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Targeting atherosclerotic inflammation: Advances in NLRP3 inflammasome inhibitors beyond LDL-C

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ABSTRACT

Atherosclerosis, the main pathological background of cardiovascular diseases, is not only characterized by lipid metabolism disorders but also chronic inflammation as a major driver of disease progression. As a key regulator of inflammatory immune responses, the NLRP3 inflammasome is involved in the development and instability of atherosclerotic plaques. Although reducing low-density lipoprotein cholesterol (LDL-C) confers benefits, residual cardiovascular risk persists, necessitating novel anti-inflammatory therapies. This review provides a comprehensive overview of NLRP3 inflammasome activation mechanisms and its role in plaque inflammation. We systematically summarize current NLRP3 inhibitors under preclinical and clinical development, including small molecules and biologics, with emphasis on design strategies, structural characteristics and pharmacological activities. Challenges in clinical translation, such as tissue targeting and safety, are also discussed. By integrating recent advances in molecular mechanisms and medicinal chemistry, this article aims to provide a theoretical basis for targeted anti-inflammatory therapies beyond lipid lowering.

Keywords: atherosclerosis, NLRP3 inflammasome, inflammatory immunity, small molecule inhibitors, drug design, plaque instability, cardiovascular residual risk

INTRODUCTION

Atherosclerosis remains the primary pathological foundation of cardiovascular diseases (CVD), the leading cause of global morbidity and mortality (1). It is a progressive chronic disease starting in childhood, characterized by lipid-rich plaque accumulation on arterial walls, leading to vascular dysfunction and ischemic events (1, 2). Low-density lipoprotein cholesterol (LDL-C) is a causal factor in atherogenesis (2). However, even after

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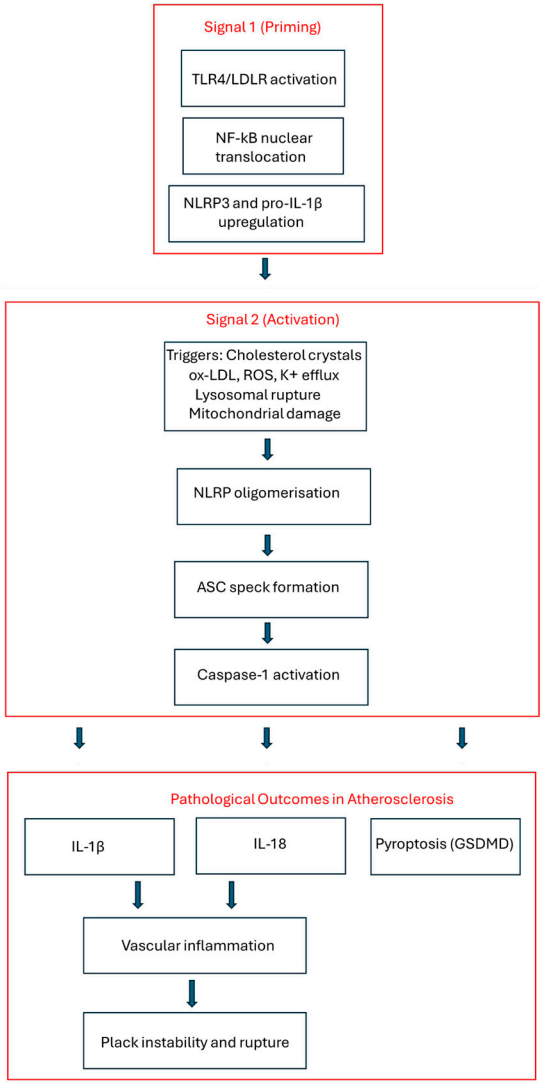

Fig. 1. Schematic representation of NLRP3 inflammasome activation in atherosclerosis. NLRP3 inflammasome activation follows a two-signal mechanism in atherosclerosis: signal 1 (priming) is mediated by TLR4/LDLR activation and NF-κB nuclear translocation, leading to upregulation of NLRP3 and pro-IL-1β; signal 2 (activation) is triggered by atherogenic stimuli such as cholesterol crystals, oxidized LDL (ox-LDL), reactive oxygen species (ROS), potassium efflux, lysosomal rupture, and mitochondrial damage, leading to NLRP3 oligomerization, ASC speck formation, and caspase-1 activation; activated caspase-1 processes pro-IL-1β and pro-IL-18 into mature IL-1β and IL-18, and induces pyroptosis *via* gasdermin D (GSDMD). These events ultimately promote vascular inflammation, plaque instability and rupture.

successful LDL-C control, significant residual cardiovascular risk persists, indicating involvement of other pathogenic processes, including inflammation (3).

Conventional therapies targeting plasma lipids, such as statins and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, reduce LDL-C and plaque burden but do not eliminate cardiovascular risk (3). The interplay between lipid accumulation and vascular inflammation is critical in plaque formation and destabilization (4). Oxidized low-density lipoprotein (ox-LDL) and cholesterol crystals act as powerful triggers of inflammatory signaling, enhancing vascular damage and plaque vulnerability (5).

The nucleotide-binding oligomerization domain, leucine-rich repeat and pyrin domain-containing protein 3 (NLRP3) inflammasome is central to the inflammatory cascade in atherosclerosis (3, 5). It is activated by cholesterol crystals and ox-LDL, leading to interleukin-1β (IL-1β) and interleukin-18 (IL-18) maturation and secretion, thereby amplifying local and systemic inflammation (5, 6). The canakinumab anti-inflammatory thrombosis outcomes study (CANTOS) trial confirmed that IL-1β inhibition reduces recurrent cardiovascular events, providing proof-of-concept that targeting NLRP3 inflammasome signaling offers benefits beyond lipid lowering (7, 8).

Nevertheless, translating NLRP3 inhibitors into clinical use faces challenges such as off-target effects and poor stability. Small-molecule inhibitors like MCC950 and tranilast show efficacy in preclinical models (9, 10), and natural compounds such as baicalin also inhibit NLRP3-mediated inflammation (11). Machine learning and molecular dynamics simulations are accelerating inhibitor discovery (12).

Thus, this review synthesizes current knowledge on NLRP3 inflammasome in atherosclerosis pathophysiology and critically evaluates the development status of NLRP3 inhibitors, focusing on preclinical and clinical drug design approaches (13–15). Fig. 1 provides a schematic view of NLRP3 inflammasome activation in atherosclerosis.

NLRP3 INFLAMMASOME: STRUCTURE, ACTIVATION AND PATHOPHYSIOLOGICAL ROLES IN ATHEROSCLEROSIS

NLRP3 inflammasome structure and assembly mechanism

The NLRP3 inflammasome is a multiprotein complex of the innate immune system, consisting of the NLRP3 receptor, the adaptor protein [apoptosis-associated speck-like protein containing a caspase recruitment domain (CARD)](ASC), and caspase-1 (16). Structurally, NLRP3 contains a nucleotide-binding oligomerization domain (NACHT), leucine-rich repeats (LRRs), and a pyrin domain (PYD). Upon activation, NLRP3 oligomerizes and recruits ASC *via* PYD-PYD interactions. ASC aggregates then recruit and activate pro-caspase-1, which processes pro-IL-1β and pro-IL-18 into mature IL-1β and IL-18 (16, 17). In addition, caspase-1 cleaves gasdermin D to initiate pyroptosis (17).

NLRP3 activation follows a two-signal mechanism: signal 1 (priming) upregulates NLRP3 and pro-IL-1β *via* NF-κB; signal 2 (activation) triggers inflammasome assembly upon danger signals such as reactive oxygen species (ROS), potassium efflux, lysosomal rupture, and mitochondrial dysfunction (18). Cryo-electron microscopy has revealed an inactive double-ring NLRP3 structure that prevents spontaneous activation (19). NEK7 is

required for NLRP3 oligomerization (20), and receptor for activated C kinase 1 (RACK1) promotes active conformation (21). Ubiquitination and deubiquitination (*e.g.*, by ABRO1) regulate NLRP3 stability (22). Atranorin directly targets ASC to block inflammasome assembly (23). These findings identify multiple steps as promising therapeutic targets (16–24).

Function of NLRP3 inflammasome in atherosclerotic plaque formation and instability

NLRP3 inflammasome activation in plaque macrophages releases IL-1β and IL-18, promoting inflammatory cascades, immune cell recruitment, and foam cell formation (25, 26). It also triggers pyroptosis of endothelial cells and macrophages, contributing to necrotic core expansion and plaque vulnerability (27). Moreover, NLRP3 regulates matrix metalloproteinases (MMPs), degrading the fibrous cap and predisposing to plaque rupture (28).

Clinical and experimental evidence shows elevated NLRP3 activity in human plaques, correlating with disease severity (25). Tranilast, which enhances NLRP3 ubiquitination, attenuates vascular inflammation and atherosclerosis in murine models (10). Genetic or pharmacological NLRP3 ablation reduces endothelial inflammation, adhesion molecules (*e.g.*, ICAM-1, VCAM-1), and macrophage infiltration (26, 27). Non-coding RNAs, such as microRNAs and lncRNAs, have emerged as novel regulators of NLRP3 expression (29). Thus, the NLRP3 inflammasome is a key therapeutic target for preventing acute cardiovascular events (8, 10, 25–32).

Related signaling pathways and regulatory mechanisms

Table I systematically summarizes major signaling pathways and regulatory mechanisms involved in NLRP3 inflammasome activation, emphasizing their relevance to atherosclerosis. The table classifies priming pathways (*e.g.*, NF-κB), activation triggers (*e.g.*, potassium efflux, mitochondrial ROS), post-translational modifications, autophagy, epigenetic regulation, and non-coding RNA networks. It highlights key molecular constituents, their specific functions, and pathophysiological consequences in plaque formation and instability (33–38).

NF-κB activation *via* TLRs upregulates NLRP3 and pro-IL-1β (33, 34). Post-translational modifications, including ubiquitination, phosphorylation and deubiquitination, regulate NLRP3 stability and assembly. For example, ABRO1 promotes deubiquitination and activation, while tranilast enhances ubiquitination to inhibit inflammasome formation (22, 35). Mitochondrial dysfunction releases mtROS and mtDNA as danger signals (36). Signal transducer and activator of transcription 3 (STAT3) facilitates NLRP3 translocation to mitochondria (37). Potassium efflux *via* P2X7 and gasdermin D pores is a well-known activation trigger (38). Endoplasmic reticulum (ER) stress and lysosomal damage also promote NLRP3 activation (39). Autophagy, especially chaperone-mediated autophagy, degrades NLRP3 components (40). Histone deacetylase 3 (HDAC3) epigenetically regulates NLRP3 transcription (41), and microRNAs fine-tune its expression (29). These interconnected regulatory processes offer numerous potential therapeutic targets (10, 29, 33–41).

Table I. Key signaling pathways and regulators of NLRP3 inflammasome activation in atherosclerosis

Pathway/ regulatory process	Key regulatory molecules/ components	Role in NLRP3 activation	Implications in atherosclerosis	Therapeutic targeting potential	Ref.
NF-κB priming (signal 1)	TLR2/4, MyD88, IκB kinase (IKK), NF-κB subunits (p65/p50)	Upregulates NLRP3 and pro-IL-1β transcription *via* NF-κB nuclear translocation	Enhances inflammasome priming in endothelial cells and macrophages; linked to plaque initiation	Inhibitors of TLR/NF-κB pathway (*e.g.,* IKK inhibitors)	3, 33
Potassium efflux	P2X7 receptor, Pannexin-1, TWIK2, GSDMD pores	Decreased intracellular K^+ triggers NLRP3 oligomerization; common activation signal	Cholesterol crystals and ATP from damaged cells promote K^+ efflux in plaques	P2X7 antagonists (*e.g.,* AZD9056); K^+ channel modulators	34
Mitochondrial dysfunction & ROS	mtROS, mitochondrial DNA (mtDNA), cardiolipin, mitofusin-2	Mitochondrial damage releases ROS and mtDNA, activating NLRP3 *via* redox sensing	Oxidative stress in plaques amplifies inflammasome activation	Mitochondrial antioxidants; mitophagy inducers	5, 36
Lysosomal disruption	Cathepsin B, LMP (lysosomal membrane permeabilization)	Lysosomal rupture releases cathepsins and particulates that activate NLRP3	Cholesterol crystals induce lysosomal damage in foam cells	Cathepsin inhibitors; lysosomal stabilizers	5, 35
ER stress & unfolded protein response	IRE1α, PERK, ATF6, CHOP, XBP1	ER stress induces ROS and Ca^{2+} flux, promoting NLRP3 assembly	Hyperlipidemia and hyperglycemia induce ER stress in vascular cells	ER stress inhibitors (*e.g.,* 4-PBA, TUDCA)	35, 39
Post-translational modifications	ABRO1 (deubiquitinase), BRCC3, TRIM31, PKA, JNK1	Ubiquitination, phosphorylation, SUMOylation regulate NLRP3 stability and activity	Altered PTM profiles in plaques affect inflammasome activity	PTM-targeting drugs (*e.g.,* deubiquitinase inhibitors)	9, 22
Autophagy regulation	LC3, p62, ATG5, beclin-1, Chaperone-mediated autophagy (CMA)	Autophagic degradation limits NLRP3 availability; CMA degrades NLRP3 components	Impaired autophagy in plaques leads to excess NLRP3 activation	Autophagy enhancers (*e.g.,* rapamycin analogs)	25, 40
Epigenetic regulation	HDAC3, SIRT2, DNMTs, specificity protein 1 (SP1) acetylation status	Histone acetylation/methylation and DNA methylation control NLRP3 expression	Epigenetic changes in aging and diabetes promote NLRP3 upregulation	Epigenetic modulators (HDAC inhibitors, SIRT activators)	36, 41

Pathway/ regulatory process	Key regulatory molecules/ components	Role in NLRP3 activation	Implications in atherosclerosis	Therapeutic targeting potential	Ref.
Non-coding RNA networks	miRNA-223, miRNA-7, lncRNA NEAT1, circRNAs	miRNAs and lncRNAs fine-tune NLRP3 expression and inflammasome assembly	Dysregulated ncRNAs in plaques correlate with NLRP3 activity	RNA-based therapeutics (antisense, miRNA mimics)	7, 29
Ion channel & transporter dynamics	TRPM2, VDAC, NCX, Cl^- channels	Modulate Ca^{2+}, Cl^-, and other ion fluxes that influence NLRP3 activation	Ionic imbalances in plaque microenvironment sustain inflammation	Ion channel blockers (TRPM2 inhibitors)	34, 38
Metabolic sensor integration	AMPK, mTOR, HIF-1α, SREBP	Link cellular energy status and lipid metabolism to NLRP3 activity	Metabolic syndrome components (obesity, diabetes) exacerbate NLRP3 activation	Metabolic modulators (AMPK activators, mTOR inhibitors)	31, 37

[a] For each pathway or regulatory process, the key molecular components, specific role in NLRP3 activation, pathophysiological implications in atherosclerotic plaque formation and progression, therapeutic targeting potential, and supporting references (far-right column) are listed.

Table II. Representative NLRP3 inflammasome inhibitors and their preclinical/clinical development status[a]

Compound	Class/category	Mechanism of action	Preclinical efficacy (*in vivo* models)	Clinical trial phase	Key challenges/safety notes	Ref.
MCC950 (CRID3)	Small molecule (diarylsulfonylurea)	Selective ATPase inhibitor of NLRP3 NACHT domain; blocks inflammasome assembly	Reduces plaque size, IL-1β secretion, and macrophage infiltration in ApoE-/-mice	Phase I completed (rheumatoid arthritis); no CV trials yet	Liver toxicity in high doses; narrow therapeutic window; oral bioavailability limited	42, 44, 47
IFM-2427	Small molecule (sulfonylurea derivative)	Potent NLRP3 ATPase inhibitor; high oral bioavailability	Attenuates atherosclerosis and improves plaque stability in murine models	Phase I/II in inflammatory diseases (NCT05128487)	Long-term safety unknown; potential immunosuppression risk	40, 42
Tranilast	Repurposed drug (anti-allergic)	Enhances NLRP3 ubiquitination *via* K48 linkage; inhibits inflammasome assembly	Reduces vascular inflammation and plaque burden in ApoE-/-mice	Approved for asthma/ allergies; repurposing studies ongoing	Off-target effects; requires high doses for NLRP3 inhibition	10, 11

Compound	Class/category	Mechanism of action	Preclinical efficacy (*in vivo* models)	Clinical trial phase	Key challenges/safety notes	Ref.
Canakinumab	Biologic (mAb) Monoclonal antibody against IL-1β	Human monoclonal antibody against IL-1β; blocks downstream signaling	Not applicable (direct cytokine neutralization)	Phase III (CANTOS: CV outcome trial) completed	Increased infection risk; high cost; subcutaneous administration	7, 8
Colchicine	Repurposed drug (anti-inflammatory)	Inhibits microtubule assembly; indirectly suppresses NLRP3 inflammasome activation	Reduces atherosclerosis and plaque inflammation in animal models	Phase III (COLCOT, LoDoCo2) completed for CVD	Gastrointestinal side effects; narrow therapeutic index	53, 57
Baicalin	Natural compound (flavonoid)	Inhibits NLRP3 inflammasome activation; antioxidant and anti-lipid effects	Ameliorates atherosclerosis in ApoE-/- mice; reduces IL-1β and oxidative stress	Preclinical only (herbal medicine studies)	Poor oral absorption; rapid metabolism; dose optimization needed	11, 13
CY-09	Small molecule (sulfonylurea analog)	Direct NLRP3 binder; inhibits ATPase activity and oligomerization	Reduces renal inflammation in diabetic nephropathy models; CV data emerging	Preclinical only	Limited pharmacokinetic data; tissue distribution unclear	45, 47
OLT1177 (Dapansutrile)	Small molecule (β-sulfonyl nitrile)	Direct NLRP3 inhibitor; oral bioavailability demonstrated	Reduces inflammation in gout and HF models; limited atherosclerosis data	Phase II in gout, HF, COVID-19	Safety profile under evaluation; CV outcome data lacking	47, 58
INF39	Small molecule (acrylate derivative)	Covalent inhibitor of NLRP3; blocks NEK7-NLRP3 interaction	Inhibits NLRP3 assembly in macrophages; *in vivo* atherosclerosis data limited	Preclinical only	Irreversible binding may increase off-target risk	19, 42
Atranorin	Natural compound (lichen metabolite)	Targets ASC speck formation; inhibits NLRP3-ASC interaction	Protects against NLRP3-driven diseases in mice; CV studies ongoing	Preclinical only	Low solubility; delivery challenges	22, 23

[a] For each inhibitor, the compound class, mechanism of action, preclinical efficacy in atherosclerosis models, clinical trial status, key translational challenges, and supporting references (far-right column) are summarized. Citation numbers correspond to the main reference list.

NLRP3 INFLAMMASOME INHIBITORS: DESIGN STRATEGIES AND PHARMACOLOGICAL PROPERTIES

As shown in Fig. 2, NLRP3 inflammasome inhibitors are divided into three major groups based on their mode of action: (*i*) small-molecule inhibitors (*e.g.*, MCC950, IFM-2427) which directly inhibit NLRP3 ATPase activity or protein-protein interactions; (*ii*) biologic inhibitors (*e.g.*, canakinumab) which block downstream cytokines; (*iii*) direct assembly disruptors (*e.g.*, atranorin) which inhibit ASC oligomerization or caspase-1 activation (42, 43).

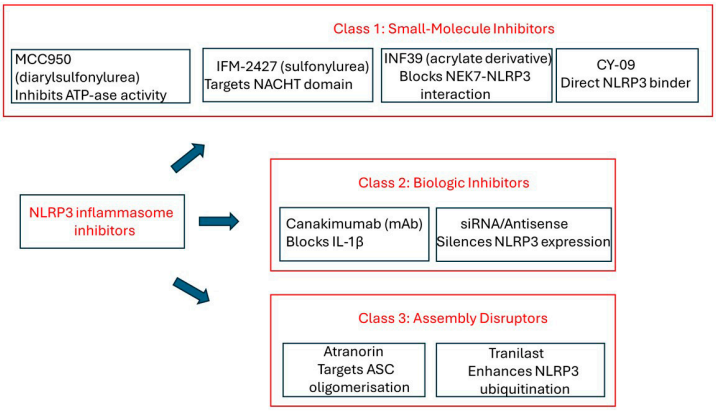

Fig. 2. Classification of NLRP3 inflammasome inhibitors by mechanism of action: class 1 including small-molecule inhibitors that directly inhibit NLRP3 ATPase activity, or block protein-protein interactions (*e.g.*, MCC950, IFM-2427, INF39, CY-09); class 2 comprising biological inhibitors, including monoclonal antibodies targeting IL-1-09 that directly inhibit NLRP3 ATPase activity, or block protein-protein interactions (*e.g.*, canakinumab); class 3 including direct assembly disruptors which inhibit ASC oligomerization and promote NLRP3 ubiquitination (*e.g.*, atranorin, tranilast).

Chemical structures and mechanisms of small-molecule inhibitors

Small-molecule NLRP3 inhibitors show great therapeutic potential. MCC950, a diarylsulfonylurea-containing molecule, selectively inhibits NACHT domain ATPase activity, preventing NLRP3 oligomerization and inflammasome assembly (42, 44). IFM-2427, a sulfonylurea derivative with good oral bioavailability, targets NLRP3 ATPase and shows efficacy in preclinical cardiovascular models (45). Chalcone-based scaffolds contain α,β-unsaturated carbonyl groups as Michael acceptors, allowing covalent or non-covalent interactions with cysteine residues (46). INF39 irreversibly blocks NEK7-NLRP3 and NLRP3-ASC interactions (19). Molecular docking studies have guided structure-activity relationship (SAR) optimization to improve pharmacokinetics and reduce off-target effects (47). Future optimization will focus on selectivity, stability and oral bioavailability (19, 42–47).

Biologics and novel drug delivery systems

Biologic agents, including monoclonal antibodies and nucleic acid therapeutics [small interfering RNA (siRNA), antisense oligonucleotides], are being explored for NLRP3 inhibition (48, 49). However, they face challenges in cellular uptake and stability.

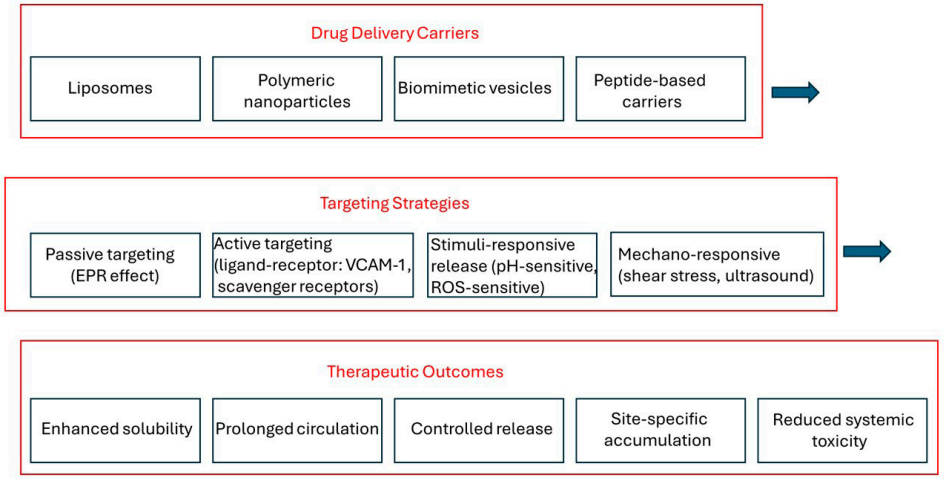

Fig. 3. Schematic overview of advanced drug delivery systems for NLRP3 inflammasome inhibitors in atherosclerosis. Nanocarriers (liposomes, polymeric nanoparticles, biomimetic vesicles, peptide-based carriers) enhance drug solubility and prolong circulation time. Targeting strategies include passive accumulation *via* the enhanced permeability and retention (EPR) effect, active targeting through ligand-receptor interactions (*e.g.*, VCAM-1 or scavenger receptors on macrophages), stimuli-responsive release triggered by acidic or oxidative plaque microenvironment, and mechano-responsive activation by shear stress or ultrasound. These approaches achieve site-specific drug accumulation, controlled release, and reduced systemic toxicity.

Fig. 3 details advanced drug delivery systems to improve targeted delivery of NLRP3 inhibitors to atherosclerotic plaques. These include liposomes, polymeric nanoparticles, and biomimetic vesicles, which enhance solubility, prolong circulation, and enable controlled release (50). Targeting strategies such as ligand-receptor interactions (*e.g.*, VCAM-1 or scavenger receptors) and stimuli-responsive release (pH- or ROS-sensitive systems) exploit the plaque microenvironment for site-specific delivery (51). Peptide-based carriers and DNA nanodevices offer biocompatibility and programmability (52). Despite advances, further optimization of stability, scalability and penetration depth is needed before clinical application (48, 49).

Pharmacological data and preclinical research outcomes

Preclinical studies in animal models of atherosclerosis show that NLRP3 inhibitors reduce plaque inflammation and volume and enhance stability. MCC950 treatment in murine models suppresses IL-1β release, reduces macrophage recruitment, and limits necrotic core growth (42, 47). Dose-dependent efficacy is observed, with higher doses showing greater inflammasome suppression. Safety profiles indicate that selective NLRP3 inhibition does not cause broad immunosuppression, reducing infection risk compared to upstream cytokine blockade (53). CY-09 has shown renoprotective effects in diabetic nephropathy models (54). However, limitations remain, including lack of pharmacokinetic data, off-target interactions, and difficulty achieving therapeutic tissue concentrations in

humans (55). Biomarkers to monitor inflammasome activity are lacking, hindering clinical translation. These issues must be addressed through thorough pharmacological characterization and development of sensitive diagnostic tools (42, 47, 53–55).

CLINICAL PROGRESS AND CHALLENGES OF NLRP3 INFLAMMASOME INHIBITORS

Representative clinical candidate drugs and their clinical trial data

Table II summarizes representative NLRP3 inflammasome inhibitors, classifying them by compound type, mechanism of action, preclinical efficacy in atherosclerosis models, clinical trial status, and key translational challenges. The table lists small-molecule inhibitors (*e.g.*, MCC950, IFM-2427, tranilast) and biologic agents (*e.g.*, canakinumab), demonstrating the variety of therapeutic approaches targeting the NLRP3 pathway. Several compounds have advanced to clinical trials, while others remain in preclinical development, each facing distinct hurdles such as bioavailability, tissue specificity, and long-term safety (56, 57).

IFM-2427 is a promising candidate in clinical trials for inflammatory diseases, including atherosclerosis (53). Trial designs are generally randomized, placebo-controlled, evaluating biomarkers (*e.g.*, IL-1β levels) and clinical endpoints (cardiovascular event reduction). Safety assessments focus on liver toxicity and gastrointestinal adverse effects (55). Early-phase data for IFM-2427, ZYIL1, DFV890, and OLT1177 show good pharmacokinetics and pharmacodynamics, with evidence of inflammasome inhibition (58). However, long-term cardiovascular outcome data and off-target effects remain insufficient. The anti-inflammatory benefits must be balanced against risks such as immunosuppression and infection vulnerability (53, 55, 58).

Challenges of tissue targeting and drug delivery

Plaque heterogeneity, including lipid cores, fibrous caps, inflammatory infiltrates and calcifications, affects drug distribution and bioavailability (59). Dense extracellular matrix and altered vascular permeability hinder small-molecule penetration. To overcome these barriers, chemical modification to increase lipophilicity and receptor-mediated targeting have been explored. Nanoparticle-based delivery systems, including liposomes, polymeric nanoparticles, and biomimetic nanovesicles, have shown promise (50, 51). These systems exploit ligand-receptor interactions (*e.g.*, targeting integrins or scavenger receptors) and stimuli-responsive release triggered by acidic or oxidative plaque microenvironment (52). Mechano-responsive nanoplatforms activated by shear stress or ultrasound are also being developed. Nevertheless, achieving precise targeting while minimizing systemic exposure and off-target effects remains challenging. Optimization of nanoparticle size, surface chemistry and payload stability are critical.

Safety issues and balancing immune regulation

Long-term NLRP3 inhibition raises concerns about immunosuppression and increased infection risk, given the inflammasome's role in innate immunity and host defense. Chronic blockade may impair pathogen response, leading to opportunistic infec-

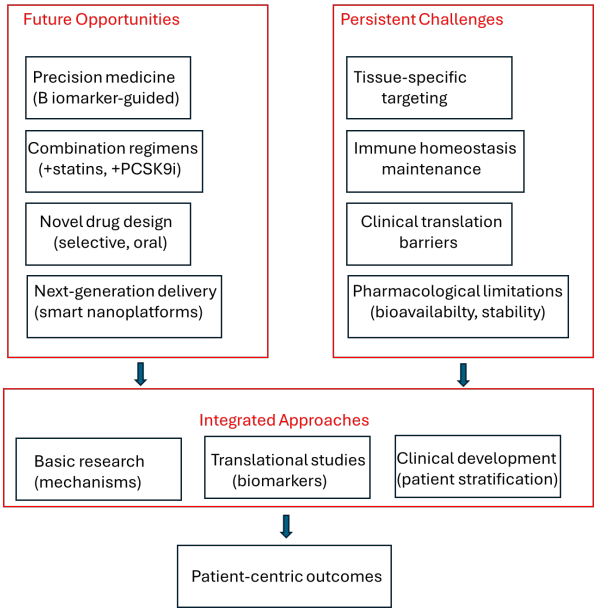

Fig. 4. Future directions and challenges in NLRP3 inflammasome-targeted therapy for atherosclerosis. Developmental scheme includes precision medicine using biomarkers, combination regimens with statins or PCSK9 inhibitors, novel drug design for improved selectivity and oral bioavailability, and next-generation smart nano-platforms for targeted delivery. Persistent challenges stay still in achieving tissue-specific targeting, maintaining immune homeostasis, overcoming clinical translation barriers, and addressing pharmacological limitations such as poor bioavailability and stability – success depending on integrated, multidisciplinary approaches bridging basic research, translational studies, and clinical development, with an emphasis on patient-centric outcomes and personalized treatment strategies.

tions. Some inhibitors show manageable safety profiles in trials, but vigilance against immunosuppressive adverse events is essential (53). Strategies to minimize risks include specific targeting of activation pathways, intermittent dosing, and development of inhibitors that preserve basal immune functions while blocking pathological activation. Patient selection and monitoring based on biomarkers may help identify suitable candidates. Localized delivery systems to limit systemic exposure may also improve safety. Natural small-molecule inhibitors offer favorable biocompatibility profiles (53). Ultimately, balancing anti-inflammatory efficacy with immune homeostasis requires a deep understanding of inflammasome biology and careful clinical assessment (53). A comprehensive overview of future opportunities and ramaining challenges in this field is presented in Fig. 4.

CONCLUSIONS

The NLRP3 inflammasome has emerged as a key modulator of inflammatory pathways in atherosclerosis, providing insights into residual cardiovascular risk. Recent prog-

ress in small-molecule inhibitors and biologics shows promising therapeutic potential. However, challenges such as poor tissue-specific targeting, off-target effects, and the delicate balance of immune homeostasis remain major hurdles. Future research should enhance mechanistic understanding of NLRP3 activation in the vascular microenvironment, guiding the rational design of next-generation inhibitors with improved specificity and pharmacokinetics. Novel drug delivery systems enabling targeted release to diseased vascular tissues are also promising. Integrating these approaches with precision medicine, using biomarkers and patient stratification, will be essential to optimize clinical effectiveness and safety.

Overall, inhibition of the NLRP3 inflammasome holds the potential to revolutionize atherosclerosis treatment by addressing residual inflammatory risk, ultimately reducing cardiovascular morbidity and mortality.

Acronyms, abbreviations, symbols. – ASC – apoptosis-associated speck-like protein containing a CARD, CANTOS – canakinumab anti-inflammatory thrombosis outcomes study, CARD – caspase recruitment domain, CVD – cardiovascular diseases, ER – endoplasmic reticulum, HDAC3 – histone deacetylase 3, IL-1β – interleukin-1β, IL-18 – interleukin-18, LDL-C – low-density lipoprotein cholesterol, LRR – leucine-rich repeat, MMP – matrix metalloproteinase, NACHT – nucleotide-binding oligomerization domain, NLRP3 – nucleotide-binding oligomerization domain, leucine-rich repeat and pyrin domain-containing protein 3, ox-LDL – oxidized low-density lipoprotein, PCSK9 – proprotein convertase subtilisin/kexin type 9, PYD – pyrin domain, RACK1 – receptor for activated C kinase 1, ROS – reactive oxygen species, SAR – structure-activity relationship, siRNA – small interfering RNA, SP1 – specificity protein 1, STAT3 – signal transducer and activator of transcription 3.

Data availability. – The data used to support the findings of this study are included within the article.

Declaration. – During the preparation of this manuscript, the author(s) used KIMI (https://kimi.moonshot.cn/) for language editing. After its use, the author(s) thoroughly reviewed, verified, and revised all AI-assisted content to ensure accuracy and originality. The authors take full responsibility for the integrity and final content of the published article.

Conflict of interest. – The author declares no conflicts of interest.

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Author's contribution. – Conceptualization X.D.; data collection and data analysis L.B.; writing, original draft preparation, X.D; writing, review and editing X.D. and L.B. Both authors have read and agreed to the published version of the manuscript.

REFERENCES

1. J. Pedro-Botet, E. Climent and D. Benaiges, El colesterol LDL como agente causal de la aterosclerosis [LDL cholesterol as a causal agent of atherosclerosis], *Clin. Invest. Arterioscler.* **36**(Suppl. 1) (2024) S3-S8; https://doi.org/10.1016/j.arteri.2024.07.001
2. C. Guijarro and J. Cosín-Sales, Colesterol LDL y aterosclerosis: evidencias [LDL cholesterol and atherosclerosis: The evidence], *Clin. Invest. Arterioscler.* **33**(Suppl. 1) (2021) 25–32; https://doi.org/10.1016/j.arteri.2020.12.004

3. B. Z. Shao, H. Y. Xu, Y. C. Zhao, X. R. Zheng, F. Wang and G. R. Zhao, NLRP3 inflammasome in atherosclerosis: Putting out the fire of inflammation, *Inflammation* **46**(1) (2023) 35–46; https://doi.org/10.1007/s10753-022-01725-x
4. A. Liaqat, M. Asad, F. Shoukat and A. U. Khan, A spotlight on the underlying activation mechanisms of the NLRP3 inflammasome and its role in atherosclerosis: A review, *Inflammation* **43**(6) (2020) 2011–2020; https://doi.org/10.1007/s10753-020-01290-1
5. M. Yalcinkaya and A. R. Tall, Cholesterol crystals as triggers of NLRP3 inflammasome activation in atherosclerosis, *Curr. Atheroscler. Rep.* **27**(1) (2025) Article ID 77 (9 pages); https://doi.org/10.1007/s11883-025-01323-w
6. M. Takahashi, NLRP3 inflammasome as a common denominator of atherosclerosis and abdominal aortic aneurysm, *Circ. J.* **85**(12) (2021) 2129-2136; https://doi.org/10.1253/circj.CJ-21-0258.
7. S. I. S. Al-Hawary, S. A. Jasim, R. M. Romero-Parra, G. S. Bustani, A. Hjazi, M. I. Alghamdi, A. K. Kareem, E. R. Alwaily, R. S. Zabibah, J. Gupta, R. Mahmoudi and S. Hosseini-Fard, NLRP3 inflammasome pathway in atherosclerosis: Focusing on the therapeutic potential of non-coding RNAs, *Pathol. Res. Pract.* **246** (2023) Article ID 154490; https://doi.org/10.1016/j.prp.2023.154490
8. J. Hettwer, J. Hinterdobler, B. Miritsch, M. A. Deutsch, X. Li, C. Mauersberger, A. Moggio, Q. Braster, H. Gram, A. A. B. Robertson, M. A. Cooper, O. Groß, M. Krane, C. Weber, W. Koenig, O. Soehnlein, N. H. Adamstein, P. Ridker, H. Schunkert, P. Libby, T. Kessler and H. B. Sager, Interleukin-1β suppression dampens inflammatory leucocyte production and uptake in atherosclerosis, *Cardiovasc. Res.* **118**(13) (2022) 2778–2791; https://doi.org/10.1093/cvr/cvab337
9. Y. Qin and W. Zhao, Posttranslational modifications of NLRP3 and their regulatory roles in inflammasome activation, *Eur. J. Immunol.* **53**(10) (2023) e2350382 (9 pages); https://doi.org/10.1002/eji.202350382
10. R. Yuan, W. Zhang, P. Nie, K. Lan, X. Yang, A. Yin, Q. Xiao, Y. Shen, K. Xu, X. Wang, X. Pan, L. Shen and B. He, Nur77 deficiency exacerbates macrophage NLRP3 inflammasome-mediated inflammation and accelerates atherosclerosis, *Oxid. Med. Cell. Longev.* **2022**(1) (2022) Article ID 2017815 (14 pages); https://doi.org/10.1155/2022/2017815
11. S. Chen, Y. Wang, Y. Pan, Y. Liu, S. Zheng, K. Ding, K. Mu, Y. Yuan, Z. Li, H. Song, Y. Jin and J. Fu, Novel role for tranilast in regulating NLRP3 ubiquitination, vascular inflammation, and atherosclerosis, *J. Am. Heart Assoc.* **9**(12) (2020) e015513; https://doi.org/10.1161/jaha.119.015513
12. V. Agarwal, R. Haldhar, A. H. Hirad, B. Ahmed, S. B. Han, A. Gupta, V. Raj and S. Lee, Repurposing FDA-approved drugs as NLRP3 inhibitors against inflammatory diseases: machine learning and molecular simulation approaches, *J. Biomol. Struct. Dyn.* **43**(8) (2025) 4327–4339; https://doi.org/10.1080/07391102.2024.2308072
13. J. Zhao, Z. Wang, Z. Yuan, S. Lv and Q. Su, Baicalin ameliorates atherosclerosis by inhibiting NLRP3 inflammasome in apolipoprotein E-deficient mice, *Diab. Vasc. Dis. Res.* **17**(6) (2020) Article ID 1479164120977441 (10 pages); https://doi.org/10.1177/1479164120977441
14. J. Luo, X. Wang, X. Jiang, C. Liu, Y. Li, X. Han, X. Zuo, Y. Li, N. Li, Y. Xu and S. Si, Rutaecarpine derivative R3 attenuates atherosclerosis via inhibiting NLRP3 inflammasome-related inflammation and modulating cholesterol transport, *FASEB J.* **34**(1) (2020) 1398–1411; https://doi.org/10.1096/fj.201900903RRR
15. B. Ahmad, A. Achek, M. Farooq and S. Choi, Accelerated NLRP3 inflammasome-inhibitory peptide design using a recurrent neural network model and molecular dynamics simulations, *Comput. Struct. Biotechnol. J.* **21** (2023) 4825–4835; https://doi.org/10.1016/j.csbj.2023.09.038
16. L. Y. El-Sharkawy, D. Brough and S. Freeman, Inhibiting the NLRP3 inflammasome, *Molecules* **25**(23) (2020) Article ID 5533 (14 pages); https://doi.org/10.3390/molecules25235533

17. H. Sharif, L. Wang, W. L. Wang, V. G. Magupalli, L. Andreeva, Q. Qiao, A. V. Hauenstein, Z. Wu, G. Núñez, Y. Mao and H. Wu, Structural mechanism for NEK7-licensed activation of NLRP3 inflammasome, *Nature* **570**(7761) (2019) 338–343; https://doi.org/10.1038/s41586-019-1295-z

18. Y. Duan, L. Zhang, D. Angosto-Bazarra, P. Pelegrín, G. Núñez and Y. He, RACK1 mediates NLRP3 Inflammasome activation by promoting NLRP3 active conformation and inflammasome assembly, *Cell Rep.* **33**(7) (2020) Article ID 108405 (11 pages + e5); https://doi.org/10.1016/j.celrep.2020.108405

19. Y. Shi, Q. Lv, M. Zheng, H. Sun and F. Shi, NLRP3 inflammasome inhibitor INF39 attenuated NLRP3 assembly in macrophages, *Int. Immunopharmacol.* **92** (2021) Article ID 107358 (11 pages); https://doi.org/10.1016/j.intimp.2020.107358

20. G. Ren, X. Zhang, Y. Xiao, W. Zhang, Y. Wang, W. Ma, X. Wang, P. Song, L. Lai, H. Chen, Y. Zhan, J. Zhang, M. Yu, C. Ge, C. Li, R. Yin and X. Yang, ABRO1 promotes NLRP3 inflammasome activation through regulation of NLRP3 deubiquitination, *EMBO J.* **38**(6) (2019) e100376 (17 pages); https://doi.org/10.15252/embj.2018100376

21. Y. Yang, H. Wang, M. Kouadir, H. Song and F. Shi, Recent advances in the mechanisms of NLRP3 inflammasome activation and its inhibitors, *Cell Death Dis.* **10**(2) (2019) Article ID 128 (11 pages); https://doi.org/10.1038/s41419-019-1413-8

22. H. Y. Wang, X. Lin, G. G. Huang, R. Zhou, S. Y. Lei, J. Ren, K. R. Zhang, C. L. Feng, Y. W. Wu and W. Tang, Atranorin inhibits NLRP3 inflammasome activation by targeting ASC and protects NLRP3 inflammasome-driven diseases, *Acta Pharmacol. Sin.* **44**(8) (2023) 1687–1700; https://doi.org/10.1038/s41401-023-01054-1

23. C. Jiang, S. Xie, G. Yang and N. Wang, Spotlight on NLRP3 Inflammasome: Role in pathogenesis and therapies of atherosclerosis, *J. Inflamm. Res.* **14** (2021) 7143–7172; https://doi.org/10.2147/jir.S344730

24. Z. Wan, Y. Fan, X. Liu, J. Xue, Z. Han, C. Zhu, and X. Wang, NLRP3 inflammasome promotes diabetes-induced endothelial inflammation and atherosclerosis, *Diabetes Metab. Syndr. Obes.* **12** (2019) 1931–1942; https://doi.org/10.2147/dmso.S222053

25. L. Qiao, J. Ma, Z. Zhang, W. Sui, C. Zhai, D. Xu, Z. Wang, H. Lu, M. Zhang, C. Zhang, W. Chen and Y. Zhang, Deficient chaperone-mediated autophagy promotes inflammation and atherosclerosis, *Circ. Res.* **129**(12) (2021) 1141–1157; https://doi.org/10.1161/circresaha.121.318908

26. M. Takahashi, NLRP3 inflammasome as a key driver of vascular disease, *Cardiovasc. Res.* **118**(2) (2022) 372–385; https://doi.org/10.1093/cvr/cvab010

27. Y. Lv, Z. Jiang, W. Zhou, H. Yang, G. Jin, D. Wang, C. Kong, Z. Qian, Y. Gu, S. Chen and L. Zhu, Low-shear stress promotes atherosclerosis via inducing endothelial cell pyroptosis mediated by IKKε/STAT1/NLRP3 pathway, *Inflammation* **47**(3) (2024) 1053–1066; https://doi.org/10.1007/s10753-023-01960-w

28. Z. Peng, H. Zhan, Y. Shao, Y. Xiong, L. Zeng, C. Zhang, Z. Liu, Z. Huang, H. Su and Z. Yang, 13-Methylberberine improves endothelial dysfunction by inhibiting NLRP3 inflammasome activation via autophagy induction in human umbilical vein endothelial cells, *Chin. Med.* **15** (2020) Article ID 8 (12 pages); https://doi.org/10.1186/s13020-020-0286-1

29. M. J. M. Silvis, E. J. Demkes, A. T. L. Fiolet, M. Dekker, L. Bosch, G. P. J. van Hout, L. Timmers and D. P. V. de Kleijn, Immunomodulation of the NLRP3 inflammasome in atherosclerosis, coronary artery disease, and acute myocardial infarction, *J. Cardiovasc. Transl. Res.* **14**(1) (2021) 23–34; https://doi.org/10.1007/s12265-020-10049-w

30. J. Ye, L. Li, M. Wang, Q. Ma, Y. Tian, Q. Zhang, J. Liu, B. Li, B. Zhang, H. Liu and G. Sun, Diabetes mellitus promotes the development of atherosclerosis: The role of NLRP3, *Front. Immunol.* **13** (2022) Article ID 900254 (12 pages); https://doi.org/10.3389/fimmu.2022.900254

31. S. Paik, J. K. Kim, P. Silwal, C. Sasakawa and E. K. Jo, An update on the regulatory mechanisms of NLRP3 inflammasome activation, *Cell. Mol. Immunol.* **18**(5) (2021) 1141–1160; https://doi.org/10.1038/s41423-021-00670-3

32. N. Kelley, D. Jeltema, Y. Duan and Y. He, The NLRP3 inflammasome: An overview of mechanisms of activation and regulation, *Int. J. Mol. Sci.* **20**(13) (2019) Article ID 3328 (24 pages); https://doi.org/10.3390/ijms20133328

33. L. Luo, F. Wang, X. Xu, M. Ma, G. Kuang, Y. Zhang, D. Wang, W. Li, N. Zhang, K. Zhao, STAT3 promotes NLRP3 inflammasome activation by mediating NLRP3 mitochondrial translocation, *Exp. Mol. Med.* **56**(9) (2024) 1980–1990; https://doi.org/10.1038/s12276-024-01298-9

34. Z. Xu, Z. M. Chen, X. Wu, L. Zhang, Y. Cao and P. Zhou, Distinct molecular mechanisms underlying potassium efflux for nlrp3 inflammasome activation, *Front. Immunol.* **11** (2020) Article ID 609441 (7 pages); https://doi.org/10.3389/fimmu.2020.609441

35. X. Chen, X. Guo, Q. Ge, Y. Zhao, H. Mu and J. Zhang, ER stress activates the NLRP3 inflammasome: A novel mechanism of atherosclerosis, *Oxid. Med. Cell. Longev.* **2019** (2019) Article ID 3462530 (18 pages); https://doi.org/10.1155/2019/3462530

36. L. Chen, W. Zhang, H. Chen, Y. Zhang, B. Guo, L. Yang, C. Yin, Q. Zuo, L. Ren, L. Bai, R. Wang, S. Zhao, E. Liu and W. Wang, HDAC3 activates endothelial NLRP3 inflammasome and promotes atherosclerosis via inhibiting the acetylation of specificity protein 1, *Cell Death Differ.* **33** (2026) 930–944; https://doi.org/10.1038/s41418-025-01620-6

37. D. Liu, X. Zeng, X. Li, C. Cui, R. Hou, Z. Guo, J. L. Mehta and X. Wang, Advances in the molecular mechanisms of NLRP3 inflammasome activators and inactivators, *Biochem. Pharmacol.* **175** (2020) Article ID 113863 (12 pages); https://doi.org/10.1016/j.bcp.2020.113863

38. T. Kodi, R. Sankhe, A. Gopinathan, K. Nandakumar and A. Kishore, New insights on NLRP3 Inflammasome: Mechanisms of activation, inhibition, and epigenetic regulation, *J. Neuroimmune Pharmacol.* **19**(1) (2024) Article ID 7 (26 pages); https://doi.org/10.1007/s11481-024-10101-5

39. A. Zahid, B. Li, A. J. K. Kombe, T. Jin and J. Tao, Pharmacological inhibitors of the NLRP3 inflammasome, *Front. Immunol.* **10** (2019) Article ID 2538 (10 pages); https://doi.org/10.3389/fimmu.2019.02538

40. S. Agarwal, J. P. Pethani, H. A. Shah, V. Vyas, S. Sasane, H. Bhavsar, D. Bandyopadhyay, P. Giri, K. Viswanathan, M. R. Jain and R. Sharma, Identification of a novel orally bioavailable NLRP3 inflammasome inhibitor, *Bioorg. Med. Chem. Lett.* **30**(21) (2020) Article ID 127571 (4 pages); https://doi.org/10.1016/j.bmcl.2020.127571

41. P. Thapa, S. P. Upadhyay, V. Singh, V. C. Boinpelly, J. Zhou, D. K. Johnson, P. Gurung, E. S. Lee, R. Sharma and M. Sharma, Chalcone: A potential scaffold for NLRP3 inflammasome inhibitors, *Eur. J. Med. Chem. Rep.* **7** (2023) Article ID 100100 (13 pages); https://doi.org/10.1016/j.ejmcr.2022.100100

42. E. Mezzaroma, A. Abbate and S. Toldo, NLRP3 Inflammasome inhibitors in cardiovascular diseases, *Molecules* **26**(4) (2021) Article ID 976 (19 pages); https://doi.org/10.3390/molecules26040976

43. S. Moon, S. Muniyappan, S. B. Lee and B. H. Lee, Small-molecule inhibitors targeting proteasome-associated deubiquitinases, *Int. J. Mol. Sci.* **22**(12) (2021) Article ID 6213 (19 pages); https://doi.org/10.3390/ijms22126213

44. S. E. Alavi, S. Alharthi, S. Z. Alavi, A. Raza and H. E. Shahmabadi, Bioresponsive drug delivery systems, *Drug Discov. Today* **29**(1) (2024) Article ID 103849; https://doi.org/10.1016/j.drudis.2023.103849

45. M. Yang and L. Zhao, The selective NLRP3-inflammasome inhibitor CY-09 ameliorates kidney injury in diabetic nephropathy by inhibiting NLRP3- inflammasome activation, *Curr. Med. Chem.* **30**(28) (2023) 3261–3270; https://doi.org/10.2174/0929867329666220922104654

46. S. Lou, M. Wu and S. Cui, Targeting NLRP3 inflammasome: Structure, function, and inhibitors, *Curr. Med. Chem.* **31**(15) (2024) 2021–2051; https://doi.org/10.2174/0109298673289984231127062528

47. S. Kiran, A. Rakib and U. P. Singh, The NLRP3 inflammasome inhibitor dapansutrile attenuates cyclophosphamide-induced interstitial cystitis, *Front. Immunol.* **13** (2022) Article ID 903834 (13 pages); https://doi.org/10.3389/fimmu.2022.903834

48. T. Y. Zhang, X. Y. Chen, X. Y. Duan, Q. R. Zhao, L. Ma, Y. Q. Yan, Y. Wang, T. Liu and S. X. Wang, [Research progress on natural small molecule compound inhibitors of NLRP3 inflammasome], *Zhongguo Zhong Yao Za Zhi* **50**(3) (2025) 644–657; https://doi.org/10.19540/j.cnki.cjcmm.20240828.701

49. Z. Yuan, D. Yu, T. Gou, G. Tang, C. Guo and J. Shi, Research progress of NLRP3 inflammasome and its inhibitors with aging diseases, *Eur. J. Pharmacol.* **957** (2023) Article ID 175931; https://doi.org/10.1016/j.ejphar.2023.175931

50. M. Su, W. Wang, F. Liu and H. Li, Recent progress on the discovery of NLRP3 inhibitors and their therapeutic potential, *Curr. Med. Chem.* **28**(3) (2021) 569–582; https://doi.org/10.2174/0929867327666200123093544

51. P. Chen and X. Li, NLRP3 inflammasome in atherosclerosis: Mechanisms and targeted therapies, *Front. Pharmacol*. **15** (2024) Article ID 1430236 (15 pages); https://doi.org/10.3389/fphar.2024.1430236

52. O. Beltrán, A. Costa-Santos, M. Luna, O. Abelenda, A. Ogando, A. Topete, J. Juarez, S. Barbosa and P. Taboada, Cell membrane-based nanovesicles as potential drug delivery systems for atherosclerosis therapy, *Colloids Surf. B Biointerfaces* **257** (2026) Article ID 115190 (15 pages); https://doi.org/10.1016/j.colsurfb.2025.115190.

53. Y. Zhang, F. Li, L. Liu, Z. An, H. Luo, H. Zhang, R. Ma, R. Zhang, Q. Dai, M. Zhang, J. Tian, C. Liu, X. Song and Y. Lu, Nanoparticle drug delivery systems for atherosclerosis: Precision targeting, inflammatory modulation, and plaque stabilization, *Adv. Sci.* **12**(36) (2025) e04990 (25 pages); https://doi.org/10.1002/advs.202504990

54. P. Karakasis, P. Theofilis, P. K. Vlachakis, K. Grigoriou, D. Patoulias, A. P. Antoniadis and N. Fragakis, Reprogramming atherosclerosis: Precision drug delivery, nanomedicine, and immune-targeted therapies for cardiovascular risk reduction, *Pharmaceutics* **17**(8) (2025) Article ID 1028 (36 pages); https://doi.org/10.3390/pharmaceutics17081028

55. D. Nurhidayah, A. Maruf, X. Zhang, X. Liao, W. Wu and G. Wang, Advanced drug-delivery systems: Mechanoresponsive nanoplatforms applicable in atherosclerosis management, *Nanomedicine* **14**(23) (2019) 3105–3122; https://doi.org/10.2217/nnm-2019-0172

56. R. Y. Pan, X. X. Kong, Y. Cheng, L. Du, Z. C. Wang, C. Yuan, J. B. Cheng, Z. Q. Yuan, H. Y. Zhang and Y. J. Liao, 1,2,4-Trimethoxybenzene selectively inhibits NLRP3 inflammasome activation and attenuates experimental autoimmune encephalomyelitis, *Acta Pharmacol. Sin.* **42**(11) (2021) 1769–1779; https://doi.org/10.1038/s41401-021-00613-8

57. F. P. Kreutzer, A. Meinecke, K. Schmidt, J. Fiedler and T. Thum, Alternative strategies in cardiac preclinical research and new clinical trial formats, *Cardiovasc. Res.* **118**(3) (2022) 746–762; https://doi.org/10.1093/cvr/cvab075

58. H. Tang, X. Zou, P. Chen, Y. Wang, S. Gao, T. Wang, Y. Xu and S.-L. Ji, Broxyquinoline targets NLRP3 to inhibit inflammasome activation and alleviate NLRP3-associated inflammatory diseases, *Int. Immunopharmacol.* **156** (2025) Article ID 114687; https://doi.org/10.1016/j.intimp.2025.114687

59. C. T. Vong, H. H. L. Tseng, P. Yao, H. Yu, S. Wang, Z. Zhong and Y. Wang, Specific NLRP3 inflammasome inhibitors: promising therapeutic agents for inflammatory diseases, *Drug Discov. Today* **26**(6) (2021) 1394–1408; https://doi.org/10.1016/j.drudis.2021.02.018