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Review article

NLRP inflammasome as a key role player in the pathogenesis of environmental toxicants

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ABSTRACT

Exposure to environmental toxicants (ET) results in specific organ damage and auto-immune diseases, mostly mediated by inflammatory responses. The NLRP3 inflammasome has been found to be the major initiator of the associated pathologic inflammation. It has been found that ETs can trigger all the signals required for an NLRP3-mediated response. The exaggerated activation of the NLRP3 inflammasome and its end product IL-1β, is responsible for the pathogenesis caused by many ETs including pesticides, organic pollutants, heavy metals, and crystalline compounds. Therefore, an extensive study of these chemicals and their mechanisms of inflammasome (INF) activation may provide the scientific evidence for possible targeting of this pathway by proposing possible protective agents that have been previously shown to affect INF compartments and its activation. Melatonin and polyunsaturated fatty acids (PUFA) are among the safest and the most studied of these agents, which affect a wide variety of cellular and physiological processes. These molecules have been shown to suppress the NLRP3 inflammasome mostly through the regulation of cellular redox status and the nuclear factor-κB (NF-κB) pathway, rendering them potential promising compounds to overcome ET-mediated organ damage. In the present review, we have made an effort to extensively review the ETs that exert their pathogenesis via the stimulation of inflammation, their precise mechanisms of action and the possible protective agents that could be potentially used to protect against such toxicants.

1. Introduction

The inflammasome (INF) as a part of the innate immune system plays a pivotal role in the host defense against harmful threats. It consists of intracellular multi-protein compartments possessing typical structures of sensory, adaptor and effector functions. The sensory compartment is responsible for the detection of damage- and pathogen-associated molecular patterns (DAMPs and PAMPs, respectively). The adaptor compartment is typically the apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC) and the effector compartment is the pro-caspase 1, which is cleaved and activated following the INF assembly [1,2]. The NLRP3 inflammasome belongs to the NOD-like receptor (NLR) family and has been widely studied [3,4]. NLRP3 consists of three main domains including an ASC-interacting N-terminal domain known as the pyrin domain, a C-terminal leucine rich domain with modulatory function and an intermediate domain known as the nucleotide tri-phosphatase domain, responsible for oligomerization [5]. Oligomerization is an essential step, which initiates the subsequent events required for NLRP3 activation. During this process, the nucleotide tri-phosphatase domains interact with each and enable the pyrin domain to interact with ASC, which finally ends up in pro-caspase 1 clustering and caspase 1 activation [6]. Detailed steps of NLRP3 oligomerization have been illustrated in Fig. 1. The proteins of this complex are widely expressed in immune cells including macrophages, monocytes, T-cells, B-cells and many non-immune cells such as hepatic satellate cells, osteoblasts and fibroblasts [7]. Since many none-

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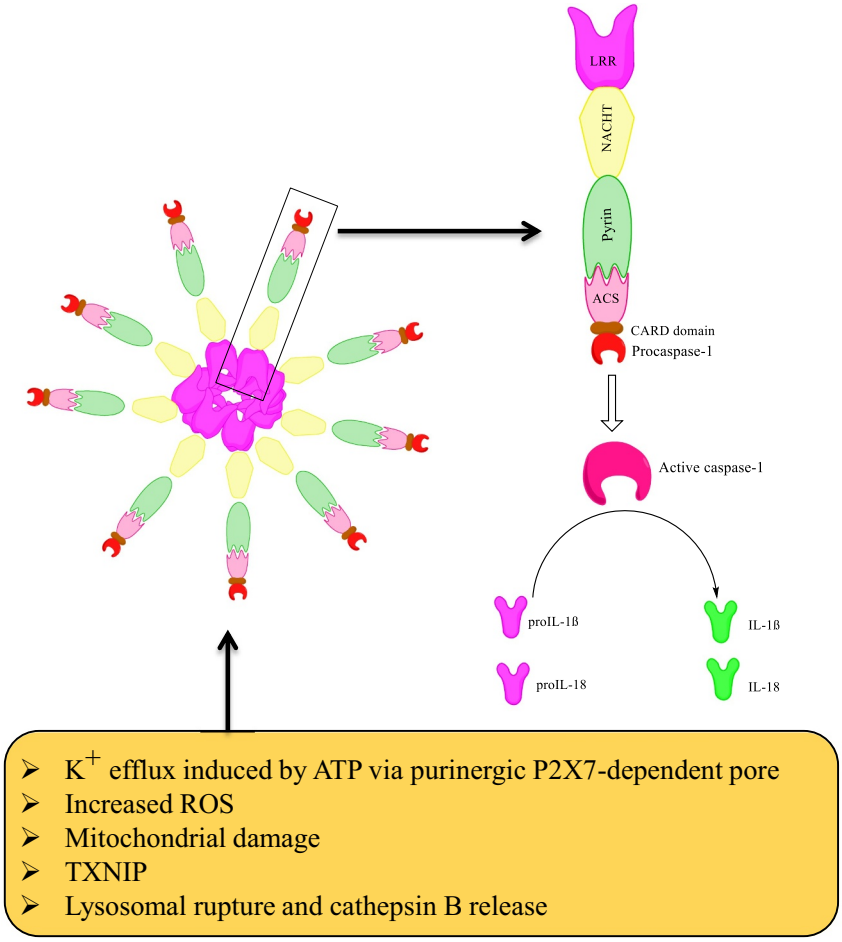

Fig. 1. Molecular mechanisms of NLRP3 oligomerization: Upon an insult, the transcription of NLRP3 and interleukins (proIL-1β, and proIL-18) is induced via PRR mediated activation of MAPK signaling pathway followed by nuclear translocation of NF-κB; this step is known as priming. Secondary insults (cell threatening signals) trigger NLRP3 oligomerization. Either of the initiating signals such as K+ efflux induced by ATP via purinergic P2X7-dependent pores, increased ROS, mitochondrial damage, TXNIP, lysosomal rupture or cathepsin B release may affect the LRR domain of the INF, which results in oligomerization. The oligomerization occurs through the interaction of the NATCH domains. This, further gives rise to the interaction of the clustered PYD domains with ACS, which per se, facilitates the interaction of the clustered caspase activation and recruitment domains (CARDs) with procaspase-1.

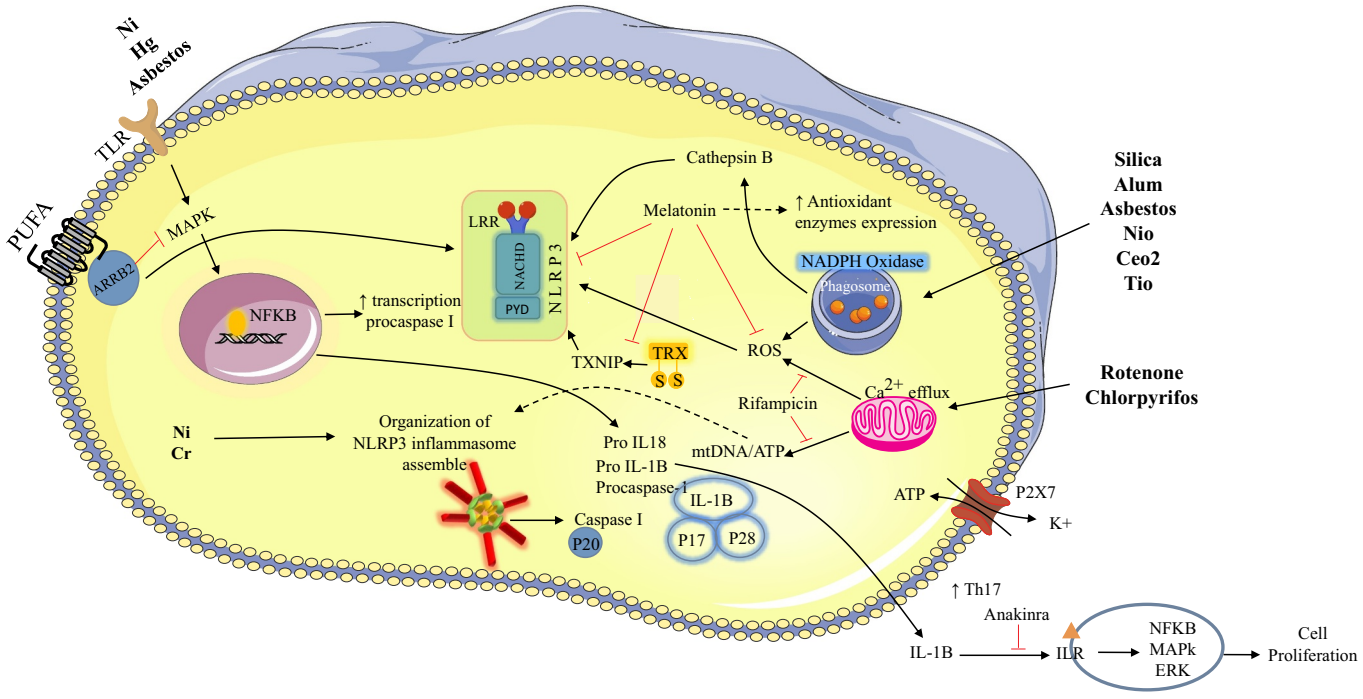

Fig. 2. The underlying mechanisms of ET–induced NLRP3 activation and the protective agents.

Table 1
The underlying mechanisms of ET–induced NLRP3 activation.

Ref	Toxicant class	Toxicant	Specific organ damage	Outcome	In vitro/in vivo
[45]	Pesticides	Paraquat	Kidney damage	Activation of NLRP3, DAPK and NF-κB ↑ Secretion of IL-1β and IL-18	In vivo; male wistar rat
[40]		Paraquat	Lung injury	↑NLRP3, ASC, caspase 1 expression, ↑ cytokines,IL-1β and IL-18 levels	In vitro/ in vivo; RAW264.7 mouse macrophages, rat
[60,62]		Chlorpyrifos	Skin inflammation	↑NLRP3, ASC, caspase 1 expression; ↑ IL-1β secretion; ↑ ROS generation; ↑ mitochondrial Ca^{2+} efflux; ↑ pro-apoptotic proteins	Invitro; Human skin keratinocyte cell line
[50]		Rotenone	–	Mitochondrial dysfunction; ↑ NLRP3 inflammasome activation Solely: no effect on caspase 1 activation	In vitro; Bone marrow-derived macrophages
[59]		Rotenone	Reduced aldestrone induced renal injury	↓ Aldestrone induced renal injury Inhibition mitochondrial complex I; ↓ Aldestrone induced ROS generation and NLRP3 activation	In vivo; Sprague-Dawley rats
[53]		Rotenone	Dendritic cells injury	↑ROS generation; Activate NLRP3 indirectly	In vitro
[54]		Rotenone	Macrophage	↑ Caspase 1 activation;stimulated IL-1β cleavage	In vitro
[67]	Organic compounds	DBP	liver	↑Caspase 1 and IL-1β expression	In vitro; HepG2 and L02 Cells
	Heavy metals				
[18]		Chromium (hexavalent)	Skin(delayed type hypersensivity)	No effect on IL-1β expression; ↑ Release IL-1β and its cleaved products:p17,P28	In vitro
[78]		Chromium	Human macrophages	↑ Release IL-1β; lysosomal destabilization	In vitro
[80]		Nickel	Antigen-presenting cells (contact dermatitis murine alveolar	↑ Mitochondrial reactive oxygen species; ↑ Release IL-1β	In vitro
[81]		Nickel oxide nanoparticle	Rat, RAW264.7 cells	↑Inflammatory cell infiltration; ↑Cytokine secretion ion; ↑ Expression of Nlrp3, caspase 1; ↑ IL-1β secretion	In vitro/ In vivo
[82]		NiO and CeO2 engineered nanomaterial	C57BL/6 J mice	↑ Cathepsin B activity; ↑Pro-inflammatory cytokine release; NLRP# inflammasome activation	In vivo
[84]		Mercury	DBA/2 J mice /B10·S	↑ mRNA expression IL-1β; ↑TNF-alpha; ↑ INF- gamma; ↑ Gamaglobulinemia; CD4 + T cell activation; ↑ Cathepsin B	In vivo
	Crystaline environmental toxicant				
[90]		Silica	Lung injury	↑ IL-1β secretion ↑ IL-18 secretion ↑ Caspase 1 activation ↑ ROS generation ↑ IL-1β, bFGF and HMGB1 secretion	In vitro Immortalized human Bronchial epithelial cell line BEAS 2B, macrophage like cell line THP-1/ In vivo
[86]		Silisca	Pleural fibrosis and malignant mesotheliomas	↑ IL-1β release and mRNA level of pro IL-1β ↑Caspase 1 activity ↑Cathepsin B ↑ Acid sphingomyelinase activity	In vivo; malignant mesothelioma xenograft mice model
[95]		Silica	–	Inflammasome actination ↑immunoglobulin E ↑NLRP3 independent prostaglandin E2 secretion	In vitro; In vivo
[99]		Sio2/tio2	Intestinal dendritic cells	MHC-II up regulation; CD80 and CD86 upregulation ↑ Release IL-1β ↑Rrelease IL-1β ↑ ROS generation	In vitro (BMDC) In vivo;C57BL/6 mice caspase 1- or NLRP3-deficient mice
[100]		Amorphous silica particles	–	↑ Release IL-1β indirect correlation with particle size (invitro) Phagocytosis NLRP3 activation (invitro) ↑ ROS ↑ NLRP3 inflammasome activation ↑Cathepsin B Invivo: ↑Inflammation; ↑ release IL-1β in peritoneal cavity lavage fluid (PCLF); ↓ Viable cells in peritoneal cavity lavage fluid (PCLF)	THP-1 human macrophage like cells/ Female C57BL/6 mice

(*continued on next page*)

Table 1 (*continued*)

Ref	Toxicant class	Toxicant	Specific organ damage	Outcome	In vitro/in vivo
[93]		Silica and ATP	Sterile inflammation	↑ Caspase 1 activation; ↑ IL-1β secretion in cells pretreated with TNF-alpha ↑ NLRP3 inflammasome activation	In vivo
[101]		Asbestos/Erionite	Pleural injury	Activate IL-1 receptor ↑Transcription of NLRP3 mRNA ↑Release alarmin, HMGB1 from human mesothelial cells ↑Release IL-1β, IL-6, IL-8, ↑ ReleaseVascular Endothelial Growth Factor (VEGF)	In vitro (human mesothelial cells); In vivo (human xenograft model of peritoneal MM)
[106]		Asbestos	Malignant mesothelioma	Up-regulation of IL-1b, IL-18; ↑ Vimentin and N-cadherin upregulation Ecadherin downregulation	Invitro Immortalized human peritoneal [LP9/hTERT (LP9)], primary Human pleural (HPM-3), and peritoneal (HM3) Mesothelial cells In vivo
[8]		Chrysotile asbestos /Libby six-mix	Lung injury	↑ROS; ↑Activation ERK; ↑ IL-1β, IL-6; ↑Cell death; ↑Activation of caspase 1 and release of IL-1 β; Activation MAPK cascade; Increased phosphorylation of ERK and Cot (MAP3K8), Increased AP-1 binding activity ↑Induced IL-6 release	THP-1 cells (macrophage cell line)/ BEAS-2B cells(bronchial epithelium representor)
[108]		Asbestos	Mesothelioma		In vivo (mice)

NLRP3, Nucleotide-binding domain and Leucine-rich Repeat containing Protein 3; **MAPK**, Mitogen-Activated Protein Kinase; **NF-κB**, nuclear factor-κB; **ROS**, Reactive Oxygen Species; **ASC**, Apoptosis-associated speck-like protein containing caspase 1 activator domain.

homologous molecules can activate NLRP3, a wide spectrum of danger signals can induce its assembly. The activation of this INF consists of two major steps including an induction step mediated by different environmental stimuli and the subsequent production of NF-κB-upregulating pro-inflammatory cytokines. The oligomerization may be triggered by increased generation of reactive oxygen species (ROS), K^+ efflux or reduced intra-cellular cAMP followed by the intracellular Ca^{2+} accumulation and mitochondrial destruction [8,9]. Although the INF pathway is one of the key mechanisms of the innate immunity required for defense against pathogens and other non-pathogenic insults, its inappropriate activation can lead to the excessive secretion of pro-inflammatory cytokines and the aberrant activation and differentiation of some subtypes of immune cells mainly Th1 and Th17, which have been implicated in the pathogenesis of many immune-mediated and autoinflammatory diseases. Such a process plays an inevitable role in the chronic inflammation underlying many metabolic disorders including gout and type II diabetes as well as some autoimmune diseases such as rheumatoid arthritis (RA), inflammatory bowel disease (IBD) and systemic lupus erythromatous [10–13]. Moreover, the purinergic receptor P2X7 (P2X7R)-mediated activation of the NLRP3 inflammasome has been reported to induce the progression of atherosclerotic plaques [14]. NLRP3 over activation is also involved in cerebral and myocardial ischemic diseases including ischemic strokes and myocardial ischemia/reperfusion models [15,16]. Furthermore, the increased levels of IL-1β results in increased T cell survival, IL-2 upregulation and increased B-cell proliferation. Enhanced expression of IL-18, another product of INF, also leads to increased Th-1 proliferation and enhancement of Th-17 activity [17].

The new life style of the modern human and his increasing need for food along with the industrialization of societies and the tremendous advances in agriculture has led to an extensive use of synthetic materials as well as organic compounds such as pesticides, putting millions of people at a high risk of exposure to life-threatening environmental pollutants. Exposure to these toxic agents leads to specific organ damage, including liver injuries, respiratory tract damage and fibrosis, mostly caused by the inflammatory responses to these toxicants. Some toxicants increase mitochondrial ROS production, which per se leads to increased LDH levels and the depletion of antioxidant enzymes. Some of them alter the efflux of the potassium and calcium ions and change cellular homeostasis [18], while others exert their noxious effects via inducing intracellular organ damage, which consequently disrupts normal cell differentiation or causes cell apoptosis [19]. There are plenty of studies in the literature, that provide evidence on the involvement of NLRP3 inflammasome in the pathology caused by many environmental toxicants (ET). The observation during which the knock down of NLRP3 resulted in the abrogation of inflammatory responses caused by these toxicants further confirmed the involvement of this pathway [18,20]. Therefore, an extensive study of ETs involved in the exaggerated activation of the INF pathway will increase our knowledge of the precise mechanisms responsible for their toxicities and may provide the evidence to introduce the NLRP3 inflammasome as a possible target to protect against these toxicities.

In this regard, the fundamental role of INF in the development of inflammatory diseases has encouraged scientists to look for agents that inhibit its activation. Since ET-induced inflammation is not an exception, it seems logical to hypothesize that proper targeting of NLRP3 may alleviate the damage caused by such pollutants. The IFN inhibitors are categorized into four major groups including small molecules, type I interferons (IFN) such as IFN-β, autophagy inducers, and microRNAs [7]. However, their use is strongly limited due to the significant side effects of these agents that most frequently overweigh their benefits. For instance, two small molecules benzenesulfunamides and CY-09 could induce myocardial injuries and cognition and metabolic disorders when they were used as INF inhibitors [21,22]. Despite various attempts that have been made for discovering new inhibitors so far, there is still need for more selective and safer ones. Melatonin, a pleiotropic small molecule which freely penetrates cell membranes, exerts a wide range of biological effects including autophagy regulation, immunomodulation, homeostasis, proliferation induction, anti-angiogenesis and anti-oxidant activities [23,24]. It also has been used to overcome pesticide-induced toxicity mostly by protecting mitochondrial structure and its biological activity [25]. Moreover, it has been found to be effective in radiotherapy-induced mucositis and sepsis through interference with NLRP3 assembly [26]. Dietary polyunsaturated fatty acids (PUFA), are among potent and safe anti-inflammatory agents. These compounds regulate the immune response via INF inhibition in various pathologic conditions such as metabolic disorders, chronic obstructive disease and ET-induced neuro-degenerative diseases [27–29].

Table 2
The protective agents against NLRP3 inflammasome-mediated injuries.

Ref	Environmental pollutant	Protecting agent	Dosage of protecting agent	Proposed mechanisms of protecting agent	In vivo/in vitro study
[72]	Cadmium	Melatonin	10 mg/kg Ip: daily 3 days before	↓ ALT/AST ↓Production of pro-inflammtory cytokines ↓ NLRP3 ↓ expression of TXNIP	In vivo C57BL/6 mice
[57]	Rotenone	Rifamicin	25–100 μM Optimum concentration:50	↓ rotenone-induced cytotoxicity; ↓ IL-1β gene expression ↓ ROS generation ↓ NLRP3 inflammasome activation	In vitro
[116]	Sepsis	Melatonin	30 mg/kg	↓ Mitochondrial ROS generation ↓Transcriptional activity of NF-κB ↓ Protein level of NLRP3 ↓ Caspase 1 and active IL-1β Noeffect on expression of ASC and pro-caspase 1 ↑RORa mRNAexpression	In vivo and in vitro C57BL/6 J mice NF-κB -RE-luc mice
[26]	Radiotherapy induced gut toxicities	Melatonin	45 mg/kg Local administration into mouth	↓ Intestinal apoptosis ↑ Mucosal recovery ↓ Mitochondrial dysfunction ↓ NF-kB /NLRP3 signaling activation	In vivo
[118]	Sepsis	Melatonin	30 mg/kg	↓Rev Erbα expression ↑Nampt expression and further increased SIRT1and consequent ↑RORα expression Similar inhibitory effects between melatonin and NLRP3 deficient mice	Wild-type and NLRP3 −/− mice
[120]	LPS-induced acute lung imjury	Melatonin	30 mg/kg IT	↓Infiltration of macrophages and neutrophils into lung Blockage the release of extracellular histones Blockage NLRP3 activation	In vivo
[127]	Diabetes retinopathy	Resolvin D1 (RvD1)	1000 ng/kg	Suppress NF-kB activation ↓NLRP3 inflammasome expression Decrease NLRP3 activation	In vivo
[129]	Hyperhomocysteinemia Glomerular injury	Resolvin D1 (RvD1) and 17S-HDHA	50 mg/kg/day by oral gavage: large dose of DHA (to reach blood concentration of DHA about 2.54 mM).	↓ NLRP3 inflammasome assemble ↓ROS	C57BL/6 J WT and NLRP3 KO mice
[130]	Concavalin A Liver injury	Protectin D1	20 or 10 μg/kg	↓ Tumor necrosis factor-α; interferon-γ; IL-2, Il-1β and Il −6. Downregulate cluster differentiation of CD4+, CD8+ ↓ NK cell infiltration ↓ TLR and NLRP3 component mRNA and protein level ↓ phPosphorylation NF-kB and further NF-κB/CX3CL1/CX3CR1 activation	C57BL/6 mice
[125]	Saturated Fatty acid induced Hepatic injury	PUFA		↓NF-κB; p65 protein expression	In vitro; In vivo C57BL/6 mice

ALT, alanine aminotransferase; **AST**, aspartate aminotransferase; **NLRP3**, Nucleotide-binding domain and Leucine-rich Repeat containing Protein 3; **ROS**, Reactive Oxygen species; **NF-κB**, nuclear factor-κB; **ASC**, Apoptosis-associated speck-like protein containing caspase 1 activator domain; **SIRT 1**, sirtuin 1; **CX3CL1/CX3CR1**, chemokine (C-X-C motif) ligand 1 CX3C chemokine receptor 1.

In the present work, we have made an extensive review of the studies focusing on the commonly used ETs that induce NLRP3 over activation to provide the scientific evidence to introduce this pathway as a target of therapeutic interventions. We have introduced melatonin and PUFAs as safe protective candidates for overcoming INF-mediated pathologies of ETs by summarizing the underlying mechanisms through which these agents induce their inhibitory effects.

2. Pesticides and NLRP3 activation

2.1. Paraquat

1, 1′-dimethyl-4,4′-bipyridinium dichloride known as paraquat is a none-selective but highly efficient herbicide. Accidental or voluntary paraquat poisoning leads to high mortality rate due to the lack of selective antidotes [30,31]. It causes damage in multiple organs including the liver, kidneys, lung and the heart [32]. ARDS (acute respiratory distress syndrome) due to bronchial and alveolar injury and subsequent lung fibrosis is the most frequent underlying cause of paraquat fatality. This organ-specific injury could be due to the high expression of NLRP3 in the alveolar fluid resident macrophages [33]. Paraquat poisoning has been linked to changes in redox cycle and ROS production that initiate the immune responses of the innate immune system [30]. In response to the increased ROS levels, the production of IL-1β and the expression of NF-κB is enhanced. Furthermore, it has been shown that NF-κB acts as a transcription factor that enhances interleukin-1β (IL-1β) and tumor necrosis factor α (TNF-α) production [34]. In fact, there is a reciprocal association between NF-κB expression and TNF-α levels such that the increased levels of TNF-α also alters NF-κB expression [35]. Moreover, ROS activate NOD-like receptors and the effector component of NLRP3 inflammasome that results in the production of IL-1β and IL-18 [36]. According to previous studies, NLRP3 levels increase in hemorrhagic

shock and hypoxia-induced lung injuries [20,37–39]. In a previous study, to explore whether or not NLRP3 was involved in a paraquat-induced lung injury, histopathological parameters of the lung, NLRP3 expression and changes in interleukin levels were evaluated after intraperitoneal (IP) administration of paraquat in rats. It has been shown that malonyldialdehyde levels in the bronchial alveolar lavage fluid (BALF) had increased displaying excess ROS production. The expression of NLRP3, ACS and caspase 1 as well as their protein levels had also increased in a time dependent manner. In fact, NLRP3 had increased initially and the rise in ASC and caspase 1 levels was observed at later times. IL-1β and IL-18 levels were also increased in the BALF. To verify the role of NLRP3 in lung injury glibenclamide, an ATP-induced K channel inhibitor, was used as the NLRP3 an inhibitor. As expected, glibenclamide had no effect on malonyldialdehyde levels, while it reduced alveolar myeloperoxidase, IL-1β and IL-18 levels [40]. Likewise, it was shown that ROS could induce NF-κB production, which was associated with transcriptional regulation of TNF-α, interleukin production through NLRP3 inflammasome [41,42].

Kidney injury, another major complication of paraquat toxicity, has been demonstrated to be the result of alterations in the oxide/redux cycle [43]. In a previous study, paraquat produced excess ROS resulting in the reduction of superoxide dismutase and catalase levels in rat kidney [44]. In another study, paraquat administration altered the histopathological and biochemical parameters of kidney including BUN and serum creatinine levels and caused renal proximal tubular congestion and interstitial hemorrhage. Moreover, it could provide both signals required for NLRP3 inflammasome activation via inducing excess ROS generation and translocation of NF-κB to the nuclei of kidney cells [45]. To explore the underlying mechanism, an NF-κB inhibitor was administered before paraquat exposure. It significantly reduced NLRP3, dephosphorylated DAP (death associated protein) and serum cytokine levels and finally improved kidney biochemical markers. The pivotal role of NF-κB in INF activation is also observed in lupus nephritis [46]. It is shown that phosphorylation status of the death-associated protein kinase (DAPK) is involved in cell survival and apoptosis during oxidative stress [47]. In this regard, the treatment of NRK-52E cells with a DAPK-targeted siRNA inhibited caspase 1 activation; however, no change was observed in the levels of NLRP3, ACS and pro-inflammatory cytokines [45]. It is suggested that the DAPK inhibitor interferes with NLRP3 inflammasome assembly leading to lower levels of pro-inflammatory cytokines and consequently reduced injury [45,48]. Moreover, it was shown that although NF-κB activation is involved in the elevation of TNF-α levels, DAPK inhibition displayed no alteration in TNF-α levels indicating that both TNF-α and NF-κB play roles upstream of DAPK [45].

2.2. Rotenone

Rotenone, an active ingredient of pesticides, inhibits electron transfer complex chain I, which results in impaired mitochondrial respiration, disrupted mitochondrial membrane potential and the consequent ROS generation [49]. It is shown that rotenone co-stimulation with ATP or simultaneous stimulation with rotenone and ATP facilitates INF assembly and triggers NLRP3-mediated caspase 1 activation, while it does not alter the transcriptional level of NLRP3 [50]. Since mitochondrial damage is one of the most important deteriorative effects of rotenone exposure, this agent may be regarded as an stimulator of NLRP3 INF. Furthermore, it is proved that excess ROS activates caspase 1 and increases mitochondrial membrane potential that finally results in mitochondrial damage and potassium efflux [50]. Conversely, some studies suggest that rotenone may not activate the INF through mitochondrial damage [4,51]. Moreover, in contrast to some studies that report the crucial role of mitochondrial membrane permeability transition pores in rotenone-induced NLRP3 activation [50,52], the blockage of these pores showed no inhibitory effects on the rotenone-induced activation, demonstrating the involvement of other mechanisms. In some cases extracellular signal regulated-kinases (ERK) have been found to be involved in NLRP3 inflammasome activation, the inhibition of these kinases had no effect on rotenone/ATP induced activation of inflammasome [50]. Treating dendritic cells with rotenone indirectly activates NLRP3 inflammasome which increases oxidative DNA damage by prolonging P53 activation causing cell death [53]. Rotenone, alum and mono-urate sodium crystals stimulate double-stranded RNA dependent protein kinase (PKR) phosphorylation; this kinase interacts with the activator components of NLRP3 and increases the translocation of high motility group box 1 (HBMG1) from the nucleus to the cytoplasm in the subsequent inflammatory cascades [54]. Stimulation of $PKR^{-/-}$ macrophages with rotenone had no effect on caspase 1 activation confirming the important role of upstream PKR in INF activation [54]. It has been reported that the rotenone-induced oxidative stress and the increased release of pro-inflammatory mediators through a p38-mediated cascade are involved in the development of Parkinson's disease [55,56]. Rifampicin reverses the rotenone-induced increase of IL-1β mRNA levels through NLRP3 suppression as well as decreased caspase 1 cleavage, which is due to reduced ROS generation and decreased disruption of mitochondrial membrane proteins [57]. Controversially, rotenone has been shown to play protective roles in kidney disease via the inhibition of mitochondrial respiratory chain resulting in less ROS generation. [58]. An in vivo study demonstrated that rotenone ameliorates aldosterone-induced kidney injury via the reduction of ROS generation and NLRP3, ASC, IL-1 β, and IL-18 expression that could be mainly due to the inhibition of mitochondrial complex chain I [59].

2.3. Chlorpyrifos

Chlorpyrifos, an organophosphorus pesticide, causes none organ-specific toxicity through respiratory and skin exposure [60]. It is found that chlorpyrifos-induced oxidative stress mediated by mitochondrial ROS generation results in neural cell damage and dermatitis [61]. Chlorpyrifos induces oxidative stress, stimulates the intrinsic pathway of apoptosis, and increases active IL-1β levels, which is associated with inflammatory skin diseases. Treating human keratinocytes HaCaT cells with chlorpyrifos resulted in decreased cell viability in a dose dependent manner with an IC50 of 820 μM, which was due to an increase in the pro-apoptotic proteins, Apaf-1 and caspase 9. Furthermore, pretreatment of cells with mitochondria-targeted ROS scavengers diminished the assembly of the components. The role of INF and the associated cytokines in skin hypersensivities has been also reported [62,63]. Regarding chlorpyrofos toxicity, caspase 1 inhibitors and mitochondrial ROS scavengers may be assumed as effective therapies.

3. Organic pollutants and NLRP3-mediated autoimmune diseases

3.1. Plasticizers

DBP, ditubyl phthalate, DEHP, and di (2-ethylhexyl) phthalate, known as air and water pollutants, are phthalate esters commonly used in plastic industry to maintain the flexibility of the products and are widely found in toys, in medications as coating agents and in food industry as food packaging material [64]. These chemicals most frequently affect the endocrine and the immune systems and cause elevated inflammatory cytokine production following their exposure. Plasticizers cause immune cells to accumulate in the liver and activate the INF. They also cause chronic and acute liver pathologies including increased beta oxidation and structural damage [65,66]. In a previous study, the treatment of liver cells with DBP increased extracellular ATP and caspase 1 and IL-1β expression that all together indicate NLRP3 activation. A mechanistic study showed that ROS and cathepsin B, a lysosomal rupture product, do not show any alteration during NLRP3 activation; however, the inhibition of the ATP-gated P2X7 ion channels can interfere with NLRP3 activation resulting in reduction of caspase 1

cleavage and IL-1β production [67].

4. Heavy metal-induced NLRP3 activation

4.1. Cadmium

Cadmium (Cd), an environmental and occupational pollutant, causes damage in the bone, heart, liver and the endocrine system through exposure to water, food, industrial materials and cigarette smoke [68,69]. Cd enters the cells by means of membrane receptors, stimulates ROS production and causes endothelial cell injury in the cardiovascular system, which finally results in hypertension, atherosclerosis induced by vascular endothelial lipid peroxidation and nonealcoholic and alcoholic fatty liver and fibrosis [70,71].

Cd elevates hepatic enzymes, IL-1β, IL-6, and TNF-α and causes neutrophil infiltration and caspase 1 activation, which is a strong evidence of the fundamental role of NLRP3 inflammasome activation in Cd-mediated hepatic cell death. The liver injury was due to the oxidative stress, which also increased LDH and MDA levels [72]. To assure the role of NLRP3 in Cd-induced liver injury, $NLRP3^{-/-}$ mouse were exposed to Cd resulting in lower levels of IL-1β and caspase 1. In previous studies, targeting TXNIP as a cellular regulator of oxidative stress led to the alleviation of liver damage [73,74]. Thioredoxin interacting protein (TXNIP) interacts directly with NLRP3 resulting in its activation [74]. Furthermore, it was found that TXNIP mRNA levels increase in Cd liver toxicity and histological examination displays their co-localization. The use of TXNIP siRNA inhibits NLRP3 activation, while the depletion of NLRP3 has no effect on TXNIP, indicating the upstream role of TXNIP in NLRP3 activation [75].

4.2. Chromium

In a previous study, the hexavalent chromium caused allergic dermatitis that is categorized as one of T cell-mediated delayed type hypersensitivities, while no hypersensitivity reaction was detected in trivalent chromium exposure [76]. Initiating a delayed type hypersensitivity requires priming of naïve T-cells through the activation of innate immune responses [77]. Treating the human monocytic cell line THP1 with $CrO4^{2-}$ and $Cr2O7^{2-}$ caused no alteration in IL-1β expression. However, enhanced levels of pro-IL-1β and its cleaved products were observed. Depletion of NLRP3 reversed these effects indicating the upstream role of NLRP3 [18]. The immune response to Cd even in the Co-Cr-Mo alloy used in joint replacement is a major concern resulting in the aseptic loss of the replaced joint through NLRP3-mediated excess release of IL-1β, which may be possibly abolished by caspase 1 inhibition [78].

4.3. Nickel

Nickel released from jewelries and clothing buttons causes contact dermatitis through interactions with the toll like receptor 4 (TLR 4) and the subsequent activation of NF-κB and mitogen-activated proteins [79]. The involvement of PRRs in Ni^{2+}-induced contact dermatitis was confirmed by exposing antigen presenting cells to Ni^{2+} result in caspase 1 activation and IL-1β secretion. Sensory protein deficient cell lines, with the exception of the $Nlrp3^{-/-}$ cells, are able to release IL-1β following exposure to Ni^{2+} indicating that IL-1β secretion may have been mediated by NLRP3 inflammasome activation. To explore the activation mechanism of NLRP3 by Ni^{2+}, cells were pretreated with apyrase (an ATP-hydrolyzing enzyme), uricase (degrading uric acid), and cytochalasin D (actin polymerization inhibitor involving in phagocytosis). This caused no alteration in IL-1β secretion demonstrating that the activation was independent of ATP and uric acid as endogenous activators of NLRP3 and phagocytosis. This is while, Mito-TEMPO diminished mitochondrial ROS generation in response to Ni^{2+} exposure indicating the involvement of mitochondrial ROS in NLRP3 activation, which is accompanied by potassium depletion and cytosolic Ca^{2+} elevation [80]. The release of endoplasmic Ca^{2+} into the cytosol leads to the pumping of Ca^{2+} into the mitochondria resulting in more ROS generation [10]. On the other hand, it was pointed out that Ni oxide nanoparticles induce lung injury via NLRP3-mediated IL-1β secretion triggered by both excess ROS generation and actin-mediated phagocytosis [81]. However, nickle and cerium oxide (NiO / CeO_2) nanoparticles only activate NLRP3 inflammasome through the disruption of phagolysosomes and surprisingly they also exhibit antioxidant activity in a pH-dependent manner [82].

4.4. Mercury

Exposure to mercury results in autoimmunity that is believed to be associated with increased pro-inflammatory cytokines and IFN-γ. It was suggested in a previous study that protection against systemic autoimmunity is genetically regulated since HgCl2 exposure of DBA/2 J mice, which are resistance to activation of polyclonal B cells, autoantibody responses and deposits of immune complex, caused no significant local inflammation. However, genetically sensitive B10·S mice responded potently to HgCl2. Increased expression of NLRP3 inflammasome components were observed in B10.s mice, which was shown to be caused by phagolysosome disruption [83,84]. Moreover, the pivotal role of phagosome disruption was further confirmed by pretreatment with a selective cathepsin B inhibitor, which suppressed the inflammatory responses.

5. Crystalline compounds and asbestosis

5.1. Silica

Inhalation of silica causes silicosis and fibrotic lung disease, which re known as occupational diseases since most exposures occur in industries like mining and constructions [85]. Inflammation mediated by macrophages is the fundamental pathology behind such diseases. Inhaled silica is recognized by alveolar macrophages via MARCO, a phagocytic receptor belonging to class A scavenger receptors. Exposure of $MARCO^{-/-}$ mice to silica showed increased lysosomal release of cathepsin B and higher levels of NLRP3 mediated inflammation comparing to wild type mice. This finding was further confirmed using an anti-MARCO antibody which caused higher IL-1β secretion [86]. MARCO deficiency also triggers the activity of acid sphingomyelinase, the enzyme involved in sphingomyelin production, resulting in ceramide accumulation and cell injury [87]. Moreover, silica induces cholesterol uptake that is involved in preserving lysosomal integrity [88] and finally increased lysosomal rupture followed by cathepsin B release [86]. Silica was shown in previous studies to induce excess ROS generation through nicotinamide adenine dinucleotide phosphate (NADPH) oxidase upon particle phagocytosis and the extent of lysosomal disruption correlated with the surface area of silica particles [5,89–91]. The consequent upregulation of NLRP3 inflammasome transcription and translation led to the increased release of caspase-1 mediated IL-1β, alarmins, basic fibroblast growth factor (bFGF) and high mobility group box 1 protein (HMGB1) [92]. These could be abrogated by either thioredoxin (TRX) overexpression or pretreatment with recombinant TRX that could rescue cells from ROS-mediated oxidative activation of the inflammatory response [90]. It has been observed that silica exposure induces the activation of P2X7 receptor. Moreover, in the absence of microbial stimulation TNF-α sensitizes macrophages to ATP and silica by binding to TNFR-I and TNFR-II, affecting gene transcription of NF-κB. The coincidence of NF-κB and P2X7 stimulation triggers the INF activation [93,94]. In addition to NLRP3 activation, particles like alum and silica induce PGE2 production in macrophages, which is independent of INF [95]. The particle-induced PGE2 production and IgE regulation play an important roles in the induction of adaptive immunity; however, there are controversial

studies regarding the role of NLRP3 in the adjuvant properties of particles in type 2 immunization [96,97]. The use of nanomaterials containing TiO_2 and SiO_2 as food additives has raised great concerns since in addition to their uptake by the respiratory system, they can also be absorbed through the intestine [98]. Exposing bone marrow derived dendritic cells to crystalline and amorphous silica and TiO_2 results in the maturation of the dendritic cells expressing MHC-II, CD80 and CD86 on their surface as well as the secretion of IL-1β. The secretion of IL-1β was diminished in caspase 1 deficient mice indicating the involvement of NLRP3 inflammasome in the initiation of silica and TiO_2-induced inflammatory response. Although TiO_2 induced no alteration in apoptosis status of the cells, crystalline and amorphous silica selectively increased apoptosis. Crystalline and amorphous silica led to higher apoptosis rates in cells bearing lower levels of MHC-II on their surfaces. TiO2 induced ROS generation depending on the particle size; however, SiO2 nanoparticles had no significant effects on the cellular redox status [99]. In addition, treating human macrophage like THP-1 cells with a wide range of micronized silica particle caused ROS generation and lysosomal rupture in a size dependent manner [100].

5.2. Asbestos

Asbestos is a biopersistence silicate mineral, widely used for construction purposes. Poor control of asbestos use, especially in the third world countries has led to significant health concerns. Asbestos induces pleural disease, asbestosis, lung cancer, and mesothelioma. Its complications are dependent upon the fiber size such that longer fibers display higher toxicities [101,102]. In addition, NLRP3 gene polymorphism is another pivotal factor in the development of asbestos-induced lung injury. The rs35829419 variant allele increases the risk of lung injury development [103]. Asbestos targets mesothelial cells that are natural linings of the peritoneal, pericardial and pleural cavities [104]. Asbestos inhalation leads to macrophage accumulation engulfing fibers and transporting them to the lymph nodes or lung interstitium and releasing cytokines, which cause neutrophil influx, hyperplasia and further fibrosis [5]. Chronic exposure to asbestos causes peritoneal mesothelium cancer and mesothelioma that has been found to be associated with chronic inflammation [105]. Exposing human mesothelial cells to asbestos fibers increased mRNA levels of NLRP3 which further caused caspase 1 activation. Asbestos fibers also enhanced both the transcription and secretion of IL-1β, IL-6 and IL-8 that was abolished using NLRP3-targeted siRNA. Moreover, it was shown that asbestos-triggered inflammatory responses are dependent upon the activation of IL-1 receptor. Inhibition of IL-1 receptor activation by anakinra, a specific IL-1 antagonist, leads to the suppression of pathologic inflammatory response in a mice model bearing a human xenograft of malignant mesothelioma [101,106]. Chrysotile asbestos and Libby six-mix exposure results in excess ROS generation in macrophage cell lines. Libby six-mix exposure results in higher ROS generation in contrast to chrysotile asbestos. Lysosomal rupture and excessive ROS generation activate NLRP3 inflammasome that results in the secretion of IL-1β. The secreted IL-1β stimulates IL-1 receptors and mitogen-activated protein kinases (MAPK), which further activates the AP-1 transcription factor involved in IL-6 secretion. The production of IL-6, an autocrine growth factor, has been demonstrated to be the consequence of NLRP3 inflammasome activation. It plays a pivotal role in the inflammation induced in epithelium cell lines [8,107]. In addition, exposing mesothelial cells to 5 mg/cm^2 of asbestos for 1 week leads to morphological changes followed by the reduction of E-cadherin expression and vimentin and N-cadherin mesenchymal marker upregulation, involved in conversion of mesential to fibroblastic transition. These changes were mediated by NLRP3 activation and further IL-1 receptor activation [106]. Erionite, a zeolite fiber, also triggers macrophages and initiates the same inflammatory response that has been found to be even more potent than asbestos [101]. Unexpectedly, an in vivo study on NLRP3 deficient and wild type mouse models exposed to asbestos showed that NLRP3 is not involved in long term survival of mice since the incidence of frank malignancy showed no significant difference between the two groups. The accumulation of immune cells, including natural killer (NK), $CD4^+$ T, and $CD8^+$ T cells as well as macrophages and neutrophils was lower in $NLRP3^{-/-}$ mice during 3 days post-exposure, however the difference vanished in long-term. The obtained results demonstrated although NLRP3 played important roles in the short term inflammatory responses to asbestos, it may not be involved in the chronic effects. Conversely, it was demonstrated that NLRP3 is critically involved in chemical-induced papilloma models of carcinogenesis after the observation that the $NLRP3^{-/-}$ mice were resistance to developing papilloma [108]. In this regard, there is need a for further investigations to explore the involvement of NLRP3 in chronic effects of asbestos.

6. Protective agents against NLRP3-induced inflammation

N-acetyl-5-methoxytryptamine known as melatonin is secreted in the pineal gland and peripheral tissues, including retina, immune cells, etc. As a pleiotropic compound, melatonin exerts a wide variety of effects, including anti-inflammatory activity, selective apoptosis induction, chemosensitizing effects, and reduction of the adverse effects and toxicities of chemotherapy and radiotherapy [109,110]. Melatonin effectively reduces ROS generation and enhances cell capability to neutralize ROS and overcomes oxidative stress by enhancing the protein levels of antioxidant enzymes [72]. Melatonin also inhibits NF-kB mediated inflammation [111]. Acknowledging the fact that many of the targets of melatonin act as initiators of INF activation or at least contribute to its assembly of compartments, it seems quite logical to think of this molecule as a protective agent against the toxicities induced by various ETs reviewed throughout this paper. This small highly soluble indole amine can freely penetrate cells and their compartments and has been previously used to control the toxicities of toxicants through mechanisms including preservation of mitochondrial function and structure. This results in maintaining cell energy and inhibiting the release of its components that are identified as danger signals, providing cellular protection against oxidative stress and apoptosis regulation [25,112,113]. Here we discuss some examples of how melatonin can protect against the exaggerated toxicant-induced INF activation and the consequent production of inflammatory cytokines, which are known to be the main culprits of organ damage.

In various liver injuries including ischemia, viral hepatitis and fibrosis, the application of melatonin alleviates the complications [114,115]. Pretreatment of mice with melatonin before Cd exposure reduced ROS generation and abrogated the activation of NLRP3, the fundamental pathogenesis factor of cadmium, at the mRNA level. It also inhibited the elevation of liver enzymes and LDH secretion displaying increased cell viability. Moreover, melatonin regulates IL-1β, IL-6 and TNF-α in the liver at the gene level [72]. Regulation of TNF-α decreases the cell sensitization to ATP and ETs, leading to lower NF-kB and MAPK activation in response to toxicants; this prevents NLRP3-mediated inflammation, the fundamental mechanism underlying the pathology caused by many ETs [19,26]. In vivo and in vitro studies demonstrate that melatonin diminishes NF-κB accumulation in the nucleus and also reduces its capacity for DNA binding, thus affecting its transcription activity by enhancing sirtuin 1 (Sirt1) mRNA and regulation of the RAR-related orphan receptor alpha (ROR-α). ROR-α depletion has been shown to reverse the regulatory effects of melatonin on NF-κB and mitochondrial redox status preservation [116]. In fact melatonin increases SIRT1 through the elevation of NAMPT1 expression, which finally results in ROR-α regulation [117,118]. Moreover, although melatonin had no effect on ASC and pro caspase 1 in sepsis, it reduced the expression of caspase 1 and IL-1β [116]. ROR-α knock down blocked melatonin's effects at mRNA levels. However, it showed no alterations in caspase 1 activity and IL-1β levels demonstrating that ROR-α is not the underlying mechanism of melatonin's regulatory role in NLRP3-

mediated caspase 1 and IL-1β activation [116]. In another study, treatment with melatonin led to comparable results with complete knock down of NLRP (NLRP3/NLRP3$^{-/-}$) in terms of both NF-κB and NLRP3 regulation [118]. Likewise, local melatonin administration in mice models exposed to external irradiation results in the blockade of NF-κB / NLRP3 signaling via the reduction of mitochondrial ROS generation as well as the suppression of pro-inflammatory cytokines [26,119]. Surprisingly, the administration of melatonin to an LPS-induced mouse model of acute lung injury led to no alterations in mitochondrial ROS generation despite its regulatory role against NLRP3 inflammasome activation. This is while melatonin could suppress extracellular histone release, a secondary signal for the activation of this pathway [120]. Melatonin also exerts its effects via regulating the levels of TXNIP, a protein involved intracellular redox homeostasis and INF assembly [72,74]. Pretreatment with melatonin reduced the co-localization of TXNIP and NLRP3, which resulted in reduced NLRP3 inflammasome activation. Nonetheless, melatonin had no effect on the expression of NLRP3 proteins. Knock down of TXNIP eliminates melatonin's protective effects confirming the hypothesis that the protective role of melatonin in Cd liver toxicity is mediated by the regulation of TXNIP [72]. These findings all together are suggestive of the potential effectiveness of melatonin as a candidate protective agent against ET-induced inflammation. Melatonin induces its protective effects mainly via inhibiting the production of the triggering signals inside the cells and decreasing the expression and the transcriptional activity of NF-kB, all of which finally result in the prevention of INF assembly.

Two major poly unsaturated fatty acids, including docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), are biologically safe compounds belonging to the omega-3 (ω-3) fatty acids, which display various biological activities including beneficial anti-inflammatory properties by reducing pro-inflammatory cytokines and anticancer properties through selective growth inhibitory effects [121,122]. Possessing well-established anti-inflammatory properties, these fatty acids are among other candidates, which may potentially protect against toxicant-induced inflammation. Omega 3 fatty acids bind to their receptors, GPR40 and GPR 120 on the cell surface [123]. The ligand and the receptor then internalize and subsequently, through b-arrestin-2 and other mediators, inhibit TAB1 and TAK1, finally interfering with NF-kB. In addition, the internalized complex directly interacts with NLRP3 inflammasome activation [27,124]. Although saturated fatty acids are detected as DAMP by TLRs and activate NLRP3 INF, PUFAs reverse these effects through reduction of NF-κB p65 protein expression [125]. It was demonstrated that the enzymatic resolvin-D1 (RVD1), a derivative of ω-3, is a beneficial compound in chronic inflammatory diseases including asthma and rheumatoid arthritis [126]. Treating with RVD1 reduces NLRP3, caspase 1 and ASC mRNA and protein levels in the retina of mice with streptozotocin-induced retinopathy. RVD1 also reverses NF-kB upregulation, thus suppressing the first signal that is required for NLRP3 activation [127]. Hyperhomocysteinemia-induced chronic inflammation leads to various complications including end stage renal disease that are found to be induced by increased ROS generation and altered metabolism resulting from NLRP3 activation [128]. In addition, DHA and its metabolite 17-oxo-DHA, have been found to inhibit INF-dependent glucocorticoid receptor degradation increasing the efficacy of glucocorticoids against inflammations [129]. Protectin D1 another DHA metabolite, exhibits anti-inflammatory activities, which has proved beneficial in liver injuries. This metabolite interacts with TLR4 which results in the suppression of NF-κB phosphorylation. The dephosphorylated form of NF-κB is unable to activate the chemokine (C-X-C motif) ligand 1 CX3C chemokine receptor 1)CX3CL1/CX3CR1(resulting in reduced NLRP3 mRNA and protein levels [130]. DHA lipoxygenase obtained metabolites, RvD1 and 17S-hydroxy DHA (17S-HDHA), reduced the co-localization of NAPPH oxidase and lipid rafts resulting in the inhibition of redox signaling and further abrogation of the assembly of NLRP3 inflammasome compartments. However, DHA solely exhibits no effects on hyperhomocysteinemia injuries proving the fact that its metabolites are crucial in its inhibition of NLRP3-mediated inflammation [129]. On the other hand, it was demonstrated that enzymatic products of ω-3 fatty acids are not involved in nigericin-induced NLRP3-mediated inflammatory cytokine production [27]. Although there is controversy regarding DHA or its bioactive metabolites as inhibitors of INF activation, it is verified that this protective effect is mediated through the regulation of the NF-κB pathway. The mechanisms of action of the NLRP INF-induced toxicity and the mechanisms of the aforementioned protective agents have been illustrated in Fig. 2. In addition, the underlying mechanisms of ET-induced NLRP3 activation and the protective agents have been summarized in the Tables 1 and 2.

7. Conclusion

NLRP3 is a pattern recognition receptor, which senses danger signals via forming a cytoplasmic protein complex, the so-called NLRP3 INF. This pathway is activated during exposure to a diverse range of compounds including, ETs, pathogens, endogenous danger molecules, ATP and crystalline structures. INF activation requires two signals including signal 1 mediated by TLR followed by NF-κB activation and the subsequent upregulation of pro IL-1β and signal 2 resulting in NLRP3 inflammasome assembly. This leads to the conversion of procaspase 1 into its active form. ETs persistently threaten humans and animals and cause diseases with inflammatory pathologies that are mostly mediated by INF activation. In a total view, ETs can activate the INF assembly via the initiation of either signal 1 or signal 2. Some toxicants might interact with TLRs and may mediate NF-κB translocation. The most frequent underlying mechanism of toxicant-induced injuries might be due to NLRP3 inflammasome activation that is followed by inflammation, cell necrosis and cell death. ETs can activate both signals required for NLRP3 inflammasome activation. ET-induced TLR activation, NF-κB translocation, mitochondrial dysfunction, excess ROS generation, and lysosomal disruption followed by the release of cathepsin B are defined as the most probable triggers involved herein. Various attempts have been made to overcome NLRP3 activation. Among many biological safe compounds, melatonin and PUFAs display anti-inflammatory properties through abrogation of NLRP3 inflammasome activation. The underlying mechanisms include diminished cell sensitization to triggers, regulation of TLR expression, NF-κB translocation and preservation of cellular redox status resulting in the the abrogation of pro-inflammatory cytokine transcription and expression, NLRP3 inflammasome assembly and IL-1β secretion. Finally, it is suggested that melatonin and PUFAs would be promising therapeutic agents against pathologies caused by environmental toxicities, which are mainly due to the exaggerated activation of INF and the subsequent inflammatory response.

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