OPEN ACCESS

Scholars International Journal of Biochemistry

Abbreviated Key Title: Sch Int J Biochem
ISSN 2616-8650 (Print) | ISSN 2617-3476 (Online)
Scholars Middle East Publishers, Dubai, United Arab Emirates
Journal homepage: https://saudijournals.com

Review Article

Nutraceutical Regulations of Inflammasome Signaling in Non-Communicable Diseases: A Review

Adeoye Bayo Olufunso[1*], Owie Mercy Iriagbonse[1], Olanrewaju Okikiola Olamide[1], Omobude-Aisagbonhi Elizabeth[1], Akinn-Akanbi Funmilayo Ajaere Sandra Onyinyechi[1], Adeyemi Funmilayo Elizabeth[1], Bolade Damilola Comfort[1], Olawuyi Faith Abiola[1]

[1]Department of Biochemistry, School of Basic Medical Sciences, Babcock University, Ilisan-Remo, Ogun State, Nigeria

DOI: https://doi.org/10.36348/sijb.2025.v08i01.003 | **Received:** 12.11.2024 | **Accepted:** 16.12.2024 | **Published:** 19.02.2025

***Corresponding author:** Adeoye Bayo Olufunso
Department of Biochemistry, School of Basic Medical Sciences, Babcock University, Ilisan-Remo, Ogun State, Nigeria

Abstract

Inflammasome protein cascades are very crucial as endogenous defence mechanisms. Nevertheless, their deregulation usually exacerbates deleterious chronic diseases. It is a large multicomplex cytosolic protein that plays a vital role in the innate immune system, therefore, acting as a vital mediator in the pathogenesis of non-communicable diseases. Pro-inflammatory cytokines like IL-1β and IL-18 are produced as a result of inflammatory reactions triggered by key inflammasomes. Notably, rheumatoid arthritis is largely caused by inflammasomes, particularly NLRP1 and NLRP3, which cause excessive inflammation and tissue damage by releasing cytokines that promote bone resorption and cartilage degradation. The development of stroke is facilitated by the NLRP3 inflammasome, which promotes inflammation and neuroinflammation, both of which cause brain damage. The pathogenesis of hypertension are significantly influenced by inflammasomes, especially NLRP3, which promote oxidative stress and inflammation, which worsen high blood pressure, cause cardiac fibrosis, and contribute to vascular and renal dysfunction. In asthma, inflammasomes primarily cause tissue damage and airway inflammation by activating NLRP3, which in turn causes the release of IL-1β and IL-18. This activation worsens asthma symptoms like inflammation and airway hyperresponsiveness while also boosting immunological responses, especially in Th2 and Th17 cells. The mechanisms governing inflammasome construction and activation, as well as the possibility of targeting inflammasomes to treat a variety of disorders, have thus become the focus of more recent study.

Keywords: Inflammasome, Rheumatoid Arthritis, Stroke, Hypertension, Asthma.

INTRODUCTION

Inflammasomes are large multicomplex cytosolic proteins that play significant role in the innate immune system. As a feedback to cellular damage or infectious agents inflammasome is formed. Inflammasome activation yields inflammation which aids in the growth of various non-communicable diseases. The inflammasome assembly consists of the sensor proteins (usually NLRs which includes a central nucleotide-binding and oligomerization domain (NACHT), C-terminal leucine-rich repeats (LRRs) *(Chen & Xu, 2022)* and an N-terminal effector domain that can either be pyrin domain (PYD), or a caspase recruitment domain (CARD) in the case of NLRC4), the adaptor apoptosis-associated speck-like protein containing CARD (ASC) and pro-caspase-1 *(Bulté et al., 2023)*

Pattern recognition receptors (PRRs) are activated to identify both damage-recognition associated patterns (DAMPs) and pathogen-recognition associated pattern (PAMPs), initiated by microbial invasion, cellular damage or injury *(Evavold et al., 2019).* The PRRs are grouped into five major classes, namely: Absent in melanoma 2-like receptors (ALRs), Nucleotide-binding domain and leucine-rich repeat receptors (NLRs), Toll-like receptors (TLRs), C-type lectin receptors (CLRs), and RIG-I-like receptors (RLRs) *(Bulté et al., 2023).* Some inflammasomes which are large cytoplasmic complexes are mainly formed by several NLRs and ALRs, for instance NLRP1, NLRP3, NLRC4, and AIM2 *(Xu et al., 2024).*

Non-Communicable disease have gradually become a worldwide health concern affecting the health structure and populations. According to World Health

Organization (WHO), Non-communicable diseases are referred to as chronic diseases, caused by physiological, behavioral, genetic and environmental factors and tend to be long-term. Types of Non-communicable diseases include cardiovascular diseases, Cancer, Diabetes and chronic respiratory disease *(WHO, 2023)*.

Per year 41 million people perish due to Non-communicable diseases, which is equal to 74% of all deaths globally. Before the age 70, 17 million people die annually from NCDs; 86% of these premature deaths arises in low- and middle-income countries. In the NCDs death, cardiovascular diseases accounts for 17.9 million annually, Cancer (9.3 million), chronic respiratory disease (4.1million) and diabetes (2.0 million including kidney disease caused by diabetes). The harmful use of alcohol or tobacco, poor physical activity, unhealthy diets and air pollution increases the chances of dying from NCDs. In 2019, the World Health Assembly extended the WHO Global action plan to reduce by one third premature mortality from NCDs through prevention, and treatment *(WHO, 2023)*.

The activation of immune cells and inflammatory activators could lead to the progression of various diseases if improperly controlled. For example, in Arthritis especially Rheumatoid Arthritis immune cells intensify inflammation resulting to degradation of bone and cartilage and bone resorption. Likewise, in Alzheimer's disease it could contribute to neuronal damage. Hence, this research aims to illuminate the role of inflammasome signaling in various Non-Communicable diseases.

The Canonical Pathway of Inflammasome Activation

The activation of the NLRP3 inflammasome involves a two-signal process; priming and activation.

A-Signal 1 (Priming the NLRP3 Inflammasome):

The priming amplifies the transcription of pro-IL-1β and NLRP3 proteins in the presence of ASC and pro-caspase1. The priming begins when macrophages are subjected to PAMPs and DAMPs to activate their respective cell surface receptors like TLR. This promotes the nuclear factor-kappaB (NF-κB) signaling pathway and increases the production of NLRP3 and cytokines. The TLRs are triggered by PAMPs/DAMPs, nuclear factor-kappaB (NF-κB) signaling is increased through MyD88 and TRIF molecules. Apoptoic signaling molecules (caspase-8 and FADD) influence (NF-κB) activation during priming as they are involved in NLRP3 transcription. Priming not only boosts the transcription of pro-IL-1β and NLRP3 but also triggers the ionic flux (K^+, CL-efflux, Ca^{2+} influx) events necessary for its activation *(Xu et al., 2024)*.

B-Signal 2 (Activating the NLRP3 Inflammasome):

Whilst the priming step prepares the main components of NLRP3 inflammasome for assembly into active multiprotein complex, the assembly is activated by the second signal (B-signal 2) resulting to the maturation and release of cytokines and triggers pyroptosis. This process begins when activated caspase-1 cleaves gasdermin (GSDMD) to facilitate the release of mature cytokines and yield pyroptosis. Normally, both NLRP3 and pro-IL-1β are of subthreshold concentration in unstimulated macrophages. Hence, the priming prepares them for activation by stimuli by enhancing their expression. The activation of NRLP3 is conditioned by 3 vital mechanisms: Lysomal damage, Ionic flux and Reactive oxygen species (ROS). Although various mechanism of NLRP3 activation are extensively researched, some remain contradictory *(Xu et al., 2024)*.

The Non-Canonical Pathway of Inflammasome Activation

This pathway activates the non-canonical caspases such as caspase-4, caspase-5, and caspase-11; where caspase-4 acts as the main caspase for NLRP3 activation. The activation of NLRP3 inflammasome in this pathway is triggered by Gram-negative infections *(Yao et al., 2024)*. Lipopolysaccharide is released into the cytosol of phagocytes to stimulate any of the caspases (independent of TLR4) *(Xu et al., 2024)* leading to the opening of pannexin 1 channel. This causes the ATP to enter through this channel to promote potassium efflux and upregulates the NLRP3 inflammasome to release of the cytokines *(Kodi et al., 2024)*. This also causes the caspases the cleavage of GSDMD to produce a N terminal domain to induce membrane pores causing the release of mature cytokines which consequently yields pyroptosis. *(Xu et al., 2024)*.

Inflammasome Signaling in Non-Communicable Diseases

Alzheimer's Disease

Alzheimer's disease is a neurodegenerative disease caused by the progressive decline in cognitive function and is common in older people. It develops due to the aggregation of atypical form of protein tau (Tau Tangles) inside the neurons and protein fragment β-Amyloid into clumps (β-Amyloid plagues) outside the neurons, followed by the destruction of neurons and damage to brain tissue (Neurodegeneration). The β-amyloid destroys the neurons by disrupting the neuron-neuron synapses, while the tau tangles obstructs the translocation of nutrients and other molecules vital for the optimal function and viability of neurons while damaging the connections between neurons. It is assumed that the presence of toxic tau proteins and β-amyloid initiates the innate immune system cells called Microglia. Chronic inflammation commences when the microglia can not continue to eliminate toxic proteins and residues from dead cells *(Alzheimer's Association, 2024)*.

Apart from β-amyloid and tau proteins, oxidative stress, neuroinflammation and metal ion accumulation are also significant hallmarks in Alzheimer's disease. Inflammasome (such as NLRP3,

NLRP1 and NLRC4) plays a key role in the pathogenesis of Alzheimer's disease. The β-amyloid activates the NLRP3 inflammasome, subsequently releasing IL-1β to stimulate neuroinflammation *(Shen et al., 2022)*. β-amyloid is mainly synthesized in neurons and released into the cerebrospinal fluid (CSF) and blood from the brain. Upon surpassing a critical limit, β-amyloid creates oligomers, fibrils and stores it in neurotic plaques that acts as DAMPSs to activate NLRP3 inflammasome *(Yao et al., 2024)*. The NLRP3 inflammasome can also be stimulated by dying neurons releasing ATP. The release of ATP causes the P2X7 receptors on microglia to activate NLRP3 inflammasome and gradually aggravate inflammation and damage *(White et al., 2017)*.

In contrast to NLRP3 known for being produced in microglia *(White et al., 2017)*, the NLRP1 is primarily expressed in neurons associated by K+/Ca2+ alteration due to the neurotoxic effects of β-amyloid on ion channels *(Bulté et al., 2023*) resulting to axonal degeneration and neuronal death *(White et al., 2017)*.

Fatty acid metabolism is expressed as a risk factor in the development of Alzheimer's disease. This is because NLRC4 inflammasome is activated on response to palmitate fatty acid in astrocytes. The NLRC4 is activated in astrocytes when IL-1β is secreted to palmitate, causing upregulation of ASC and NLRC4 *(White et al., 2017)*.

Parkinson's Disease

Parkinson's disease is a chronic neurodegenerative disease that affects the motor system. The pathological hallmarks of Parkinson's disease include the gradual loss of dopaminergic neurons in the substantia nigra (SN) pars compacta and the presence of Lewy bodies consisting of fibrillar aggregates of α-synuclein (α-syn) in neurons. Also, infiltration of peripheral immune cell and the activation of astrocytes and microglia could result to Parkinson's disease development *(Shen et al., 2022)*.

Chronic inflammasome is activated by pathogenic accumulating misfolded protein aggregates. The NLR3 Inflammasome activated by the accumulating misfolded α-synuclein results in dopaminergic (DA) neuronal cell death via the secretion of proinflammatory cytokines *(Jewell et al., 2022)*. It requires both cathepsin B- and caspae-1to activate. TLRS inhibitors could obstruct the release of IL-1β by α-syn in the monocytes and microglia *(Yao et al., 2024)*. The caspase-1 associates with lewy bodies by direct cleavage of α-synuclein generating aggregation prone fragments that are toxic to neuronal culture *(Bulté et al., 2023)*. The nuclear factor kappaB (NF-kB) signaling regulates the synthesis of cytokines *(Shen et al., 2022)*. Overall, the activation of NLRP3 by the α-synuclein shows the link between inflammasome and Parkinson's disease.

PSORIASIS

Psoriasis is an inflammatory skin disease where the skin cells, keratinocytes, and immune cells relates actively with each other. It develops as a result of abnormal differentiation, excessive expansion of keratinocytes and immigration of neuroinflammatory cells *(Wu et al., 2023)*. Psoriasis inflammation may be induced by air pollutants, drugs, sun exposure or mechanical stress *(Sieminska et al., 2024)*.

Immune cells are mobilized and activated to secrete cytokines (IL-17, IL-22, and tumor necrosis factor TNF-α) by external stimuli to promote keratinocytes expansion *(Wu et al., 2023)*. Hence, the interaction between the immune cells and keratinocytes leads to the secretion of cytokines. NLRP3 inflammasome was discovered to be four times higher in psoriasis samples when analyzed with normal skin biopsy samples. Extracellular ATP acts as an alarmin to induce IL-23/IL-17 axis and NF-κB activation via P2X7R signaling in NLRP3 expression. Also, in Langerhans and melanocytes AIM2 is expressed in normal conditions, and elevated in keratinocytes in inflammatory condition. The presence of cytosolic DNA triggers the AIM2 inflammasomes, secreting proinflammatory cytokines in keratinocytes only. Another inflammasome is NLRP1 and is found to have a relationship between its complex variations and psoriasis. The biochemical outcomes of different single nucleotide polymorphisms such as rs12150220, rs6502867 and rs878329 was evaluated in psoriasis. And the over transmission of NLRP 1 rs878329C and rs8079034C genotypes in psoriasis was reported. Aside from the NLRs members, TLRs plays a vital role in the innate immune system facilitating the development of psoriasis *(Ci ̨a ̇zy ́nska et al., 2021)*.

CANCER

Abnormal cells that develop frantically and go pass its usual boundaries to invade the adjacent parts of the body is known as Cancer *(WHO, 2023)*. The major pathological hallmark of cancer is tumor immune microenvironment. It consists of cell types such as pericytes, endothelial cells, and immune inflammatory cells. These cells stimulate IL-1β, IL-17, etc. which causes proliferation of cancer cells. The secretion of these cytokines by cancer cells leads to malignant proliferation and produces matrix metalloproteinases (MMPs) and other adhesion factors that promotes neovascularization for the nutrition supplementation of tumor cells proliferation *(Wu et al., 2023)*.

In the manifestation and development of tumors, inflammasomes could act as a protector or a foe. Inflammasome activations trigger the immune response to restrict the invasion of pathogens by regulating caspase-1-dependent cell pyroptosis to cause cell death under chronic inflammation and stress, hence, playing its role as a protector. And acting as a foe, when the irregulation of inflammasome activation results in

hyperinflammatory state, thereby, creating an environment that promotes metastasis and tumor growth *(Deng et al., 2023)*.

The NLRP1 is said to have a biological function in the *in vivo* and *in vitro* melanoma circumstances. They discovered that in the cells of the cytoplasm, NLRP1 was present and that knocking tumor-promoting events results from NLRP1 down regulation *(Balahura et al., 2020)*.

Though, the inflammasomes exacts its protective roles than its cons, the cytokines produced is found to be highly present in cancer patients such as breast cancer, colon cancer or melanomas. Following the activation of PAMPs, IL-1β is produced but its activation is joined to DAMPs, a secondary stimulus. IL-1β molecules are secreted in the cytosol, once they are produced by inflammasome, they bind to IL-1RI to form heterodimer with the IL-1R accessory protein. These events result in IL-1 signaling pathway activation. Thereafter, intracellular adaptor protein, MyD88, phosphorylates IL-11R via cytoplasmic Toll/IL-1 receptor (TIR) domain. Thus, interleukin-1 receptor associated kinases (IRAKs) and TNF receptor-associated factors are triggered to activate specific NF-κB and MAP Kinases. Afterwards, NF-κB is moved to the nucleus to initiate the transcription of several proinflammatory molecules; within them are vascular endothelial growth factor (VEGF), IL-6, tumor necrosis factor alpha (TNFα), and inducible nitric oxide synthase *(Balahura et al., 2020)*.

Rheumatoid Arthritis

Rheumatoid arthritis is a chronic autoimmune disease that majorly affects the synovial joints lining and is related with premature death, progressive disability and socioeconomic burdens. Bone erosion, systemic consequences, cartilage damage and hyperplastic synovium are the various hallmark of Rheumatoid arthritis *(Guo et al., 2018)*. Genetic factors such as gene mutations, also play a key role in the pathogenesis of Rheumatoid Arthritis. Inflammasomes like NLRP1 and NLRP3 aids in the development of Rheumatoid Arthritis, such that NLRP1 is highly expressed due to the disparities in NLRP1 gene and the inflammatory complex-related genes of NLRP3 is produced in the peripheral blood mononuclear cells (PBMCs). Overstimulation of NLRP3 complex results in excess inflammation and unneeded host tissue damage which aids the intensity of RA *(Yang et al., 2022)*.

Pro-inflammatory cytokines namely, IL-1, IL-16, Tumor necrosis factor (TNF), and IL-18, are excessive in the synovial fluid and membrane of rheumatoid patients. Therefore, facilitating osteoclast production by Macrophage colony-stimulating factor (M-CSF) and RANKL expression by its synovial fibroblasts and TNF. These proinflammatory cytokines stimulate cartilage-degrading enzymes like aggrecanases and Matrix Metalloproteinases (MMPs), which activate the production of synovial fluid and inhibit the production of extracellular matrix by chondrocytes in synovial fibroblasts. As a result, cartilage decomposition occurs in rheumatoid patients due to its excessive response. The production of proinflammatory cytokines promote Th17 cell differentiation which decreases the synthesis of cartilage components and inhibit osteoblast generation through several mechanisms *(Yang et al., 2022)*.

Also, in rheumatoid patients, bone resorption is highly increased in the osteoclast lineage cells by the NLRP3 inflammasomes, which promotes IL-1β and IL-18 production. The DAMPs or PAMPs increase involved in osteolysis aids polynuclearization and the production of IL-1β and IL-18, which increases the inflammasome activity in osteoclasts and osteoclast progenitors. The multinucleation and expansion of osteoclasts is gotten from RANKL and M-CSF is induced by IL-1β. Nevertheless, it stimulates the translocation of osteoclasts precursors, which leads to quantitative change osteoprotegerin (OPG), M-CSF, and C-X3-C motif ligand 1 (CX3CL1) involved in hyper differentiation *(Yang et al., 2022)*.

Stroke

A stroke is caused by an abrupt disruption of cerebral blood flow, which happens when cerebral arteries burst or become occluded *(Jung & Seong, 2021)*. It is classified into two, namely Ischemic Stroke and Hemorrhagic Stroke. The latter is caused by disruption of a cerebral blood artery, and the former, caused by blood vessel and supply to a portion of the brain becoming occluded, which results to loss of function *(Masenga & Kirabo, 2024)*. Pathological hallmarks responsible for cell death and injury includes endothelial dysfunction, atherosclerosis, and neuroinflammation. However, early pathological mechanisms such as ATP depletion, oxidative stress, mitochondrial damage, and influx of Ca^{+}, lead to inflammasome activation and upregulation in ischemic stroke. This in turn, facilitates the activation and migration of vascular smooth tissue cells, macrophages, neutrophils, etc. to the ischemic are thereby, aggravating tissue injury and fibrotic changes *(Masenga & Kirabo, 2024)*.

It was discovered that ischemic stroke triggers NF-κB and MAPK signaling pathway activation in ischemic neurons in the brain, which encourages the NLRP3 inflammasome activation and afterwards, brain injury and neuronal cell death *(Masenga & Kirabo, 2024)*. PRRs recognize DAMPS from mitochondrial ROS and dying neurons *(Jung & Seong, 2021)*, and cellular debris from the damaged parenchyma in ischemic stroke causing the activation of NF-κB, following priming. However, adapter proteins such as TRIF and MyD88 are implicated in the NLRP3 inflammasome activation. After priming, JAMM domain-containing Zn2+ metalloprotease called

BRCC36, facilitates NLRP3 activation after the phosphorylation of ASC and deubiquitination. The ASC is recruited to stimulate the inflammasome cascade *(Masenga & Kirabo, 2024)*.

Similar to the NLRP3 inflammasome, NLRP1 is expressed in the microglia and neurons after the ischemic stroke. However, AIM2 and NLRC4 are activated to trigger the inflammatory response along with pyroptosis in microglia during the ischemic stroke *(Jung & Seong, 2021)*.

HYPERTENSION

A diastolic pressure of more than 80 mmHg and a systolic pressure of more than 130 mmHg refers to Hypertension *(Miguel et al., 2021)*. High salt intake, increased sympathetic nervous system activation and a compromised renin-angiotensin-aldosterone system (RAAS) response, lead to the development of hypertension *(Iqbal & Jamal, 2023)*. Inflammation is also a major contributor to the development of hypertension *(Miguel et al., 2021)*.

It has been frequently shown that during hypertension, inflammatory cells (T cells and macrophages) can enter the brain, kidney and vasculature organs, involved in blood pressure regulation. IL-1, IL-6, IL-17, and TNF-α, inducers of vascular and renal dysfunction, are synthesize and released by activated inflammatory cells. Activation of the inflammatory cells, particularly T cells, can facilitate the local production of prohypertensive stimuli (Angiotensin II) and can further elevate blood pressure by promoting fluid retention and vascular constriction. Therefore, in hypertension, there is an elevated increase of NLRP3 expression caused by the DAMPs detected by the PRRs on antigen-presenting cells *(Miguel et al., 2021)*.

ASTHMA

Asthma is an inflammatory disease driven by the action of the airway, resulting in airway remodeling, obstruction, hyperresponsiveness and mucus hyper-production *(Kudo et al., 2013)*. T lymphocyte inflammation involving CD4 aggregation and eosinophilic inflammation are involved in the pathogenesis of asthma. Chronic airway inflammation is induced by strong chemical mediators by inflammatory cells, resulting in airway remodeling in asthma *(Wu et al., 2021)*.

It was shown that the NLRP3 receptor detects Charcot-Leyden crystals, which can form after eosinophil degranulation. These crystals encourage ASC-involved NLRP3 inflammasome assembly and IL-1β production, sustaining chronic inflammation following eosinophilic inflammation *(Wu et al., 2021)*. Also, in the asthmatic airway, exposure to pathogens or allergens; cigarette smoke, causes the production of ROS cytokines, and NETs. These substances can then activate the NLRP3 inflammasome in airway epithelial cells as well as infiltrating eosinophils. Increased Th1 Th2 and/or Th17 cell infiltration and related pathological effects, including airway remodeling, AHR, mucus hypersecretion, and, are the outcomes of this augmented release of IL-1β and IL-18 *(Theofani et al., 2019)*.

Table 1: Bioactive compounds with anti-inflammasome properties

Bioactive Compounds	**Natural Source**	**Mechanisms of Inflammasome Inhibition**	**References**
W-3-fatty acid	Sea foods	Hinders NLRP3, AIM2, and NAIP5/NLRC4 inflammasomes expression	*(Adeoye et al., 2024)*
Docosahexaenoic acid (DHA)	Fish oil	Decreases in TNF-α production triggered by the NF-kB receptor activator ligand (RANKL).	(*Wang et al., 2021*)
Berberin	*Hydrastis canadensis*, *Coptis chinensis*,	Pathway inhibition of NF-kB	(*Wang et al., 2021*)
Curcumin	Tumeric (*Curcuma longa)*	Inactivates NF-kB, thereby reducing the upregulation of proinflammatory cytokines	(*Wang et al., 2021*)
Epigallocatechin-3-gallate (EGCG)	Green tea	Inhibits AIM2 inflammasome by reducing the amount of IFN- -γ-induced priming signal	*(Ci ̨azy ́nska et al., 2021)*
Ellagic Acid	Berries	Protects DA neurons by suppressing Microglia's NLRP3 inflammasome activation	*(Shen et al., 2022)*
Brevilin A (BA)	*Centipeda minima*	Inhibits ASC oligomerization and NLR inflammasomes.	*(Chen & Xu 2022)*
Resveratol	Blueberries, Grapes, Mulberries	Inhibits the production of activation of NLRP3 inflammasome-induced pyroptosis by modifying the Sirt1/AMPK pathway	*(Olufunso et al., 2024: Wang et al., 2021)*

CONCLUSION AND FUTURE DIRECTIONS

Several recent studies have shown that inhibiting inflammasomes acts as a therapeutic target for treatments. Tranilast, an allergy medication is used to hinder NLRP3 assembly formation by directly binding to the NACHT domain. This blocks biochemical binding between NLRP3 molecules, thus, preventing ASC from binding *(Yao et al., 2024)*. Canakinumab, a monoclonal antibody IL-1β inhibitor targets the IL-1 receptor and IL-1α inhibiting the tumor growth *(Li et al., 2021)*. Caspase-1 inhibitors like Ritonavir and Disulfiram inhibits synthesis of GSDMD pores and IL-1β release. MCC950 (also called CP-456773), an extensively researched NLRP3 inhibitor is a chemical compound that contains diaryl sulfonylurea and directly targets the walker B motif in the NACHT domain of NLRP3, keeping NLRP3 in an inactive state. P2X7R inhibitor such as Avastin prevents the NLRP3 activation by ATP *(Chen & Xu 2022)*. However, the inflammasomes plays different roles in the pathogenesis of diseases, therefore more clinical trials are conducted to develop more drug inhibitors.

REFERENCES

- Adeoye B., David, A. A., Phillips, A. O., Bangsi, A. C., Olajoju, O. M., Oluwadunsin, A. I., Babatunde, O. O., Olubukola, A. O., Moore, A. G. S., Adebola, A. O., Ezekiel, A. A., Emmanuel, K. O., Temitope, A. B., Olusayo, O. G., Oyebimpe, O. I., & Blessing, F. (2024). Molecular crossfires between inflammasome signalling and dietary small molecule inhibitors in neurodegenerative diseases: Implications for medical nutrition therapy. *EAS Journal of Biotechnology and Genetics*, *6*(4), 68–75. https://doi.org/10.36349/easjbg.2024.v06i04.002
- Bulté, D., Rigamonti, C., Romano, A., & Mortellaro, A. (2023). Inflammasomes: Mechanisms of action and involvement in human diseases. *Cells*, *12*(1766). https://doi.org/10.3390/cells12131766
- Carvalho, R. V. H. de, & Zamboni, D. S. (2020). Inflammasome activation in response to intracellular protozoan parasites. *Trends in Parasitology*, *36*(4), 304–317. https://doi.org/10.1016/j.pt.2020.02.006
- Chen, C., & Xu, P. (2022). Activation and pharmacological regulation of inflammasomes. *Biomolecules*, *12*(7), 1005. https://doi.org/10.3390/biom12071005
- Chen, H., & Jiang, Z. (2013). The essential adaptors of innate immune signaling. *Protein & Cell*, *4*(1), 27–39. https://doi.org/10.1007/s13238-012-2063-0
- Ciążyńska, M., Olejniczak-Staruch, I., Sobolewska-Sztychny, D., Narbutt, J., Skibińska, M., & Lesiak, A. (2021). The role of NLRP1, NLRP3, and AIM2 inflammasomes in psoriasis: A review. *International Journal of Molecular Sciences*, *22*(11), 5898. https://doi.org/10.3390/ijms22115898
- De Miguel, C., Pelegrín, P., Baroja-Mazo, A., & Cuevas, S. (2021). Emerging role of the inflammasome and pyroptosis in hypertension. *International Journal of Molecular Sciences*, *22*(3), 1064. https://doi.org/10.3390/ijms22031064
- Deng, Z., Lu, L., Li, B., Shi, X., Jin, H., & Hu, W. (2023). The roles of inflammasomes in cancer. *Frontiers in Immunology*, *14*, Article 1195572. https://doi.org/10.3389/fimmu.2023.1195572
- Evavold, C. L., & Kagan, J. C. (2019). Inflammasomes: Threat assessment organelles of the innate immune system. *Immunity*, *51*(4), 609–624. https://doi.org/10.1016/j.immuni.2019.08.005
- Guo, Q., Wang, Y., Xu, D., Nossent, J., Pavlos, N. J., & Xu, J. (2018). Rheumatoid arthritis: Pathological mechanisms and modern pharmacologic therapies. *Bone Research*, *6*, 15. https://doi.org/10.1038/s41413-018-0016-9
- Iqbal, A. M., & Jamal, S. F. (2023, July 20). *Essential hypertension*. In *StatPearls* [Internet]. StatPearls Publishing. Available from https://www.ncbi.nlm.nih.gov/books/NBK539859/
- Jewell, S., Herath, A. M., & Gordon, R. (2022). Inflammasome activation in Parkinson's disease. *Journal of Parkinson's Disease, 12*(Suppl. 1), S113–S128. https://doi.org/10.3233/JPD-223338
- Jung, K. H., & Seong, S. Y. (2021). Role of inflammasomes in neuroinflammation after ischemic stroke. *Encephalitis*, *1*(4), Article e2021.00073. https://doi.org/10.47936/encephalitis.2021.00073
- Kodi, T., Sankhe, R., Gopinathan, A., Nandakumar, K., & Kishore, A. (2024). New insights on NLRP3 inflammasome: Mechanisms of activation, inhibition, and epigenetic regulation. *Journal of Neuroimmune Pharmacology*, *19*(7). https://doi.org/10.1007/s11481-024-10101-5
- Kudo, M., Ishigatsubo, Y., & Aoki, I. (2013). Pathology of asthma. *Frontiers in Microbiology*, *4*, Article 263. https://doi.org/10.3389/fmicb.2013.00263
- Li, Y., Huang, H., Liu, B., Zhang, Y., Pan, X., Yu, X. Y., Shen, Z., & Song, Y. H. (2021). Inflammasomes as therapeutic targets in human diseases. *Signal Transduction and Targeted Therapy*, *6*(1), Article 247. https://doi.org/10.1038/s41392-021-00650-z
- Lu, H. F., Zhou, Y. C., Hu, T. Y., Yang, D. H., Wang, X. J., Luo, D. D., Qiu, S. Q., Cheng, B. H., & Zeng, X. H. (2024). Unraveling the role of NLRP3 inflammasome in allergic inflammation: Implications for novel therapies. *Frontiers in Immunology*, *15*, 1435892. https://doi.org/10.3389/fimmu.2024.1435892
- Masenga, S. K., & Kirabo, A. (2024). The NLRP3 inflammasome in ischemic stroke. *Frontiers in Stroke*, *3*, Article 1382379. https://doi.org/10.3389/fstro.2024.1382379

- Mi, L., Min, X., Chai, Y., Zhang, J., & Chen, X. (2022). NLRP1 inflammasomes: A potential target for the treatment of several types of brain injury. *Frontiers in Immunology, 13,* Article 863774. https://doi.org/10.3389/fimmu.2022.863774
- Theofani, E., Semitekolou, M., Morianos, I., Samitas, K., & Xanthou, G. (2019). Targeting NLRP3 inflammasome activation in severe asthma. *Journal of Clinical Medicine, 8*(10), Article 1615. https://doi.org/10.3390/jcm8101615
- Wang, R. X., Zhou, M., Ma, H. L., Qiao, Y. B., & Li, Q. S. (2020). The role of chronic inflammation in various diseases and anti-inflammatory therapies containing natural products. *ChemMedChem*. https://doi.org/10.1002/cmdc.202000996
- White, C. S., Lawrence, C. B., Brough, D., & Rivers-Auty, J. (2016). Inflammasomes as therapeutic targets for Alzheimer's disease. *Brain Pathology, 27*(6), 736–749. https://doi.org/10.1111/bpa.12478
- World Health Organization. (2023). *Noncommunicable diseases*. World Health Organization. Retrieved November 10, 2024, from https://www.who.int/news-room/fact-sheets/detail/noncommunicable-diseases
- Wu, X., Ma, Y., Wang, L., & Qin, X. (2023). A route for investigating psoriasis: From the perspective of the pathological mechanisms and therapeutic strategies of cancer. *International Journal of Molecular Sciences, 24*(18), 14390. https://doi.org/10.3390/ijms241814390
- Xu, Z., Kombe Kombe, A. J., Deng, S., Zhang, H., Wu, S., Ruan, J., Zhou, Y., & Jin, T. (2024). *Molecular Biomedicine, 5*(14). https://doi.org/10.1186/s43556-024-00179-x
- Yang, G., Kang, H. C., Cho, Y. Y., Lee, H. S., & Lee, J. Y. (2022). Inflammasomes and their roles in arthritic disease pathogenesis. *Frontiers in Molecular Biosciences, 9*, 1027917. https://doi.org/10.3389/fmolb.2022.1027917
- Yao, J., Sterling, K., Wang, Z., Zhang, Y., & Song, W. (2024). The role of inflammasomes in human diseases and their potential as therapeutic targets. *Signal Transduction and Targeted Therapy, 9*, 10. https://doi.org/10.1038/s41392-023-01687-y
- Zheng, Y., Xu, L., Dong, N., & Li, F. (2022). NLRP3 inflammasome: The rising star in cardiovascular diseases. *Frontiers in Cardiovascular Medicine, 9*, 927061. https://doi.org/10.3389/fcvm.2022.927061