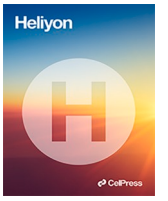
Heliyon 10 (2024) e28917

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Review article

Deciphering the molecular mechanism of NLRP3 in BPA-mediated toxicity: Implications for targeted therapies

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ARTICLE INFO

Keywords:
Bisphenol A
Pathogenesis
Organ toxicity
NLRP3 inflammasome
Signaling pathways

ABSTRACT

Bisphenol-A (BPA), a pervasive industrial chemical used in polymer synthesis, is found in numerous consumer products including food packaging, medical devices, and resins. Detectable in a majority of the global population, BPA exposure occurs via ingestion, inhalation, and dermal routes. Extensive research has demonstrated the adverse health effects of BPA, particularly its disruption of immune and endocrine systems, along with genotoxic potential. This review focuses on the complex relationship between BPA exposure and the NOD-like receptor protein 3 (NLRP3) inflammasome, a multiprotein complex central to inflammatory disease processes. We examine how BPA induces oxidative stress through the generation of intracellular free radicals, subsequently activating NLRP3 signaling. The mechanistic details of this process are explored, including the involvement of signaling cascades such as PI3K/AKT, JAK/STAT, AMPK/mTOR, and ERK/MAPK, which are implicated in NLRP3 inflammasome activation. A key focus of this review is the wide-ranging organ toxicities associated with BPA exposure, including hepatic, renal, gastrointestinal, and cardiovascular dysfunction. We investigate the immunopathogenesis and molecular pathways driving these injuries, highlighting the interplay among BPA, oxidative stress, and the NLRP3 inflammasome. Finally, this review explores the emerging concept of targeting NLRP3 as a potential therapeutic strategy to mitigate the organ toxicities stemming from BPA exposure. This work integrates current knowledge, emphasizes complex molecular mechanisms, and promotes further research into NLRP3-targeted interventions.

1. Introduction

BPA, a synthetic compound derived from diphenylmethane, assumes a pivotal role within industrial applications. It serves as a fundamental constituent in the production of thermal papers, polycarbonate plastics, and epoxy resins. An extensive array of plastic commodities, including infant feeding bottles and beverage receptacles. Notably, the prevalence of BPA extends to its integration in epoxy resin coatings utilized in the lining of food and beverage containers, which reflects a pervasive presence in our modern packaging infrastructure [1]. BPA exerts a pervasive influence on the endocrine milieu, precipitating multifaceted perturbations in hormonal dynamics. It orchestrates a symphony of dysregulations encompassing sex hormones, leptin, insulin, and thyroxin. And it engenders a complex interplay that ultimately culminates in a spectrum of hepatotoxicity, immunotoxicity, genotoxicity, and carcinogenicity [2]. Furthermore, BPA exposure has been implicated in a spectrum of adverse health outcomes, including obesity, cardiovascular diseases, and diabetes [3]. These health concerns have become increasingly significant in light of evolving research into

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https://doi.org/10.1016/j.heliyon.2024.e28917
Received 8 January 2024; Received in revised form 26 March 2024; Accepted 27 March 2024
Available online 30 March 2024

BPA's impact on human physiology.

The pervasive dissemination of BPA into the environment primarily stems from anthropogenic activities, constituting a substantial driver of migration and environmental exposure. Industrial waste and the disposal of plastics contribute significantly to the release of BPA, predominantly into aquatic ecosystems and landfills. Herein, BPA undergoes a gradual decomposition process, culminating in forming minuscule particles known as microplastics. This phenomenon instigates their entry into the food chain, impacting marine ecosystems and terrestrial fauna alike. Moreover, the omnipresence of BPA is exacerbated by its ubiquitous use in consumer products such as water bottles, baby feeding bottles, tins, and cans, where it serves as a common coating material. Consequently, human exposure to BPA becomes virtually unavoidable due to routine interactions with these items.

Notably, a recent study conducted to assess BPA content in Polyethylene Terephthalate (PET) bottled water samples employed a range of temperatures (8 °C, 18 °C, 28 °C, 38 °C, and 48 °C). The results revealed a temperature-dependent variation in BPA concentration. Specifically, at 8 °C, BPA was detected at a maximum concentration of 11.30 ng/L. Between 18 °C and 28 °C, the BPA content remained relatively stable, averaging around 10.3 ng/L. However, the temperature of 38 °C yielded the lowest observed concentration, measuring 5.19 ng/L. Interestingly, when the water temperature reached 48 °C, the BPA concentration exhibited an increase, reaching 7.84 ng/L. These findings underscore the sensitivity of BPA leaching from PET bottles to temperature variations, shedding light on a critical aspect of human exposure dynamics [4]. Evidence from contemporary research underscores the formidable capacity of BPA to traverse the placental barrier, thereby infiltrating fetal biological matrices, including cord blood and amniotic fluid. This phenomenon has garnered substantial attention within the scientific community due to its discernible implications, including but not limited to delayed fetal development, heightened susceptibility to premature birth, recurrent miscarriages, and perturbations in male anogenital distance [5].

Prenatal exposure to BPA has exhibited a correlative nexus with a spectrum of adverse consequences on the reproductive system. These repercussions transcend the realm of behavioral and emotional aspects, encompassing heightened indices of anxiety, melancholia, and hyperactivity. Furthermore, this exposure nexus extends its reach to encompass deleterious influences on the reproductive system. It is characterized by perturbations in the form of reproductive organ impairment, metabolic dysregulation, augmented susceptibility to obesity, and a proclivity towards the emergence of metabolic maladies. Additionally, prenatal BPA exposure has emerged as a contemporary concern, with connections being drawn to an elevated propensity for infantile asthma, a facet of growing significance in the current medical landscape [6]. Intriguingly, BPA exposure extends into the human milieu through multiple inescapable pathways, encompassing respiratory inhalation, oral ingestion, and epidermal contact with environmental contaminants, household particulate matter, and printed paper products. Notably, BPA ingress into the endocrine system is facilitated through dietary consumption, particularly when food items are enfolded or encased within plastic, metal cans, or tins, as these materials have the propensity to facilitate BPA leaching [7].

In accordance with the rigorous standards outlined in the OECD Test Guideline 428, a comprehensive investigation into the dermal penetration kinetics of BPA within human skin has been undertaken, yielding noteworthy findings. The study discloses a discerning penetration rate of 8.6%, coupled with an accrued reservoir of bio-available BPA, quantified at 9.3%. These pivotal outcomes underscore the imperative role of cutaneous exposure pathways in augmenting the overall systemic burden of BPA [8]. In the findings of Lee et al., in 2018, a pervasive presence of BPA was ascertained within the physiological matrices of pregnant women, fetuses, and neonates. Characterization of these individuals as BPA-exposed was predicated upon meticulous correlative assessments and the calculation of BPA concentration ratios within the paired samples derived from maternal-neonate cohorts. In a cohort encompassing 318 mother-child dyads, spanning a spectrum of biological samples, including maternal serum, urine, placental tissues, breast milk, and neonatal cord serum, it was discerned that the most pronounced BPA concentrations were consistently observed within urinary specimens, followed in descending order by serum, breast milk, and placental tissues [9].

NLRP3, formally known as Pyrin domain-containing protein 3 (PYCARD3), represents a pivotal constituent within the nucleotide-binding and oligomerization domain-like receptors (NLRs) family, occupying a central role within the realm of innate immunity. In response to both pathogenic incursion and cellular distress, the NLRP3 inflammasome orchestrates the activation of Caspase 1, thereby precipitating the synthesis of potent proinflammatory cytokines, including Interleukin 1 Beta (IL-1β) and Interleukin 18 (IL-18). This pivotal molecular machinery exemplifies a paradigmatic nexus of modern immunological inquiry, amid the contemporary thrust towards understanding intricate host-defense mechanisms [10]. A comprehensive understanding of the intricate molecular mechanisms governing NLRP3 inactivation holds profound therapeutic promise in the quest for novel antioxidative stress, anti-inflammatory, and anti-autoimmune therapeutics. Contemporary scientific endeavors are actively exploring the identification and characterization of specific inhibitors and modulators targeting NLRP3 activation, representing a burgeoning frontier in therapeutic research.

Notably, BPA-induced deleterious effects underscore the pivotal role of NLRP3 inflammasome activation, marking this review as a pioneering endeavor elucidating the crucial molecular facets of NLRP3 signaling within the context of BPA-induced toxicity. By doing so, this review endeavors to catalyze critical insights that will steer future investigations aimed at unraveling the intricate landscape of NLRP3 activation in the context of BPA toxicity, thus contributing to the current thrust in cutting-edge research.

2. Search strategy refinement

This review comprehensively assesses the detrimental effects of BPA exposure through a critical analysis of experimental studies. Specifically, it delves into the deleterious consequences of BPA on various organs, including the hepatic, renal, gastrointestinal tract, cardiovascular system, and neurological system. Furthermore, it explores the intricate molecular mechanisms underlying BPA-induced NLRP3 inflammasome activation and associated signaling pathways. Additionally, the review critically evaluates potential therapeutic interventions targeting the NLRP3 inflammasome to mitigate BPA-mediated organ toxicities.

A comprehensive literature search strategy was employed, utilizing the Scopus, Web of Science, PubMed, and ScienceDirect (Elsevier) databases. Boolean operators ("AND," "OR," and "NOT") were strategically combined with relevant search terms encompassing BPA, its toxicity ("Bisphenol A-induced toxicity," "bisphenol A analogs," and "endocrine disruptor"), and specific organ toxicities (BPA-induced hepatotoxicity, renal toxicity, gastrotoxicity, cardiotoxicity). Additionally, the search included the "Mechanism of NLRP3 in inflammation" to capture relevant literature.

To ensure the quality and relevance of retrieved articles, a set of stringent inclusion and exclusion criteria were meticulously applied. a) only original research articles were considered; b) encompassing studies conducted on both animal models and human samples; c) articles evaluating potential therapeutic strategies; d) detailing BPA exposure at various concentrations; e) investigating the molecular mechanisms of BPA and NLRP3; f) assessing the impact of BPA on organ toxicities; g) NLRP3-associated signaling pathways were prioritized. Conversely, review articles, editorials, commentaries, and studies with poorly characterized populations or duplicate, unrelated, inaccessible, or non-English content were excluded.

This meticulous selection process, based on pre-defined inclusion and exclusion criteria, ensured the review's focus on high-quality, relevant research directly addressing the relationship between BPA exposure, NLRP3 inflammasome activation, and associated organ toxicities.

3. BPA-induced organ toxicity

Drawing from a compendium of toxicological and epidemiological investigations, it is unequivocally evident that BPA exposure instigates a multifaceted spectrum of deleterious outcomes in human physiology. These ramifications encompass neurotoxicity, immunomodulation, perturbation of endocrine homeostasis, genotoxic insult, organ system impairments, and disruptions in the intricate nexus governing reproductive and developmental pathways [11]. Through the initiation of oxidative stress pathways via the production of Reactive oxygen species (ROS), BPA stands as a formidable contributor to the pathological cascade affecting vital organs, including but not limited to the liver, kidneys, and cerebral tissues, as illustrated in Fig. 1.

Within the hepatocellular milieu of rodent models, BPA disrupts the finely tuned equilibrium between endogenous antioxidants and pro-oxidant species, thus instigating a profound cascade of hepatic perturbations [12]. In a controlled experimental paradigm, juvenile murine subjects were exposed to a spectrum of BPA concentrations (0.5, 5, and 50 mg/kg/day). The ensuing observations unveiled a cascade of adverse repercussions on spermatogenic processes. It manifests a dose-dependent decline in critical parameters, including sperm count, sperm motility, and the expression levels of occluding a significant constituent in the integrity of the blood testis barrier. This dose-response relationship underscores the nuanced impact of BPA exposure on male reproductive health, in line with contemporary investigations into endocrine disruptors and reproductive toxicity [13].

Experimental subjects, notably rats subjected to BPA exposure, exhibited a pronounced augmentation in body mass, concomitant with the development of renal hyperplasia, serving as compelling evidence of BPA's nephrotoxic potential. Notably, chronic and recurring BPA exposure elicited discernible alterations in key renal biomarkers, including heightened serum creatinine and blood urea nitrogen levels, elevated urinary protein excretion, and diminished creatinine clearance rates. Concurrently, a notable decrement in the urinary protein-to-creatinine ratio was observed, unequivocally substantiating BPA's deleterious impact on renal physiology, thus contributing to a discernible decline in renal functionality [14].

In a contemporary investigation exploring the ramifications of acute BPA exposure across a spectrum of doses (5, 25, 125 μg/kg bw/day), a discernible exacerbation of hepatic injury emerged. This exacerbation manifested as a consequential decline in key hepatic biomarkers, notably encompassing Aspartate aminotransferase (AST), Alkaline phosphatase (ALP), and Alanine transaminase (ALT)

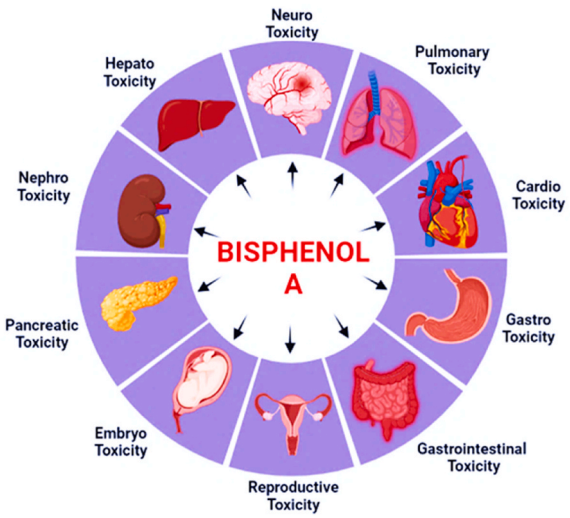

Fig. 1. Diagrammatic representation of BPA-inducing toxicity in various organs.

levels [15].

3.1. BPA-induced hepatotoxicity

3.1.1. The Liver's multifaceted role

The liver, a pivotal organ within the human body, orchestrates a multitude of essential processes. These encompass the biotransformation of xenobiotics and the metabolism of endogenous metabolic byproducts, the detoxification of pharmaceutical agents, and the intricate processing of nutritional constituents [16].

3.1.2. BPA-induced perturbations in hepatic function

BPA, imposes a profound impact on the liver's physiological equilibrium. It diminishes the liver's competence in detoxifying reactive oxygen species, while concurrently inciting an escalation in the production of free radicals [17].

3.1.3. Insights from cutting-edge research

A recent scientific inquiry conducted by Ibrahim Salih et al. (2022) has unveiled compelling insights. Their investigation has unveiled that exposure to BPA culminates in the augmentation of the central vein's wall thickness. Concomitantly, this exposure is accompanied by the presence of obstructed bile ducts, the development of sclerosis, fibroblast infiltration, lymphocytic infiltration, and occurrences of hemolysis [18].

3.1.4. NLRP3 inflammasome in hepatotoxicity

Modern studies have convincingly demonstrated that NLRP3 inflammasome activation plays a pivotal role in the realm of hepatotoxicity. This activation is associated with the promotion of inflammation and hepatocyte demise. Notably, the administration of the NLRP3 inhibitor MCC950 has shown remarkable efficacy in mitigating hepatic injury in murine models, as exemplified by Wree et al. (2014) [19].

3.1.5. Elucidating BPA's hepatotoxic mechanisms

Recent research conducted by Wang et al. (2021) has unraveled the intricate hepatotoxic mechanisms instigated by BPA exposure. These mechanisms encompass the induction of heightened oxidative stress, potentiation of mitochondrial apoptosis, and suppression of the SIRT1/PGC-1 signaling pathway, collectively leading to liver damage. Moreover, BPA exposure has been observed to induce perturbations in the gut microbiota and a concomitant reduction in Short-chain fatty acid (SCFA) levels, both of which have been implicated in hepatotoxicity [20].

3.1.6. Impairment of hepatic antioxidant defenses

BPA exerts a notable detrimental effect on the enzymatic activity of hepatic antioxidant enzymes, including Glutathione peroxidase (GPx) and Glutathione reductase (GR), concurrently augmenting Malondialdehyde (MDA) levels. Such exposure is further linked to hepatic lipid accumulation, elevated levels of serum ALT, Creatine kinase MB (CK-MB), Lactate dehydrogenase (LDH), and histological aberrations within the liver tissue [21].

3.1.7. In vitro insights into BPA-induced toxicity

Cutting-edge *in vitro* toxicity studies, as elucidated by Pang et al. (2021) offers profound insights into the intricate web of BPA-induced cellular responses. These investigations reveal an upsurge in ROS generation and the subsequent accumulation of pro-inflammatory cytokines, including IL-1β, Tumor necrosis factor-alpha (TNF-α), and Interleukin 6 (IL-6). This, in turn, triggers a cascade of toxicity, prominently involving the NLRP3 inflammasome and activation of the Nuclear factor kappa B (NF-κB) pathway [22].

3.2. BPA-induced renal toxicity

Exposure to BPA has been substantiated as a causative agent of renal damage, a phenomenon substantiated by contemporary animal studies have unveiled intricate mechanistic pathways. BPA exposure has emerged as a catalyst for orchestrating a cascade of pathophysiological events within renal cells, encompassing the initiation of oxidative stress, incitement of proinflammatory responses, and instigation of apoptosis. These orchestrated events collectively culminate in a nuanced portrait of compromised renal function, structural aberrations within the renal architecture, and an escalated susceptibility to renal carcinogenesis. Clinical evidence corroborates these mechanistic insights, as human studies have unveiled notable perturbations in renal health indicators. Notably, a discernible decrease in Glomerular filtration rate (GFR), augmented urinary albumin excretion, and elevated serum creatinine levels have been demonstrated in human samples following BPA exposure. Moreover, contemporary research accentuates BPA's multifaceted role in hormonal dysregulation and oxidative perturbation. This disruptive influence extends to the modulation of Estrogen receptor (ER) and Androgen receptor (AR), as elucidated by Teng et al. (2013) [23], thus heralding an era of evolving the interplay between BPA exposure and renal pathogenesis, particularly within the realm of chronic kidney diseases.

Recent investigations have revealed that the administration of BPA elicits a substantial upregulation in renal biomarkers, concomitant with a marked attenuation in the pro-inflammatory cytokines IL-1β, IL-6, and TNF-α. These findings underscore the profound impact of BPA on renal homeostasis. Furthermore, meticulous assessment has unveiled several intricacies in the renal

response to BPA exposure, including the extension of edema in renal epithelial cells. Concurrently, alterations in critical oxidative stress parameters, such as MDA, Glutathione (GSH), Superoxide dismutase (SOD), and GPx levels, have been observed. These changes illuminate the complex interplay between BPA and oxidative stress pathways. Notably, contemporary research has documented a subtle yet noteworthy increase in the accumulation of Nuclear factor erythroid 2 (NRF2), a key transcription factor orchestrating cellular antioxidant defenses. This observation aligns with the evolving trend of exploring NRF2-mediated responses as a pivotal axis in the cellular defense against environmental stressors, including BPA-induced renal perturbations [24].

BPA exerts deleterious effects on renal physiology by instigating a cascade of events that commence at the mitochondrial level, ultimately culminating in profound organ pathology. At the forefront of this intricate mechanism is the direct impact of BPA on mitochondrial function within the kidney, inciting an escalating oxidative stress milieu. This dysregulated redox equilibrium precipitates a series of debilitating consequences, including mitochondrial dysfunction, tissue malformation, and structural impairment of the renal organ. Noteworthy in this context is the persistent manifestation of renal hypertrophy in BPA-administered rodent models, constituting a burgeoning area of concern in contemporary research. The relentless progression of renal hypertrophy, discernible in these experimental subjects, significantly encumbers their physiological capabilities. Notwithstanding concurrent phenomena such as attenuated growth rates, elevated levels of Blood urea nitrogen (BUN) and serum creatinine, and a conspicuous decline in creatinine excretion through the urinary route. These discernible clinical markers underscore the gravity of BPA-induced renal derangement and underscore the pressing need for comprehensive investigations to illuminate novel therapeutic avenues [25].

In conditions characterized by proteinuria, glomerular podocytes, specialized epithelial cells of the renal filtration apparatus, are frequently affected, resulting in impaired waste clearance. This phenomenon is associated with a dose-dependent escalation of urinary protein excretion and Urinary protein-to-creatinine ratio (UPCR) over a 5-week timeframe following intraperitoneal administration of BPA at varying doses (50, 100, and 150 mg/kg) [26]. In a study conducted by Yuan et al. (2019), the deleterious effects of BPA exposure on Marc-145 cells manifested as a significant reduction in SOD activity and GSH levels. Simultaneously, there was a concomitant escalation in apoptotic markers, including LDH activity, intracellular levels of ROS, and the accumulation of reactive thiobarbituric acid substances (TBARs) [27]. BPA's multifaceted influence extends to the renal domain, as substantiated by Charaya et al. (2022). Their research underscores alterations in the NRF2 profile, variations in proliferating cell nuclear antigen levels, perturbations in Metallothionein (MTH) and kelch-like ECH-associated protein 1 (KEAP1) dynamics, modifications in SOD activity, and the induction of apoptotic processes [28].

3.3. BPA-induced gastro toxicity

BPA has been substantiated as a potent instigator of Gastrointestinal (GI) toxicity, primarily attributed to its capacity to provoke oxidative stress, thereby augmenting the production of ROS within the confines of the gastrointestinal tract. This consequential surge in ROS levels precipitates a cascade of events characterized by compromised integrity of the gastric and intestinal epithelial barriers, along with perturbation of the gut microbiota composition [29]. BPA was shown to be absorbed at a higher rate in the colon than in the proximal jejunum, according to research by Hiroki Inoue et al. (2003) [30]. Recent research conducted by Ismail et al. (2022) reveals that BPA exerts a profound adverse influence on the gastric glandular region, primarily through fibrotic and apoptotic mechanisms. Furthermore, BPA induces deleterious morphological alterations in enteroendocrine, chief, and parietal cells, along with vascular dilation and congestion. These detrimental effects coincide with diminished Periodic acid-Schiff (PAS)-positive reactivity, heightened collagen fiber deposition, decreased immunoexpression of B-cell lymphoma 2 (BCL2), increased Proliferating cell nuclear antigen (PCNA) immunoexpression, and a reduction in gastric mucosal height [31]. BPA induced notable histopathological changes in the gastric tissue, marked by vascular congestion within the muscular layer of the glandular region and submucosal edema in the non-glandular portion [32].

In the seminal study conducted by Abo-Elsoud et al. (2002), the induction of gastric ulcers by BPA was ascribed to a constellation of intricate molecular alterations within the gastric tissue microenvironment. These perturbations encompassed a reduction in gastric juice volume, a decline in GSH levels, diminished Prostaglandin E2 (PGE2) concentrations, and a depletion of Interleukin 10 (IL-10). Simultaneously, a decrease in the activity of SOD and PCNA proteins was noted. Furthermore, an observable upsurge in MDA levels heightened titratable acidity, increased TNF-α, and IL-6 levels, augmented Caspase 3 activity, and an elevated presence of NF-κB proteins were documented within the gastric tissue milieu. These intricate biochemical and molecular transformations underscore the profound impact of BPA-induced gastric ulcers, reflecting the contemporary understanding of the complex interplay between BPA exposure and gastric tissue pathophysiology [33]. The administration of BPA (50 mg/kg) resulted in a pronounced perturbation of various physiological parameters. Specifically, the experimental group exhibited a significant increase in white blood cell count, neutrophil-lymphocyte ratio, mucin concentration, Nitric oxide (NO), and MDA levels, while concurrently experiencing a decrease in bicarbonate levels, SOD activity, and GSH content within the gastric juice. Additionally, histological examination of the stomach mucosa revealed inflammation-related aberrations. These findings underscore BPA-induced gastrointestinal toxicity, characterized by heightened gastric acidity, diminished bicarbonate production, and an imbalance in the pro-oxidant/antioxidant homeostasis [34].

3.4. BPA-induced cardiotoxicity

BPA exerts its potential to disrupt endocrine signaling, notably affecting estrogen pathways. Estrogen, a pivotal hormone in human physiology, plays a vital role in cardioprotection, as corroborated by Iorga et al. (2017) [35]. BPA-induced perturbations extend to the cardiovascular system, manifesting in alterations of heart rate, blood pressure, and electrocardiographic parameters, alongside disturbances in cardiac cellular function [36]. These disturbances stem from intricate intracellular mechanisms orchestrated by BPA,

including inhibition of primary ion channels, perturbations in Ca^{2+} handling, induction of oxidative stress, and the initiation of epigenetic modifications [37]. Furthermore, BPA exposure exacerbates susceptibility to cardiovascular diseases, notably atherosclerosis, and amplifies associated risk factors such as hypertension and diabetes mellitus [38].

Valokola et al. (2019) conducted a revealing study characterizing histopathological effects induced by BPA, unveiling nuclear degenerative changes, focal lymphatic inflammation, and cytoplasmic vacuolation. Electrocardiographic assessment under BPA exposure reveals prolongation of RR, QT, and PQ intervals, signaling cardiac dysfunction. Western blot analyses conducted in the same study demonstrated elevated phosphorylation of p38-mitogen-activated protein kinase (p38) and c-jun NH2 terminal kinases (JNK), accompanied by a decreased phosphorylation state of protein kinase B and Extracellular signal-regulated protein kinases 1 and 2 (ERK1/2) [39].

In rodent models, Bana et al. (2019) explored the dose-dependent effects of BPA administration, observing notable weight gain alongside histopathological changes in cardiac tissue. Notably, at 25 mg/kg BPA, modest histological impacts were observed, including changes in myofibrillar structure and mild inflammation in ventricular regions. The 50 mg/kg BPA dosage revealed profound alterations in heart muscle fibers, characterized by dilation, fragmentation, disorganized sarcomeric organization, and inter-sarcomeric connective tissue, underscoring the multifaceted nature of BPA's impact on cardiac physiology [40].

3.5. BPA-induced reproductive toxicity

BPA exerts deleterious effects on the reproductive system, precipitating reproductive toxicity with repercussions spanning fertility, pregnancy, and developmental processes [41]. Robust evidence underscores the adverse consequences of BPA exposure in male subjects, evincing diminished sperm count and structural alterations within spermatozoa. In the female cohort, BPA disrupts menstrual regularity, instigates malformations in mammary gland development, curtails fertility, infiltrates the placental barrier, impinges on fetal development, and heightens the susceptibility to miscarriages and preterm births. Recent investigations by Liu et al. (2022) delved into the ramifications of BPA-induced toxicity in male Sprague Dawley rats, revealing pronounced testicular damage, a reduction in sperm count, and an upsurge in sperm abnormalities. Intriguingly, this inquiry unveiled the orchestration of oxidative stress and the initiation of cellular apoptosis within testicular tissues.

Concurrently, perturbations in histone composition elevated histone H3 and H2A, alongside diminished ubiquitin histone H2B (ub-H2B) and H2A (ub-H2A) signify the multifaceted nature of BPA-induced perturbations. Notably, the surge in ROS contributes to oxidative stress and potentially reconfigures apoptotic cascades, manifesting as heightened cleaved Caspase 3 activity. Moreover, the activation of the phosphoinositide-3-kinase-protein kinase B pathway (PI3K/AKT) was discerned, illuminating a novel facet of BPA-mediated pathogenesis [42].

Parallelly, investigations by Adegoke et al. (2022) [43] offered insights into the intricate repercussions of BPA exposure on female reproductive physiology. Employing human normal ovarian epithelial cells IOSE80 as a model system, their discernments unveiled conspicuous perturbations across KEGG pathways modulated by BPA. Notable among these were cellular senescence, RNA transport, oocyte meiosis, and progesterone-mediated oocyte maturation. As BPA concentrations escalated, the presence of the ERK inhibitor U0126 elicited a modest reduction in protein expression of ERK, concurrent with alterations in relative mRNA levels and Cyclin-dependent kinase inhibitor 3 (CDKN3). Consequently, a diminished ratio of cells in the S phase and G0/G1 phase signaled impediments in cellular progression through these specific phases of the cell cycle, underscoring the intricate consequences of BPA on female reproductive biology [44].

3.6. BPA-induced other organ toxicities

3.6.1. Neurotoxic effects and implications for neurological disorders

BPA leads to neurotoxicity by impairing cognitive functions and contributing to the pathogenesis of neurological disorders. Additionally, it has adverse effects on atherosclerosis and hypertension. For example, a study by Huang et al. (2020) demonstrated that high-dose BPA administration elevated intracellular Ca^{2+} levels in KGN cells, leading to increased intracellular ROS production. This, in turn, reduced cellular antioxidant capacity and induced deleterious alterations to biomolecules [45].

3.6.2. Impact on vascular function and molecular pathways

Exposure to BPA can modulate the vasorelaxant response of the Human umbilical artery (HUA) by affecting key pathways such as NO/cyclic Guanosine monophosphate (cGMP)/soluble Guanylate cyclase (sGC)/Protein kinase G (PKG). Recent research revealed decreased expression of Human umbilical artery smooth muscle cells (HUASMC) and increased expression of the BKCa channel β1 subunit as a result of BPA exposure [46].

3.6.3. Disruption of glucose metabolism and implications for diabetes

BPA-induced disruptions in glucose metabolism impact crucial pathways including Pdx1, Gck, Igf2, Srebf1, and Srebf2, leading to insulin resistance and diabetes. These disruptions affect insulin secretion, promote lipogenesis, cause oxidative damage, and induce β cell apoptosis [47].

3.6.4. Endocrine effects and impacts on prostate development

Exposure to BPA in pubertal male rat results in notable upregulation of ER and messenger RNA (mRNA) expression within hypothalamic structures, persisting into adulthood. Prenatal BPA exposure transiently affects AR expression, leading to alterations in

periductal stromal cell proliferation and reduced Prostatic acid phosphatase (PAP) expression in the ventral prostate of peripubertal rats [48].

3.6.5. Disruption of developmental signaling pathways

During the early developmental stages of Xenopus laevis, BPA disrupts the Notch signaling pathway by inhibiting γ-secretase, an enzyme crucial for cleaving the Notch intracellular domain (NICD). This interference with γ-secretase activity results in various abnormal morphological changes, including scoliosis, eye dysplasia, and pigmentation loss [49].

3.6.6. Inflammation, oxidative stress, and gene expression

Extended exposure to BPA is associated with pronounced inflammation and oxidative stress response, as evidenced by elevated levels of MDA, SOD levels, and increased IL-18 expression in pulmonary tissue. Furthermore, persistent BPA exposure influences the expression of genes linked to fibrosis [50] empirically demonstrated these effects.

3.6.7. Gene expression and immune regulation

Prolonged BPA exposure correlates with numerous anomalies, including increased ROS levels, impaired adaptive and innate immune responses, and elevated blood glucose and insulin concentrations. Gene expression analysis revealed that differentially exposed genes were enriched in immune function and pancreatic cancer-related pathways. Of note, the Signal transducer and activator of transcription 3 (STAT3) plays a crucial role in regulating these processes. BPA exhibits stable binding to both STAT3 and IL-10, suggesting that STAT3 could serve as a potential target for BPA-induced pancreatic cancer by modulating immune responses [51].

4. Molecular mechanism of NLRP3 in BPA-mediated toxicity

The precise mechanism governing NLRP3 activation remains an ongoing subject of inquiry, yet multiple initiating triggers have been discerned. Pattern recognition receptors (PRRs) play a pivotal role in sensing and instigating downstream inflammatory cascades upon the ingress of deleterious entities into the cellular milieu, encompassing pathogens, cellular debris, and environmental contaminants such as BPA [52]. Among the five members constituting the PRR inflammasome ensemble, the Nucleotide-binding oligomerization domain (NOD)-like receptor (NLR) family includes NLRP1, NLRP3, NLRC4, Absent in melanoma 2 (AIM2), and Pyrin [53]. Notably, the NLRP3 inflammasome assumes a pivotal role in orchestrating immune responses against inflammatory ailments.

The NLRP3-associated mechanism of toxicity is intricate, yet prior investigations have provided salient insights into its signaling cascade.

i. **Activation of NLRP3:** NLRP3 activation ensues in response to various stimuli, such as uric acid and cholesterol crystals, extracellular Adenosine triphosphate (ATP), and microbial components [54,55].
ii. **Assembly of the NLRP3 Complex:** These stimuli incite the recruitment and activation of the adaptor protein Apoptosis-associated spec-like protein containing a CARD (ASC), culminating in the activation of Caspase 1 [56].
iii. **Cleavage of Pro-IL-1β and Pro-IL-18:** Caspase 1 cleaves the pro-forms of IL-18 and IL-1β within the intracellular milieu, inducing their activation and thus instigating the inflammatory response [57].
iv. **Induction of Pyroptosis:** NLRP3 activation concurrently triggers pyroptosis, a programmed cell death modality characterized by the extrusion of intracellular contents through the formation of plasma membrane pores. Gasdermin D (GSDMD), cleaved by Caspase 1, constitutes the agent responsible for pore formation, generating oligomers that permeate the membrane [58].

Two discrete signaling modalities, priming and activation, govern NLRP3 activation. In the priming phase, Pathogen-associated molecular patterns (PAMPs) engage with Toll-like receptors (TLR), Interleukin-1 receptors (IL-1R), and Tumor necrosis factor receptors (TNFR), thereby initiating the priming of NLRP3, pro-IL-18, and pro-IL-1β via the NF-κB signaling pathway. In the subsequent activation phase, Damage-associated molecular patterns (DAMPs) elicit Chloride (Cl^-) efflux, Potassium (K^+) efflux, Sodium (Na^+) efflux, and Calcium (Ca^{2+}) mobilization, collectively impairing mitochondrial function and other cellular processes [59]. As a consequence, the NLRP3 protein complexes with NIMA-related kinase 7 (NEK7) form the active NLRP3 inflammasome. Subsequently, the inactive form of Caspase 1 undergoes auto-proteolytic cleavage, yielding the active Caspase 1 enzyme. Active Caspase 1 then orchestrates the conversion of GSDMD, pro-IL-18, and pro-IL-1β into their N-terminal cleavage products GSDMD-N terminal (GSDMD-NT), IL-18, and IL-1β. This sequential cascade culminates in pyroptosis, a prominent mode of programmed cell death, concurrently triggering an inflammatory milieu [60].

The NLRP3 complex encompasses diverse constituents, including sensors, adaptors, and effectors such as the Caspase recruitment domain (CARD), Pyrin domain (PYD), Nucleotide-binding and oligomerization domain NACHT, and Leucine-rich repeat domain (LRR). Notably, NLRP3 recruits ASC through PYD interactions, thereby facilitating ASC's CARD/CARD interactions with Caspase 1, which in turn regulates key factors in the inflammatory cascade [61,62].

4.1. Oxidative stress and NLRP3-mediated toxicity

Intrinsically, TLRs are integral membrane-bound receptors belonging to the family of PRRs. TLRs are renowned for their discernment of PAMPs and DAMPs [63]. Upon the infiltration of an environmental toxicant, such as BPA, into an organ, it interfaces with TLRs, eliciting a cascade of events [64]. Notably, this interaction triggers a rapid perturbation in the electron transport chain

(ETC) within mitochondria, resulting in the instigation and accumulation of ROS [65]. The crux of this oxidative phenomenon hinges on the mitochondrial membrane potential (ΔΨm), where high values propel heightened ETC activity and consequently amplify ROS production. Conversely, a diminished ΔΨm mitigates ROS generation [66]. Extensive prior investigations underscore the robust nexus between oxidative stress and the activation of NLRP3 inflammasomes. Moreover, ROS catalyzes the release of pro-inflammatory cytokines, instigating deleterious tissue alterations [67]. A study by Lei et al. (2023) has proved that ROS triggered the TLR4/MyD88/NF-κB pathway and upregulates pyroptosis and necroptosis genes/proteins which leads to disruption of neuroendocrine [68].

Intriguingly, the lysosomal NADPH oxidase (NOX) complex further perpetuates NLRP3 inflammasome activation via ROS induction [69]. A fascinating mechanistic insight emerges from the interaction between ROS and Thioredoxin (TRX), whereby ROS-mediated binding of Thioredoxin-interacting protein (TXNIP) to TRX activates NLRP3 [70]. Consequently, this intricate interplay between oxidative stress and NLRP3 inflammasome activation conveys a profound cellular detriment, culminating in toxicity and cellular damage (Fig. 2).

4.2. *Immunopathogenesis and NLRP3-mediated toxicity*

Immunopathogenesis, the complex interplay between the immune system's response to pathogens or stimuli and resulting in tissue damage and pathology, is a multifaceted process. NLRP3, an integral component of this process, exhibits context-dependent intricacies. The NLRP3 inflammasome plays a pivotal role in immunogenesis, orchestrating the effective resolution of pathogens and the restoration of tissue homeostasis.

BPA's impact on the immune system is evident. At concentrations ranging from 0.054 to 5.4 mg/L, BPA stimulates lymphocyte proliferation, while concentrations spanning from 0.005 to 50 mg/L enhance macrophage activity [70]. Additionally, Yetro et al. (2003) documented BPA's discernible influence on murine thymocytes, promoting their proliferation while concurrently elevating Interferon-gamma (IFN-γ) levels and suppressing IL-4 production [71]. These cytokines, including IL-4, IL-5, and IFN-γ, are crucial regulators of anti-inflammatory responses, originating from $CD4^+$ T lymphocytes (Th1 & Th2) [72]. Furthermore, BPA administration in adult mice led to a reduction in $CD4^+$ cell counts, known for their role in pro-inflammatory response regulation [73].

Previous studies reveal that BPA induces B cell activity, enhancing the production of IgA and IgG2a, while also elevating IFN-γ levels [74]. In a murine model of systemic lupus erythematosus, B1 cell-secreted IgM antibodies showed an increased level [75]. Similarly, exposure to BPA within the RAW264 macrophage cell line led to heightened LPS levels, resulting in NO and TNF-α generation [76].

Furthermore, exposure to 17β-estradiol influences immune responses. It enhances IL-12 production in response to TLR ligands, modulates dendritic cell development and function, and elevates IFN-γ production in C57BL/6 mice [76]. Research indicates that estradiol significantly impacts macrophage TNF-α production. Notably, macrophage TNF-α release is inhibited at both extremely high

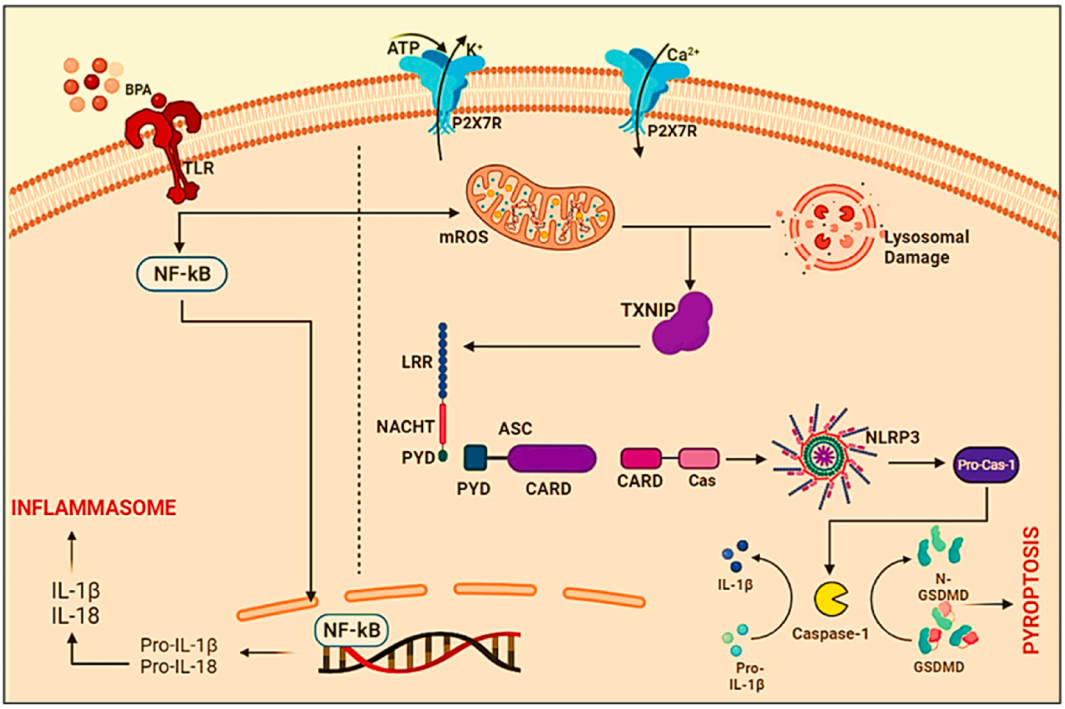

Fig. 2. A Simplified schematic mechanism of NLRP3 activation.

and very low estradiol dosages, while intermediate levels induce its elevation [77].

Endocrine-disrupting chemicals (EDCs) wield considerable influence over nuclear receptors involved in hormone signaling, including AR, ERα, ERβ, Thyroid receptor (TRα, TRβ), Peroxisome proliferator-activated receptor (PPARα, PPARγ), and Retinoid X receptor (RXRα, RXRβ, RXRγ). These EDCs disrupt normal cellular functions by interacting with these nuclear receptors, leading to T-cell proliferation inhibition and suppression of inflammatory cytokine secretion [78].

5. The signaling mechanism associated with NLRP3-mediated toxicity

Critical to our understanding of NLRP3 inflammasome activation is the intricate orchestration of signaling pathways, encompassing gene expression modulation, post-translational modifications, and dynamic regulation of cellular energy metabolism. Notably, these multifaceted processes operate within a context-dependent framework, exhibiting remarkable diversity in mechanistic interactions. The precise interplay among these pathways and their regulation of NLRP3 inflammasome activity is inherently contingent upon cell type, microenvironment, and the nature of encountered stimuli, as graphically depicted in Fig. 3.

5.1. PI3K/AKT

Within the context of the innate immune response, the PI3K/AKT signaling complex assumes a central role in orchestrating NLRP3 inflammasome activity, governing a wide spectrum of cellular processes encompassing cellular growth, viability, and metabolic functions. The interplay between the PI3K/AKT pathway and the NLRP3 inflammasome is intricate and contingent upon cellular phenotype and contextual cues.

Emerging insights indicate that, within specific cellular milieus, PI3K/AKT pathway activation initiates NLRP3 inflammasome activation, instigating an inflammatory cascade. External signaling events, such as ligand binding to cell membrane-bound Receptor Tyrosine Kinases (RTKs), trigger PI3K activation. Subsequently, active PI3K catalyzes the phosphorylation of Phosphatidylinositol 4,5-bisphosphate (PIP2) into Phosphatidylinositol 3,4,5-trisphosphate (PIP3), serving as a pivotal second messenger in the PI3K/AKT pathway. PIP3 recruits serine and threonine residues, facilitating AKT activation, which in turn phosphorylates the substrate, thereby modulating NLRP3 inflammasome activation [78].

Remarkably, BPA demonstrates the capacity to downregulate proteins within the PI3K/AKT pathway [79]. Wang et al. (2020) corroborate the existence of an association between the PI3K/AKT pathway and the NLRP3 inflammasome in the context of lipopolysaccharide-induced lung injury [80]. Notably, recent findings reveal that exposure to particulate matter (PM 2.5) induces macrophage activation via the PI3K/AKT signaling pathway in murine lung tissue and RAW264.7 cells [81].

An investigation into chickens with selenium deficiency exposed to BPA unveils elevated levels of ROS and MDA, coupled with a reduction in SOD and GPx expression. Furthermore, the perturbation of the PI3K/AKT pathway, coupled with an imbalance in BCL/

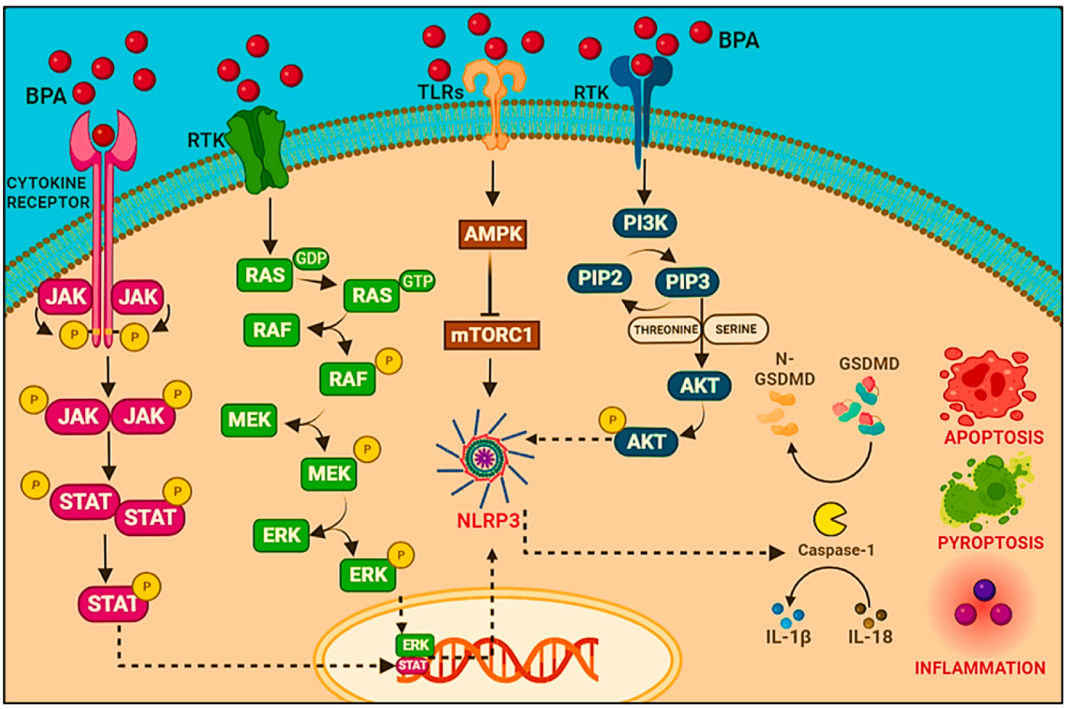

Fig. 3. A simplified schematic figure of the signaling pathway associated with NLRP3-mediated toxicity.

BAX protein ratios, triggers the activation of Caspase 9 and Caspase 3, ultimately culminating in apoptosis within chicken renal tissues [82].

In the realm of testicular toxicity induced by BPA, DPY30-mediated germ cell cycle alterations stem from the blockade of the PI3K/AKT pathway through histone modification [83]. Notably, EDCs perturb PI3K/AKT signaling through molecular mechanisms involving the upregulation of ERα, ERβ, and BCL2, concomitant with the downregulation of Aryl Hydrocarbon Receptor Nuclear Translocator 2 (ARNT2). This disruption fosters cell proliferation and apoptosis [84]. Recent investigations by Gao et al. (2020) unearthed the dysregulation of Treg/Th17 cell populations in the context of the PI3K/AKT pathway, attributable to enhanced NF-κB protein expression mediated by ERα and ARNT2 activation. This dysregulation subsequently culminates in elevated IL-17 and TNF-α levels in the serum, ultimately potentiating the release of pro-inflammatory cytokines and chemokines that impact immune responses [85].

Furthermore, Western blot analyses have elucidated that BPA augments the expression of components within the PI3K pathway, encompassing the catalytic and regulatory subunits, concomitant with heightened AKT phosphorylation [86].

5.2. ERK/MAPK

The Extracellular Signal-Regulated Kinase/Mitogen-Activated Protein Kinase (ERK/MAPK) pathway serves as a linchpin in a wide spectrum of biological processes, encompassing cellular proliferation, differentiation, viability, and programmed cell death, notably apoptosis. This intricate signaling cascade is elicited by extracellular stimuli, including hormones, cytokines, and growth factors, which engage specific receptors [87].

Activation of the ERK/MAPK pathway commences with the conversion of the small GTPase Ras from GDP to GTP, triggering a kinase cascade. Ras activation initiates a cascade involving key players such as PI3K's catalytic subunit, p110, eventually leading to the sequential activation of kinases Raf, MEK, and ERK [88]. Noteworthy is the Modulator of Nongenomic ER (MNAR), an activator of ERα, which also phosphorylates MAPK [89]. MNAR's role is pivotal as it interacts with ERα and Src, thereby instigating Src-mediated activation of the ERK/MAPK pathway.

Upon activation, ERK translocates to the nucleus, where it phosphorylates various transcription factors, resulting in pronounced alterations in gene expression patterns [90]. Dysregulation of the ERK/MAPK pathway has far-reaching implications, contributing to the development of conditions such as cancer, cardiovascular diseases, and neurological disorders.

Recent research advances have underscored the ERK/MAPK pathway's significance in the context of cytokine production during acute lung injury. Studies have demonstrated that pretreatment with SB203580, a specific inhibitor of the p38 MAPK signaling pathway, mitigates LPS-induced upregulation of TLR2, Caspase 1, NLRP3, IL-1β, and IL-6 in NR8383 cells [91]. Additionally, this pathway is implicated in the activation of NLRP3 and subsequent IL-1β expression.

Intriguingly, recent investigations by Sevastre-Berghian et al. (2022) shed light on BPA's adverse effects on the hippocampus in rats, uncovering a reduction in MAPK levels and activation, a decrease in γH2AX, and an upregulation in NF-κB and pNF-κB expression, leading to discernible histopathological changes [92].

Moreover, BPA exposure in hippocampal tissues was found to substantially inhibit the Akt and p44/42 MAPK pathways, indicative of ERK/MAPK pathway inhibition [93]. Further exploring the nexus between BPA and inflammatory processes, Zhou et al. (2019) probed the modulation of NLRP3/Caspase 1 within rat brain models and observed an upregulated expression of inflammatory factors and enhanced phosphorylation of p38MAPK/ERK [94]. Of particular note is the intriguing role of Pin1 in the p38 MAPK pathway. Recent studies have illuminated its influence on NLRP3, ASC, Caspase 1, IL-1β, and IL-6 or TNF-α expression [95]. Pin1's regulatory impact on the pathway appears to hinge on the phosphorylation of p38 MAPK, rather than direct binding, with potential implications for the synthesis of inflammatory proteins [96].

Additionally, the latest research emphasizes the contributions of MAPK signaling pathways, including P38, ERK, and JNK, in priming the NLRP3 inflammasome and facilitating the production of cytokines like IL-1β and IL-18 [96]. In the context of BPA exposure, cell viability is significantly compromised, leading to increased Fas, FasL, and Caspase 3 production, protein expression, and activation of JNKs/p38 MAPK pathways. This elucidates the mechanism through which BPA induces Sertoli cell death [97].

Furthermore, BPA's impact on Vascular Smooth Muscle Cells (VSMCs) extends to modulating the phosphorylation of MAPK while concurrently diminishing AKT phosphorylation. These effects are intricately linked to BPA's ability to hinder VSMC invasiveness and migratory capacity, mediated through the affinity modulation of transcription factors NF-κB, AP-1, and SP-1 for their respective binding sites [98].

5.3. JAK/STAT

The Janus kinase/Signal transducer and activation of transcription (JAK/STAT) pathway represents a pivotal signaling cascade with far-reaching implications in contemporary molecular biology. This pathway orchestrates critical biological processes such as inflammation, cellular differentiation, growth regulation, and immune responses [99]. Within this intricate network, the STAT proteins, members of the transcription factor family, reign as master regulators of gene expression. Their activation occurs in response to extracellular signaling molecules that engage cell surface receptors, subsequently initiating the activation of JAKs. This activation leads to the phosphorylation of STAT proteins, which, upon binding to DNA, undergo dimerization and translocate into the nucleus. Here, they execute their precise control over the transcription of inflammatory genes.

In the current scientific landscape, JAK/STAT signaling emerges as a linchpin in numerous pathological and physiological processes. Dysregulated JAK/STAT activity has been unequivocally linked to autoimmune disorders, inflammatory conditions, and cancer onset. Notably, this intricate family of kinases is finely tuned by a multitude of cytokines, including IL, Interferons (IFN), and

endogenous signaling molecules such as erythropoietin, thrombopoietin, and growth hormone. The activation of JAK proteins, facilitating receptor phosphorylation upon ligand binding to cytokine and hormone receptors, constitutes a central theme in this pathway's dynamic regulation [100].

Highlighting the clinical relevance, the inhibition of STAT3 signaling has demonstrated the potential to induce apoptosis in human U266 myeloma cells [101]. Notably, genetic alterations in cancerous cell populations have established a compelling connection between STAT3 and the pro-inflammatory milieu, playing a pivotal role in tumorigenesis [102].

Furthermore, contemporary research has unveiled the roles of STAT4 and STAT6 in T helper cell polarization during the inflammatory cascade. The IFN/STAT1 pathway has assumed a central role in eliciting inflammatory responses, encompassing the upregulation of chemokine synthesis, the modulation of hematopoietic cell differentiation, programmed cell death, and the initiation of ROS and NO production [103].

Recent investigations, exemplified by Castejon et al. (2022), have shed light on novel connections between JAK/STAT signaling and regulatory pathways. Their work elucidates the potential of Ligstroside aglycon to modulate pro-inflammatory cytokines and protein expression, revealing intriguing correlations with NRF2 activation and the suppression of NF-κB, MAPKs, and JAK2/STAT3 signaling pathways [104]. Li et al. (2023) studied the effect of Tetrabromobisphenol A, as a result, it significantly induces oxidative stress, disrupts mitochondrial membrane potential, activates the JAK2/STAT3 signaling pathway, and elevates the levels of Caspase 3 and 9. These events culminate in the upregulation of *p*-JAK2/p-STAT3, ultimately leading to an activated JAK2/STAT3 signaling axis and the promotion of apoptosis [105].

In the context of environmental influences, hormone-disrupting compounds such as 17β-estradiol (E2), β-sitosterol (βS), and 4-*n*-nonylphenol (NP) have been found to exert a regulatory impact on the JAK/STAT, ERK, and AKT pathways. Recent studies by Hanson et al. (2021) have highlighted the interaction between these compounds and JAK2 inhibition [104].

Within the purview of immunology, emerging evidence underscores the connection between BPA exposure and the NLRP3 inflammasome. Investigations involving $CD11b^{+}$ bone marrow cells have revealed that BPA exposure leads to significant elevations in NLRP3, Caspase 1, and IL-1β levels. Similarly, in NZB NZW F1 female cells, a consistent increase has been observed in the constitutive levels of ERα, NLRP3, activated STAT1, active Caspase1, and mature IL-1β upon exposure to BPA. Furthermore, even at low concentrations (10 nM), BPA exposure in human peripheral blood mononuclear cells ($CD14^{+}$) has demonstrated a substantial rise in NLRP3, IFI16, STAT1, and procaspase-1 (p45) levels [106].

In a study exploring BPA exposure in red common carp, Liu et al. (2020) conducted a KEGG enrichment analysis, revealing extensive alterations in the NF-κB, TLR, B Cell Receptor (BCR), and JAK/STAT pathways. These findings collectively underscore the profound impact of BPA on the immune system, with NLRP3 emerging as a key player intricately intertwined with the JAK/STAT signaling pathway [107].

5.4. AMPK/mTOR

Adenosine-monophosphate activated-protein kinase (AMPK) and the mammalian target of rapamycin (mTOR) represent pivotal components governing the intricate orchestration of cellular metabolism and energy homeostasis [108]. This regulatory nexus has garnered increased attention due to its central role in governing cellular responses to environmental cues and cellular energy status. Activation of AMPK, often prompted by intracellular energy depletion, instigates a metabolic reprogramming characterized by heightened glucose uptake and enhanced fatty acid oxidation. Concurrently, AMPK exerts its energy-saving influence by suppressing energy-intensive processes, including protein and lipid synthesis [109].

On the other hand, mTOR, a kinase sensitive to nutrient and growth factor availability, plays a key role in modulating cell growth and protein synthesis. The interplay between AMPK and mTOR has emerged as a focal point in physiological processes such as glucose and lipid metabolism, autophagy, and cellular growth and proliferation. Dysregulation of this delicate balance between AMPK and mTOR has been associated with a spectrum of disorders, ranging from metabolic dysfunctions to neurodegenerative diseases and cancer [110].

Crucially, the intricate relationship between AMPK, mTOR, and NLRP3 inflammasome activation has recently come under scrutiny. Activation of AMPK not only influences energy metabolism but also serves as a modulator of the mTOR signaling pathway, which, in turn, affects NLRP3 activation. This intricate signaling cascade underscores its relevance in diverse cellular processes and disease pathogenesis [111].

Recent investigations have unveiled the impact of BPA on this intricate network. BPA, a pervasive environmental endocrine disruptor, has been shown to inhibit the phosphorylation of mTOR downstream of AMPK, thus influencing the AMPK/mTOR axis. Furthermore, BPA exposure has been linked to the activation of Unc-51-like-kinase activity (ULK1), mediated by glucose deprivation and AMPK activation, reinforcing its role in autophagy regulation [110].

Notably, the influence of BPA extends beyond cellular processes. BPA exposure has been associated with disruptions in autophagy dynamics, as evidenced by altered ratios of autophagy flux proteins LC3II/I and p62. Moreover, BPA-induced changes in the BAX/BCL2 ratio, Caspase 3 expression, and apoptosis rates underscore its potential role in cellular apoptosis pathways [112].

Recent Western blot analyses have provided additional insights, demonstrating the elevated phosphorylated AMPK and decreased phosphorylated mTOR expression in response to BPA exposure, further highlighting the intricate interplay between BPA and AMPK/mTOR signaling [113,114]. In vivo studies have unraveled the implications of BPA-induced Akt/mTOR pathway activation, offering potential insights into its impact on spermatogenic capacity and testicular cell fate [113].

Additionally, investigations in murine models have pointed to the role of the mTOR/NLRP3 pathway in modulating intestinal inflammation, shedding light on the intricate regulatory network that governs autophagy and inflammation, both of which are

Table 1
List of pre-clinical studies on NLRP3-mediated Bisphenol toxicity.

Environmental toxicants	Exposure concentration of BPA	Mechanism of action	Impact	Model	Reference
BPA	1 nM to 100 μM	Pyroptosis	- Elevated caspase-1 mRNA in IMR-32 cells. - Decreased caspase-1 mRNA in SK-N-SH cells.	SK-N-SH, IMR-32 cell lines	[117]
BPA	0.05 g/kg^{-1}	Pyroptosis	Induction via NF-κB/NLRP3/Caspase-1 pathway	chicken	[118]
BPA	1–400 μmol/L	Pyroptotic cell death	- Stimulation of intracellular ROS. - Elevated MDA levels. - Decreased SOD levels. - Upregulation of CARD(ASC), NLRP3, IL-1β/pro-IL-1β, and IL-18/pro-IL-18.	osteocytes MLO-Y4	[119]
BPS	10^{-3} M -10^{-10} M	NLRP3 inflammasome, TLR4, Nrf2, MAPK pathway	ROS production and activation of NLRP3, TLR4, and MAPK pathways	Murine macrophage RAW264.7 cells	[120]
BPA	20 μg/kg	NLRP3 inflammasome and apoptosis	- Enhanced free radicals generation. - Increased Nrf-2, TLR4, and NLRP3 inflammasome expression. - Elevated levels of IL-8, IL-18, and TGF-β1	Wistar rats	[121]
BPA	10–100 nM	Inflammasome activity	Increased ER-α, IFN-β mRNAs, and NLRP3 Elevated levels of STAT1, Caspase-1, IL-1β Increased in level of IRF5, IL-18, NLRP3, STAT1, Procaspase-1 and activate STAT-1. Increase in AIM2 protein in mononuclear cells.	Murine Bone marrow-derived cells [(NZB × NZW) F_1], Female C57BL/6J (B6) mice Cell line of human monocyte THP-1	[122]
BPA	50 μg/kg	Activation of the Inflammasome Pathway and Oxidative Stress	- Activation of inflammasome pathway and oxidative stress. - Upregulation of adaptor ASC, Casp-1, and IL-1 synthesis. - Recruitment of monocytes/macrophages in the liver.	C57Bl/6J mice	[123]
BPA	3–3000 μg/kg	Upregulates immune response	Increases anti-HEL IgG, splenic lymphocyte proliferation, $CD3^+CD4^+$, and $CD3^+CD8^+$ cells.	DBA/1 J mice	[124]
BPA	3–3000 μg kg−1	The synergistic modulation of lymphoid cells, TH1 and TH2, in the context of immune response	- Elevated anti-HEL IgG and IgG1 antibodies. - Increased lymphoid cell proliferation rates. - Enhanced synthesis of IgG2a and IgG1. - Augmented secretion of IFN-γ and IL-4.	DBA/1J mice	[125]
BPA	150 mg/kg	TREM-2/DAP-12/Syk Pathway	Upregulation of hippocampal signaling pathway with tau phosphorylation; increased oxidative stress; altered antioxidant machinery; disrupted Nrf-2/HO-1 signaling and Trx-1/Grx-1 system	Wistar albino rats	[126]
BPA & Nonylphenol	100 μM	Apoptosis	Increased Ca2+, PLC activation, and ADAM17 activation	Reproductive tract cancer cell lines	[127]
BPA	50 μg/kg	Cognitive dysfunction and oxidative stress	Oxidative stress in brain areas, reduced NMDA receptor expression, increased MDA levels	Male Swiss albino mice	[128]
BPA	50 μg/kg	Estrogen Receptor Alpha Regulation	Altered ER mRNA and protein expression, reduced ER phosphorylation	Male rats	[129]
BPA	50 μg/kg	Apoptosis & Inflammatory response	Increased ROS, RNS, MDA, and H2O2; decreased antioxidant enzyme activity; elevated proinflammatory cytokines; enhanced caspase activity	CD-1 male mice	[130]
BPA & Nonylphenol	50 mg/kg	Apoptosis	Increased TUNEL-positive cells, cleaved PARP, and active caspase-3	Male Sprague–Dawley rats	[131]
BPA & BPS	50 μg BPA & BPS/kg	Glucose Intolerance & Hepatic Mitochondrial Changes	Elevated HDL-C levels; mitochondrial H2O2 production; DRP1 expression; reduced mitochondria; altered PGC1 expression	Wistar albino rat	[132]
BPA	0 - 5000 μg/kg	Gene expression	Altered gene expression associated with fat production and plasma insulin levels; increased liver triglycerides and cholesteryl esters	CD1 mice	[133]
BPA & BPS	0.05 mg/mL	Expression of Anti-Mullerian Hormone (AMH)	Increased expression of AMH and AMHRII proteins; DNA fragmentation	Bovine oocyte maturation and early embryo development	[134]
BPA	40 μg/kg	Mitigation of Dynamin-Related Protein 1 Inhibition	Down-regulated autophagic markers; up-regulated caspase-3; increased MDA levels; mitochondrial changes; Drp-1 involvement	Wistar rats	[135]

intimately linked to NLRP3-mediated signaling [115].

6. The therapeutic target of NLRP3 in BPA toxicity

The intricate molecular mechanisms underlying the initiation of the NLRP3 inflammasome by BPA have undergone rigorous scrutiny. BPA instigates NLRP3 inflammasome activation in macrophages through a well-established NF-κB/TLR4 signaling axis, resulting in the augmented secretion of potent pro-inflammatory cytokines, specifically IL-18 and IL-1β. This discernible linkage between BPA and the NLRP3 inflammasome assumes paramount significance within the context of an expanding landscape of inflammatory pathologies. Consequently, therapeutic interventions targeting the NLRP3 inflammasome have gained substantial momentum as a contemporary strategy for mitigating the deleterious consequences of BPA exposure.

Notably, a compendium of compounds, including MCC950, β-hydroxybutyrate, and glyburide [116,115], have surfaced as promising inhibitors of the NLRP3 inflammasome, unveiling an exciting avenue for potential intervention strategies. Moreover, BPA has demonstrated its remarkable versatility by instigating NLRP3 inflammasome activation through a plethora of molecular pathways, encompassing TLR4/NF-κB signaling, ROS-dependent NF-κB activation, and the STING-TBK1-IRF3 axis. This nuanced interplay underscores the NLRP3 inflammasome as an auspicious therapeutic target, poised to effectively ameliorate the multifaceted toxicity inflicted by BPA exposure (see Table I).

7. Future perspective

The activation of the NLRP3 inflammasome stands as a fundamental determinant in the onset and progression of diverse toxicological manifestations. To unveil novel paradigms and therapeutic avenues for addressing NLRP3 inflammasome-related pathologies, an in-depth comprehension of the intricate interplay between mitochondria and NLRP3 inflammasome activation during organ injury emerges as a critical imperative. This heightened understanding serves as the compass guiding the development of innovative methodologies and pharmaceutical agents. Moreover, a profound elucidation of mitochondria's role in the orchestration of NLRP3 inflammasome activation paves the way for future research endeavors squarely focused on designing and implementing precision-targeted therapeutic interventions.

One promising avenue entails the meticulous scrutiny of compounds or pharmacological agents capable of interacting with the NLRP3-NACHT domain, consequently curtailing its ATPase activity. This strategic inhibition of NLRP3 inflammasome activation holds profound potential for the attenuation of organ-specific toxicities.

Remarkably, a spectrum of natural compounds has been posited as potent inhibitors of both organ toxicity and NLRP3 inflammasome activation. Pre-clinical investigations have unequivocally underscored the pivotal role played by NLRP3 activation in the context of toxicological studies. Therefore, the strategic targeting of the NLRP3 inflammasome emerges as a pivotal approach for mitigating the burden of toxicity-associated ailments. This therapeutic pursuit can be driven by a rich repertoire of natural compounds or synthetic pharmaceuticals, exemplified by the synthetic chemicals MCC950, CY-09, and OLT1177, all of which substantively interact with the NLRP3-NACHT domain, leading to a conspicuous attenuation of its ATPase activity [136]. The recent elucidation of the crystal structure of NLRP3 bound to the MCC950 complex has unfurled a compelling avenue toward the identification of potential NLRP3 inhibitors characterized by enhanced efficacy and selectivity [137]. This structural elucidation serves as the cornerstone for an expedition into the innovation and design of novel compounds, peptides, and monoclonal antibodies, each meticulously tailored to selectively target the NLRP3 inflammasome. This groundbreaking revelation usher in a new era, replete with the promise of more efficacious and precisely targeted therapeutic modalities.

Simultaneously, extensive research efforts have been directed towards chalcone derivatives, which indirectly hamper NLRP3 inflammasome activation via the inhibition of ROS production. Researchers have channelled their scientific acumen into the synthesis of a myriad of chalcone derivatives, each boasting inhibitory efficacy over LPS-induced ROS generation within macrophages [138].

In aggregate, the future prospects in this dynamic domain unfurl a tapestry of heightened enlightenment concerning NLRP3 inflammasome activation, the quest for innovative compound and drug entities capable of finely modulating this cascade, and the seamless translation of this scholarly corpus into the clinical realm, where NLRP3 inflammasome-associated afflictions can be more effectively managed. The emergence of precision-targeted therapies, the untapped potential of natural compounds, the synthetics armamentarium, and the ever-expanding repertoire of chalcone derivatives form the veritable keystones of this unfolding narrative. The enduring pursuit of scientific inquiry, bolstered by robust collaboration amongst researchers, pharmaceutical enterprises, and clinical practitioners, will indubitably catalyze the unlocking of NLRP3 inflammasome inhibition's profound potential in elevating patient outcomes.

8. Conclusion

In summation, this review underscores the pivotal role of NLRP3 in the deleterious repercussions stemming from pervasive environmental exposure to BPA. BPA's propensity to incite NLRP3 inflammasome activation engenders a cascade of events that intricately contribute to the genesis and progression of diverse pathologies. The ubiquity of NLRP3 involvement in multiple inflammatory cascades accentuates its prominence, particularly within the context of pathological conditions.

Our comprehensive elucidation lays the groundwork for prospective therapeutic strategies aimed at NLRP3 modulation. Notably, contemporary pre-clinical investigations have made significant strides in probing the prospect of modulating NLRP3 activation as a viable countermeasure against BPA-induced toxicity across various organ systems. Yet, a nuanced comprehension of the mechanistic

intricacies remains paramount. This imperative lies in pinpointing precise therapeutic nodes within the expansive web of NLRP3 signaling pathways a quest that holds immense promise for the amelioration of BPA-associated pathogenic manifestations in the current landscape of scientific inquiry.

Funding

This review did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Data availability statement

All data supporting the findings of this study are available within the paper.

CRediT authorship contribution statement

Doveit Antony Charles: Writing – original draft, Methodology. **Sabina Evan Prince:** Supervision.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Corresponding author served as Associate Editor in Heliyon journal in the section of Pharmacology and Toxicology - Sabina Evan Prince If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgment

The authors would like to thank the Vellore Institute of Technology for the opportunity to contribute to this work.

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