

Role of the NLRP3 inflammasome in diabetes and its complications (Review)

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Abstract. Diabetes and its complications are systemic metabolic disorders triggered by chronic hyperglycemia, with the NOD-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome carrying out a central role in disease progression. Activation of the NLRP3 inflammasome is involved not only in the onset of diabetes but also in its complications, including cardiovascular disease, nephropathy and retinopathy. The present review outlines the core mechanisms of the NLRP3 inflammasome and its specific contributions to diabetes and associated conditions. Additionally, emerging therapeutic strategies that target the NLRP3 inflammasome were explored, offering novel insights into the management of diabetes and its associated complications.

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1. Introduction

Diabetes mellitus is a chronic metabolic disorder marked by persistent hyperglycemia. It is broadly classified into type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM),

each characterized by distinct pathophysiological mechanisms. T1DM is primarily caused by autoimmune-mediated destruction of pancreatic β -cells, leading to an absolute deficiency in insulin (1). By contrast, T2DM is associated with insulin resistance and a gradual decline in β -cell function, often influenced by modifiable factors such as poor diet, sedentary lifestyle and obesity. As increasing longevity, urbanization and unhealthy dietary habits become more widespread, the global burden of diabetes continues to escalate. According to the International Diabetes Federation, the number of individuals with diabetes worldwide is projected to reach 783.2 million by 2045 (2).

Chronic metabolic dysregulation in diabetes (particularly in T2DM) is a key contributor to a range of complications, including diabetic retinopathy (DR), diabetic kidney disease (DKD), diabetic cardiomyopathy (DCM) and diabetic encephalopathy (DE). These complications considerably diminish the quality of life of patients and increase morbidity and mortality (3). A growing body of evidence has identified inflammation as a key driver of diabetes progression, particularly in T2DM (4,5). In particular, chronic low-grade systemic inflammation is now recognized as a core mechanism underlying insulin resistance. Diabetic individuals frequently exhibit elevated levels of various pro-inflammatory factors, such as TNF- α , IL-6 and CRP (6). These mediators interfere with insulin signaling by activating the NF- κ B and JNK pathways, which inhibit the tyrosine phosphorylation of insulin receptor substrates (IRS), thereby exacerbating insulin resistance and pancreatic β -cell dysfunction (7-9).

An inflammasome is a multiprotein complex that forms in response to cellular stress and microbial signals. It acts as an intracellular sensor that activates caspase-1, leading to the cleavage of pro-IL-1 β and pro-IL-18 into their active forms, which then mediate inflammatory responses. In the field of inflammation research, the concept of the inflammasome was first proposed by Tschopp *et al* (10) in 2002. Recent studies have focused on the mechanistic role of the NOD-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome in the context of diabetes (11-13). Studies have revealed that under hyperglycemic conditions, oxidative stress, mitochondrial dysfunction and accumulation of advanced glycation end products (AGEs) can activate the NLRP3 inflammasome (14-16). This activation process promotes the activation of caspase-1, subsequently leading to the maturation and release of the pro-inflammatory factors IL-1 β and IL-18 (17,18). These

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inflammatory cytokines not only intensify local inflammatory responses but also induce pyroptosis, leading to pancreatic β -cell damage and other tissue injuries, suggesting that the inflammatory response is not only a key pathological feature of diabetes, but also a key pathophysiological mechanism in its development process.

2. Molecular mechanisms of the NLRP3 inflammasome

The NLRP3 inflammasome is one of the most representative inflammasomes in the NLRP family, often referred to as a 'molecular sensor' for detecting intracellular and extracellular stimuli (18). The NLRP3 inflammasome is composed of three core components: The sensor protein NLRP3, the adaptor protein apoptosis-associated speck-like protein containing a CARD (ASC) and the effector protein caspase-1. Structurally, NLRP3 interacts with ASC through homotypic pyrin domain (PYD)-PYD interactions at their N-termini, thereby recruiting procaspase-1 to form a fully functional inflammasome complex (19,20).

The activation of the NLRP3 inflammasome is strictly regulated and involves a two-step process: Priming and activation (Fig. 1). During the priming phase, extracellular or intracellular stimuli, including pathogens, cellular damage or metabolic disturbances, are detected by Toll-like receptors (TLRs) or cytokine receptors. This recognition event triggers both the MAPK and NF- κ B signaling pathways, leading to the transcriptional upregulation of NLRP3 and pro-IL-1 β , and the formation of the initial 'sensing complex' (21,22). In the activation phase, various agonists, including extracellular ATP, nigericin, particulate matter such as alum, or intracellular RNA (23-26), can be employed. These agonists induce NLRP3 inflammasome activation primarily through potassium efflux (25). Upon activation, NLRP3 recruits ASC via its PYD domain, and ASC subsequently interacts with pro-caspase-1 through caspase activation and recruitment domain (CARD)-CARD interactions. This cascade culminates in the activation of caspase-1, a key step in the maturation of pro-inflammatory cytokines (such as, IL-1 β and IL-18) and the initiation of pyroptosis, a form of inflammatory programmed cell death.

3. Role of the NLRP3 inflammasome in the pathology of diabetes: Mechanisms of NLRP3 activation by diabetes

Diabetes, as a chronic metabolic disorder, potently activates the NLRP3 inflammasome through multiple mechanisms. At the same time, the activation of NLRP3 further exacerbates the pathological progression of diabetes and the development of its associated complications (14,15,27-29).

Hyperglycemia and downstream pathways. One of the primary characteristics of diabetes is chronic hyperglycemia, which triggers the NLRP3 inflammasome through various pathways, including the production of AGEs. AGEs are formed when blood glucose undergoes non-enzymatic glycation with proteins under hyperglycemic conditions (30). This process involves the nucleophilic addition of the carbonyl group of glucose to the free amino groups of proteins, which produces unstable Schiff bases. These Schiff bases are rearranged to

create stable ketoamines or Amadori products, which are then further converted into irreversible AGEs through intermediary substances, such as 3-deoxyglucosone (31).

By attaching themselves to the receptor for AGEs (RAGE), AGEs trigger the activation of the pro-inflammatory transcription factor NF- κ B (32). The functional NF- κ B binding sites located in the proximal promoter region of the RAGE gene are likely necessary for this process (33). Additionally, AGEs increase the generation of reactive oxygen species (ROS), which triggers the NLRP3 inflammasome (34).

One of the main ways that diabetes and hyperglycemia cause cellular damage is through oxidative stress (35). In hyperglycemia, glucose undergoes glycolysis to produce pyruvate, which then enters the mitochondria to participate in oxidative phosphorylation and the tricarboxylic acid (TCA) cycle. ROS are produced in greater quantities during this process due to electron leakage at complexes I and III caused by overactivation of the electron transport chain, which also produces superoxide. The TCA cycle is the primary source of ROS formation induced by hyperglycemia, according to the study by Nishikawa *et al* (36). The NLRP3 inflammasome may be activated when ROS buildup causes thioredoxin-interacting protein (TXNIP) to separate from its binding partner thioredoxin (TRX) (37,38). Furthermore, oxidative stress induces NLRP3 inflammasome activation by dysregulating intracellular calcium homeostasis (39,40).

Mitochondrial dysfunction and damage-associated molecular patterns (DAMPs). Oxidative stress and hyperglycemia can cause damage to the mitochondria, which release mitochondrial ROS and mitochondrial DNA (mtDNA), functioning as DAMPs to trigger the NLRP3 inflammasome (37). Furthermore, impaired mitophagy in diabetes leads to the accumulation of damaged mitochondria, exacerbating NLRP3 inflammasome activation (41,42). Diabetes is often accompanied by dyslipidemia and the accumulation of free fatty acids and cholesterol crystals can also serve as activation signals for the NLRP3 inflammasome (43-45). Additionally, hyperuricemia, frequently associated with diabetes, may contribute to inflammation by generating uric acid crystals that act as DAMPs to activate the NLRP3 inflammasome (46).

In the state of insulin resistance, tissues such as adipose tissue, liver and muscle release large amounts of inflammatory cytokines (such as, TNF- α and IL-6), which promote NLRP3 expression through the activation of the NF- κ B signaling pathway. Moreover, adipose tissue inflammation releases ROS and inflammatory cytokines, creating a positive feedback loop that continuously activates the NLRP3 inflammasome. This perpetuates inflammatory responses and exacerbates the pathological progression of diabetes.

Beyond mitochondrial dysfunction, endoplasmic reticulum (ER) stress represents a key upstream signal for NLRP3 inflammasome activation in diabetes. Under chronic hyperglycemia and metabolic overload, misfolded proteins accumulate in the ER, triggering the unfolded protein response (UPR). The activation of UPR sensors, such as PERK, IRE1 α and ATF6, can enhance NLRP3 expression either directly or through downstream mediators, including CHOP and ROS production (47). ER stress also induces calcium release into

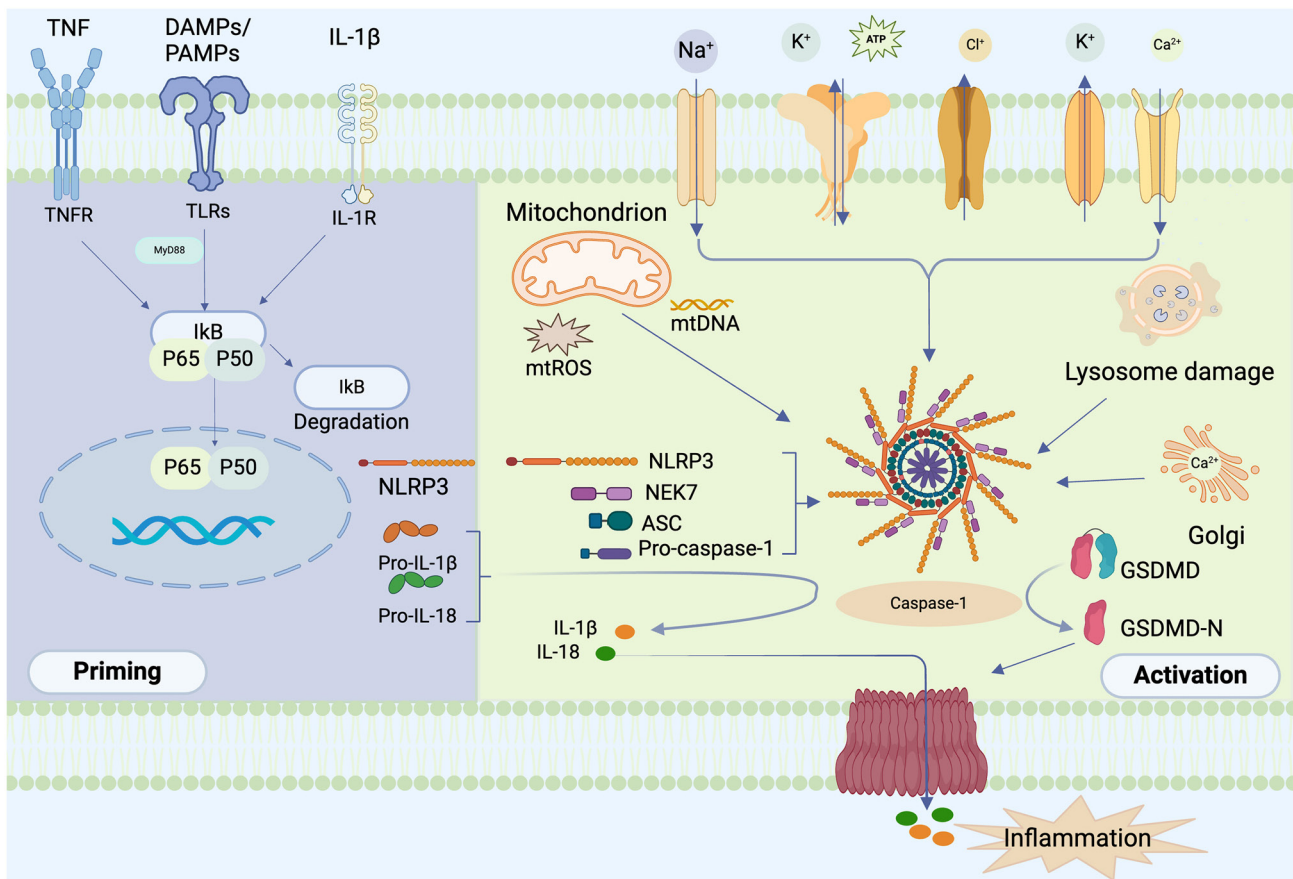


Figure 1. Schematic of the initiation and activation steps of the NLRP3 inflammasome. The activation of the NLRP3 inflammasome is divided into two signals: Initiation and activation. During the initiation stage, the transcription factor NF- κ B is activated by cytokines or PAMPs and DAMPs, inducing the upregulation of NLRP3 and pro-IL-1 β and pro-IL-18 expressions. Activation phase is induced by various PAMPs and DAMPs, such as the outflow of K⁺ plasma, ATP production, mtROS production, the release of oxidized mitochondrial DNA, lysosomal damage and Golgi dissociation. The assembly of the NLRP3 inflammasome triggers the auto-lysis of caspase-1, further lysing pro-IL-1 β and pro-IL-18. Activated caspase-1 cleaves GSDMD to generate its N-terminal fragment GSDMD-N, which executes pyroptosis. GSDMD, Gasdermin D; DAMPs, pathogen-associated molecular patterns; pro-IL-1 β , IL-1 β precursor; PAMPs, pathogen-associated molecular patterns; TNFR, tumor necrosis factor receptor; TLRs, toll-like receptors; NLRP3, NOD-like receptor family pyrin domain-containing 3; mtDNA, mitochondrial DNA; mtROS, mitochondrial reactive oxygen species; NEK7, NIMA-related kinase 7; ASC, apoptosis-associated speck-like protein containing a CARD. Created using biorender.com.

the cytoplasm, contributing to mitochondrial dysfunction and subsequent NLRP3 activation (37). These findings suggest that ER stress may be a key link between metabolic stress and inflammation in diabetes.

In addition to mitochondrial impairment, other diabetes-induced stress responses contribute to NLRP3 inflammasome activation. Chronic hyperglycemia in diabetes can alter post-translational modifications (PTMs) of inflammasome components, thereby sustaining NLRP3 activation. Changes in the ubiquitination and phosphorylation states of NLRP3 modulate its activity (48). For instance, hyperglycemia-induced deubiquitination promotes inflammasome activation, while specific kinases can enhance NLRP3 oligomerization through phosphorylation (49). These PTMs may present a molecular basis for the persistent, low-grade inflammation observed in diabetic conditions and highlight potential regulatory checkpoints for therapeutic intervention.

Non-canonical pathway of NLRP3 activation. In addition to the canonical pathway, NLRP3 can be activated via non-canonical mechanisms. In this pathway, intracellular lipopolysaccharide (LPS) directly binds to and activates caspase-4

and caspase-5 in humans (caspase-11 in mice), independent of TLR4. These caspases cleave gasdermin D (GSDMD), which forms pores in the cell membrane, leading to pyroptosis and potassium efflux, an upstream signal that triggers the canonical NLRP3 inflammasome assembly. Non-canonical activation is particularly relevant in metabolic endotoxemia, obesity and T2DM, in which gut-derived LPS may chronically stimulate this pathway. Understanding both pathways provides a comprehensive view of NLRP3 regulation in diabetes-related inflammation (50,51).

4. NLRP3 and the multisystem complications of diabetes mellitus

DKD. DKD is one of the most severe microvascular complications associated with diabetes mellitus (52). Epidemiological studies indicate that ~40% of patients with diabetes progress to develop DKD (53-55). Research has demonstrated that inflammatory responses carry out a key role in the pathogenesis and progression of DKD, primarily by altering renal vascular permeability and disrupting the integrity of the glomerular filtration barrier (56).

Pathological mechanisms of DKD. Using gene knockout in a diabetic mouse model, Wu *et al* (57) has revealed that the absence of NLRP3 markedly reduces renal pathological alterations. These alterations include glomerular hypertrophy, glomerulosclerosis, mesangial expansion and interstitial fibrosis, along with a marked reduction in renal inflammatory responses. At the molecular level, a study has shown that a high-glucose environment activates the NLRP3 inflammasome in a time-dependent manner, promoting the secretion of IL-1 β and the activation of caspase-1, ultimately leading to injury in HK-2 cells (58). Notably, oxidative stress induced by high glucose levels is considered a central link in the various pathological mechanisms of DKD (59), with ROS generated from mitochondrial dysfunction potentially serving as a key upstream signal for NLRP3 activation (60). Recent research has further elucidated the multiple activation mechanisms of NLRP3 in DKD. Firstly, a high-glucose environment can stimulate macrophages to secrete exosomes, which activate mesangial cells via an NLRP3-dependent pathway, accelerating the progression of renal injury (61). Secondly, endoplasmic reticulum stress induced by high glucose levels can also activate the NLRP3 inflammasome, leading to pyroptosis in podocytes (62).

Additionally, a study revealed that the activation of the NLRP3 inflammasome in models of DKD results in the abnormal function of connexin 43 hemichannel, thereby promoting the cascade amplification of inflammatory responses (63). In addition to inflammation, impaired autophagy under hyperglycemic conditions also carries out a key role in the progression of DKD. Renal cells, including podocytes and tubular epithelial cells, exhibit suppressed autophagic flux, leading to the accumulation of damaged mitochondria and protein aggregates. This dysfunction amplifies oxidative stress and facilitates the activation of the NLRP3 inflammasome. Restoration of autophagy has been shown to mitigate renal inflammation and fibrosis in diabetic models (64). These findings collectively underscore the central role of NLRP3 in the pathogenesis of DKD.

Signaling pathways in DKD. Research indicates that the NLRP3 inflammasome carries out a role in the pathological progression of DKD through multiple signaling pathways (65-67). Among these, the NF- κ B/NLRP3 signaling axis is the most extensively studied regulatory pathway. Activation of NF- κ B can induce the expression of various pro-inflammatory factors (such as IL-1 β , IL-18, TNF- α and IL-6). Beyond directly mediating inflammatory responses, these cytokines also positively regulate NLRP3 activation and priming, inducing further release of IL-1 β and IL-18. This establishes a self-perpetuating inflammatory cycle that ultimately exacerbates chronic inflammation (68). Pharmacological or genetic modulation of the NF- κ B/NLRP3 axis has been revealed to markedly attenuate the progression of DKD (69-72). The NLRP3 regulatory network is dependent on nuclear factor erythroid 2-related factor 2 (Nrf2) signaling, which counteracts NLRP3-driven inflammation through dual mechanisms: Heme oxygenase-1 induction to directly inhibit NLRP3 activation, and I κ B phosphorylation blockade to disrupt NF- κ B/NLRP3 crosstalk, collectively mitigating renal inflammation (73-75).

Therapeutic inhibitors of DKD. Novel inhibitors and various natural substances have revealed potential as therapeutics for DKD in recent years (76-78). Pomegranates contain a natural polyphenolic component called punicalagin, which is well known for its potent anti-inflammatory and antioxidant properties. By blocking the TXNIP/NLRP3 signaling pathway, punicalagin efficiently slows the progression of renal fibrosis and improves renal function in diabetic rats. The mechanism of action may involve reducing NOX4 expression levels, which inhibits TXNIP/NLRP3 axis activation (79). Ginsenoside Rg5, another potent plant-derived compound, has several pharmacological effects when used to treat DKD. In high-fat diet/streptozotocin-induced diabetic C57BL/6 mice, a study revealed that ginsenosides not only successfully inhibit the activation of the NLRP3 inflammasome but also markedly improve metabolic parameters, including reductions in insulin levels, fasting blood glucose, creatinine, urea and uric acid. This effect involves the suppression of p38 MAPK phosphorylation and the activation of the NF- κ B signaling pathway (80).

The biphenyl diester derivative AB-38b has demonstrated potential medicinal use in the field of new drug development. By inhibiting the activation of the NLRP3 inflammasome through the TXNIP/NLRP3 pathway and suppressing NLRP3 activation by modulating the Nrf2 signaling pathway, this compound carries out its therapeutic effects in two ways to markedly attenuate disease progression of DKD (81). MCC950, a leading NLRP3 inhibitor, has revealed efficacy in numerous trials in the field of specific inhibitors. By selectively blocking NLRP3 activation, this medication potently suppresses pyroptosis and associated inflammatory reactions. Preclinical studies indicate that MCC950 is a novel therapeutic strategy for DKD, as it considerably delays the progression of renal fibrosis and ameliorates renal pathology in diabetic mice (82,83). It has been demonstrated that NLRP3 activation in HK-2 cells is inhibited by CAY10603, a selective inhibitor of histone deacetylase 6 (Table I) (84).

Diabetic retinopathy (DR). DR is one of the most common microvascular complications of diabetes. Epidemiological study reveals ~30% of patients with diabetes develop retinopathy (85). Notably, hyperglycemia-induced retinal damage is irreversible. Even stringent glycemic control fails to arrest progression, frequently resulting in permanent vision loss (86).

Pathological mechanisms of DR. By initiating inflammatory cascades and pyroptosis pathways that collectively cause retinal tissue destruction, the NLRP3 inflammasome carries out a key regulatory role in the onset and progression of DR. The NLRP3 inflammasome in retinal glial cells is aberrantly activated in response to prolonged hyperglycemic stimulation. This results in an excessive production of pro-inflammatory cytokines, such as IL-1 β and IL-18, which damages the retinal neurovascular unit both structurally and functionally. Mitochondrial dysfunction induced by oxidative stress generates free mtDNA and mitochondrial reactive oxygen species (mtROS), which serve as danger signal molecules and interact with the NLRP3 inflammasome to establish a positive feedback loop that amplifies the inflammatory response. A clinical study has demonstrated that the gene transcription levels and protein expression levels of important components of the NLRP3 inflammasome

Table I. Potential pharmacological applications of NLRP3 inflammasome inhibition in the treatment of diabetic kidney disease.

First author/s, year	Treatment	Experimental model	Inducer and dose	Regimen duration	Effects	(Refs.)
An <i>et al</i> , 2020	Punicalagin	C57BL/6 mice	HFD + STZ (100 mg/kg)	8 weeks	Downregulates NLRP3, IL-1 β , GSDMD, caspase-1, NOX4 and TXNIP.	(79)
Zhu <i>et al</i> , 2020	Ginsenoside Rg5	C57BL/6 mice	HFD + STZ (40 mg/kg)	5 weeks	Downregulates ROS, MDA, SOD, GSH-Px, NOX4, TXNIP, NLRP3, ASC, caspase-1, IL-1 β , IL-18, NF- κ B p65, p-ERK, p-JNK and p-p38.	(80)
Lv <i>et al</i> , 2023	Triptolide	C57BL/6 mice	HFD + STZ (50 mg/kg)	12 weeks	Upregulates Nrf2, HO-1, SOD, GSH, NLRP3, ASC, pro-caspase-1 and GSDMD-N.	(74)
		MPC5 cells	HG (25 mM)	48 h	Downregulates ROS, MDA, IL-1 β and IL-18. Upregulates Nrf2, HO-1, SOD, GSH.	
Zhang <i>et al</i> , 2019	MCC950	db/db mice	/	12 weeks	Downregulates MDA, IL-1 β , IL-18, NLRP3, ASC, pro-caspase-1 and GSDMD-N.	(82)
					Downregulates NLRP3, caspase-1 p20, pro-caspase-1, Pro-IL-1 β , IL-1 β p17, TGF- β 1, collagen I and α -SMA.	
		HBZY-1 cells	HG (30 mM)	48 h	Downregulates NLRP3, caspase-1 p20, Pro-caspase-1, IL-1 β p17, TGF- β 1, collagen I and α -SMA.	
Hou <i>et al</i> , 2022	CAY10603	CD-1 mice	STZ (150 mg/kg)	3 weeks	Downregulates HDAC6, Coll1a1, α -SMA, NLRP3, pro-caspase-1, cleaved-caspase-1.	(84)
		HK-2 cells	TGF- β (2.5 ng/ μ l); 5 ng/ μ l)	48 h	Downregulates HDAC6, NLRP3, GSDMD-NT, caspase-1.	
		iBMDM cells	LPS-ATP (2.5 mM); Nig (20 μ M)			

HFD, high fat diet; HG, high glucose; STZ, Streptozotocin; NLRP3, NOD-like receptor family pyrin domain containing 3; ASC, apoptosis-associated speck-like protein containing a CARD; caspase-1, cysteinyl aspartate-specific protease-1; GSDMD, gasdermin D; NOX4, nicotinamide adenine dinucleotide phosphate oxidase 4; TXNIP, thioredoxin-interacting protein; ROS, reactive oxygen species; SOD, superoxide dismutase; MDA, malondialdehyde; GSH-Px, glutathione peroxidase; ASC, apoptosis-associated speck-like protein containing a caspase recruitment domain; HO-1, heme oxygenase-1; Nrf2, nuclear factor-erythroid 2-related factor 2; α -SMA, α -smooth muscle actin; HDAC6, histone deacetylase 6; Coll1a1, collagen type I α 1 chain.

(NLRP3, ASC and caspase-1) in peripheral blood mononuclear cells are elevated in patients with DR compared with healthy controls (87). Vitreous NLRP3 levels are considerably increased in the PDR eyes with tractional retinal detachment (TRD) as compared with PDR eyes (88), suggesting that NLRP3 inflammasome activation may be a key molecular event driving the progression of PDR to TRD.

Activation of the NLRP3 inflammasome has also been implicated in promoting retinal neovascularization by upregulating vascular endothelial growth factor (VEGF). IL-1 β and IL-18, released upon NLRP3 activation, induce VEGF expression in retinal pigment epithelial cells and glial cells. Elevated VEGF levels increase vascular permeability and disrupt the integrity of the blood-retinal barrier (BRB), leading to macular edema and progression to PDR. Inhibition of NLRP3 or its downstream cytokines has been revealed to attenuate VEGF expression levels and improve retinal vascular stability in diabetic models (89).

Signaling pathways in DR. Several types of retinal cells, including Müller glial cells, vascular endothelial cells and retinal ganglion cells, express the P2X7 receptor (P2X7R). The P2X7R is triggered by elevated hyperglycemia, which facilitates the assembly and activation of the NLRP3 inflammasome, as well as the maturation and release of IL-1 β (90). The pro-inflammatory, pro-apoptotic and pro-pyrototic effects of hyperglycemia combined with LPS are markedly attenuated by blocking the P2X7R/NLRP3 signaling pathway, as demonstrated by decreased expression levels of pyroptosis markers (such as GSDMD-N), apoptosis-related proteins (such as cleaved caspase-3) and inflammatory factors (such as IL-6 and TNF- α) (91). A high glucose environment causes excessive ROS generation in human retinal microvascular endothelial cells, which in turn upregulates the expression of TXNIP. Through direct binding to NLRP3, TXNIP facilitates the activation of the NLRP3 inflammasome, which, in turn, increases the release of inflammatory proteins, such as IL-1 β and IL-18. The TXNIP/NLRP3 axis carries out a key role in DR, as evidenced by experiments revealing that inhibiting the TXNIP/NLRP3 axis notably reduces the release of inflammatory factors (92-94).

MicroRNAs (miRs) carry out a key role in regulating the NLRP3 inflammasome. A recent study revealed that miR-17-5p upregulates TXNIP expression under the control of the long non-coding RNA KCNQ1OT1, thereby activating the NLRP3 inflammasome and impairing retinal Müller cell function (95). By contrast, miR-20a and miR-22-3p directly target NLRP3 mRNA to suppress inflammasome activation, thereby exerting neuroprotective effects (96,97). High oxidative stress is a hallmark of hyperglycemia, as reported by Park *et al* (98), levels of ROS are elevated in the cytoplasm and mitochondria of ARPE-19 cells when glucose levels are high. Inhibition of the NF- κ B/NLRP3 pathway successfully protects ARPE-19 cells from high glucose-mediated oxidative stress, inflammation and apoptosis, demonstrating the NF- κ B/NLRP3 pathway's role in maintaining retinal cell homeostasis.

Therapeutic inhibitors of DR. Polydatin, a natural substance, primarily found in the dried roots and stems of *Polygonum cuspidatum*, demonstrates anti-inflammatory

properties (99,100). By activating sirtuin (SIRT) 1 and blocking the NLRP3 inflammasome pathway, it prevents high glucose from damaging Müller cells. This reduces the production of pro-inflammatory and pro-angiogenic factors as well as oxidative stress, which may have therapeutic benefits for DR (101). Additionally, lycopene seed polyphenols have revealed considerable retinal protective effects in db/db mouse models, increasing the thickness of various retinal layers (including the ganglion cell layer, inner plexiform layer, inner nuclear layer, outer plexiform layer and outer nuclear layer and improving blood-retinal barrier (BRB) damage by inhibiting the NLRP3 inflammasome (102). Similarly, spermidine and sarsasapogenin, as natural compounds, have demonstrated protective effects against high glucose-induced inflammatory damage in human retinal pigment epithelial cells, with mechanisms involving the inhibition of ROS production and NF- κ B/NLRP3 pathway activation (103,104). These studies suggest that natural compounds, by modulating inflammatory and oxidative stress pathways, hold potential for treating DR (105,106) (Table II).

In addition to natural compounds, several synthetic inhibitors that specifically target the NLRP3 inflammasome have revealed potential in treating DR. MCC950, a potent and selective NLRP3 inhibitor, blocks the ATPase function of NLRP3 and prevents inflammasome assembly. In diabetic mouse models, MCC950 has been revealed to suppress retinal IL-1 β levels and protect the BRB (107). Similarly, OLT1177 (dapan-sutirle), an orally active NLRP3 inhibitor, has demonstrated anti-inflammatory effects in various models of metabolic and inflammatory disease (108). While clinical data are still limited, these inhibitors represent potential adjuncts to current DR therapies by directly targeting upstream inflammatory signaling (109).

DCM. Myocardial fibrosis, ventricular hypertrophy and heart failure are some of the pathological characteristics of DCM, a cardiac condition that results from persistent hyperglycemia in diabetes. Research suggests that chronic inflammation is a key factor in the development and progression of DCM (110,111), although the exact pathophysiology of the condition remains unclear. The pathophysiology of DCM is associated with the overactivation of the NLRP3 inflammasome. This intracellular immune complex is considered to be a key mechanism causing cardiomyocyte injury, fibrosis and cardiac dysfunction (112).

Pathological mechanisms of DCM. A primary way the NLRP3 inflammasome contributes to the pathogenic mechanisms of DCM is by inducing pyroptosis, which exacerbates cardiac dysfunction (113-116). Through various pathways, hyperglycemia in diabetes triggers the NLRP3 inflammasome, which induces pyroptosis in several cardiac cell types, including cardiomyocytes, fibroblasts and vascular endothelial cells, thereby accelerating the structural and functional alterations in the heart. In particular, oxidative stress induced by hyperglycemia and increased ROS levels encourage TXNIP to bind to NLRP3, which in turn activates the NLRP3 inflammasome and causes cardiomyocyte pyroptosis (117). Furthermore, in diabetic conditions, where high glucose environments, through AGEs and other metabolites, promote fibroblast differentiation into myofibroblasts, increasing

Table II. Potential pharmacological applications of NLRP3 inflammasome inhibition in the treatment of diabetic retinopathy.

First author/s, year	Treatment	Experimental subjects	Inducer and dose	Regimen duration	Effects	(Refs.)
ElSayed <i>et al.</i> , 2023	Memantine	Swiss albino mice	Alloxan (180 mg/kg)	8 weeks	Downregulates glutamate, TXNIP, NLRP3, IL-1 β and MDA.	(105)
Yang <i>et al.</i> , 2024	Scutellarin	SD rats	STZ (60 mg/kg)	42 days	Downregulates TNF- α , IL-1 β , IL-18, NLRP3, ASC and Pro-Caspase-1.	(106)
Wang <i>et al.</i> , 2024	Polydatin	Müller (MIO-M1) cells	HG (30 mM)	24 h	Downregulates GPx, SOD and CAT. Downregulates IL-6, TNF- α , IL-1 β , VEGF, HGF, ROS, MDA, NLRP3 and ASC. Upregulates SOD and SIRT1.	(101)
Xiang <i>et al.</i> , 2023	Lycopene seed polyphenol	db/db mice	/	6 weeks	Downregulates Bax/Bcl-2, caspase-9, IL-1 β , IL-18, TNF- α , NLRP3, ASC, pro-caspase-1, caspase-1 p10, NF- κ B, ve-cadherin, VEGF-A, VEGF-R1 and VEGF-R2.	(102)
		hREC cells	HG (200 mM)	/	Downregulates Bax/Bcl-2, caspase-3, cleaved-caspase-3, NF- κ B, NLRP3, ASC, pro-caspase-1, caspase-1 p20, caspase-1 p10, VEGF-A, VEGF-R1 and VEGF-R2.	
Bang <i>et al.</i> , 2023	Spermidine	ARPE-19 cells	HG (25 mM)	48 h	Downregulates IL-1 β , IL-18, pro-IL-1 β , cleaved-IL1 β , pro-IL18, cleaved-IL-18, NF- κ B, p-I κ B- α , TXNIP, NLRP3, ASC and cleaved caspase-1.	(103)

SD, Sprague Dawley; HFD, high-fat diet; HG, high glucose; STZ, streptozotocin; NLRP3, NOD-like receptor family pyrin domain containing 3; ASC, apoptosis-associated speck-like protein containing a CARD; caspase-1, cysteinyl aspartate-specific protease-1; TXNIP, thioredoxin-interacting protein; ROS, reactive oxygen species; SOD, superoxide dismutase; VEGF, vascular endothelial growth factor; GPx, glutathione peroxidase; CAT, catalase; HGF, hepatocyte growth factor; SIRT1, sirtuin 1; NLRP3, NOD-like receptor family pyrin domain containing 3; MDA, malondialdehyde.

collagen deposition and ultimately leading to myocardial fibrosis, the NLRP3 inflammasome regulates cardiac fibroblasts (118,119). Endoplasmic reticulum stress (ERS) can trigger NLRP3 inflammasome-mediated inflammation and establish a link between inflammatory responses and oxidative stress in myocardial tissue (120). Together, these processes demonstrate the key role the NLRP3 inflammasome carries out in DCM and offer a theoretical foundation for targeted treatments that target this inflammasome.

One of the primary characteristics of DCM is mitochondrial dysfunction, which is also key for the activation of the NLRP3 inflammasome. When cardiomyocytes experience hyperglycemia and lipid overload, they produce more ROS and damage their mitochondrial membranes, which causes mtDNA to leak into the cytosol. NLRP3 recognizes these mitochondrial DAMPs, which encourages its activation. Furthermore, NLRP3 activation and mitochondrial damage are further exacerbated in diabetic rats by decreased mitophagy (121). In DCM, myocardial inflammation, fibrosis and contractile dysfunction are all influenced by persistent activation of the inflammasome. Therefore, focusing on mitochondrial health may be a potential mechanism that can be exploited to reduce inflammasome-driven cardiac damage in patients with diabetes (98).

Signaling pathways in DCM. Degenerative processes of DCM are markedly influenced by the TXNIP/NLRP3 signaling axis, which is implicated in the consequences of diabetes (122). Inhibiting the TXNIP/NLRP3 signaling axis in primary cardiomyocytes from neonatal mice and db/db mouse cardiac cells has been revealed to reduce pyroptosis levels, thereby considerably decreasing myocardial damage (114,123). Furthermore, through binding to and suppressing the production of their target mRNAs, miRs, a type of short non-coding RNA, carry out key roles in controlling cellular inflammatory responses, cell death and fibrosis. For example, increased expression of miR-223-3p protects cardiomyocytes from damage in DCM by inhibiting NLRP3 inflammasome activation in cardiomyocytes via the miR-223-3p/NLRP3 pathway (124). These investigations not only clarify the key functions of miRs and the TXNIP/NLRP3 signaling axis in DCM, but they also offer a theoretical framework for creating tailored treatment plans based on these pathways (125-127).

In DCM, the spleen tyrosine kinase (Syk)/JNK signaling pathway has been associated with NLRP3 inflammasome activation in addition to mitochondrial dysfunction (128). Syk is active in hyperglycemic environments and phosphorylates JNK, which increases NLRP3 transcriptional activation. This exacerbates cardiac inflammation and fibrosis by increasing the production of IL-1 β and caspase-1 activity in cardiomyocytes (129,130). In diabetic animals, inhibition of the Syk/JNK pathway has been revealed to decrease NLRP3 activation and improve cardiac function, suggesting that it may hold therapeutic potential in DCM (128).

Therapeutic inhibitors of DCM. Studies have indicated that NLRP3 carries out a key role in DCM (131,132). An *in vitro* study has demonstrated that, in contrast to the H9C2 cardiac cell group receiving high-glucose therapy, NLRP3 knockdown markedly increases the survival rate and ATP levels of H9C2

cardiac cells while reducing the production of lactate dehydrogenase (LDH) (133). The NLRP3 inhibitor MCC950 has been demonstrated in a study to considerably suppress LDH release in diabetic rats, decrease peripheral inflammatory cell infiltration and relieve cardiomyocyte hypertrophy (133). Furthermore, exogenous hydrogen sulfide shields cardiomyocytes by reducing ROS generation and preventing the activation of the NLRP3 inflammasome (134,135). With research showing that MSCs shield cardiomyocytes by enhancing miR-223-3p expression and preventing NLRP3 activation, mesenchymal stem cell therapy has demonstrated notable potential in the treatment of DCM (124). By blocking NLRP3, natural plant extracts have also been revealed to offer protection against DCM. For instance, in both *in vitro* and *in vivo* models, berberine, a natural extract from *Coptis chinensis*, decreases pyroptosis and NLRP3-dependent inflammation via the mTOR/mtROS pathway (136).

Furthermore, silymarin and puerarin also shield cardiomyocytes by blocking NLRP3 (137,138). In contrast to current aloe-emodin compounds, recent research has synthesized a new molecule called aloe-emodin derivative and revealed that it is more effective at reducing cardiomyocyte pyroptosis in DCM by inhibiting NLRP3 (139). These studies highlight the key function of the NLRP3 inflammasome in the development of DCM and offer a variety of prospective treatment approaches (Table III).

DE. One of the notable signs of diabetes-related central nervous system issues is DE, which is typified by neurodegenerative alterations and cognitive dysfunction (140,141). Hyperglycemia is a considerable risk factor for poor brain neuronal function, according to accumulating research (142-144). Chronic high blood glucose levels in hyperglycemic settings harm neurons and glial cells by triggering oxidative stress, inflammatory reactions and metabolic abnormalities, which ultimately lead to cognitive impairment (144). Among these, hyperglycemia-induced chronic inflammation is considered to be a key pathogenic mechanism in the onset and advancement of DE (145). By breaking down the blood-brain barrier, encouraging glial cell activation and escalating neuroinflammation, the aberrant activation of inflammatory substances and pathways not only directly affects neuronal function but also exacerbates cognitive decline (146).

Pathological mechanisms of DE. Numerous intricate molecular and cellular processes are involved in the pathogenic causes of DE, with inflammatory responses being key to the development and course of diabetic cognitive impairment (147). Ma *et al* (148) used single-cell sequencing of the hippocampus in db/db mice to demonstrate the involvement of inflammation in diabetic cognitive damage. Since microglia are the primary home of the NLRP3 inflammasome, hyperglycemia stimulates these cells, encouraging the production of pro-inflammatory chemicals that ultimately cause neuronal damage (149). Furthermore, recent research reveals that neuroinflammation can be reduced by efficiently suppressing excessive NLRP3 activation-induced microglial responses through the deletion of the microglial cleavage-activating protein (13). Furthermore, studies have demonstrated that the NLRP3 inflammasome is present in both neurons and glial cells, where it regulates tau

Table III. Potential pharmacological applications of NLRP3 inflammasome inhibition in the treatment of diabetic cardiomyopathy.

First author/s, year	Treatment	Experimental subjects	Inducer and dose	Regimen duration	Effects	(Refs.)
Yang <i>et al</i> , 2024	Mesenchymal stem cells	C57BL/6 mice	HFD + STZ (60 mg/kg)	8 weeks	Downregulates NLRP3, Caspase-1, GSDMD and IL-1 β .	(124)
Zhang <i>et al</i> , 2024	Teneligliptin	H9C2 cells	HG (33 mM)	48 h	Downregulates NLRP3, Caspase-1, GSDMD and IL-1 β .	(116)
		C57BL/6 mice	STZ (55 mg/kg)	4 weeks	Downregulates NOX4, NLRP3, caspase-1 and IL-1 β .	
		Primary cardio- myocyte cells	HG (30 mM)	24 h	Downregulates caspase-1, IL-1 β . Upregulates p-AMPK.	
Liu <i>et al</i> , 2024	H ₂ S	SD rats	STZ (60 mg/kg)	8 weeks	Downregulates CBS, CSE, 3-MST, N-GSDMD, cleaved-caspase-1, NLRP3, ASC, IL-18, IL-1 β , ROS and MDA.	(134)
		NRVMs and H9C2 cells	HG (50 mM)	/	Upregulates SOD and GSH. Downregulates CBS, CSE, 3-MST, N-GSDMD, cleaved-caspase-1, NLRP3 and ASC.	
Gao <i>et al</i> , 2022	Cycloviro- buxine D	C57BL/6 mice	HFD + STZ (30 mg/kg)	2 months	Downregulates NLRP3, p-caspase-1, cleaved-caspase-1, GSDMD, GSDMD-N, IL-18 and IL-1 β .	(115)
		PNRCM cells	HG (40 mM)	24 h	Downregulates NLRP3, pro-caspase-1, cleaved-caspase-1, GSDMD, GSDMD-N, IL-18 and IL-1 β .	
Wang <i>et al</i> , 2024	Ghrelin	SD rats	HFD + STZ (35 mg/kg)	2 weeks	Downregulates NLRP3, IL-1 β , cleaved-caspase-1, cleaved-GSDMD, cleaved-caspase-12, CHOP and GRP78.	(120)
		H9C2 cells	HG (33.3 mM) Saturated free fatty acid palmitate (200 μ M)	24 h	Upregulates p-PI3K and p-AKT.	
Zhong <i>et al</i> , 2024	Berberine	db/db mice	/	8 weeks	Downregulates NLRP3, pro-IL-1 β , cleaved-IL-1 β , pro-IL-18, cleaved-IL-18, pro-caspase-1, cleaved caspase-1, pro-GSDMD and cleaved-GSDMD.	(136)
		H9C2 cells	HG (33 mM)	24 h	Downregulates p-mTOR, NLRP3, pro-IL-18, cleaved-IL-18, pro-caspase-1, cleaved caspase-1 p20, cleaved caspase-1 p10 and cleaved-GSDMD.	
Hu <i>et al</i> , 2023	Aloe-Emodin derivative	SD rats	HFD + STZ (30 mg/kg)	4 weeks	Downregulates NLRP3, GSDMD-N and caspase-1.	(139)
Sun <i>et al</i> , 2023	Puerarin	H9C2 cells	HG (50 mM)	24 h	Downregulates NLRP3, ASC, GSDMD-N and caspase-1.	(137)
		H9C2 cells	HG (25 mM)	24 h	Downregulates NLRP3, cleaved-caspase-1, N-GSDMD and P2X7	

PNRCM, primary neonatal rat cardiomyocytes; NRVMs, neonatal rat ventricular myocytes; HFD, high-fat diet; STZ, streptozotocin; HG, high glucose; NLRP3, NOD-like receptor family pyrin domain containing 3; ASC, apoptosis-associated speck-like protein containing a CARD; GSDMD, gasdermin D; NOX4, nicotinamide adenine dinucleotide phosphate oxidase 4; ROS, reactive oxygen species; SOD, superoxide dismutase; MDA, malondialdehyde; GSH-Px, glutathione peroxidase; ASC, apoptosis-associated speck-like protein containing a caspase recruitment domain; HO-1, heme oxygenase-1; Nrf2, nuclear factor-erythroid 2-related factor 2; CBS, cystathionine β -synthase; CSE, cystathionine γ -lyase; 3-MST, 3-mercaptopropionate sulfoxidase; GRP78, glucose-regulated protein 78.

protein phosphorylation to contribute to neurodegenerative processes (150,151). These findings reveal the critical involvement of the NLRP3 inflammasome in the pathogenesis of DE.

Signaling pathways in DE. Through its involvement in several signaling pathways, the NLRP3 inflammasome carries out a key role in the pathogenic processes of DE. Firstly, in mouse models of DE, the SIRT1/NLRP3 signaling pathway reveals notable neuroprotective effects. According to studies, NLRP3-related inflammatory protein expression levels can be suppressed by activating SIRT1, which in turn reduces neuroinflammation and preserves neuronal function (152,153). Secondly, by encouraging autophagy-mediated NLRP3 degradation through the exogenous overexpression of the transcription factor EB, a key regulator of the autophagy/lysosome-nuclear signaling system, microglial activation is reduced, and cognitive impairment and neuronal injury are ameliorated (154). Furthermore, DE is notably influenced by the TXNIP/NLRP3 signaling axis. Inhibiting the TXNIP/NLRP3 axis decreases the inflammatory response of microglia under high-glucose stimulation, whereas overexpression of TXNIP and NLRP3 increases levels of ROS, malondialdehyde and inflammatory cytokines (155,156). Lastly, in diabetic mice, Syk activation causes neuronal pyroptosis via the traditional NLRP3/Caspase-1/GSDMD pathway, which impairs cognitive performance (157).

The TLR4/myeloid differentiation primary response protein 88 (MyD88) signaling axis has a considerable influence on the priming phase of NLRP3 inflammasome activation. The NF- κ B pathway is activated when TLR4 binds the adaptor protein MyD88 in response to DAMP or pathogen-associated molecular pattern (PAMP) recognition (158). This prepares the cell for inflammasome assembly by increasing the transcription of NLRP3, pro-IL-1 β and pro-IL-18 (159). TLR4 signaling is particularly important in diabetes because endogenous ligands or increased LPS persistently stimulate this axis (160).

Therapeutic inhibitors of DE. Due to its anti-inflammatory qualities, the hypoglycemic medication metformin has recently been revealed to alleviate diabetes-induced encephalopathy (161,162). Metformin has neuroprotective benefits via activation of SIRT1 and inhibition of NLRP3 inflammasome activation, which reduces the production of inflammatory markers (such as TNF- α and IL-6) in the hippocampus of db/db mice (153). Both the NLRP3-specific inhibitor MCC950 and exogenous hydrogen sulfide can ameliorate diabetes-associated cognitive dysfunction by inhibiting NLRP3 inflammasome activation (163,164). The compound harmine exerts its effects by inhibiting NLRP3 inflammasome activation and enhancing the BDNF/TrkB signaling pathway (165). Similarly, studies have found that various natural compounds can improve diabetic cognitive impairment (166-168). For example, a study demonstrated that quercetin, a naturally occurring substance, reduces neuroinflammation and preserves neuronal function via the SIRT1/NLRP3 pathway (152). Furthermore, a study demonstrated that gastrodin, a naturally occurring substance with neuroprotective properties, enhances learning and memory in db/db mice while reducing NLRP3 inflammasome activation and endoplasmic reticulum stress (169). Walnuts, known for their brain-boosting properties (170,171), have

recently been revealed to contain walnut-derived peptides that act as NLRP3 inhibitors, alleviating cognitive impairment in T2DM mice (172). These studies not only reveal the potential of metformin and various natural compounds in treating DE but also provide a scientific foundation for developing novel therapeutic strategies targeting the NLRP3 inflammasome and its associated pathways (Table IV).

5. Conclusion and future prospects

The pathophysiology and progression of diabetes mellitus, particularly the development of its numerous comorbidities, are markedly influenced by the NLRP3 inflammasome. Studies have revealed that NLRP3 hyperactivation is the primary cause of chronic inflammation in diabetes, which is associated with insulin resistance, poor glucose management and damage to multiple organs (173,174). A mechanistic understanding of the role that NLRP3 inflammasome hyperactivation carries out in insulin resistance has been made possible by recent research (175).

IL-1 β and IL-18, two important pro-inflammatory cytokines that disrupt insulin signaling pathways (176-178), are cleaved and secreted by the NLRP3 inflammasome when it is activated. By encouraging serine phosphorylation via the JNK and NF- κ B pathways, IL-1 β , in particular, has been demonstrated to disrupt IRS phosphorylation in hepatocytes and adipocytes (179). Aside from its systemic effects, IL-1 β also disrupts the function of pancreatic β -cells by encouraging local inflammation (180). Glycemic imbalance and insulin deficiency are made worse by this β -cell malfunction. Additionally, through macrophage-mediated inflammation in adipose tissue, IL-18 has been associated with the exacerbation of insulin resistance (181).

Additionally, increased M1-polarized macrophage infiltration in insulin-sensitive organs, such as the liver, muscle and adipose tissue, has been associated with NLRP3 inflammasome activation, which intensifies inflammatory signaling (182). NLRP3 carries out a key role in the pathophysiology of insulin resistance in diabetes, as evidenced by the considerable improvements in insulin sensitivity and restoration of normal glucose homeostasis observed in mouse models when it is genetically or pharmacologically inhibited (183,184). The NLRP3 inflammasome sustains systemic inflammatory responses by promoting the release of pro-inflammatory cytokines, such as IL-1 β (185). In addition to worsening diabetes, this persistent inflammation is a considerable contributing factor to complications such as DKD, retinopathy and cardiovascular disorders (122,186).

In patients with diabetes, persistent hyperglycemic conditions activate the NLRP3 inflammasome, triggering a cascade of inflammatory responses (187). Although current therapeutic strategies for diabetes primarily focus on glycemic control, conventional glucose-lowering treatments have limited efficacy in alleviating NLRP3-mediated systemic inflammation (23). Therefore, the development of targeted therapeutic strategies against the NLRP3 inflammasome is warranted. The present review summarizes advances in pharmacological research on targeting NLRP3 inflammasome inhibition for the amelioration of diabetic complications. MCC950, an NLRP3 inhibitor, has demonstrated notable anti-inflammatory

Table IV. Potential pharmacological applications of NLRP3 inflammasome inhibition in the treatment of diabetic encephalopathy.

First author/s, year	Treatment	Experimental subjects	Inducer and dose	Regimen duration	Effects	(Refs.)
Zhai <i>et al</i> , 2018	MCC950	db/db mice	/	12 weeks	Downregulates NLRP3, ASC, IL-1 β and pro-IL-1 β .	(163)
Hu <i>et al</i> , 2024	Metformin	db/db mice	/	8 weeks	Downregulates MDA, NLRP3, cleaved-caspase-1, ASC, IL-1 β and IL-18. Upregulates SOD, CAT, GSH-Px, NGF, PSD95 and SIRT1.	(153)
Liu <i>et al</i> , 2020	Harmine	SD rats	STZ (60 mg/kg)	12 weeks	Downregulates NLRP3, ASC, cleaved-caspase-1, IL-1 β and IL-18. Upregulates BDNF and p-TrkB.	(165)
Chen <i>et al</i> , 2024	H ₂ S	SH-SY5Y cells	HG (33 mM)			
		SD rats	HFD+STZ (40 mg/kg)	30 days	Downregulates NLRP3, ASC, caspase-1 p10, IL-1 β p17 and IL-18. Upregulates CBS, Nrf-2, HO-1 and Lamin B.	(164)
Hu <i>et al</i> , 2020	Quercetin	db/db mice	/	12 weeks	Downregulates NLRP3, cleaved-caspase-1, ASC, IL-1 β and IL-18. Upregulates PSD93, PSD95, BDNF, NGF and SIRT1.	(152)
Ye <i>et al</i> , 2018	Gastrodin	db/db mice	/	12 weeks	Downregulates GRP78, CHOP, p-PERK, p-IRE, TXNIP, NLRP3 and ASC.	(169)
Zhai <i>et al</i> , 2018	Notoginsenoside R1	db/db mice	/	10 weeks	Downregulates NLRP3, ASC, IL-1 β , Pro-IL-1 β , TNF- α , IL-6, CD11b, MDA and TXNIP. Upregulates p-Akt, Nrf2, HO-1 and SOD.	(166)
Li <i>et al</i> , 2024	Walnut-derived peptide	HT22 cells C57BL/6 mice	HG (50 mM) HFD+STZ (50 mg/kg)	4 weeks	Downregulates NLRP3, ASC, caspase-1, NEK7, IL-18, IL-1 β and TNF- α . Upregulates BDNF, MAP2, SNAP25 and SYP.	(172)
Lu <i>et al</i> , 2021	Dioscin	HT22 cells SD rats PC12 cells	HG (75 mM) HFD+STZ (25 mg/kg) methylglyoxal (2.0 mM)	24 h 12 weeks 24 h	Downregulates P2X7R, NLRP3, ASC, caspase-1, IL-18 and IL-1 β .	(168)

HFD, high-fat diet; HG, high glucose; caspase-1, cysteinyl aspartate-specific protease-1; STZ, Streptozotocin; NLRP3, NOD-like receptor family pyrin domain containing 3; ASC, apoptosis-associated speck-like protein containing a CARD; GSDMD, gasdermin D; NOX4, nicotinamide adenine dinucleotide phosphate oxidase 4; TXNIP, thioredoxin-interacting protein; ROS, reactive oxygen species; SOD, superoxide dismutase; MDA, malondialdehyde; GSH-Px, glutathione peroxidase; ASC, apoptosis-associated speck-like protein containing a caspase recruitment domain; HO-1, heme oxygenase-1; Nrf2, nuclear factor-erythroid 2-related factor 2; CBS, cystathionine β -synthase; TrkB, tropomyosin receptor kinase B; PSD, postsynaptic density protein; SYP, synaptophysin; BDNF, brain-derived neurotrophic factor; NGF, nerve growth factor; MFN1, mitofusin 1; OPAL, optic atrophy 1; SIRT1, Sirtuin 1; CD11b, integrin subunit α M; GRP78, glucose-regulated protein 78; P2X7R, P2X purinoceptor 7 receptor.

effects in experimental studies and is progressing to clinical trials (188-190), offering novel therapeutic perspectives for diabetes and its complications. However, emerging evidence of its hepatotoxicity necessitates further safety evaluations.

Metformin, recognized as the optimal initial therapeutic agent for diabetes (191) has been reported in the present review to potentially exert anti-inflammatory effects through modulation of the NLRP3 inflammasome. Furthermore, traditional herbal medicines, characterized by their high safety profile and minimal side effects, have emerged as potential sources for regulating the NLRP3 inflammasome. Natural compounds, such as ginsenosides and berberine, have shown potential in inhibiting NLRP3 activation through multiple mechanisms, not only alleviating diabetes-associated chronic inflammation but also improving pancreatic islet function and glycemic control, thereby demonstrating substantial clinical application prospects.

Enhancing the selectivity, stability and targeted delivery of NLRP3 inflammasome inhibitors should be the primary goals of future research. Delivery technologies based on nanotechnology, including liposomes, nanoparticles and exosomes, offer intriguing avenues for enhanced tissue-specific distribution and improved bioavailability. Furthermore, new inhibitors, such as dapansutride and CY-09, have demonstrated promising outcomes in preclinical models and warrant additional clinical testing (192). Therapeutic targeting of upstream components of the inflammasome cascade, such as TLR4/NF- κ B or downstream components, such as IL-1 β , may offer supplementary or alternative approaches. The practical applicability and effectiveness of inflammasome-targeted therapies in diabetes and associated complications could be markedly improved by integrating precision medicine techniques, such as genetic screening, patient stratification and biomarker-guided therapy (193).

The novelty of the present review lies in the systematic integration of the multidimensional mechanisms by which hyperglycemia activates the NLRP3 inflammasome, overcoming the limitations of previous single-pathway studies (34,194). To the best of our knowledge, the present review incorporates the classical AGEs-RAGE-NF- κ B pathway, the mitochondrial oxidative stress-TXNIP pathway, the endoplasmic reticulum stress-UPR pathway and non-canonical pathways into a unified framework for the first time, revealing the core pathological mechanism of the 'metabolism-inflammation vicious cycle'. In terms of diabetic complications, it provides a relatively comprehensive discussion of the role of NLRP3 in DKD, DCM, DR and DE, along with associated signaling pathways and existing inhibitors. By bridging fundamental mechanisms with clinical translation, the present review not only analyzes the limitations of current inhibitors but also prospectively explores novel therapeutic strategies in the discussion section, such as the application prospects of nanodrug delivery systems and precision medicine. These insights could inform future research on diabetic chronic inflammation mechanisms and therapeutic development.

However, certain limitations exist. The majority of the NLRP3 inhibitors included (such as, MCC950) are still limited to animal models or early-stage clinical trials, and their long-term efficacy and safety require validation in large-scale

human studies. Additionally, NLRP3 inflammasome activation exhibits tissue-specific differences (for example, pancreatic β -cells vs. adipose tissue) and current research has yet to fully elucidate its precise regulatory networks in various target organs. In conclusion, future research focusing on novel NLRP3 inhibitors and optimization of existing treatment regimens holds promise for delivering more effective and safer therapeutic options for patients with diabetes.

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Competing interests

The authors declare that they have no competing interests.

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