as allocation concealment, random housing, and investigator blinding. Third, polyphenols generally display low

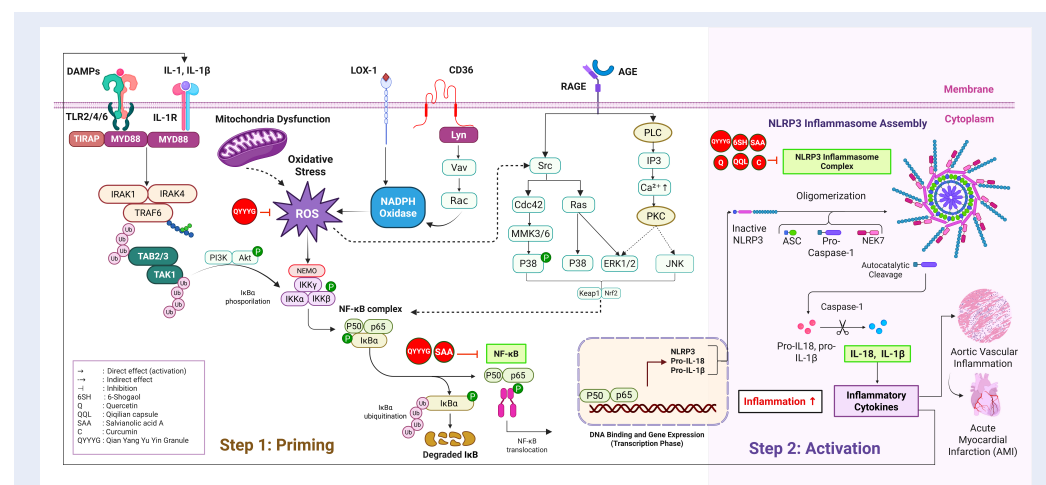


Figure 4: Schematic illustration of the molecular mechanisms and inhibitory targets of polyphenolic compounds within the NLRP3 inflammasome signaling pathway. The diagram illustrates the two-step activation mechanism and polyphenol targets. Step 1 (Priming): SAA and QYYYG inhibit NF- κ B activation; QYYYG, 6-shogaol, and SAA quench ROS; QQL and curcumin suppress assembly. Polyphenols also stimulate Nrf2 and enhance autophagy.

systemic bioavailability, rapid phase II metabolism, and poor water solubility *in vivo*, which limits the direct translation of nominal *in vitro* concentrations to clinical settings. Future research should prioritize standardized preclinical study designs, novel delivery systems (e.g., nanoparticle encapsulation, liposomal formulations) to improve polyphenol bioavailability, and well-designed early-phase clinical trials to evaluate therapeutic efficacy and safety in human cardiometabolic diseases.

CONCLUSION

Current preclinical evidence indicates that polyphenols act as effective multitarget modulators of the NLRP3 inflammasome signaling cascade in cardiometabolic diseases. By mitigating oxidative stress, inhibiting Akt/NF- κ B priming pathways, restoring autophagic flux, and activating Nrf2-mediated antioxidant responses, polyphenols attenuate caspase-1 activation and IL-1 β /IL-18 maturation, thereby reducing atherosclerosis, endothelial dysfunction, vascular calcification, and cardiac remodeling. However, clinical translation remains constrained by methodological variability, uncharacterized pharmacokinetics, and a lack of robust human trials. Future efforts should focus on standardized preclinical methodologies, advanced bioavailability-enhancing delivery platforms, and rigorously designed clinical trials to determine the clinical utility of polyphenol-based therapeutics in cardiometabolic medicine.

ABBREVIATIONS

6-SH (6-Shogaol), AGE (Advanced glycation end-product), Akt (Protein kinase B), ALP (Alkaline phosphatase), Ang II (Angiotensin II), ApoE (Apolipoprotein E), ASC (Apoptosis-associated speck-like protein containing a CARD), BMC (BioMed Central), CD36 (Cluster of differentiation 36), DAMPs (Danger-associated molecular patterns), EGCG (Epigallocatechin-3-gallate), GSDMD (Gasdermin D), HAEC (Human aortic endothelial cell), HASMC (Human artery smooth muscle cell), HFD (High-fat diet), hs-CRP (High-sensitivity C-reactive protein), HUVEC (Human umbilical vein endothelial cell), IL-1 β (Interleukin-1 beta), IL-6 (Interleukin-6), IL-10 (Interleukin-10), IL-18 (Interleukin-18), ISO (Isoproterenol), LDH (Lactate dehydrogenase), LDLR (Low-density lipoprotein receptor), MAPK (Mitogen-activated protein kinase), MCP-1 (Monocyte chemoattractant protein-1), MDA (Malondialdehyde), NF- κ B (Nuclear factor-kappa B), NLRP3 (Nucleotide-binding

oligomerization domain-like receptor family pyrin domain-containing 3), Nrf2 (Nuclear factor erythroid 2-related factor 2), OCN (Osteocalcin), OPN (Osteopontin), ox-LDL (Oxidized low-density lipoprotein), PICO (Population, Intervention, Comparison, Outcome), PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses), PROSPERO (International Prospective Register of Systematic Reviews), QQL (Qiqilian capsule), QUIN (Quality Assessment Tool for *In Vitro* Studies), QYYYG (Qian Yang Yu Yin Granule), ROS (Reactive oxygen species), SAA (Salvianolic acid A), SHR (Spontaneously hypertensive rat), SIRT1 (Sirtuin 1), SOD (Superoxide dismutase), SYRCLE (Systematic Review Centre for Laboratory Animal Experimentation), T2DM (Type 2 diabetes mellitus), TNF- α (Tumor necrosis factor-alpha), VED (Vascular endothelial dysfunction), and ZDF (Zucker diabetic fatty)

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AUTHOR'S CONTRIBUTIONS

Conceptualization, methodology, literature search, study screening, data extraction, quality appraisal, formal analysis, and drafting of the original manuscript were performed by the authors. All authors reviewed, critically revised, and approved the final version of the manuscript.

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AVAILABILITY OF DATA AND MATERIALS

All data generated or analyzed during this systematic review are included within this published article and its accompanying tables and figures. Additional

dataset details are available from the corresponding author upon reasonable request.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable. This study is a systematic review of previously published preclinical literature and did not involve direct experimentation with human participants or live animals by the review authors.

CONSENT FOR PUBLICATION

Not applicable.

DECLARATION OF GENERATIVE AI AND AI-ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

During the preparation of this manuscript, the authors utilized AI-assisted language editing tools solely for the purpose of improving English language fluency, grammar, and scientific medical style. The authors reviewed and edited the content as needed and take full responsibility for the integrity, accuracy, and scientific content of the publication.

COMPETING INTERESTS

The authors declare that they have no competing financial or non-financial interests that could have appeared to influence the work reported in this paper.

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