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Review Article

Research Progress of Programmed Cell Death Induced by Acrylamide

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Acrylamide exposure through environment pollution and diet is very common in daily life. With the deepening of the study on the toxicity of acrylamide, it has attracted widespread attention for the effects of acrylamide on multiple organs through affecting a variety of programmed cell death. Multiple studies have shown that acrylamide could exert its toxic effect by inducing programmed cell death, but its specific molecular mechanism is still unclear. In this review, the research on the main forms of programmed cell death (apoptosis, autophagy, and programmed necrosis) induced by acrylamide and their possible mechanisms are reviewed. This review may provide basic data for further research of acrylamide and prevention of its toxicity.

1. Introduction

Food safety involves not only the toxic and harmful substances added to food in various food processes but also a series of harmful substances produced by some chemical reactions in food production. Acrylamide (AA) has been detected in potato chips, coffee, and some grain foods, such as all kinds of cakes, cookies, bread, and toast (Figure 1) [1, 2]. The content of AA in different foods is listed in Table 1. The content of AA in potato crisps, bread, coffee, and biscuits is very high. Moreover, the content of AA in these fried or baked foods is much higher than the content standard (0.5 μg/L) in drinking water stipulated by the World Health Organization. Table 1 shows that the level of AA in different food changed depending on the ingredients and processing conditions. Several pathways of AA formation in food have been reported [3, 4], but the most probable pathway of AA formation in food is the Maillard route (Figure 2). Asparagine is considered to be the most important precursor of AA [5, 6]. When asparagine is heated alone, a very limited amount of AA is formed. So it needs a carbonyl group to accelerate its conversion to AA. The classical pathway (Figure 2(a)) occurs in the heating of asparagine in the presence of compounds that have α-hydroxyl carbonyl groups (such as the reducing sugars), which leads to the formation of Schiff bases in the Maillard reaction. Schiff bases can be decarboxylated directly by Schiff betaine or indirectly by an intermediate of oxazolidin-5-1 to form azomethine ylide. Afterward, AA may be produced directly from azomethine ylide, through the deamination of 3-aminopropionamide (3-APA), which is regarded to be a direct precursor of AA. In addition to compounds containing carbonyl α-OH groups, other active carbon groups may also take a part in the formation of AA [7]. When α-dicarbonyl groups are available, alternative pathways (Figure 2(b)) appear to be activated. A significantly related reaction is the Strecker degradation of amino acids by these intermediates, in which an aldehyde is formed through decarboxylated and deaminated of amino acid. Therefore, food exposure is a common way. In addition, chemical poly-AA synthesized from AA are widely used in the treatment of drinking water and industrial wastewater, oil mining, papermaking, production of textile, adhesive, dye and cosmetics, and other fields. In the process of polymer synthesis

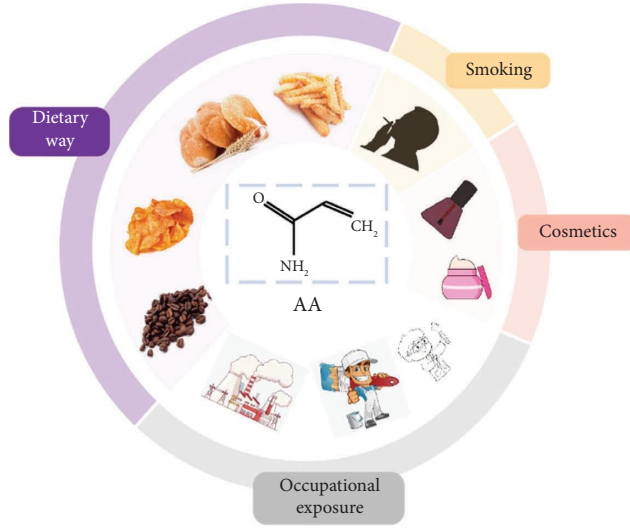

Figure 1: Major source of exposure to AA. There are four main routes of exposure to AA: dietary way, occupational exposure, cosmetics, and smoking.

Table 1: Contents of AA in different food categories.

Category	Food groups	AA levels ($\mu g \cdot kg^{-1}$)	Reference
Cereal product	White wheat bread	121	[8]
	Rye bread	432	[8]
	Whole wheat bread	479	[8]
	Whole grain bread	151	[8]
	Wafer	233.94	[9]
	Traditional flat bread	218.26	[9]
	Biscuit	200.67	[9]
	Cracker	190.50	[9]
	Cake	186.39	[9]
	Cookie	156.10	[9]
	Leavened bread	100.22	[9]
	Fried instant noodles	32.75	[10]
Potato product	Potato crisps	630	[11]
	French fries	357	[12]
Coffee product	Roasted coffee	222.3 ± 218.8	[13]
	Instant coffee	166.7 ± 71.8	[13]

and application, a small amount of AA monomer may inevitably remain or decompose, polluting the atmosphere, water, and soil [8–13].

A tide of research shows that AA can be absorbed through the digestive and respiratory tract, skin, and mucous membranes and transported to various body tissues through the blood. AA even enters into fetuses and infants through the placenta and milk [14, 15]. AA has been reported to produce reproductive toxicity, developmental toxicity, neurotoxicity, immunotoxicity, and carcinogenicity after entering the human and animal body [14, 16–19]. Therefore, the research and control of the toxicity of AA have had a high profile around the world.

The toxicity of AA not only has a broad spectrum but also causes severe harm. The research regarding to the toxic AA is no longer simply to evaluate its harmful effects on organisms, but also to explore the specific toxic mechanism. A plethora of studies have already suggested that one of the critical mechanisms of AA is to trigger programmed cell death (PCD). PCD refers to an orderly and active way of cell death to maintain homeostasis under the stimulation of certain signals or factors. Apoptosis, autophagy, pyroptosis, and necroptosis are common ways of PCD [20]. AA was previously found to induce cell apoptosis. Recent studies have shown that AA could still lead to cell autophagy. There is also evidence that AA-induced injury may be related to cell pyroptosis and necroptosis. This review mainly summarized the research of AA-induced PCD and may provide clues for the elucidation of the possible toxic mechanism and the risk control of AA.

2. Acrylamide Induces Cell Apoptosis

Apoptosis is an early, chronic, and mild reaction after injury induction. It is a highly regulated and gene PCD process during cell growth and development. It maintains the

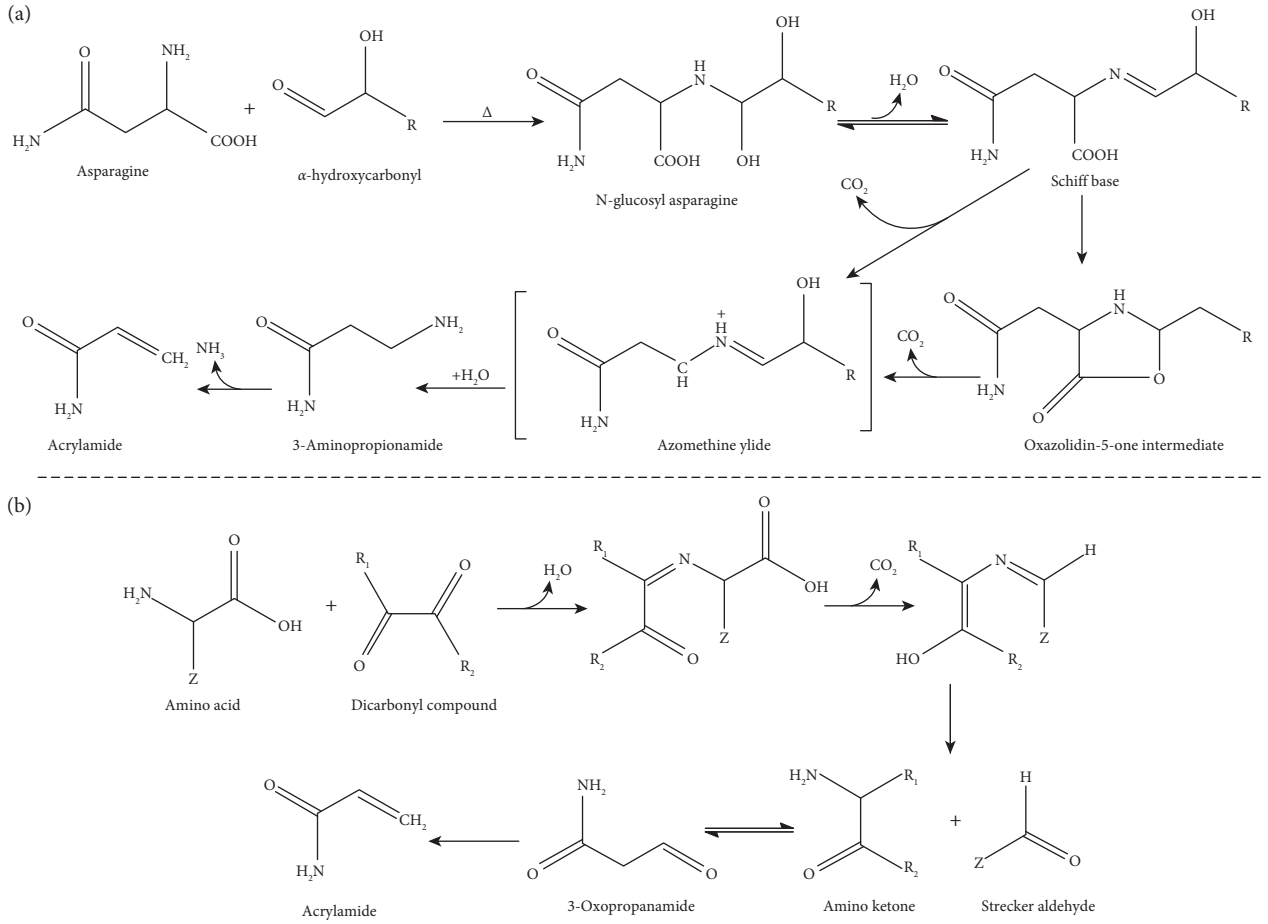

Figure 2: Mechanism of AA formation in heated foods. (a) Principle of decarboxylation of Schiff base to form AA. (b) The principle that dicarbonyl compounds are degraded by Strecker to form AA.

homeostasis of cells and biological organism by clearing off redundant, aging, and damaged cells [21, 22]. The classic apoptotic pathway includes three major signaling pathways: the extrinsic death receptor-induced pathway, the intrinsic mitochondria-mediated pathway, and endoplasmic reticulum stress pathway [23]. Apoptosis is an active process in the body, which is regulated by apoptosis-related genes. During the process of apoptosis, the bcl-2 family proteins located in the mitochondrial membrane were changed, including the expression level of proapoptotic protein bax increased and the expression level of antiapoptotic protein bcl-2 decreased. It has been found that AA can induce apoptosis in nerve cells, germ cells, retinal cells, hepatocytes, bone marrow cells, and so on, endangering the growth and function of cells.

2.1. Acrylamide Induces Apoptosis in Nervous Related Cells. An increasing number of evidence proved that AA caused severe neurotoxicity. Although the neurotoxic mechanism of AA is complex, the induction of neuronal apoptosis represents as one important mechanism. The research of apoptosis has no longer only focus on nerve cells, and more research has gone deep into the tissues and cells related to the nervous system. The apoptotic mechanism has been deeply explored, which provides an important scientific basis for intervention and prevention of AA-induced injury.

Previous animal studies have suggested that there was an early apoptosis detected in AA-induced neuropathy. For example, the results of a subchronic model in Wistar rats and SD rats showed that after exposure to AA, the expression of antiapoptotic bcl-2 decreased in the cerebral cortex and cerebellar cortex, while the expression of proapoptotic bax increased and caspase-3 was activated [24–26]. Typical apoptotic characteristics such as nuclear pyknosis occurred in cerebral cortical neurons. There were different degrees of the apoptotic phenomenon in the central and peripheral nervous system. Meanwhile, the expressions of bax and caspase-7 in cerebellum of rats exposed to AA (5 mg/kg) significantly increased, and apoptotic phenomenon were observed in more than half of the isolated cells [27].

Some researchers have suggested that AA-induced apoptosis occurs in the Purkinje cell layer and the cerebellar cortical granulosa cell layer, due to the observed condensation and pyknosis of the nucleus [28–31]. Purkinje cells are the largest neurons in the cerebellar cortex and the only neurons that can transmit impulses from the cerebellar cortex. The nuclear factor erythroid 2-related factor 2 (Nrf2)

family is a transcription factor that regulates the redox state of cells and is involved in the coordination of adaptive responses to various stimuli [32]. It has been found that AA-induced degeneration and apoptosis in cerebellar Purkinje cells were related to the inhibition of the Nrf2 pathway [33].

It has also been reported that the occurrence of nerve cell apoptosis is mediated by the PERK pathway activated by ERS (endoplasmic reticulum stress) [28]. Zebrafish is an ideal model to study the development, function, and tissue repair of the nervous system. AA also exerted severely toxic effects on zebrafish. Zebrafish after being exposed to AA experienced an injury in its brain structure, and this injury was due to cell apoptosis mediated through ERS and eIF2α-ATF4-CHOP signal cascade [34]. In SH-SY5Y cells, AA-induced phosphorylated tau protein aggregation, phosphorylated cAMP response element binding protein (CREB) decreased, and bax/bcl-2 ratio was up-regulated. AA could also activate PERK-eIF2α pathway in SH-SY5Y cells, trigger the activation of glycogen synthase kinase-3β (GSK-3β), and up-regulate activating transcription factor 4 (ATF4) and C/EBP homologous protein (CHOP) [35].

The central nervous system has active oxygen metabolism, but the activity of antioxidant enzymes is relatively low. Therefore, oxidative stress plays an important role in AA-induced neurotoxicity. Numerous studies have shown that AA can induce neuronal apoptosis in various neural cell models through mitochondrial and death receptor pathways [36–38]. For example, AA could down-regulate the expressions of miR-21, p-Akt, and bcl-2 in SH-SY5Y cells and up-regulate the levels of PTEN, bax, caspase-9, and caspase-3, thus triggering mitochondrial oxidative stress [39]. Mitogen-activated protein kinase (MAPK), a serine-threonine protein kinase including extracellular regulated protein kinases (ERK), c-JunN-terminal kinase (JNK), and p38 protein, could control apoptosis and proliferation of cell [40, 41]. The mitochondrial apoptosis induced by AA in PC12 cells was closely related to the activation of JNK and p38 pathways [37]. Nuclear factor-κB (NF-κB) could regulate a variety of target genes including those associated with proliferation and apoptosis. Moreover, the NF-κB signal is prone to crosstalk and affects a variety of signaling pathways [42]. AA could also cause the accumulation of cellular reactive oxygen species (ROS) by increasing the mRNA level of ERS-dependent apoptosis factor C/EBP homologous protein (CHOP) and inactivating the NF-κB pathway [34, 43]. Research has proved that AA could activate the NF-κB cascade, increase the ratio of Bax/Bcl-2, and cause the cleavage of caspase-3, caspase-9, and PARP to induce apoptosis [44].

In addition, a whole cell model *in vitro* was established to simulate the barrier and metabolic microenvironment in the nervous system *in vivo*. A noncontact cocultured blood-brain barrier (BBB) model *in vitro* was established with human umbilical vein endothelial cells (HUVEC) and rat glioma cells (C6). Human renal cortical proximal convoluted tubular epithelial cells (HK-2), human normal hepatocytes (L-02), and human neuroblastoma cells (SH-SY5Y) were inoculated into a cell coculture plate to establish an integrated discrete multiple organ cell coculture (IdMOC) model. Then, SH-SY5Y cells were either directly exposed to AA, or indirectly exposed to AA via the BBB model and IdMOC model. The results showed that the SH-SY5Y apoptosis rate of the indirect exposure group was significantly lower than that of the direct exposure group [45].

There are also a large number of neuroglia in the nervous system, such as astrocytes, oligodendrocytes, microglia in the central nervous system, and Schwann cells in the peripheral nervous system. Astrocytes play the role of supporting and separating nerve cells and participate in the formation of the blood-brain barrier. The toxic effects of AA on rat primary astrocytes and three human astrocytoma cell lines (U-1240MG, U-87MG, and U-251MG) have been tested. It was found that, after exposure to 2 mmol/L of AA for 48 h, an increased ratio of bax/bcl-2 was detected in primary astrocytes and U-87MG cells, whereas an overexpression of bcl-2 was observed in U-1240MG and U-251MG cells. The levels of p53 and p-p53 in primary astrocytes increased, and caspases (caspase-3, caspase-8, and caspase-9) were activated in all cell types. These results indicate the existence of a common apoptotic pathway among all astrocytes, and U-87MG cells might be a suitable *in vitro* model besides primary astrocytes [46–48]. In response to various cellular stressors, such as oxidative stress, hypoxia, DNA damage, RNA consumption, and oncogene activation, the tumor suppressor gene p53 may be activated and overexpressed, promoting cell apoptosis [49]. The latest research shows the increased apoptosis induced by AA may be due to the high increase of the p53 expression level [50].

In addition, the results in mice found that the apoptotic effect of AA on astrocytes was closely related to the deletion of metallothionein I/II (MTI/II) [51]. AA could also impair the energy metabolism of mouse microglia cell line BV2 by reducing mitochondrial respiration, anaerobic glycolysis, and the expressions of complex I, III, and IV subunits, leading to apoptosis [52]. Recent research using the zebrafish model also reported that AA could enhance microglia-induced neuronal apoptosis by impairing the capacity of oxidative repairing systems [53].

AA could also induce apoptosis in other nerve cells. For example, AA could induce apoptosis in adult hippocampal neurons and pluripotent neural precursor cells in mice [54]. AA in HT22 (mouse hippocampal neuron cell line) cells could down-regulate the bcl-2 level and up-regulate the levels of bax and cleaved caspase-3 [55]. AA could also stimulate apoptosis in motor neuron VSC4.1 cells (Spinal cord anterior horn motoneuronoma cell line) by elevating the expressions of GRP78 (glucose-regulated protein 78), ATF6 (activating transcription factor 6), and IRE1 (Inositol-requiring enzyme 1), which indicated the role of endoplasmic reticulum stress in regulating apoptosis [56]. Recently, cerebral organoids based on human embryonic stem cells (hESC) have been used to analyze human neurodevelopmental toxicity. The results by hESC-derived cerebral organoids showed that AA could significantly interfere with the transcriptional profile, elevate Nrf2-mediated gene expression, cause cell apoptosis, and promote tau hyperphosphorylation in cerebral organoids [57].

2.2. Acrylamide Induces Cell Apoptosis in Reproductive System. AA causes reproductive and developmental toxicity to rodents and humans. Inducing apoptosis in germ cells and related cells is one of the important mechanisms of AA-induced toxicity. For example, the apoptosis rate of testicular germ cells increased significantly after rats were chronically exposed to AA (20, 40, 60 mg/kg) for 8 weeks. It is revealed that AA could cause oxidative damage to mouse testicular tissue and inhibit the expressions of CK18 (Cytokeratin 18) and CK8 (cytokeratin 8) and vimentin, thus activating Fas/FasL and caspase-3 apoptosis pathway [58–60]. AA could also disrupt the dynamic balance of spermatogenic cell division, proliferation, and apoptosis in male rats and then cause spermatogenesis disorder. The specific mechanism is closely related to the reduced protein expressions of XRCC1, TERT, and PCNA, as well as the declined activity of the antioxidant enzyme (SOD, CAT, and GPX) in testicular spermatogenic cells, and the mitochondrial damage in testicular seminiferous tubules [61–63]. Recent studies suggested that AA-promoted apoptosis in rat testicular tissue was also mediated by stimulating p38α-MAPK, TNF-α, and PI3K/Akt/mTOR pathways [64].

Notably, AA exposure could also induce DNA damage and oxidative stress in mouse sperm. Thus, these may be one of the reasons why H2AX phosphorylated amplification and meiosis processes are interrupted. It is illustrated that MVH-positive cells decreased in AA-treated mice. In conclusion, DNA damage and oxidative stress may be one of the causes of germ cell apoptosis and further lead to germ cell depletion [65].

Leydig cell is an endocrine cell located in the mammalian testicular stroma. It plays an important role in promoting the differentiation and development of embryonic reproductive organs, as well as maintaining sexual function and promoting metabolism. It is already found that AA could destroy antioxidant systems and induce the mitochondrial apoptosis pathway in Leydig cells, resulting in sperm defects and various abnormal histopathological injuries [66, 67]. Recent findings suggest that AA exposure could lead to structural and functional damage of Leydig cells and mouse testis, and decreased testosterone synthesis, which may be related to activation of ERK1/2 phosphorylation [68].

AA can also damage female fertility. Prenatal development is extremely sensitive, and the effect of any poison may permanently damage its process. AA could easily pass through the placenta and breast milk. It has been reported that maternal exposure to AA could lead to weight loss at birth, and the decrease of follicles as well as oocytes apoptosis in the offspring of newborn guinea pigs [69, 70]. AA-caused follicular cell apoptosis was responsible for ovarian dysfunction [71]. Evidence by evaluating the effect of AA on apoptosis-related genes in the ovaries showed that the most increased ratio of Bax/Bcl-2 was found in the AA group compared to the normal group. AA may induce ovarian dysfunction by increasing the proportions of apoptosis-related genes [72]. It has been reported that AA exposure may inhibit the endocrine function of lutein in pregnancy through ovarian oxidative stress and apoptosis [73]. AA could also promote the apoptosis of mouse extracellular cumulus granulosa cells, delay cell maturation, and decrease developmental potential [74]. Some results are indicated that AA exposure reduces the developmental potential of GV oocytes by inducing mitochondrial dysfunction, actin assembly abnormalities, and apoptosis, which impair chromatin structure, sperm binding capacity, and embryonic development [75].

Decidualization is an important process of a successful pregnancy. It is reported that AA could significantly inhibit the decidualization of mouse endometrium by inducing apoptosis [76]. AA during pregnancy mainly caused placental development arrest by regulating the expressions of key placental AA genes and labyrinthine vessels, inhibiting proliferation and inducing apoptosis. Moreover, P-ERK1/2 and p53 may be involved in the process [73, 77]. In addition, it is also shown that benzopyrene had an obvious synergistic effect on gonadal cell apoptosis in *Caenorhabditis elegans* [78].

2.3. Acrylamide Induces Cell Apoptosis in Bone Marrow/Spinal Cord Tissues. Bone marrow mesenchymal stem cells (BMMSCs) participate in a variety of immune responses and have the ability to preferentially migrate to repair damaged tissues and organs *in vivo*. Someone reported that after AA treatment of BMMSCs for 72 h, the levels of ROS, HSP27, and IL-8 increased significantly, and NF-κB pathway was activated, but the cell cycle and apoptosis hardly changed [79]. Others found that the structure of spinal cord tissue was destroyed and obvious characteristics of apoptosis appeared after AA exposure. BMMSCs transplantation can inhibit the spinal cord cell apoptosis caused by AA, and its mechanism may be related to promoting the expression of bcl-2 and inhibiting the expression of bax [80]. It is still shown that AA can damage bone development and remodeling, which was due to the apoptosis of mesenchymal progenitor cells (HMPC) [81].

2.4. Acrylamide Induces Apoptosis in Gastrointestinal Cells. AA is also toxic to the gastrointestinal tract. Male mice (BALB/c) exposed to AA displayed alteration of morphology and histology of the small intestinal wall and decrease in proliferation, villus length, fractal dimension, crypt depth, and number, as well as the small intestinal absorptive surface. Conversely, there was an increase in apoptosis and parameters associated with nerve ganglia [82].

Ildefonso RodríGuez Ramiro et al. reported that AA can activate caspase-3 and induce apoptosis in human Caco-2 cells. The specific mechanism is related to the activation of extracellular-regulated kinases (ERK) and c-JunN-amino terminal kinases (JNK), the accumulation of intracellular ROS, and the destruction of mitochondrial structure [83]. Natural dietary antioxidants such as HTY (olive oil extract), hispidin (*phellinus igniarius* extract), and cocoa polyphenolic extract (CPE) and its main polyphenol components procyanidin B2 (PB2) can partially inhibit AA-activated apoptosis by improving the redox state of Caco-2 cells [83–85].

It has been reported that AA caused mucosal erosions and depletion of the protective surface mucus as well as widespread inflammatory infiltration in adult male albino rats. A significant increase in the expressions of caspase-3 and iNOS indicated the involvement of apoptosis and oxidative stress. Rosemary extracts exerted a protective effect against AA-induced gastric apoptosis and inflammation [86].

2.5. Acrylamide Induces Apoptosis in Liver, Kidney and Lung Cells. It has been previously reported that AA caused apoptosis in HL7702 cells (human hepatocyte) by the disturbing cell cycle, disrupting DNA function and activating protooncogene c-jun and c-fos [87]. Studies have shown that AA induces hepatocyte apoptosis, leading to an increase of bax, TGF-β1, and COX-2 and decreases the expression of bcl-2, Nrf2, HO-1, and antioxidant [88]. AA also stimulated apoptosis in HepG2 cell, rat liver cells (e.g., BRL-3A cells and IAR20 cells), and kidney cells, and the miR-27a-5p-Btf3-ATM-p53 axis might play a vital role in the promotion of AA-induced cell apoptosis through disrupting mitochondrial structure and function [89]. It was reported that the application of AA increased the level of KIM-1 in kidney tissue, as well as the expression levels of caspase-3 and bcl-2. In this study, it was observed increased expression levels of NF-κB and MAPK-1 in the renal tissue of rats treated with AA, suggesting that AA can trigger inflammation and apoptosis of renal tissue by stimulating NF-κB and MAPK-1 [90]. Meanwhile, the apoptosis could be inhibited by silymarin, morin, and rosmarinic acid by regulating the key proteins of the IRE1 pathway (p-IRE1α, XBP-1s, and TRAF2), PI3K/Akt/mTOR signal pathway and the expression of endoplasmic reticulum stress (ERS) characteristic proteins (GRP78, p-ASK1, Caspase-12, and CHOP) [91, 92].

The respiratory system was also reported to be damaged by AA. BEAS-2B cells (pulmonary epithelial cell) after AA treatment displayed obvious apoptotic characteristics, such as the significantly decreased ratio of bcl-2/bax, and the increased level of Nrf2 expression and caspase-3/7 activity [93]. It is also found that the mRNA expression levels of proapoptotic Bax and procaspase-3 significantly were higher after AA exposure, and the levels of antiapoptotic Bcl-2 were relatively lower. Moreover, the ratio of either p-ERK/ERK or p-JNK/JNK was significantly elevated by AA [94].

2.6. Acrylamide Induces Cell Apoptosis in Immune System. AA has been discovered to threaten the immune system. AA had adverse effects on peripheral blood lymphocytes (PBL) and intestinal associated lymphoid tissue (GALT) in male SD rats [95]. AA can activate caspase-3 in human lymphocytes and human monocyte macrophages and cause PARP fragmentation, inducing apoptosis [96, 97].

The results in the mouse model showed that AA could reduce the weight of thymus and spleen and cause pathological atrophy, the imbalance of the proportion of peripheral blood lymphocyte subsets, and the decrease of cytokine levels [98]. Meanwhile, the apoptosis rates of the spleen and thymus in the middle and high-dose groups of AA were significantly higher than those in the normal group. AA-induced a large number of apoptosis in mouse splenocytes through the cascade activation of caspases. Because AA caused a disorder of mitochondrial electron transfer chain complexes I and III, accompanied by the collapse of mitochondrial membrane potential and the accumulation of ROS [99].

2.7. Acrylamide Induces Apoptosis in Cell Associated with Visual Disorder. According to statistics, professional workers and experimental animals exposed to AA endure visual impairment, but the mechanism has not been clarified. Studies have confirmed that AA could induce slight or severe apoptosis in bovine lens epithelial (BEL) cells, human retinal pigment epithelium (RPE) cells, and the rod cells and cone cells of zebrafish embryos. These processes are caspase-3-dependent, accompanied by increasing ROS, inactivating antioxidant enzymes, and inhibiting Gpx1 and Nrf2 [100–102].

2.8. Acrylamide Induces Cell Apoptosis in Other Systems. AA could also affect preneoplatic lesions of the urinary tract in mice. Abnormal apoptotic/mitosis ratio and the expression of caspase-3 increased in AA-treated mice, and dietary PUFA (polyunsaturated fatty acid) such as *n*-6 PUFA (corn oil) could modulate preneoplastic proliferation in AA-treated mice [103]. Replicative senescence, characterized by a limited ability of cells to divide *in vitro*, induces endothelial dysfunction. Many compounds in food can induce earlier vascular senescence. Chronic exposure to lower concentrations of AA induces accelerated senescence and causes endothelial dysfunction *in vivo*. Since AA *in vitro* could inhibit HUVEC proliferation and induce apoptosis in dose- and time-dependent manners [104].

Apoptosis occurs continuously during tissue development to remove abnormal cells while causing minimal damage to surrounding tissues. Apoptosis can be upregulated by different signal transduction pathways under the induction of AA. The death receptor pathway, mitochondrial pathway, and ER stress pathway are all involved (Figure 3). The search for a new target as a key regulator of apoptosis signals may provide further insights into the intervention of AA toxicity.

3. Acrylamide Disturbs Cell Autophagy

Autophagy refers to the process in which some damaged proteins or organelles are encapsulated by autophagy vesicles with double-layer membrane structure and then sent to lysosomes (animals) for degradation and recycling [105]. Autophagy-related proteins include LC3 and Beclin-1. LC3-I and LC3-II are two forms of LC3. LC3-II is transformed from LC3-I by binding with phosphatidyl ethanolamine, which is a marker of autophagosome, and Beclin-1 is a key protein regulating the formation of autophagosomes. Specifically, autophagy flow is a finely regulated process, including the formation of autophagosomes, the fusion of autophagosomes and lysosomes, and the degradation of autophagolysosomes. AA can induce varying degrees of autophagy in different cells.

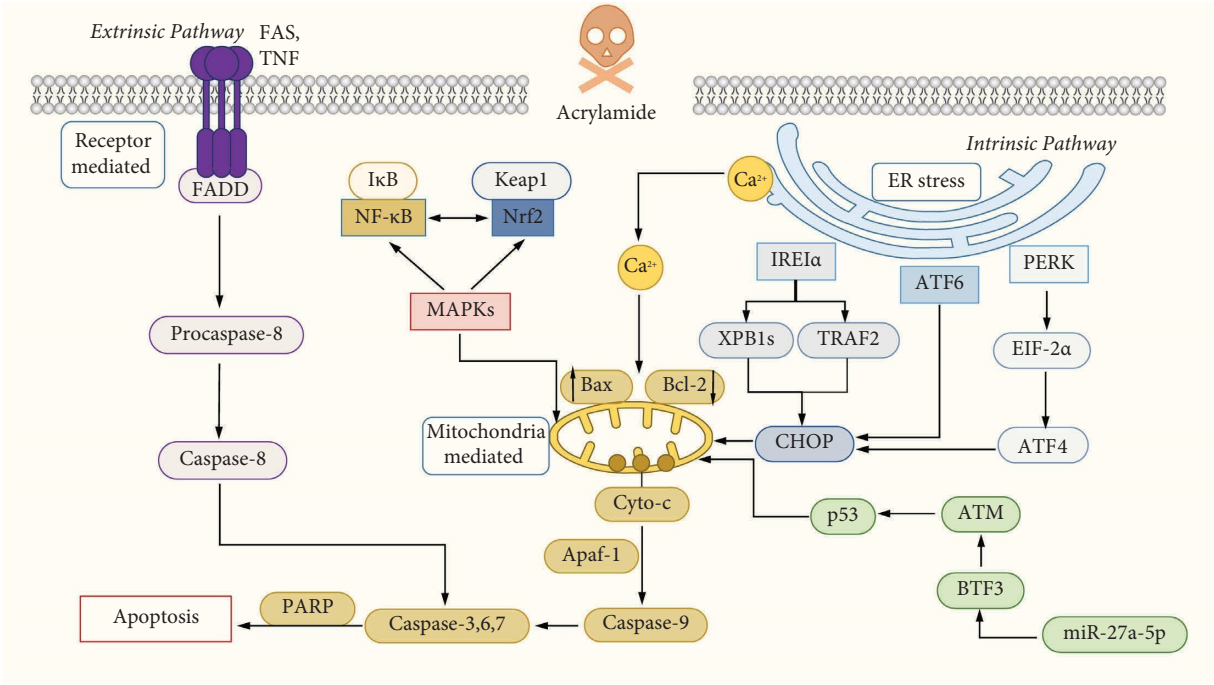

Figure 3: Molecular mechanism of apoptosis pathway induced by AA.

3.1. Acrylamide Induces Cell Autophagy in Nervous Systems. In the study of AA neurotoxicity, a large number of autophagosome, swollen mitochondria, and enlarged endoplasmic reticulum could be observed in the cerebellum of AA-exposed rats. The ratio of LC3-II/LC3-I and the protein expression of Beclin1 were significantly elevated in AA-exposed rats. ATF4 and CHOP, as well as PERK-mediated endoplasmic reticulum stress (ERS), participated in AA-induced autophagy [28]. It has also been reported that AA regulates the autophagy signaling pathway in U87-MG cells by increasing the expression of p62 and Beclin-1 and decreasing the protein expression ratio of LC3-I/LC3-II [44]. *In vitro* study with PC12 cell, it was found that AA promoted the protein expressions of Beclin-1, LC3-II as well as p62. AA-induced neuronal death was weakened by an autophagy inhibitor (3-methyladenine) and worsened by a lysosomal inhibitor (chloroquine), proving that AA could severely disturb the autophagy homeostasis. In addition, it was also found that AA-induced autophagy by activating CYP2E1, ERK, PKC-α, and PKC-δ and inhibiting AMPK, p38, and JNK pathways. Pretreatment with bioactive polyphenols blocked AA-stimulated LC3 transformation and autophagy activation [19, 106].

3.2. Acrylamide Induces Cell Autophagy in Reproductive Systems. The toxic mechanism of AA in reproductive and developmental systems still involves cell autophagy. Prenatal AA exposure significantly caused the reduction of the number of primordial follicles and primary follicles in neonatal guinea pigs. There were not only apoptosis signals but also slight autophagy signals observed in oocytes of primary and secondary follicles [69]. After rats (female Wistar-Albino of fifty days old) were exposed to AA (2.5, 10, and 50 mg/kg/day), ovarian weight and the concentrations of serum progesterone and estradiol significantly decreased. A high dose of AA (50 mg/kg/day) significantly induced the overexpressions of INSL3, CYP17α, IGF1, ESR1, ESR2, ATG5, ATG12, and LC3 in the ovary. In addition, AA-induced ovarian dysfunction was mediated by influencing steroid hormone release and activating mRNA levels of autophagy-related genes [71]. AA could also down-regulatebcl-2 and up-regulate protein levels of p38-α MAPK, TNF-α, NF-κB, IL-1β, IL-6, COX-2, cytochrome c, bax, Caspase-3, LC3, and Beclin-1 in testicular tissue/cell of male rats, indicating a large number of apoptosis and autophagy. Morin can interfere with AA-induced apoptosis and autophagy by regulating PI3K/Akt/mTOR and NF-κB signal pathway [64]. Furthermore, autophagy occurred in the oocytes of mice exposed to AA. These results suggested that AA exposure led to the reduced developmental potential of mouse germinal vesicles (GV) by damaging chromatin structure, sperm-binding capacity, and embryonic development through autophagy [75].

3.3. Acrylamide Induces Cell Autophagy in Liver and Kidney Injury. AA-induced hepatotoxicity and nephrotoxicity in rats is also related to excessive autophagy. Not only the obvious characteristics of apoptosis but also the autophagy indexes such as Beclin-1 and LC3 were significantly up-regulated in the liver and kidney of AA-treated rats. In addition, Morin also reversed the changes in levels of apoptotic and autophagic parameters by regulating p38-α MAPK, NF-κB, and PI3K/Akt/mTOR pathway [91].

3.4. Acrylamide Suppresses Cell Autophagy. Besides induction of excessive autophagy, AA also inhibits normal autophagy. For example, in AA-treated U2OS cells (human

osteosarcoma cells), autophagy was inhibited although the apoptosis rate increased. Song et al. reported that AA-induced the accumulation of autophagy markers LC3-II and p62, suggesting that AA may inhibit autophagy. It seems that the toxic mechanism of AA-induced autophagy is complex and cell-specific [107].

Apoptosis and autophagy have been observed simultaneously in AA-induced cytotoxicity. Generally speaking, AA stimulates cell apoptosis and autophagy in the liver, kidney, and nerve as well as germ cells, AA-stimulated cell apoptosis, and autophagy can be mediated by some common signal pathways. For example, AA-induced autophagic accumulation may be attributed to the blocking of autophagic flux, preventing the autophagic from binding to the lysosome. Additional information confirming the association between apoptosis and autophagy flux suggests that limiting the protective autophagy induced by AA further promotes apoptosis initiation [44]. However, the level of autophagy changes greatly sometimes, and the relationship between apoptosis and autophagy during the AA-induced damage process has not been fully elucidated.

Autophagy is an important cellular mechanism involved in a variety of cellular processes. Autophagy helps maintain cellular homeostasis under appropriate stress conditions. Either autophagy inhibition or promotion will affect the normal proliferation and function of cells. It may also induce apoptosis when stress is prolonged or aggravated. In summary, AA-induced autophagosome accumulation may be due to the blocking of autophagic flux, which prevents the binding of autophagosomes to lysosomes, and excessive autophagy may also activate apoptosis (Figure 4).

4. Acrylamide Causes Cell Pyroptosis

Cell pyroptosis has attracted more and more attention in recent years. The morphological characteristics, occurrence, and regulation mechanism of cell pyroptosis are different from other types of cell death [20, 108]. Pyroptosis is a kind of caspase-1-dependent and proinflammatory form of cell death, accompanied by the release of a large number of proinflammatory factors. Pyroptosis appears morphologically to be a combination of apoptosis and necrosis, involving the destruction of plasma membrane integrity and the release of cytoplasmic contents. During cell pyroptosis, the size of dying cells increases significantly and the nucleus becomes round and shrinks with the expansion of cells. Like apoptotic cells, the DNA fragments of pyroptotic cells were positive under TUNEL staining. Unlike apoptotic cells, pyroptosis cells maintained nuclear integrity.

4.1. Acrylamide Induces Cell Pyroptosis in Nervous Systems. In the study of AA-inducedneuro-degeneration in mice (20 mg/kg body weight for 4 weeks), it was found that proinflammatory cytokines such as tumor necrosis factor α (TNF-α), interleukin-1β (IL-1β), and inducible nitric oxide synthase (iNOS) increased, indicating the possible existence of pyroptotic events [109].

NLRP3 (Nucleotide-binding oligomerization domain, leucine rich repeat, and pyrin domain containing 3) inflammasome, an intracellular multiple protein complex, is composed of the sensor protein NLRP3, the adaptor apoptosis-associated specklike protein (ASC) and the cysteine protease-1 precursor (procaspase-1). NLRP3 inflammasome when assembling forms the effector protein caspase-1. Then, caspase-1, as a precursor of inflammatory caspase, cleaves the cytokines such as pro-IL-1β and pro-IL-18 into pro-inflammatory cytokine IL-1β and IL-18. Thus, NLRP3 plays an important role in caspase-1-dependent pyroptosis pathway. AA exposure stimulates the activation of NLRP3 inflammasome mainly through MARK, Nrf2, and NF-κB pathways [110]. The activation of NLRP3 inflammasome and its subsequent downstream inflammatory response have been detected in AA-induced neurotoxicity. For example, in AA-induced BV2 cell death, there was an obvious activation of NLRP3 inflammasome and an increase of cytokine interleukin-1β and interleukin-18 expression. These were also observed in AA-exposed C57BL/6 mice and SD rats. Either intervention with specific NLRP3 inhibitor MCC950 or NLRP3 knockout significantly reversed AA-induced cerebellar Purkinje cell degeneration and pyroptosis. AA-induced pyroptosis was also accompanied by NF-κB activation, and a significant increase of inflammatory cytokines including IL-6, COX-2, and TNF-α. AA-induced NLPR3 inflammasome cleavage can be inhibited by increasing protein p62 and activating the Nrf2 antioxidant pathway [33, 111].

4.2. Acrylamide Induces Pyroptosis in Liver, Kidney, and Lung Cells. Excessive pyroptosis was also reported in AA-induced hepatotoxicity and nephrotoxicity in rats. Not only the obvious characteristics of apoptosis and autophagy indexes but also inflammatory parameters such as IL-1β, IL-6, TNF-α, and COX-2 were significantly up-regulated in the liver and kidney of AA-treated rats [91]. AA could induce pyroptosis in rat liver kupffer cell, as indicated by NLRP3 inflammatory activation and increased levels of caspase-1, IL-1β, IL-18, IL-6, and TNF-α [112]. It was shown that AA-induced-inflammatory responses could cause pulmonary dysfunction and increase systemic inflammation. Specifically, AA resulted in significantly elevated levels of NF-κB, IL-1β, TNF-α, and COX-2 in lung tissue [94]. These evidence suggested that pyroptosis represents as one of the crucial mechanisms of AA toxicity.

Pyroptosis in which cells constantly expand until the cell membrane bursts, results in the release of cell contents and activation of inflammatory responses. Pyroptosis is a PCD mediated by GSDMD. AA-induced different degrees of pyroptosis in the nervous system, liver, kidney, and lung cells (Figure 5). NLRP3 inflammasome and NF-κB have been reported to be involved in AA induced-injury. However, other specific pathways of pyroptosis regarding to AA still need further research.

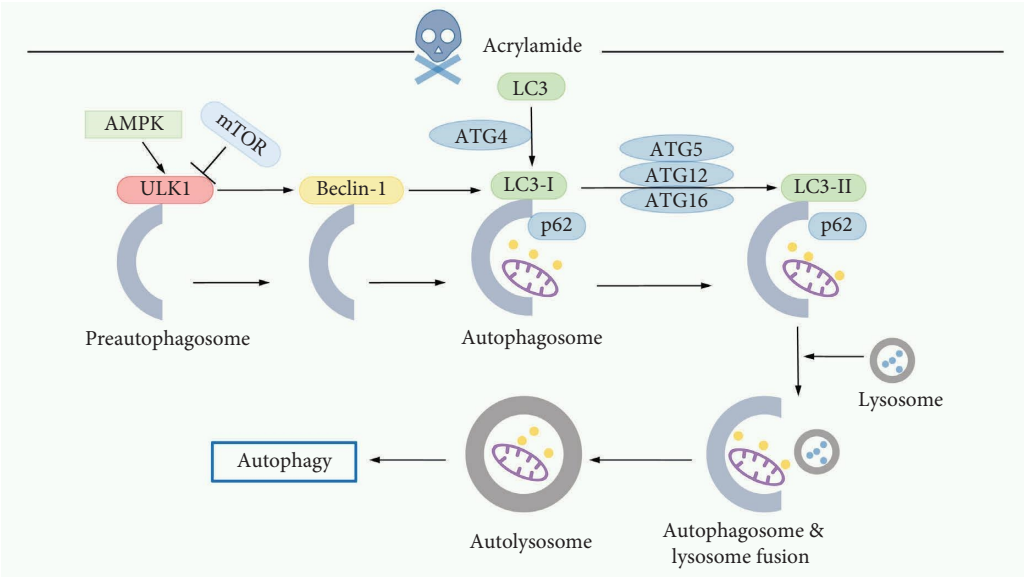

Figure 4: Molecular mechanisms of autophagy pathways in AA-induced toxicity.

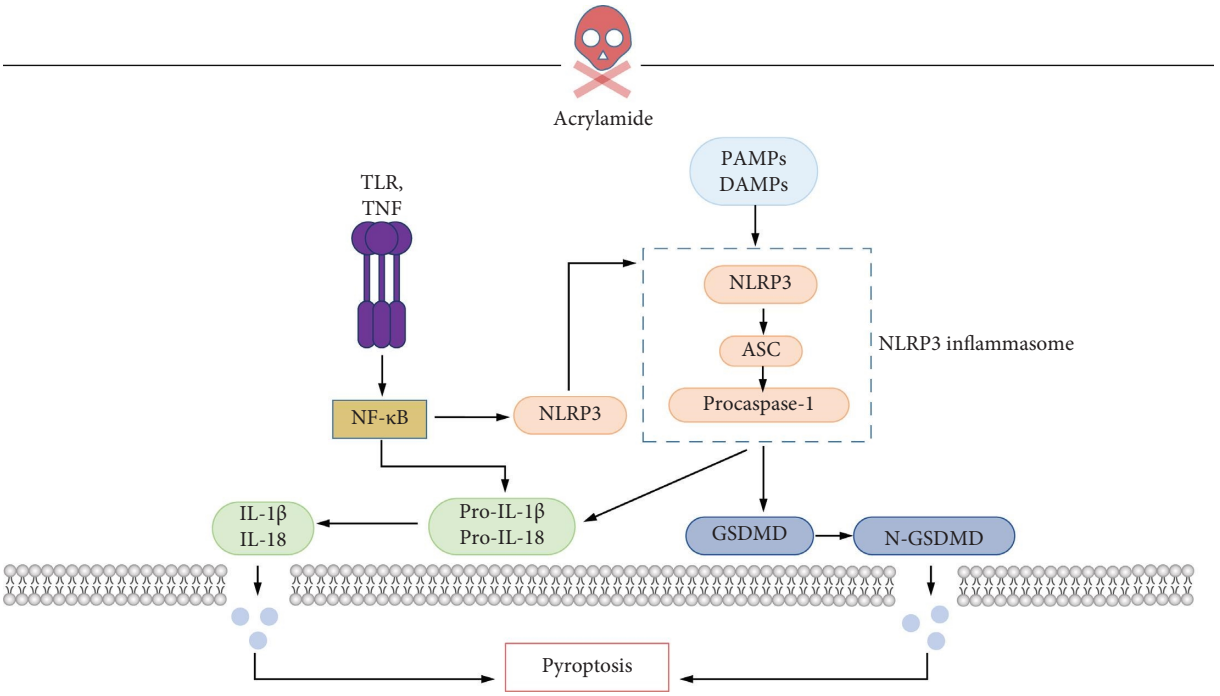

Figure 5: Molecular mechanisms of inflammation pathways in AA-induced toxicity.

5. Acrylamide Induces Cell Necrosis

The term "necrosis" (or "oncosis") refers to all forms of death that are characterized by swelling of the cells and their organelles, followed by permeabilization of the cellular membranes. Traditionally, cell necrosis is considered to be a kind of cell death induced by extreme physical and chemical factors. However, recent studies have shown that cell necrosis is not completely uncontrolled. Necrosis in some cases may be regulated, which is called necroptosis [20, 22]. Like pyroptosis, necroptosis also destroys cell membranes and causes a severe inflammatory response. Unlike pyroptosis, necroptosis has its own executive protein different from that of pyroptosis.

Necroptosis is generally mediated by receptor-interacting protein kinase-1/-3 (RIP1/RIP3) and performed through MLKL (mixed-lineage kinase domainlike protein). RIP1 and RIP3 through RHIM (RIP homotypic interaction motif) form complex IIb, also known as necrosome which mediates necroptosis [113]. Mutual phosphorylation of RIP1 and RIP3 in the necrosome can lead to MLKL recruitment and phosphorylation of MLKL.

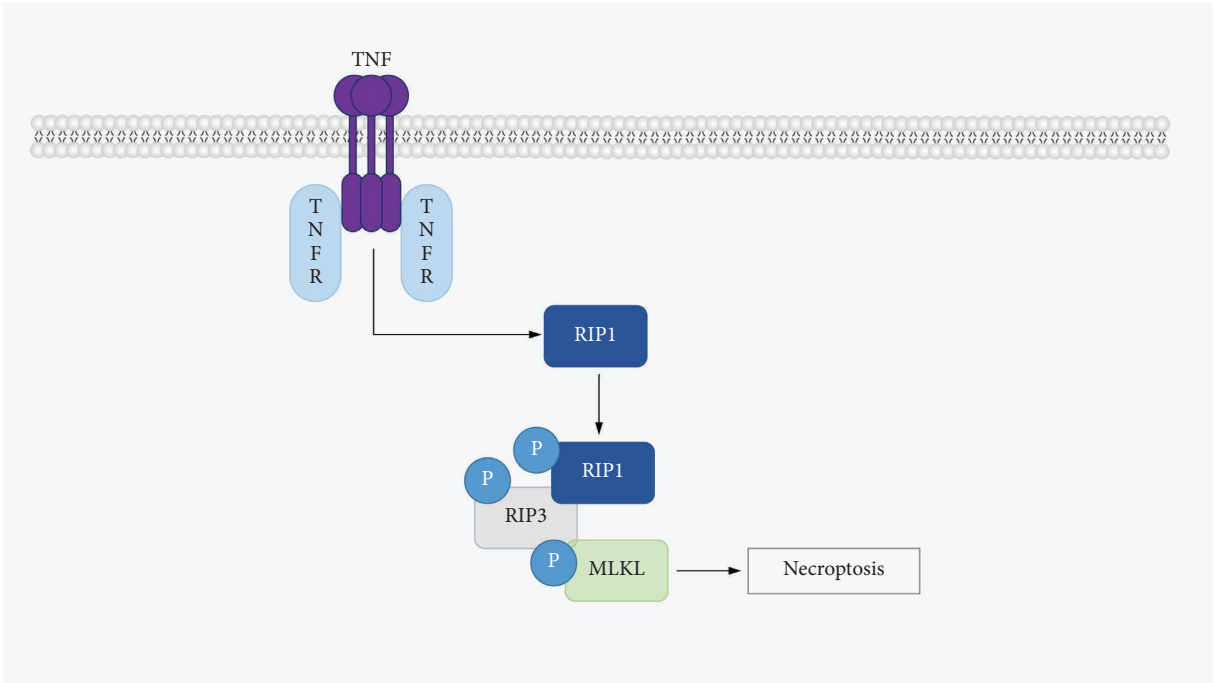

Figure 6: Molecular mechanism of necroptosis pathway.

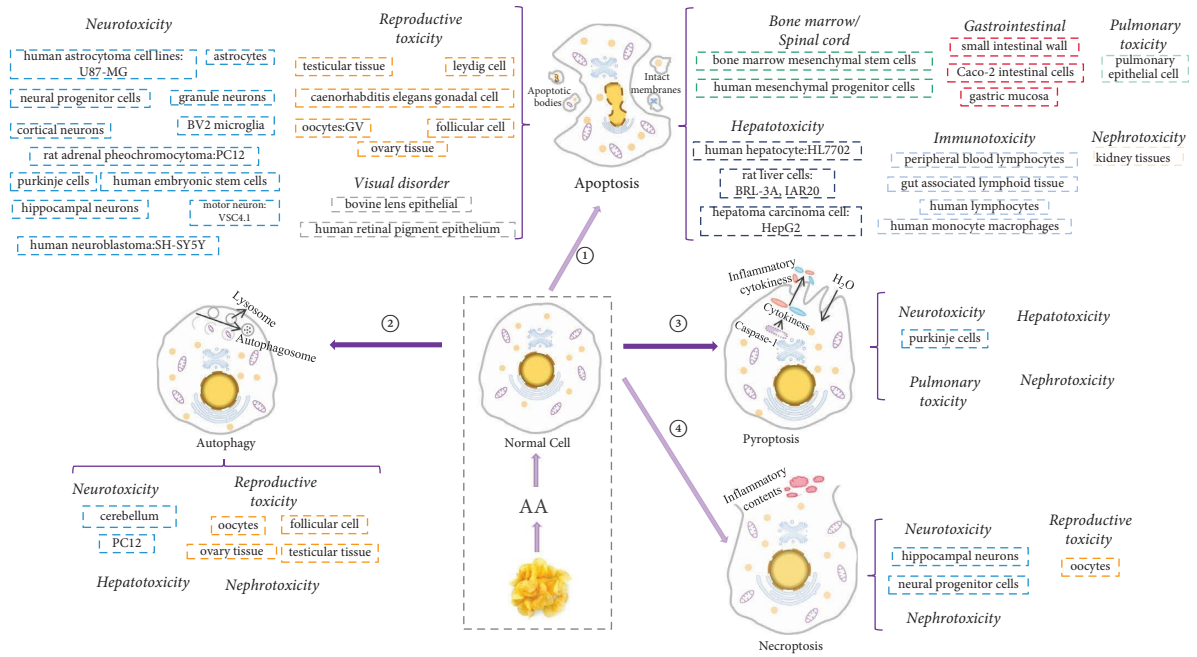

Figure 7: AA can induce PCD in different cell types. The picture shows roughly four types of PCD.

Then, phosphorylated MLKL oligomerizes and transfers to the cell membrane, followed by destroying the permeability and integrity of the membrane, thus finally leading to necroptosis. However, necroptosis is more precisely defined as a RIP3-dependent cell death, because RIP3 is essential and RIP1 is not always involved in signal transduction (Figure 6).

It has been reported that a high concentration of AA stimulated the production of reactive oxygen species and induced apoptosis and necrosis in hippocampal neurons and pluripotent neural precursor cells in mice [54]. In mussels exposed to AA, female gonads endured severe necrosis and oocyte atresia [114]. In rats exposed to AA, there was obvious inflammatory cell infiltration, hepatocellular necrosis, and hemorrhage areas in liver sections, and necrosis and glial cell activation in nervous tissues [115, 116]. These findings only suggested the occurrence of necrosis and inflammatory response in AA-induced toxicity. However, there is no direct evidence that the necrosis is some kind of

necroptosis. In addition, the signal pathway of necroptosis has not been fully understood. Further research regarding to the mechanisms of necroptosis and AA-induced necrosis is still needed.

6. Summary

AA can induce varied degrees of PCD in various types of cells. At present, plentiful research focuses on nervous, reproductive, liver, and kidney injuries. However, an increasing number of studies are expanding to other organs and systems in animals and humans (Figure 7). Inducing the disorder of the redox system is common and important for AA to exert toxic effects. Mitochondrial stress and endoplasmic reticulum stress, mediated by some kinases, are responsible for AA-induced PCD. Bioactive components to some degree ease the damage caused by AA. Although apoptosis, autophagy, and pyroptosis were all detected after AA exposure, existing studies hardly elucidate the interaction between them. Other types of PCD, such as mitotic disorder, are hardly reported and need further exploration.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

Acknowledgments

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References

[1] H. A. Deribew and A. Z. Woldegiorgis, "Acrylamide levels in coffee powder, potato chips and French fries in Addis Ababa city of Ethiopia," *Food Control*, vol. 123, Article ID 107727, 2021.

[2] C. S. Pundir, N. Yadav, and A. K. Chhillar, "Occurrence, synthesis, toxicity and detection methods for acrylamide determination in processed foods with special reference to biosensors: Occurrence, synthesis, toxicity and detection methods for acrylamide determination in processed foods with special reference to biosensors: A review review," *Trends in Food Science & Technology*, vol. 85, pp. 211–225, 2019.

[3] C. P. B. Gunduz and M. F. Cengiz, "Acrylamide contents of commonly consumed bread types in Turkey," *International Journal of Food Properties*, vol. 18, no. 4, pp. 833–841, 2015.

[4] A. Nematollahi, M. Kamankesh, H. Hosseini, J. Ghasemi, F. Hosseini-Esfahani, and A. Mohammadi, "Investigation and determination of acrylamide in the main group of cereal products using advanced microextraction method coupled with gas chromatography-mass spectrometry," *Journal of Cereal Science*, vol. 87, pp. 157–164, 2019.

[5] J. Cheng, S. Zhang, S. Wan, P. Wang, X. O. Su, and J. Xie, "Rapid and sensitive detection of acrylamide in fried food using dispersive solid-phase extraction combined with surface-enhanced Raman spectroscopy," *Food Chemistry*, vol. 276, pp. 157–163, 2019.

[6] M. Mesias and F. J. Morales, "Acrylamide in commercial potato crisps from Spanish market: trends from 2004 to 2014 and assessment of the dietary exposure," *Food and Chemical Toxicology*, vol. 81, pp. 104–110, 2015.

[7] A. P. Arisseto, M. C. Toledo, Y. Govaert et al., "Determination of acrylamide levels in selected foods in Brazil," *Food Additives & Contaminants Part A-Chemistry Analysis Control Exposure & Risk Assessment*, vol. 24, no. 3, pp. 236–241, 2007.

[8] D. S. Mottram, B. L. Wedzicha, and A. T. Dodson, "Acrylamide is formed in the Maillard reaction," *Nature*, vol. 419, no. 6906, pp. 448-449, 2002.

[9] R. H. Stadler, I. Blank, N. Varga et al., "Acrylamide from Maillard reaction products," *Nature*, vol. 419, no. 6906, pp. 449-450, 2002.

[10] D. V. Zyzak, R. A. Sanders, M. Stojanovic et al., "Acrylamide formation mechanism in heated foods," *Journal of Agricultural and Food Chemistry*, vol. 51, no. 16, pp. 4782–4787, 2003.

[11] A. Duda-Chodak, L. Wajda, T. Tarko, P. Sroka, and P. Satora, "A review of the interactions between acrylamide, microorganisms and food components," *Food & Function*, vol. 7, no. 3, pp. 1282–1295, 2016.

[12] C. Jin, X. Wu, and Y. Zhang, "Relationship between antioxidants and acrylamide formation: a review," *Food Research International*, vol. 51, no. 2, pp. 611–620, 2013.

[13] M. Surma, A. Sadowska-Rociek, E. Cieslik, and K. Sznajder-Katarzynska, "Optimization of QuEChERS sample preparation method for acrylamide level determination in coffee and coffee substitutes," *Microchemical Journal*, vol. 131, pp. 98–102, 2017.

[14] V. Matoso, P. Bargi-Souza, F. Ivanski, M. A. Romano, and R. M. Romano, "Acrylamide: Acrylamide: A review about its toxic effects in the light of Developmental Origin of Health and Disease (DOHaD) concept review about its toxic effects in the light of Developmental Origin of Health and Disease (DOHaD) concept," *Food Chemistry*, vol. 283, pp. 422–430, 2019.

[15] M. Kadawathagedara, A. C. H. Tong, B. Heude et al., "Dietary acrylamide intake during pregnancy and anthropometry at birth in the French EDEN mother-child cohort study," *Environmental Research*, vol. 149, pp. 189–196, 2016.

[16] D. Aras, Z. Cakar, S. Ozkavukcu, A. Can, and O. Cinar, "In Vivo acrylamide exposure may cause severe toxicity to mouse oocytes through its metabolite glycidamide," *PLoS One*, vol. 12, no. 2, Article ID e0172026, 2017.

[17] Y. Komoike, K. Nomura-Komoike, and M. Matsuoka, "Intake of acrylamide at the dietary relevant concentration causes splenic toxicity in adult zebrafish," *Environmental Research*, vol. 189, Article ID 109977, 2020.

[18] M. Huang, J. Jiao, J. Wang, Z. Xia, and Y. Zhang, "Exposure to acrylamide induces cardiac developmental toxicity in zebrafish during cardiogenesis," *Environmental Pollution*, vol. 234, pp. 656–666, 2018.

[19] D. Triningsih, J.-H. Yang, K. H. Sim, C. Lee, and Y. J. Lee, "Acrylamide and its metabolite induce neurotoxicity via modulation of protein kinase C and AMP-activated protein kinase pathways," *Toxicology in Vitro*, vol. 72, Article ID 105105, 2021.

[20] N. Ketelut-Carneiro and K. A. Fitzgerald, "Apoptosis, apoptosis, pyroptosis, and necroptosis—oh my! the many ways a cell can dieyroptosis, and necroptosis-oh my! the many

ways a cell can die," *Journal of Molecular Biology*, vol. 434, no. 4, Article ID 167378, 2022.

[21] S. Ünver Saraydin, D. Saraydin, and Z. D. Şahin İnan, "A study of digital image analysis on the acrylamide derivative monomers induced apoptosis in rat cerebrum," *Microscopy Research and Technique*, vol. 83, no. 4, pp. 436–445, 2020.

[22] Y. Wang and T.-D. Kanneganti, "From pyroptosis, apoptosis and necroptosis to PANoptosis: From pyroptosis, apoptosis and necroptosis to PANoptosis: A mechanistic compendium of programmed cell death pathways mechanistic compendium of programmed cell death pathways," *Computational and Structural Biotechnology Journal*, vol. 19, pp. 4641–4657, 2021.

[23] K. Wang, "Molecular mechanisms of hepatic apoptosis regulated by nuclear factors," *Cellular Signalling*, vol. 27, no. 4, pp. 729–738, 2015.

[24] S. X. Li, N. Cui, C. L. Zhang, X. l. Zhao, S. F. Yu, and K. Q. Xie, "Effect of subchronic exposure to acrylamide induced on the expression of bcl-2, bax and caspase-3 in the rat nervous system," *Toxicology*, vol. 217, no. 1, pp. 46–53, 2006.

[25] P. Zhang, H. Pan, J. Wang, X. Liu, and X. Hu, "Telomerase activity-independent function of telomerase reverse transcriptase is involved in acrylamide-induced neuron damage," *Biotechnic & Histochemistry*, vol. 89, no. 5, pp. 327–335, 2014.

[26] K. Amirshahrokhi and A. Abzirakan, "Carvedilol attenuates acrylamide-induced brain damage through inhibition of oxidative, inflammatory, and apoptotic mediators," *Iranian Journal of Basic Medical Sciences*, vol. 25, no. 1, pp. 60–67, 2022.

[27] Y. Q. Zhang, X. X. Li, and M. M. Zhao, "Toxic effects of acrylamide on primary cultured rat cortical neurons," *Journal of Neuroanatomy*, vol. 31, no. 2, pp. 208–214, 2015.

[28] Y. Wang, L. Duan, X. Zhang et al., "Effect of long-term exposure to acrylamide on endoplasmic reticulum stress and autophagy in rat cerebellum," *Ecotoxicology and Environmental Safety*, vol. 224, Article ID 112691, 2021.

[29] X. Pan, L. Zhu, H. Lu, D. Wang, Q. Lu, and H. Yan, "Melatonin Melatonin Attenuates Oxidative Damage Induced by Acrylamide In Vitro and In Vivottenuates oxidative damage induced by acrylamide in vitro and in vivo," *Oxidative Medicine and Cellular Longevity*, vol. 201512 pages, Article ID 703709, 2015.

[30] C. F. Liu, C. M. Jiang, and L. H. Zhou, "Protective effect of epigallocatechin-3-gallate on apoptosis of rat cerebellar granule neurons induced by acrylamide," *Journal of Central South University*, vol. 37, no. 9, pp. 944–950, 2012.

[31] L. H. Zhou, S. X. Xu, and C. M. Jiang, "Protective effects of genistein against apoptosis induced by acrylamide in cultured rat cerebellar granule neurons," *Carcinogenesis, Teratogenesis and Mutagenesis*, vol. 23, no. 1, pp. 46–49, 2011.

[32] J. D. Hayes and A. T. Dinkova-Kostova, "The Nrf2 regulatory network provides an interface between redox and intermediary metabolism," *Trends in Biochemical Sciences*, vol. 39, no. 4, pp. 199–218, 2014.

[33] X. Sui, J. Yang, G. Zhang et al., "NLRP3 inflammasome inhibition attenuates subacute neurotoxicity induced by acrylamide in vitro and in vivo," *Toxicology*, vol. 432, Article ID 152392, 2020.

[34] Y. Komoike and M. Matsuoka, "Endoplasmic reticulum stress-mediated neuronal apoptosis by acrylamide exposure," *Toxicology and Applied Pharmacology*, vol. 310, pp. 68–77, 2016.

[35] D. Yan, N. Wang, J. Yao, X. Wu, J. Yuan, and H. Yan, "Curcumin Curcumin Attenuates the PERK-eIF2α Signaling to Relieve Acrylamide-Induced Neurotoxicity in SH-SY5Y Neuroblastoma Cellsttenuates the PERK-eIF2α signaling to relieve acrylamide-induced neurotoxicity in SH-SY5Y neuroblastoma cells," *Neurochemical Research*, vol. 47, no. 4, pp. 1037–1048, 2022.

[36] Y. Q. Liu, L. N. Wu, X. B. Lu, W. J. Song, and M. Le, "Effects of death receptor pathway on acrylamide-induced apoptosis of PC12 cells," *Modern Preventive Medicine*, vol. 38, no. 10, pp. 1908-1909, 2011.

[37] X. Q. Pan, *The Roles of MAPKs, Nrf2, and NF-Kb Signaling Pathways in the Mechanism of Acrylamide Neurotoxicity*Huazhong University of Science & Technology, Hong Shan Qu, China, 2016.

[38] X. Pan, X. Wu, D. Yan, C. Peng, C. Rao, and H. Yan, "Acrylamide-induced oxidative stress and inflammatory response are alleviated by N-acetylcysteine in PC12 cells: Acrylamide-induced oxidative stress and inflammatory response are alleviated by N-acetylcysteine in PC12 cells: Involvement of the crosstalk between Nrf2 and NF-κB pathways regulated by MAPKsnvolvement of the crosstalk between Nrf2 and NF-kappa B pathways regulated by MAPKs," *Toxicology Letters*, vol. 288, pp. 55–64, 2018.

[39] F. F. Deng, X. T. Li, and M. M. Zhu, "Effects of acrylamide on apoptosis and Mir-21 expression of SH-SY5Y neurons," *Journal of Nan Jing Medical University*, vol. 33, no. 7, pp. 947–952, 2013.

[40] A. Cuadrado and A. R. Nebreda, "Mechanisms and functions of p38 MAPK signalling," *Biochemical Journal*, vol. 429, no. 3, pp. 403–417, 2010.

[41] E. F. Wagner and A. R. Nebreda, "Signal integration by JNK and p38 MAPK pathways in cancer development," *Nature Reviews Cancer*, vol. 9, no. 8, pp. 537–549, 2009.

[42] K. Taniguchi and M. Karin, "NF-κB, inflammation, immunity and cancer: coming of age," *Nature Reviews Immunology*, vol. 18, no. 5, pp. 309–324, 2018.

[43] X. Wu, "The inhibition effects of curcumin on acrylamide-induced apoptosis," in *SH-SY5Y Cells*Huazhong University of Science and Technology, Hong Shan Qu, China, 2017.

[44] L. Deng, M. Zhao, Y. Cui et al., "Acrylamide induces intrinsic apoptosis and inhibits protective autophagy via the ROS mediated mitochondrial dysfunction pathway in U87-MG cells," *Drug and Chemical Toxicology*, vol. 45, no. 6, pp. 2601–2612, 2022.

[45] X. Chen, D. Zhu, Y. G. Yang et al., "Effects of in vitro blood-brain barrier and simulated metabolic system on acrylamide-induced apoptosis of SH-SY5Y," *Chinese Journal of Industrial Hygiene and Occupational Diseases*, vol. 36, no. 6, pp. 401–407, 2018.

[46] J. G. Lee, Y. S. Wang, and C. C. Chou, "Acrylamide-induced apoptosis in rat primary astrocytes and human astrocytoma cell lines," *Toxicology in Vitro*, vol. 28, no. 4, pp. 562–570, 2014.

[47] J. H. Chen, C. H. Yang, Y. S. Wang, J. G. Lee, C. H. Cheng, and C. C. Chou, "Acrylamide-induced mitochondria collapse and apoptosis in human astrocytoma cells," *Food and Chemical Toxicology*, vol. 51, pp. 446–452, 2013.

[48] J. H. Chen, K. Y. Wu, I.-M. Chiu, T. C. Tsou, and C. C. Chou, "Acrylamide-induced astrogliotic and apoptotic responses in human astrocytoma cells," *Toxicology in Vitro*, vol. 23, no. 5, pp. 855–861, 2009.

[49] H. R. H. Mohamed, "Acute Acute Oral Administration of Cerium Oxide Nanoparticles Suppresses Lead

Acetate–Induced Genotoxicity, Inflammation, and ROS Generation in Mice Renal and Cardiac Tissuesral administration of cerium oxide nanoparticles suppresses lead acetate-induced genotoxicity, inflammation, and ROS generation in mice renal and cardiac tissues," *Biological Trace Element Research*, vol. 200, no. 7, pp. 3284–3293, 2022.

[50] G. Safwat, A. A. Mohamed, and H. R. H. Mohamed, "Estimation of genotoxicity, apoptosis and oxidative stress induction by TiO2 nanoparticles and acrylamide subacute oral coadministration in mice," *Scientific Reports*, vol. 12, no. 1, Article ID 18648, 2022.

[51] M. Feng, J. B. Guo, and C. Huang, "Protective effect of metallothionein-I/II on acrylamide-induced astrocyte injur," *Journal of Toxicology*, vol. 28, no. 4, pp. 265–269, 2014.

[52] Z. Liu, G. Song, C. Zou et al., "Acrylamide induces mitochondrial dysfunction and apoptosis in BV-2 microglial cells," *Free Radical Biology and Medicine*, vol. 84, pp. 42–53, 2015.

[53] C. Sharma and S. C. Kang, "Garcinol pacifies acrylamide induced cognitive impairments, neuroinflammation and neuronal apoptosis by modulating GSK signaling and activation of pCREB by regulating cathepsin B in the brain of zebrafish larvae," *Food and Chemical Toxicology*, vol. 138, Article ID 111246, 2020.

[54] H. R. Park, M. S. Kim, S. J. Kim et al., "Acrylamide induces cell death in neural progenitor cells and impairs hippocampal neurogenesis," *Toxicology Letters*, vol. 193, no. 1, pp. 86–93, 2010.

[55] Y. Q. Zhang, *Study on the Damage Effect of Acrylamide on HT22 Mouse Hippocampal Neurons*Guangdong Pharmaceutical University, Guang Dong Sheng, China, 2015.

[56] X. G. Xiao, J. S. Sun, S. Y. Li, S. X. Qu, and Y. H. Qu, "Apoptosis of motor neuron VSC4.1 induced by acrylamide through endoplasmic reticulum stress," *Journal of Environment and Occupational Medicine*, vol. 34, no. 12, pp. 1087–1092, 2017.

[57] Q. Bu, Y. Huang, M. Li et al., "Acrylamide exposure represses neuronal differentiation, induces cell apoptosis and promotes tau hyperphosphorylation in hESC-derived 3D cerebral organoids," *Food and Chemical Toxicology*, vol. 144, Article ID 111643, 2020.

[58] Q. Zhao, *The Toxic Effects of Acrylamide on Mice Testicular Tissue and the Correlation with the Expression of CKl8 and Fas, FasL, Caspase-3*Shanxi Medical University, Shanxi, China, 2012.

[59] X. L. Zhang, *The Cytotoxicity Effect of Acrylamide in Mouse Testis and its Relationship with Vimentin Expression*Shanxi Medical University, Shanxi, China, 2010.

[60] Q. Zhao, B. Q. Bai, and J. Zhang, "Effects of acute exposure to acrylamide on the expression of Caspase-3 and CK8 in mouse testis," *Journal of Environment and Health*, vol. 29, no. 1, pp. 48–50, 2012.

[61] L. Y. Yuan and P. Zhan, "Toxic effect of acrylamide on rat testis and its effect on protein expression of proliferative nuclear antigen," *Journal of Shanghai Jiaotong University*, vol. 32, no. 12, pp. 1587–1593, 2012.

[62] Y. X. Ma, S. M. Tian, J. Liu et al., "Protective roles of melatonin against acrylamide-induced testicular toxicity in rats," *Journal of Sun Yat-sen University (Social Science Edition)*, vol. 38, no. 4, pp. 517–525, 2017.

[63] Y. X. Ma, G. Y. Li, J. Liu, C. Zhou, and S. M. Tian, "Effects of melatonin on acrylamide-induced testicular oxidative damage and Bax/Bcl-2 expression in rats," *Anatomy Research*, vol. 37, no. 4, pp. 255–257, 2015.

[64] S. Kucukler, C. Caglayan, E. Darendelioğlu, and F. M. Kandemir, "Morin attenuates acrylamide-induced testicular toxicity in rats by regulating the NF-κB, Bax/Bcl-2 and PI3K/Akt/mTOR signaling pathways," *Life Sciences*, vol. 261, Article ID 118301, 2020.

[65] J. G. Gao, Y. Jiang, J. T. Zheng, and L. W. Nie, "Pubertal exposure to acrylamide disrupts spermatogenesis by interfering with meiotic progression in male mice," *Toxicology Letters*, vol. 358, pp. 80–87, 2022.

[66] H. J. Yang, S. H. Lee, Y. Jin et al., "Toxicological effects of acrylamide on rat testicular gene expression profile," *Reproductive Toxicology*, vol. 19, no. 4, pp. 527–534, 2005.

[67] J. Sun, M. Li, F. Zou et al., "Protection of cyanidin-3-O-glucoside against acrylamide- and glycidamide-induced reproductive toxicity in leydig cells," *Food and Chemical Toxicology*, vol. 119, pp. 268–274, 2018.

[68] J. Zhang, X. Zhu, W. Xu et al., "Exposure to acrylamide inhibits testosterone production in mice testes and Leydig cells by activating ERK1/2 phosphorylation," *Food and Chemical Toxicology: An International Journal Published for the British Industrial Biological Research Association*, vol. 172, Article ID 113576, 2023.

[69] M. Hulas-Stasiak, P. Dobrowolski, E. Tomaszewska, and K. Kostro, "Maternal acrylamide treatment reduces ovarian follicle number in newborn Maternal acrylamide treatment reduces ovarian follicle number in newborn guinea pig offspringuinea pig offspring," *Reproductive Toxicology*, vol. 42, pp. 125–131, 2013.

[70] M. Hułas-Stasiak, P. Dobrowolski, and E. Tomaszewska, "Chapter 5 - maternal acrylamide and effects on offspring," *Acrylamide in Food*, pp. 93–107, Academic Press, Cambridge, MA, USA, 2016.

[71] N. Aldawood, A. Alrezaki, S. Alanazi et al., "Acrylamide impairs ovarian function by promoting apoptosis and affecting reproductive hormone release, steroidogenesis and autophagy-related genes: Acrylamide impairs ovarian function by promoting apoptosis and affecting reproductive hormone release, steroidogenesis and autophagy-related genes: An in vivo studyn in vivo study," *Ecotoxicology and Environmental Safety*, vol. 197, Article ID 110595, 2020.

[72] A. M. Firouzabadi, M. Imani, F. Zakizadeh et al., "Evaluating effect of acrylamide and ascorbic acid on oxidative stress and apoptosis in ovarian tissue of wistar rat," *Toxicology Reports*, vol. 9, pp. 1580–1585, 2022.

[73] D. Yu, X. Jiang, W. Ge et al., "Gestational exposure to acrylamide suppresses luteal endocrine function through dysregulation of ovarian angiogenesis, oxidative stress and apoptosis in mice," *Food and Chemical Toxicology*, vol. 159, Article ID 112766, 2022.

[74] X. L. Chen, Z. F. Wei, C. N. Yu, H. F. Niu, X. N. Wang, and A. J. Yang, "Effect of acrylamide on oocyte maturation and developmental potential in mice," *Journal of Reproductive Medicine*, vol. 27, no. 1, pp. 71–75, 2018.

[75] J. G. Gao, J. K. Yang, L. Zhu, C. Xu, and L. W. Nie, "Acrylamide impairs the developmental potential of germinal vesicle oocytes by inducing mitochondrial dysfunction and autophagy/apoptosis in mice," *Human & Experimental Toxicology*, vol. 40, no. 12, pp. S370–S380, 2021.

[76] D. Yu, Q. Liu, B. Qiao et al., "Exposure to acrylamide inhibits uterine decidualization via suppression of cyclin D3/p21 and apoptosis in mice," *Journal of Hazardous Materials*, vol. 388, Article ID 121785, 2020.

[77] D. Yu, X. Xie, B. Qiao et al., "Gestational exposure to acrylamide inhibits mouse placental development in vivo," *Journal of Hazardous Materials*, vol. 367, pp. 160–170, 2019.

[78] W. Nie, Z. H. Tu, X. Y. Guo, and K. Z. Cai, "Study on the apoptosis of gonad cells in caenorhabditis elegans induced by acrylamide and benzopyrene," *Food Research and Development*, vol. 40, no. 2, pp. 36–41, 2019.

[79] X. L. Tao, *Effects of Acrylamide on NFκB Pathway of Porcine Bone Marrow Mesenchymal Stem Cells*Huazhong Agricultural University, Hong Shan, China, 2011.

[80] J. S. Sun, X. Y. Zhou, S. X. Qu, T. J. Bu, and S. Y. Li, "Bone marrow mesenchymaI stem ceII transpIantation inhibits apoptosis in the rat spinaI cord injured by acryIamide," *Chinese Journal of Tissue Engineering Research*, vol. 22, no. 5, pp. 680–685, 2018.

[81] L. Szewczyk, J. Ulanska, M. Dubiel, A. M. Osyczka, and G. Tylko, "The effect of acrylamide and nitric oxide donors on human mesenchymal progenitor cells," *Toxicology in Vitro*, vol. 26, no. 6, pp. 897–906, 2012.

[82] P. Dobrowolski, P. Huet, P. Karlsson et al., "Potato fiber protects the small intestinal wall against the toxic influence of acrylamide," *Nutrition*, vol. 28, no. 4, pp. 428–435, 2012.

[83] I. Rodriguez-Ramiro, S. Ramos, L. Bravo, L. Goya, and M. Á. Martín, "Procyanidin B2 and a cocoa polyphenolic extract inhibit acrylamide-induced apoptosis in human Caco-2 cells by preventing oxidative stress and activation of JNK pathway," *The Journal of Nutritional Biochemistry*, vol. 22, no. 12, pp. 1186–1194, 2011.

[84] I. Rodriguez-Ramiro, M. Á. Martín, S. Ramos, L. Bravo, and L. Goya, "Olive oil hydroxytyrosol reduces toxicity evoked by acrylamide in human Caco-2 cells by preventing oxidative stress," *Toxicology*, vol. 288, no. 1-3, pp. 43–48, 2011.

[85] W. Chen, Y. Shen, H. Su, and X. Zheng, "Hispidin derived from Phellinus linteus affords protection against acrylamide-induced oxidative stress in Caco-2 cells," *Chemico-Biological Interactions*, vol. 219, pp. 83–89, 2014.

[86] A. E. El-Mehi and N. M. El-Sherif, "Influence of acrylamide on the gastric mucosa of adult albino rats and the possible protective role of rosemary," *Tissue and Cell*, vol. 47, no. 3, pp. 273–283, 2015.

[87] R. Wang, J. J. Liu, C. Huang, Q. F. Qian, Q. Li, and X. L. Liu, "Effects of acrylamide on apoptosis and expression of proto-oncogenec-fos and c-Jun in L-02 fetal liver cell line," *Journal of Hygiene Research*, vol. 39, no. 2, pp. 183–186, 2010.

[88] M. M. Soliman, S. S. Alotaibi, S. Sayed et al., "The The Protective Impact of *Salsola imbricata* Leaf Extract From Taif Against Acrylamide-Induced Hepatic Inflammation and Oxidative Damage: The Role of Antioxidants, Cytokines, and Apoptosis-Associated Genesrotective impact of salsola imbricata leaf extract from taif against acrylamide-induced hepatic inflammation and oxidative damage: the role of antioxidants, cytokines, and apoptosis-associated genes," *Frontiers in Veterinary Science*, vol. 8, Article ID 817183, 2021.

[89] L. Zhang, L. Dong, L. Yang, Y. Luo, and F. Chen, "MiR-27a-5p regulates acrylamide-induced mitochondrial dysfunction and intrinsic apoptosis via targeting Btf3 in rats," *Food Chemistry*, vol. 368, Article ID 130816, 2022.

[90] V. Gelen, S. Yildirim, E. Sengul et al., "Naringin attenuates oxidative stress, inflammation, apoptosis, and oxidative DNA damage in acrylamide-induced nephrotoxicity in rats," *Asian Pacific Journal of Tropical Biomedicine*, vol. 12, no. 5, pp. 223–232, 2022.

[91] F. M. Kandemir, S. Yildirim, S. Kucukler, C. Caglayan, E. Darendelioglu, and M. B. Dortbudak, "Protective effects of morin against acrylamide-induced hepatotoxicity and nephrotoxicity: Protective effects of morin against acrylamide-induced hepatotoxicity and nephrotoxicity: A multi-biomarker approach multi-biomarker approach," *Food and Chemical Toxicology*, vol. 138, Article ID 111190, 2020.

[92] Z. Hong, W. Minghua, N. Bo et al., "Rosmarinic acid attenuates acrylamide induced apoptosis of BRL-3A cells by inhibiting oxidative stress and endoplasmic reticulum stress," *Food and Chemical Toxicology*, vol. 151, Article ID 112156, 2021.

[93] S. Kacar, V. Sahinturk, and H. M. Kutlu, "Effect of acrylamide on BEAS-2B normal human lung cells: Effect of acrylamide on BEAS-2B normal human lung cells: Cytotoxic, oxidative, apoptotic and morphometric analysisytotoxic, oxidative, apoptotic and morphometric analysis," *Acta Histochemica*, vol. 121, no. 5, pp. 595–603, 2019.

[94] K. Yesildag, R. Eroz, A. Genc, T. Dogan, and E. Satici, "Evaluation of the protective effects of morin against acrylamide-induced lung toxicity by biomarkers of oxidative stress, inflammation, apoptosis, and autophagy," *Journal of Food Biochemistry*, vol. 46, no. 7, Article ID e14111, 2022.

[95] Y. Yener, E. Sur, T. Telatar, and Y. Oznurlu, "The effect of acrylamide on alpha-naphthyl acetate esterase enzyme in blood circulating lymphocytes and gut associated lymphoid tissues in rats," *Experimental and Toxicologic Pathology*, vol. 65, no. 1-2, pp. 143–146, 2013.

[96] J. Blasiak, E. Gloc, K. Wozniak, and A. Czechowska, "Genotoxicity of acrylamide in human lymphocytes," *Chemico-Biological Interactions*, vol. 149, no. 2-3, pp. 137–149, 2004.

[97] D. Zapolska-Downar, A. Kosmider, M. Tornqvist, and M. Naruszewicz, "Tu-P7:173 Tu-P7:173 The effects of acrylamide on endothelial cell and monocyte-derived macrophages apoptosishe effects of acrylamide on endothelial cell and monocyte-derived macrophages apoptosis," *Atherosclerosis Supplements*, vol. 7, no. 3, p. 223, 2006.

[98] J. Fang, L. Liang Chun, D. Jia Xu, and N. Li, "Immunotoxicity of acrylamide in female BALB/c mice," *Biomedical and Environmental Sciences*, vol. 27, no. 6, pp. 401–409, 2014.

[99] E. Zamani, F. Shaki, S. Abediankenari, and M. Shokrzadeh, "Acrylamide induces immunotoxicity through reactive oxygen species production and caspase-dependent apoptosis in mice splenocytes via the mitochondria-dependent signaling pathways," *Biomedicine & Pharmacotherapy*, vol. 94, pp. 523–530, 2017.

[100] M. Arocena, "Effect of acrylamide on the cytoskeleton and apoptosis of bovine lens epithelial cells," *Cell Biology International*, vol. 30, no. 12, pp. 1007–1012, 2006.

[101] A. Albalawi, R. H. A. Alhasani, L. Biswas, J. Reilly, and X. Shu, "Protective effect of carnosic acid against acrylamide-induced toxicity in RPE cells," *Food and Chemical Toxicology*, vol. 108, pp. 543–553, 2017.

[102] A. Albalawi, R. H. A. Alhasani, L. Biswas, J. Reilly, S. Akhtar, and X. Shu, "Carnosic acid attenuates acrylamide-induced retinal toxicity in zebrafish embryos," *Experimental Eye Research*, vol. 175, pp. 103–114, 2018.

[103] X. Zhang, C. Zhao, and B. Jie, "Various dietary polyunsaturated fatty acids modulate acrylamide-induced preneoplatic urothelial proliferation and apoptosis in mice," *Experimental and Toxicologic Pathology*, vol. 62, no. 1, pp. 9–16, 2010.

[104] C. Sellier, N. Grossin, E. Boulanger, and F. J Tessier, "0080: Dietary acrylamide induces accelerated endothelial aging in murine and human cell model," *Archives of Cardiovascular Diseases Supplements*, vol. 7, no. 1, p. 83, 2015.

[105] S. Saha, D. P. Panigrahi, S. Patil, and S. K. Bhutia, "Autophagy in health and disease: Autophagy in health and disease: A comprehensive review comprehensive review," *Biomedicine & Pharmacotherapy*, vol. 104, pp. 485–495, 2018.

[106] X. Xia, Z. Zhang, C. Zheng et al., "Ameliorative effects of canolol against acrylamide toxicity in PC12 cells through modulating MAPKs pathway and autophagy," *Journal of Functional Foods*, vol. 75, Article ID 104257, 2020.

[107] D. Song, C. Xu, A. L. Holck, and R. Liu, "Acrylamide inhibits autophagy, induces apoptosis and alters cellular metabolic profiles," *Ecotoxicology and Environmental Safety*, vol. 208, Article ID 111543, 2021.

[108] Y. Wei, L. Yang, A. Pandeya, J. Cui, Y. Zhang, and Z. Li, "Pyroptosis-Pyroptosis-Induced Inflammation and Tissue Damagenduced inflammation and tissue damage," *Journal of Molecular Biology*, vol. 434, no. 4, Article ID 167301, 2022.

[109] R. Santhanasabapathy, S. Vasudevan, K. Anupriya, R. Pabitha, and G. Sudhandiran, "Farnesol quells oxidative stress, reactive gliosis and inflammation during acrylamide-induced neurotoxicity: Farnesol quells oxidative stress, reactive gliosis and inflammation during acrylamide-induced neurotoxicity: Behavioral and biochemical evidenceehavioral and biochemical evidence," *Neuroscience*, vol. 308, pp. 212–227, 2015.

[110] L. Zhang, L. Yang, Y. Luo, L. Dong, and F. Chen, *Acrylamide Induced Hepatotoxicity through Oxidative Stress: Mechanisms and Interventions*, Antioxidants & redox signaling, New Rochelle, NY, USA, 2022.

[111] Y. Liu, X. Zhang, D. Yan et al., "Chronic acrylamide exposure induced glia cell activation, NLRP3 inflammasome upregulation and cognitive impairment," *Toxicology and Applied Pharmacology*, vol. 393, Article ID 114949, 2020.

[112] B. Nan, C. Yang, L. Li et al., "Allicin alleviated acrylamide-induced NLRP3 inflammasome activation via oxidative stress and endoplasmic reticulum stress in Kupffer cells and SD rats liver," *Food and Chemical Toxicology*, vol. 148, Article ID 111937, 2021.

[113] D. Wallach, T. B. Kang, C. P. Dillon, and D. R. Green, "Programmed necrosis in inflammation: Programmed necrosis in inflammation: Toward identification of the effector moleculesoward identification of the effector molecules," *Science*, vol. 352, no. 6281, Article ID aaf2154, 2016.

[114] M. Larguinho, A. Cordeiro, M. S. Diniz, P. M. Costa, and P. V. Baptista, "Metabolic and histopathological alterations in the marine bivalve Mytilus galloprovincialis induced by chronic exposure to acrylamide," *Environmental Research*, vol. 135, pp. 55–62, 2014.

[115] S. Gedik, M. E. Erdemli, M. Gul et al., "Hepatoprotective effects of crocin on biochemical and histopathological alterations following acrylamide-induced liver injury in Wistar rats," *Biomedicine & Pharmacotherapy*, vol. 95, pp. 764–770, 2017.

[116] S. S. Elblehi, O. I. El Euony, and Y. S. El-Sayed, "Apoptosis and astrogliosis perturbations and expression of regulatory inflammatory factors and neurotransmitters in acrylamide-induced neurotoxicity under ω3 fatty acids protection in rats," *Neurotoxicology*, vol. 76, pp. 44–57, 2020.