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Effects of dietary acrylamide on kidney and liver health: Molecular mechanisms and pharmacological implications

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A B S T R A C T

Acrylamide (AA) has raised concerns throughout the world in recent years because of its potential negative effects on human health. Numerous researches on humans and animals have connected a high dietary exposure to AA to a possible risk of cancer. Additionally, higher consumption of acrylamide has also been associated with dysfunctioning of various organ systems from nervous system to the reproductive system. Acrylamide is primarily metabolised into the glycidamide inside the body which gets accumulated in different tissues including kidney and liver, and chronic exposure to this can lead to the nephrotoxicity and hepatotoxicity through different molecular mechanisms. This review summarizes the various sources, formation and metabolism of the dietary acrylamide along with the different molecular mechanisms such as oxidative stress, inflammation, DNA damage, autophagy, mitochondrial dysfunction and morphological changes in nephron and hepatocytes through which acrylamide exerts its deleterious effect on kidney and liver causing nephrotoxicity and hepatotoxicity. This review summarizes various animal and cellular studies that demonstrate AA-induced nephrotoxicity and hepatotoxicity. Lastly, the article emphasizes on underlying protective molecular mechanisms of various pharmacological interventions against acrylamide induced hepatotoxicity and nephrotoxicity

1. Introduction

A prevalent environmental toxin, acrylamide (AA), is produced when foods rich in carbs are cooked at extremely high temperatures (over 120°C) and in humid environments [6]. Maillard's reaction between carbohydrates (fructose and glucose) and amino acid (particularly asparagine) in food is primarily accountable for the production of AA [85]. "The International Agency for Research on Cancer" has identified acrylamide as a potential human carcinogen [83]. The major concern over acrylamide exposure in food was highlighted in 2002 when Swedish researchers found that several thermally processed starchy foods had a high concentration of AA [119]. Survey report published in year 2015 by "European Food Safety" authority indicating the existence of AA in 43,419 food items. According to the report, at 4.5 mg/kg, coffee had the highest AA concentration, whereas fried potato products had an average AA content of 1.0 mg/kg. The European Commission set residual acrylamide limits of 750 μg/kg for potato crisps and 400–850 μg/kg for roast coffee and other food items associated to coffee [21]. After exposure by oral consumption or inhalation, acrylamide can get deposited in different tissues throughout the body mainly in the blood and is converted by CYP2E1 into the glycidamide (GA), which is a highly harmful than AA. GA has the ability to hydrolyse and to form glutathione conjugates which then produces two mercapturic acid compounds that are excreted in urine [84].

Epidemiological studies indicated that AA intake in the diet ranges from 0.02 to 1.53 μg/kg b.w., with the greatest levels observed in European and American populations [120]. Infants, young children, and young people are most vulnerable to AA in meals. According to European statistics, "Baby foods, other than processed cereal-based" contributed the most to babies' overall AA exposure, followed by "Products based on potatoes" and "Processed cereal-based baby foods". Their estimated daily consumption of ACR is three times more than that of adults [25]. Research undertaken over the last 20 years has demonstrated that consuming AA-containing food items causes various disorders which has been seen in human and animal species including carcinogenicity, reproductive toxicity, neurotoxicity, genetic toxicity, hepatotoxicity and nephrotoxicity [19,1,50,121,123]. This impact is absolutely dependent on the AA dose, period of exposure to AA, and the type of animals utilized in the study.

Nephrotoxicity may be indicated by an increase in the excretion of

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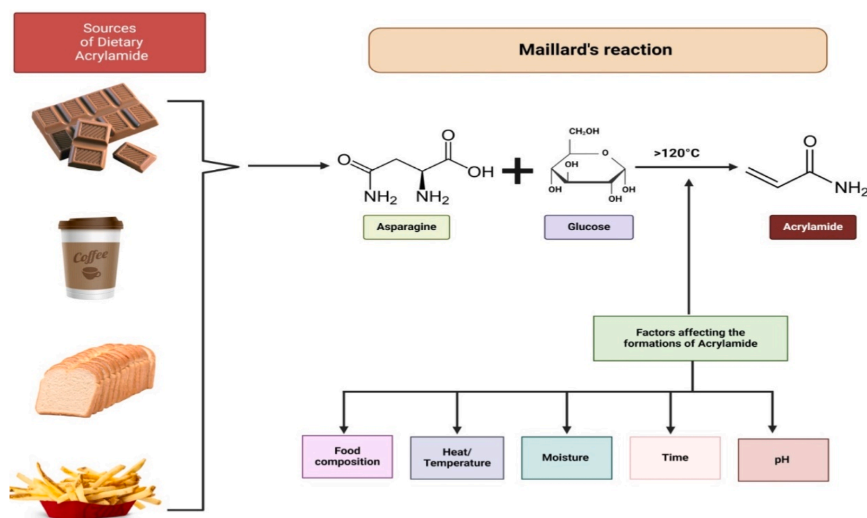

Fig. 1. Sources of dietary acrylamide, formation process and factors affecting the production of acrylamide.

Table 1
Concentration of acrylamide in different food items.

Food Item	Acrylamide Concentration (μg/kg)	Ref.
French Fries	500	Gabašová et al. [42]
Potato Chips	250–4000	Martinez et al. [78]
Toasted Bread	85–230	Alsharafani et al. [14]
Breakfast Cereals	140.93–373.25	Merhi et al. [82]
Roasted Nuts and Seeds	100–1000	Mesías et al. [86]
Roasted Coffee	249–710	Strocchi et al. [113]
Bakery biscuits	130–154	Ahmad et al. [8]

urine albumin, a reduction in the glomerular filtration rate, or both. Several studies have indicated that exposure to environmental toxicants, such as acrylamide, has a vital role in the development of kidney-related illnesses and nephrotoxicity [128]. Various *in-vivo* studies have found that acrylamide causes lipid peroxidation and DNA damage which increases the oxidative stress in the kidney. Additionally, it increases the creatinine, serum urea, kidney proinflammatory cytokine levels and uric acid causing kidney injury and nephrotoxicity [122]. Animal studies exploring the effects of AA on renal tissue have observed that the degradation of glomerular cells and tubule in the kidney is caused via oxidative stress. During oxidative stress (OS), AA lowers the levels of GSH, CAT and SOD whereas elevates levels of NO and MDA in renal cells causing cellular toxicity and apoptotic cell death via upregulating the renal caspase-3 expression [62].

Liver is a main organ where different xenobiotics like environmental toxins, pollutants, drugs and chemicals get metabolised [95]. Acrylamide metabolism utilizes GSH to make conjugates that leads to excessive consumption of GSH. Consequently, homeostasis of redox balance is disrupted that leads to OS in the hepatic cells [57]. Two enzymes used as liver function markers in clinical laboratories are "Alanine transaminase" (ALT) and "Aspartate transaminase" (AST). In acrylamide induced hepatotoxicity animal model, it has been found that level of these enzymes were significantly high [133]. Furthermore, exposure to AA caused a reduced GSH levels and lowered GST activity in the hepatic tissues, which in return increases the ROS level causing oxidative stress and consequently damaging the hepatic cells [107]. Increased OS can damage the DNA and impair cell metabolism, resulting in apoptosis causing hepatotoxicity and hepatic disorders [39].

This review attempts to unravel the underlying molecular mechanisms involved in AA-induced nephrotoxicity and hepatotoxicity. Furthermore, novel pharmacological interventions that have shown a therapeutic effect against AA-induced nephrotoxicity and hepatotoxicity are also discussed in this review.

2. Search strategy

Databases like, Google Scholar, Web of Science, SCOPUS and PubMed were utilized using Medical Subject Headings (MeSH) terms and keywords such as "acrylamide," "hepatotoxicity", "nephrotoxicity," "kidney," "liver," "dietary acrylamide toxic effects," and "acrylamide induced nephrotoxicity", "acrylamide induced hepatotoxicity" to collect the data. Latest publications which are published in previous 5 years are primarily discussed in this review.

3. Acrylamide: sources, formation and metabolism

3.1. Sources of dietary acrylamide

Acrylamide is mainly present in food items which are rich in carbohydrate such as, french fries, chips, coffee, bakery products etc. (Fig. 1). French fries have an average AA concentration of about 400 μg/kg [42]. Crisps and chips have an average AA concentration of about 250–4000 μg/kg [78]. Significant amount of AA can also be found in breads and toast with an AA concentration of about 85–230 μg/kg when baked at 250°C for 15 minutes [14]. Beverage like coffee that is commonly consumed worldwide also contain a high amount of AA, as when coffee beans are roasted at a high temperature, they produce around 272 μg/kg of AA. Other food products like cereal, bakery biscuits, and roasted nuts also contain a significantly high amount of AA in them [112]. Acrylamide concentration in different food items is demonstrated in Table 1.

3.2. Formation of acrylamide

Maillard's reaction (MR) is a chemical reaction through which acrylamide is formed in various food products [7]. MR is a series of intricate chemical events that include the reduction of proteins, amino acids (such asparagine), and carbohydrates (like glucose). At high a temperature, a non-enzymatic activity takes place that causes browning of food and changes the colour, develops taste components and releases fragrance. Additionally, in this process, the MR produces unwanted byproducts like acrylamide which are generally harmful for the human consumption [16]. According to research, raw foods often don't contain acrylamide. Nonetheless, meals that have been cooked at temperatures

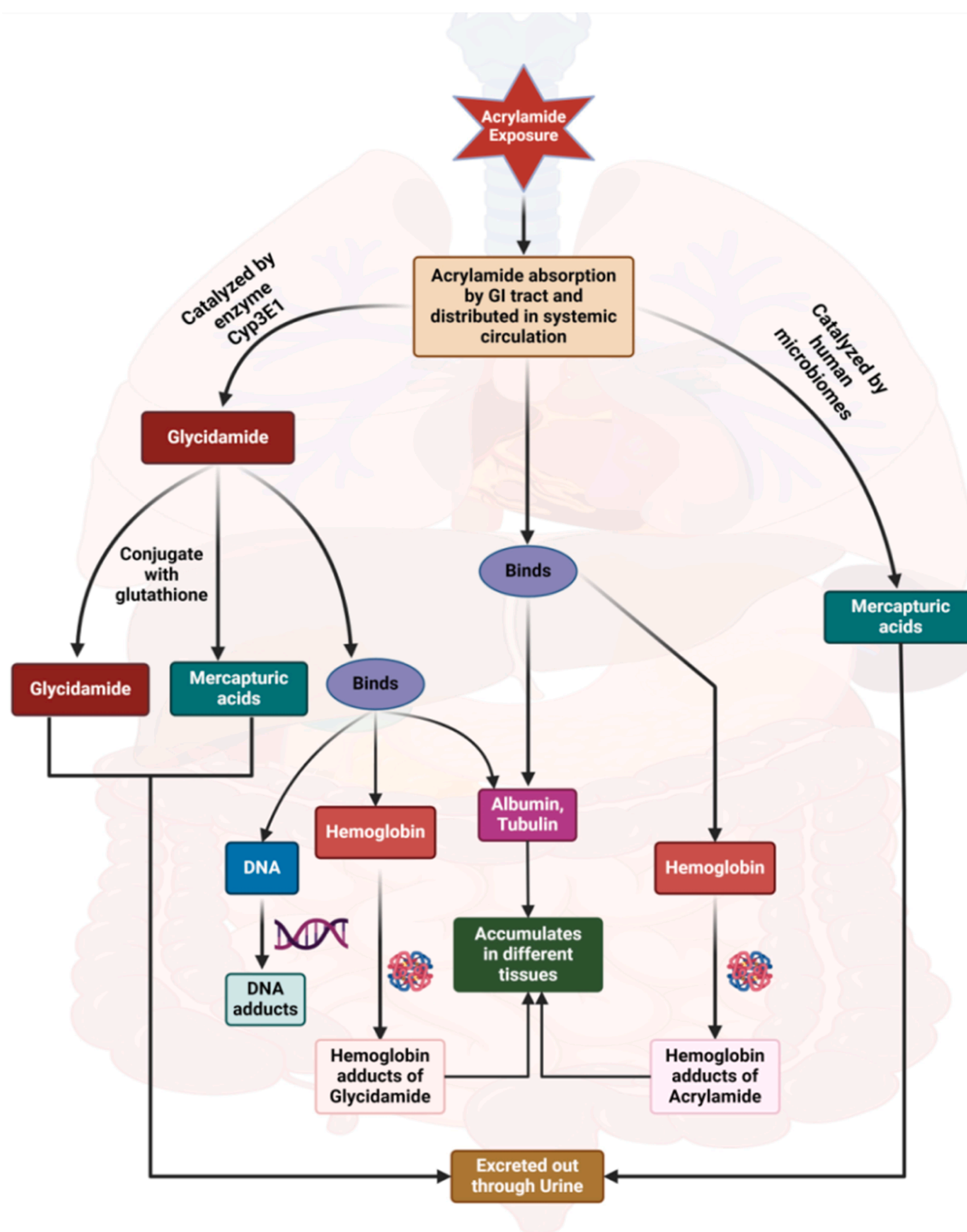

Fig. 2. Metabolic Pathway of Acrylamide.

higher than 120°C contain it. There are various other factors that can impact the MR and AA formation including, food composition, temperature, moisture, time, pH etc. (Fig. 1) [48].

3.2.1. *Food composition*

A naturally occurring amino acid found in dietary products, asparagine reacts with reducing sugars to produce acrylamide. Coffee beans, cereals bread, potatoes and other foods with greater asparagine content are more likely to produce acrylamide than foods with less asparagine [90]. The amount of sugar in food items has a direct correlation with the development of acrylamide. During heating, higher sugar levels can boost the AA's level in the food [97].

3.2.2. *Temperature*

The production of acrylamide is significantly accelerated by high temperatures, generally exceeding 120°C. The amount of acrylamide in food item cooked at 170°C was approximately 2000 μg/kg and approximately 4000 μg/kg when cooked at 190°C. Consequently, when the cooking temperature rises, acrylamide production tends to increase [76].

3.2.3. *Moisture*

Moisture content in food can influence the production of AA significantly. Higher moisture content in a food can reduces the amount of acrylamide formation as water in the food will helps to lower the cooking temperature and will prevent the high temperature which is generally required for the MR. On the other hand, in baking and frying

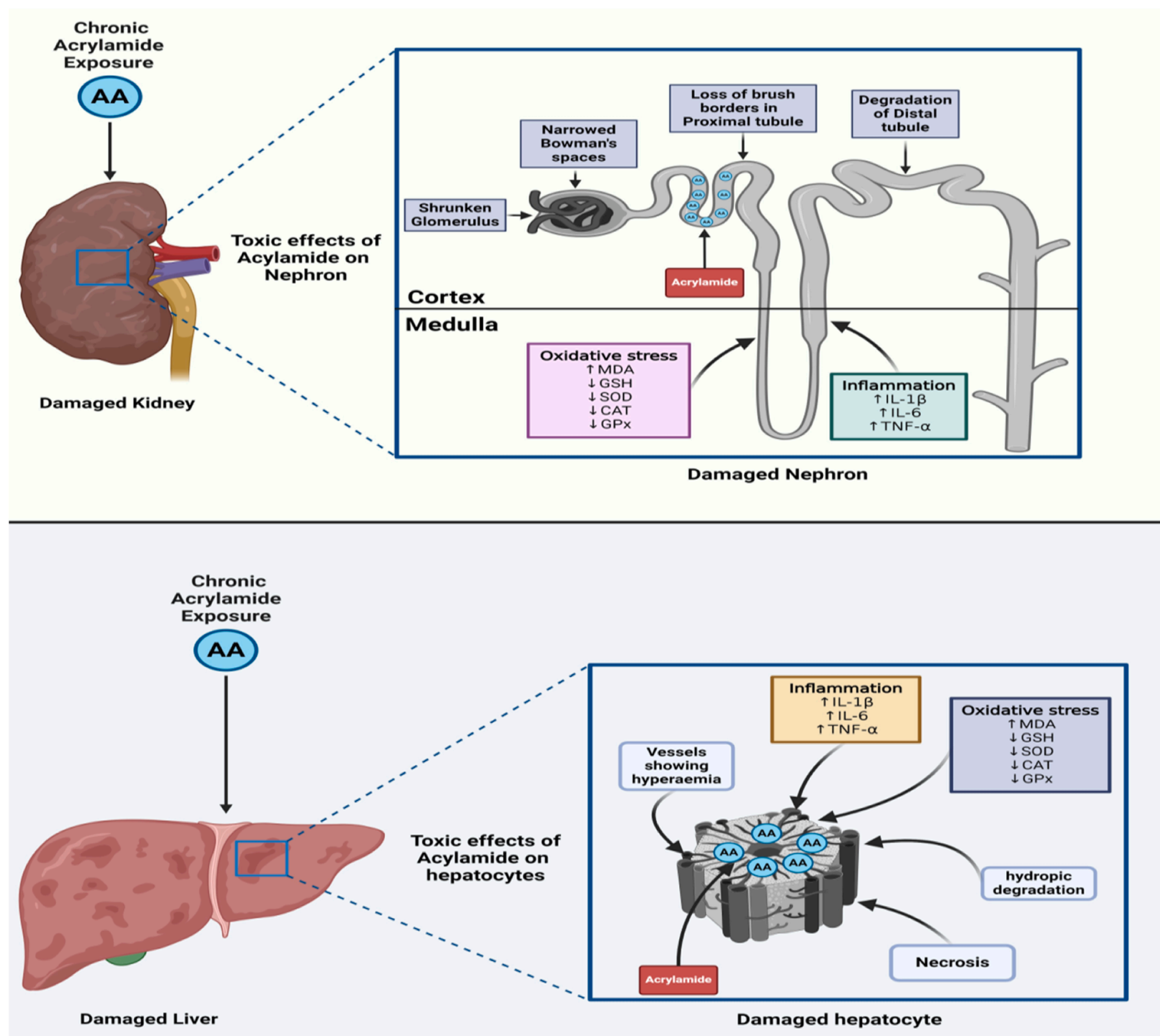

Fig. 3. Toxic effect of acrylamide on nephron and hepatocyte.

when moisture content in significantly low it promotes the formation of the acrylamide due to the prolonged exposure to the high temperature [22].

3.2.4. *Time*

The amount of acrylamide produced is greatly influenced by how long the meal is cooked or processed. Those cooked for longer periods of time may have higher levels of acrylamide than those cooked for a short period of time [87]. In a study, it was found that when French fries were fried for 2 minutes their acrylamide content was about 200 μg/kg but when they were fried for 10 minutes their acrylamide content was as high as 1000 μg/kg [64].

3.2.5. *pH*

pH of the food item can also influence the production of the acrylamide as food item having a pH level of neutral or slightly alkaline around 7–9 produced more amount of acrylamide as this range of pH helps Maillard's reaction process rapidly [16]. Whereas, lowering the pH of the food (making it acidic) can reduces the amount of acrylamide formation significantly because low pH levels slowdowns the Millard's reaction and decrease the level of AA in the food items [135].

By controlling and monitoring these factors during the cooking, frying and roasting of the food items the concentration of the acrylamide can be significantly reduced which can than lowers the risk of acrylamide incudes hepatotoxicity, neurotoxicity, reproductive toxicity nephrotoxicity, and can even reduce the risk of the cancer

3.3. *Metabolism of acrylamide*

AA is absorbed, broken down and distributed throughout the body after human exposure [75]. Acrylamide's low molecular weight and excellent solubility allow it to passively spread into every organ in the body. Every tissue is therefore susceptible to its toxic effects [11]. AA can be directly metabolised in humans by conjugation GSH, which is facilitated by GST. CYP2E1 is an enzyme which helps in the bio-transformation of acrylamide into the genotoxic metabolite called glycidamide also known as epoxy propionamide [32]. The body eliminate and remove acrylamide and glycidamide by forming conjugate with glutathione in the presence of reduced glutathione-S-transferases. The resulted glutathione conjugates readily bind with different proteins,

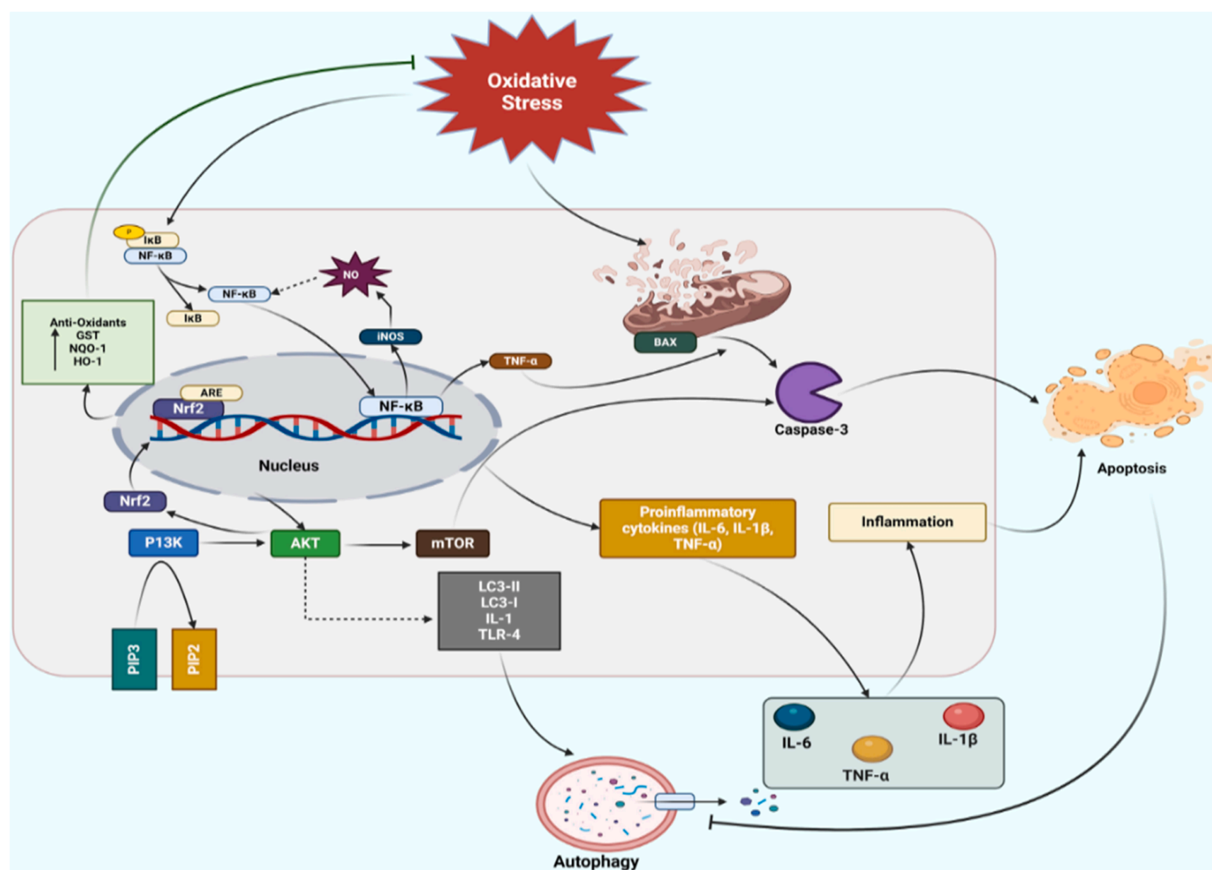

Fig. 4. Common signalling pathways in acrylamide induced nephrotoxicity and hepatotoxicity causing apoptosis and cell death.

RNA and DNA through covalent bonds. Glutathione conjugates are then converted into the mercapturic acids (MA) such as "N-acetyl-S-(2-carbamoyl-2-hydroxyethyl)N-acetyl-S-(2-carbamoylethyl)" or "cysteine-cysteine", which is then excreted out through the urine and is considered as a biomarker for AA exposure [70]. "N-(2-carbamoyl-2-hydroxyethyl) valine" and "N-(2-carbamoylethyl) valine" are the two haemoglobin adducts that are produced when plasma albumin, proteins and the valine amino acids of haemoglobin react with acrylamide and glycidamide. Additionally, these two adducts are also considered as a biomarkers to determine the AA exposure [71]. Glycidamide can also binds to the DNA and forms DNA adducts like "N7-(2-carbamoyl-2-hydroxyethyl)guanine" (N7-GA-Gua) causing genotoxicity [93,54]. Acrylamide in the body can also be metabolised through the microorganisms present in the human microbiome which catalyses and convert the acrylamide into the MA which are then excreted out through urine [105]. Previous research has demonstrated that a range of bacterial strains generate amidases at concentrations between 1 and 40 mM to catalyze the hydrolysis of acrylamide to ammonia and acrylic acid. It has been demonstrated that amidase is secreted by the human body's bacterial inhabitants, including Escherichia coli, Bacillus clausii, Enterococcus faecalis, and Helicobacter pylori. The bacterial amidases found naturally in the gastrointestinal system may result in augmentation of AA breakdown and a reduction in its adverse effects on humans [25] as shown in (Fig. 2).

4. Acrylamide and kidney

After being exposed to acrylamide, the gastrointestinal tract absorbs it, and it then travels throughout the body to all of the organs, including the kidneys. In the liver acrylamide gets metabolized in the presence of CYP2E1 and forms conjugate with the GSH and produces glycidamide, which is a more reactive metabolite of the acrylamide. Glycidamide and acrylamide both have a high affinity to bind with other proteins and form adducts. They mainly forms adduct with haemoglobin and then are circulated throughout the body via the bloodstream [100]. Kidneys are normally involved in the filtration of the blood and removal of the waste material from the body. When these adducts of glycidamide and acrylamide are filtered by the glomeruli in the kidney they can damage the renal cortex and the proximal tubules area of the kidney [106]. According to histopathological investigations of previous study, exposure to the acrylamide resulted in glomeruli shrinkage, brush borders loss in the proximal tubules, degradation of kidney epithelium, accumulation of necrotic regions in the renal parenchyma, and elevations in p53 expression and caspase-3 activity in kidney tissue [39]. Previous study on rats found that kidney sections from a group receiving acrylamide treatment had glomerular collapse, Bowman's spaces narrowing and damage as well as the tubular degeneration in the proximal and distal tubular epithelial cells (Fig. 3) [92]. Upon chronic exposure to the acrylamide, it can cause cell death that can lead to the nephrotoxicity [126]. Furthermore, acrylamide and its reactive metabolites can create adducts with DNA that damages DNA and impair mitochondria, which in turn produces ROS and cause OS in kidney [35,89].

5. Acrylamide and liver

Liver is an organ which is extremely vulnerable to toxins as well as hazardous substances. Acrylamide's detrimental effects on the liver have been demonstrated in several animal studies, but till date, there are no reports of acrylamide induced hepatotoxicity in humans. According to previous studies, acrylamide causes hepatotoxicity by raising oxidative stress levels, triggering inflammatory responses, and lowering the antioxidant defence system [132]. Enzymes which determines the normal liver functioning like, AST, ALT and bilirubin were markedly up-regulated in AA-induced hepatotoxicity animal model [96].

Furthermore, acrylamide exposure significantly up-regulated the inflammatory cytokines levels, like IL-1, TNF-α and IL6 through NF-κB signalling [96]. Moreover, it is clearly shown that acrylamide induction leads to disruption of the redox balance by increasing lipid peroxides, nitric oxide levels along with the increased protein carbonyl content. In addition, AA-induced toxicity altered the antioxidant defence enzymes like CAT, GPx, GSH as well as SOD. Acrylamide raises cytochrome C levels, P53, and Bax/Bcl-2 ratio, all of which contributes in the hepatocytes cell death [41]. In addition, Acrylamide's exposure was also linked to increase levels of total triglycerides, cholesterol and LDL [108]. On the other hand, HDL and cholesterol levels were found decreased after the administration of the acrylamide. Moreover, acrylamide (38.27 mg/kg) administration caused significant morphological changes in the central area of rat's liver including, necrosis, hydropic degradation, and vessels showing hyperaemia (Fig. 3) [68].

In a previous study, synergistic toxic effect of ochratoxin and acrylamide was assessed in human hepatic and renal cells *in-vitro,* where researcher found upregulation of apoptotic markers like BAX, Caspase3 along with an increased expression of Cytochrome P1A1 and Cytochrome P1A2 which promotes the formation of ROS in the hepatic and renal cells leading to apoptosis and cell death [102].

5.1. Effect of acrylamide on microRNAs in kidney and liver

MicroRNAs (miRNAs) are small, non-coding RNAs that can function as epigenetic regulators. These compounds can control a wide variety of cellular and molecular functions. It has been demonstrated that diverse toxicants may dysregulate miRNAs and AA is one of a such toxicant [55]. In a latest study, the inhibited expressions of miR-27a-5p and miR-122–5p were found to be linked with the inflammation and fibrosis in the rat's renal tissues. The result from this study showed the un-regulation of Kim-1, TNF-α and P53 along with the elevated levels of Keap-1, Caspase-3, cleaved Caspase-3 and BAX with a downregulation of NRF-2 gene [13]. In another study, the elevated levels of miR-27a-5p were observed in AA-induced liver toxicity in rats. Results from this study reviles that lowered expression of Bft3 was linked with upregulation of ATM and P53 levels, which are responsible for the mitochondria-mediated apoptosis. miR-27a-5p was also found to be positively regulate Caspase-3 and Caspase-9 and negatively regulating the BAX/BCL-2 ratio. These results suggest that miR-27a-5p can induce apoptosis through mitochondrial dysgunction causing cellular toxicity in rat's liver [131].

The role of microRNAs is very crucial in gene regulation and protein formations but very less information is currently available in context to the regulation mechanism of microRNAs in AA-induced kidney and liver toxicity. Therefore, more studies are required to understand the exact regulatory mechanism of microRNAs in AA-induced Nephrotoxicity and Hepatotoxicity.

6. Underlying molecular mechanism of acrylamide induced nephrotoxicity and hepatotoxicity

Acrylamide can induce nephrotoxicity and hepatotoxicity through different mechanisms which includes, oxidative stress [67,35], DNA damage [89], [103]; inflammation [12,108] mitochondrial damage [118,122] and autophagy [23] (Fig. 4).

6.1. Oxidative stress

An imbalance in cellular homeostasis known as oxidative stress promotes the body's natural antioxidant defence mechanisms and ROS production to increase [65]. Cells undergo continuous oxidation and reduction activities, but damage is often prevented by different anti-oxidative mechanisms, either by enzymatic or non-enzymatic, which maintains the homeostasis [28]. Oxidative stress occurs whenever the equilibrium shifts in favour of more oxidation. The pathological transition to oxidative stress and subsequent damage to cells and tissues leads to changes in DNA, lipid, and protein structures, which also affects their activities [80]. Apart from leading to rapid damage to tissue, oxidative stress can trigger various intracellular signalling pathways, which in turn triggers indirect effects such as cell death or proliferation, extracellular matrix synthesis, degradation and inflammation. This can leads to the dysfunction of various organ including, kidneys, lungs, pancreas, liver, heart, brain etc. [101]. Dietary acrylamide intake has been linked to morphological and functional changes of many organs, a decline in anti-oxidant system, and impairment in detoxification [20]. It is well reported that acrylamide damages the kidneys mainly through oxidative stress [122]. Several investigations demonstrated that acrylamide intoxication resulted in nephrotoxicity by lowering the concentration of GSH, SOD as well as CAT along with augmentation of NO and MDA levels [109]. Furthermore, various studies has demonstrated the reduced level of the antioxidant proteins like GSH, GPx, SOD and CAT in animal models of acrylamide induced hepatotoxicity [23,68]. An *in-vitro* study found that acrylamide exposure also elevate the production of MDA and NO in the BRL-3A liver cells causing the OS and apoptosis causing cellular toxicity [56]. Therefore, acrylamide consumption is directly linked to the higher level of the ROS and reduced level of antioxidant proteins in kidney as well as in liver which results in the increased OS leading to nephrotoxicity and hepatotoxicity.

6.2. Inflammation

Acrylamide induced nephrotoxicity is closely linked with the inflammatory response. Inflammatory cytokines like IL-1β, TNF-α, and IL-6 were shown to be highly elevated in AA-induced nephrotoxicity [2]. NF-κB plays an important role in inflammation as acrylamide interacts with NF-κB signalling pathway at cellular level, stimulating the activated form of NO, which triggers an inflammatory response. IκB phosphorylation stimulates the NF-κB translocation into the nucleus and thereby regulates the transcription of genes like TNF-α which causes inflammation [74]. In previous study, when acrylamide (20 mg/kg) was given for 30 days to albino wistar rat, it increases the TNF-α levels in acrylamide group [20]. Another study found that AA "38.27 mg/kg; i.g for 10 days" administration leads to marked kidney injury through NF-κB mediated up-regulation of IL-1β, IL-6, KIM-1 and IL-33, a potential biomarker of kidney injury also found increased in the presence of renal inflammation. Pharmacological interventions such as melatonin, selenium and Naringin attenuated AA-induced renal injury and KIM-1 augmentation through inhibition of renal inflammation [61,45,109].

Furthermore, the liver triggers the inflammatory response by a group of effector cells called Kupffer's cells (KC) [98]. The multiprotein complex known as inflammasomes detects the pathogens and then cleaves and releases proinflammatory cytokines and mediates inflammation [130]. It has been demonstrated that the NLRP3 inflammasome is essential for the inflammatory response of liver cells, particularly KCs [127]. NLRP3 oligomerizes and binds procaspase-1 and the apoptosis-related dot-like protein CARD to produce NLRP3 inflammasomes when environmental toxicants activate KCs. This causes pro-cas-1 to be cleaved and activate Pro- IL-18 and IL-1β which are then cleaved by the cas-1 to produces the mature IL-18 and IL-1β, which, in reaction to inflammatory processes, are released outside of the cell and damages liver [36]. Pollutant exposure primarily activates NLRP3 inflammasome by stimulating the MAPK, Nrf2 and NF-κB pathways. Research has demonstrated that acrylamide causes an excess ROS production as well as it activates JNK, ERK1/2 and p38 [31]. Hepatotoxicity is caused by these events because they activate the NLRP3 inflammasome, which in turn raises the production of cleaved caspase-1 and proinflammatory cytokines including TNF-α, IL-18, IL-6, and IL-1β in the liver's KCs [24]. Furthermore, AA administration in drinking water (300 ppm) leads to nephrotoxicity and hepatotoxicity by lowering the expression of Nrf2 and increasing of TNF-α and iNOS levels showing inflammation and oxidative stress [34]. This observed effect mediated through

Table 2
Pharmacological interventions against acrylamide induced nephrotoxicity.

Sr. No.	Pharmacological intervention	Acrylamide-induced nephrotoxicity model (Species, Dose, Route and Duration)	Pharmacological intervention (Dose, route and Duration)	Therapeutic effect	Ref.
1.	Selenium	Male Sprague Dawley rats, 38.27 mg/kg,(i.g) for 10 days	1 mg/kg, (i.g) for 10 days	↓ IL−6, IL−1β, IL−33, MDA and NO, ↑ GSH	Sengul et al. [110]
2.	Taxifolin	Male Albino Wistar rats, 20 mg/kg, (p.o.) for 30 days	50 mg/kg,(p.o.) for 30 days	↓ MDA, IL−1β and TNF-α, ↑ tGSH levels	Bedir et al. [20]
3.	Naringin	Sprague Dawley rats, 38.27 mg/kg,(i.g) for 10 days	100 mg/kg, (i.g) for 10 days	↓ MDA, L−1β, IL−6, TNF-α, NF-κB, IL−33, and COX−2, ↑ GPx, GSH and CAT levels	Gelen et al. [45]
4.	Melatonin	Wistar rats, 25 mg/kg, (p.o.) for 21 days	0.5 ml volume of 10 mg/kg, (i.p) for 21days	↓ MDA, IL−1β, and TNF-α, ↑ GSH, SOD and CAT levels	Demir et al. [35]
5.	Vinpocetine	Male Albino Wistar rats, 38.27 mg/kg, (p.o.) for 10 days	5 mg/kg, (p.o.) for 10 days	↓ MDA, caspase−3, ↑ GSH and SOD levels	D. S. [62]
6	Thymoquinine	Male Albino Wistar rats, 20 mg/kg, (p.o.) for 28 days	20 mg/kg, (p.o.) for 28 days	↓ MDA, ↑ GSH, CAT, SOD and GSHpx levels	Ghonim et al. [46]
7.	Gallic acid	Albino Wistar rats, 20 mg/kg, (p.o.) for 21 days	40 mg/kg, (p.o.) for 7 days	↓ MDA, TNF-α and IL6, ↑ GSH and GPx levels	Alejolowo et al. [12]
8.	Morin	Albino Wistar rats, 38.27 mg/kg, (p.o.) for 10 days	100 mg/kg, (p.o.) for 10 days	↓ caspase−3, Bax, cytochrome c, beclin−1, LC3A, LC3B, p38α MAPK, NF-κB, IL−1β, IL−6, TNF-α, COX−2 and MDA, ↑ GSH, CAT, SOD and GSHpx levels	Kandemir et al. [68]
9.	Boron	Albino Wistar rats, 38.27 mg/kg, (p.o.) for 10 days	20 mg/kg, (p.o.) for 10 days	↓ MDA and ↑ GSH, SOD, Nrf2 and Keap−1 levels	Gür et al. [49]
10.	Vitamin E	Albino Wistar rats, 20 mg/kg, (p.o.) for 21 days	100 mg/kg, (p.o.) for 21 days	↓ MDA and caspase−3, ↑ GSH, SOD and CAT	Taima et al. [116]
11.	Vitamin C	Albino Wistar rats, 20 mg/kg, (p.o.) for 60 days	200 mg/kg, (p.o.) for 60 days	↓ MDA and creatinine, ↑TAC%	Davoudimoghadam et al. [33]
12.	Curcumin	Sprague-Dawley rats, 40 mg/kg, (p.o.) for 28 days	100 mg/kg, (p.o.) for 28 days	↓ MDA, urea, creatinine and CYP2E1, ↑ GSH, SOD levels	Sun et al. [114]
13.	Spirulina platensis	Rats, 20 mg/kg, (p.o.) for 14 days	1000 mg/kg, (p.o.) for 14 days	↓ IL−1β, IL−6, and TNF-α, MDA, NO and 8-OHdG, ↑ GSH, GSH-Px, SOD, and CAT	Bin-Jumah et al. [23]
14.	Ellagic acid	Albino Wistar rats, 20 mg/kg, (p.o.) for 30 days	30 mg/kg, (p.o.) for 14 days	↓ MDA, IL−1β and TNF-α, ↑ GSH, GSH-Px, SOD and CAT	Mehrzadi et al. [81]
15.	Rutin	Female Albino Wistar rats 38.27 mg/kg, (p.o.) for 10 days	40 mg/kg, (p.o.) for 10 days	↓ MDA, ↑ GSH, SOD and CAT levels	Uthra et al. [124]
16.	Extra virgin Olive oil (EVOO)	Female Albino Wistar rats, 40 mg/kg, (p.o.) for 21 days	300 μl, (p.o.) for 21 days	↓ MDA, H_2O_2, Plasma LDH, Kidney LDH, creatinine and uric acid, ↑ GSH, SOD and CAT levels	Ghorbel et al. [47]
17.	Hesperidin	Albino Wistar rats, 20 mg/kg, (p.o.) for 14 days	10 mg/kg, (p.o.) for 14 days	↓ TNF-α, IL−1β, IL−6, MDA, OHdG and NO, ↑GSH, SOD, CAT, GSH-Px levels	Elhelaly et al. [37]
18.	Diosmin	Albino Wistar rats, 20 mg/kg, (p.o.) for 14 days	10 mg/kg, (p.o.) for 14 days	↓ TNF-α, IL−1β, IL−6, MDA, OHdG and NO, ↑GSH, SOD, CAT, GSH-Px levels	Elhelaly et al. [37]
19.	Hesperitin	Female Albino Wistar rats, 40 mg/kg, (p.o.) for 3 day	40 mg/kg, (p.o.) for 3 days	↓ LPO (TBARS), creatinine and urea, ↑GSH, SOD, CAT levels	Shrivastava et al. [111]
20.	Pomegranate peel	Albino Wistar rats, 40 mg/kg, (p.o.) for 17 days	200 mg/kg (p.o.) for 31 days	↓ IL−1β, KIM−1, iNOS, MDA and NO, ↑GSH, GPx SOD, CAT levels	Kandeil et al. [67]
21.	Trigonella foenum-graecum	Male Albino Wister rats, 20 mg/kg, (p.o.) for 14 days	5 ml TFG/ 95 g diet, (p.o.) for 14 days	↓ IL−1β, IL−6, and TNF-α, MDA, uric acid, urea, creatinine, NO and 8-OHdG, ↑ GSH, GPx SOD, CAT levels	Abdel-Daim et al. [3]
22.	Syzygium aromaticum oil (Clove)	Male Albino Wister rats, 20 mg/kg, (p.o.) for 21 days	200 mg/kg, (p.o.) for 21 days	↓creatinine, urea and MDA, ↑ SOD levels	Elkomy et al. [38]
23	Moringa oleifera leaves Nanoparticles	Adult Male rats, 50 mg/kg in drinking water for 21 days	50 mg/kg/day. (p.o) for 21 days	↓creatinine, urea and MDA, ↑ SOD and improved morphology of kidney	Abduljalil et al. [5]
24	Allicin	Adult male rat, 30 mg/kg (p.o) for 28 days	50 mg/kg/day (p.o) for 28 days	↓Caspase3, BAX, p53, ace-p53, ↑SIRT1, BCL2	L. [74]

over-activating of NF- κB signaling. A recent report indicated that AA-induced apoptotic cell death in kidney and liver might be linked with the inflammation. AA-induced inflammation has been linked to down-regulation of BCL-XL which are the anti-apoptotic proteins and elevation of apoptotic markers like caspase-9 and 3 as well as Bax [17,108]. These results indicated that AA-induced hepatotoxicity can be alleviated by using anti-inflammatory agents such as melatonin that further confirmed the detrimental role of inflammation in liver injury [96].

AA inhibits Nrf2 activation, which promotes the production of antioxidants, causing inflammation in the liver and kidney cells, resulting in nephrotoxicity and hepatotoxicity. Additionally, AA causes hyper-activation of NF-κB, which increases the gene expressions of proinflammatory cytokines like IL-1β and TNF-α.

6.3. *DNA damage*

Within cells, DNA encodes genetic information and is a vulnerable target for ROS. Oxidative DNA damage can arise from base lesions and base changes in the single and double strands caused by excessive ROS activation [59]. Because mtDNA lacks protective histones, it is more vulnerable to ROS damage than that of the nuclear DNA. Thymine can be oxidised by ROS in mtDNA causing the mutations of 8-hydroxydeoxyguanosine (8-OHdG), which then combines with adenine instead of cytosine [27]. Moreover, ROS-induced mtDNA damage and mitochondrial transport chain mutations may exacerbate mitochondrial dysfunction, which in return increase the ROS production [134].

Acrylamide is metabolized and is converted into glycidamide which is more form toxic than the acrylamide. This metabolite can make DNA adducts and thereby causing DNA damage in various cells throughout the body [54]. Substantial amount of studies has reported AA-induced

Table 3
Pharmacological interventions against acrylamide induced hepatotoxicity.

Sr. No.	Pharmacological intervention	Acrylamide-induced hepatotoxicity model (Species, Dose, Route and Duration)	Pharmacological intervention (Dose, route and Duration)	Therapeutic effect	Ref.
1.	Morin	Albino Wistar rats, 38.27 mg/kg, (p.o.) for 10 days	100 mg/kg, (p.o.) for 10 days	↓ caspase−3, Bax, cytochrome c, beclin−1, LC3A, LC3B, p38α MAPK, NF-κB, IL−1β, IL−6, TNF-α, COX−2 and MDA, ↑ GSH, CAT, SOD and GSHpx levels	Kandemir et al. [68]
2.	Pomegranate peel	Male Albino Wistar rats, 30 mg/kg, (p.o.) for 21 days	150 mg/kg (p.o.) for 21 days	↓AST, ALT, MDA, TGF-β1, IL−1β, IL−6, COX−2 and caspase−3, ↑ GSH, CAT, SOD, Nrf2 and Bcl−2 levels	Sayed et al. [108]
3.	Selenium	Male Albino Wistar rats, 50 mg/kg, (i.p.) for 11 days	0.6 mg/kg (i.p) for 11 days	↓AST, ALT, MDA and caspase−3, ↑ GSH and Bcl−2 levels	Rahbardar et al. [104]
4.	Ellagic acid	Albino Wistar rats, 20 mg/kg, (p.o.) for 30 days	30 mg/kg, (p.o.) for 14 days	↓AST, ALT, MDA, IL−1β, TNF-α and NO, ↑ GSH, CAT, SOD and GPx levels	Karimi et al. [69]
5.	Rapamycin	Albino Wistar rats, 20 mg/kg, (p.o.) for 21 days	0.5 mg/kg, (p.o.) for 21 days	↓AST, ALT, MDA, caspase−3, LC3 and p62, ↑ SOD levels	Erfan et al. [40]
6.	Punicalagin	Male Albino Wister rats, 50 mg/kg/day, (i.p.) for 11 days	40 mg/kg, (i.p.) for 11 days	↓MDA, caspase−3, Bax, ↑ GSH levels	Foroutanfar et al. [41]
7.	Quercetin	KM male mice 50 mg/kg/day, (i.p.) for 7 days	10 mg/kg, (i.p.) for 7 days	↓MDA, LC3I, LC3II, caspase−3, caspase−9 and Bax, ↑ GSH, SOD, CAT, AKT, mTOR levels	L. [73]
8.	Amifostine	Male Albino Wister rats, 50 mg/kg/day, (i.p.) for 11 days	100 mg/kg, (i.p.) for 11 days	↓MDA, caspase−3, Bax, ALT and AST, ↑ GSH and Bcl2 levels	Karimi et al. [70]
9.	Melatonin	Albino Wistar rats, 25 mg/kg, (p.o.) for 21 days	0.5 ml volume of 10 mg/kg, (i.p) for 21days	↓AST, ALT, MDA, TNF-α and NF-κB, ↑ GSH, CAT and SOD levels	Ozturk et al. [96]
10	Moringa oleifera-mediated zinc oxide nanoparticles	Sprague Dawley rats, 20 mg/kg (i.p.), for 60 days	10 mg/kg, (i.p) for 60days	↓AST, ALT, MDA, caspase−3, CYP2E1 ↑ GSH, GPx and GSR levels	Mahfouz et al. [77]
11.	Cinnamon	Male Albino Wister rats, 50 mg/kg/day, (p.o.) for 28 days	50 mg/kg, (p.o.) for 28 days mg/kg and 400 mg/kg, (p.o.) for 7 days	↓AST, ALT, urea, creatinine, MDA and TNF-α, ↑ GSH, SOD and GPx levels	Hamdey et al. [51]
12.	Ginger	Male Albino Wister rats, 50 mg/kg/day, (p.o.) for 28 day	50 mg/kg, (p.o.) for 28 days mg/kg and then 400 mg/kg, (p.o.) for 7 days	↓AST, ALT, urea, creatinine, MDA and TNF-α, ↑ GSH, SOD and GPx levels	Hamdey et al. [51]
13.	Raspberry ketone	Male Albino Wister rats, 5 mg/kg/day, (p.o.) for 60 day	6 mg/kg, (p.o) for 60 days	↓AST, ALT, MDA and caspase−3, ↑ GSH, SOD and CAT levels	Hamdy et al. [52]
14.	White tea	Male Albino Wister rats, 5 mg/kg/day, (p.o.) for 60 day	6 mg/kg, (p.o) for 60 days	↓AST, ALT, MDA and caspase−3, ↑ GSH, SOD and CAT levels	Hamdy et al. [52]
15.	Thymoquinone	Sprague Dawley rats, 20 mg/kg (p.o.), for 14 days	20 mg/kg, (p.o) for 7 days	↓ AST, ALT, TNF-α, IL−6, IL−1β, 8-OHdG MDA and NO ↑ GSH, CAT, GST and SOD levels	Abdel-Daim et al. [4]
16.	Red wine	Male Charles River Wistar rats, 250 μg/kg, (i.g) for 33 days	16.5 mg/kg, (i.g) for 33 days	↓ AST, ALT and MDA ↑ GSH, CAT, GST and SOD levels	Banc et al. [18]
17.	Allicin	Sprague Dawley rats, 30 mg/kg (p.o.), for 28 days	50 mg/kg, (p.o.) for 28 days	↓ AST, ALT, ALP, LDH, BUN, TNF-α, IL−6, IL−1β, 8-OHdG MDA, MPO, CYP2E1 NF-κB and NLRP3, ↑GSH, GPx, SOD, CAT, GR, GST level	Nan et al. [91]
18.	Carvacrol	Male Albino Wister rats, 20 mg/kg/day, (p.o.) for 30 day	50 mg/kg, (i.p) for 30days	↓AST, ALT, MDA, TNF-α and NF-κB, IL−1β and TOS ↑ GSH and TAS levels	Cerrah et al. [26]
19.	Myrtle leaf extract	Male Albino Wister rats, 20 mg/kg/day, (p.o.) for 42 day	300 mg/kg, (p.o.) alone for 7 days then concomitant with acrylamide for 35 days	↑ Cell viability Bcl−2 ↓ PD−1, ROS and DNA damage	Hassan et al. [53]
20.	Curcumin	Sprague-Dawley rats, 40 mg/kg, (p.o.) for 28 days	100 mg/kg, (p.o.) for 28 days	↓ MDA, AST, ALT, urea, creatinine and CYP2E1, ↑ GSH, SOD levels	Sun et al. [114]
21.	Lycium ruthenicum	Sprague-Dawley rats, 40 mg/kg, (i.g.) for 19 days	200 mg/kg, (i.g.) for 19 days	↓ MDA, AST, ALT, ↑ GSH, SOD, Nrf2 levels and ↑mitochondrial ATPase activity	Gao et al. [43]
22.	Hesperidin	Albino Wister rats, 20 mg/kg/day, (p.o.) for 14 day	10 mg/kg, (p.o.) for 21 days	↓ AST, ALT, ALP 8-OHdG, MDA, NO, IL−1β, IL−6 and TNF-α, ↑ GSH-Px, SOD, CAT levels	Elhelaly et al. [37]
23.	Blueberry anthocyanin extract	KM male mice 50 mg/kg/day, (p.o.) for 7 days	150 mg/kg, (i.g.) for 7 days	↓ ROS, MDA, Cyt-c ↑ ATPase, SOD levels and ↑ activities of ETC Mitochondrial membrane potential	Sun et al. [115]
24.	Carnosic acid	Sprague-Dawley rats, 40 mg/kg, (p.o.) for 21 days	60 mg/kg, (p.o.) for 21 days	↓ AST, ALT, ALP MDA and TOS, ↑Nrf2, CAT and TOC levels Restored the normal histopathological structure of liver	Cheng et al. [30]
25.	Resveratrol	Rats, 40 mg/kg (i.p.), for 10 days	60 mg/kg, (i.g.) for 10 days	↓ AST, ALT, ALP 8-OHdG, MPO, MDA, LDH, NF-κB, TNF-α, IL−6 and IL−1β, ↑ GSH, SOD, CAT and Nrf2/NQO−1 levels	Tan et al. [118]

(continued on next page)

Table 3 (*continued*)

Sr. No.	Pharmacological intervention	Acrylamide-induced hepatotoxicity model (Species, Dose, Route and Duration)	Pharmacological intervention (Dose, route and Duration)	Therapeutic effect	Ref.
26.	Ganoderma atrum polysaccharide	Sprague-Dawley rats, 20 mg/kg, (p.o.) for 30 days	200 mg/kg, (p.o.) for 30 days	↓ AST, ALT, ALP 8-OHdG, MDA, IL−1β, IL−6 and TNF-α, ↑ GSH-Px, SOD, CAT levels	Jiang et al. [66]
27.	Spirulina platensis	Albino Wister rats, 20 mg/kg/ day, (p.o.) for 14 day	1000 mg/kg (p.o.) for 21 days	↓ NO, MDA, AST, ALT, ALP TNF-α, IL−6, IL−1β and 8-OHdG, ↑ GSH, GPx, SOD, CAT levels	Bin-Jumah et al. [23]
28.	Rosmarinic acid (RosA)	BRL−3A cells, 4 ml of 4MM acrylamide was added in the cell culture and cultivated for 24 hrs	50 μM of RosA was used for the pre-treatment for 2 hrs. and then cultivated for 24 hrs. after adding acrylamide	↓ ROS and MDA, ↑ SOD, GSH levels	Hong et al. [56]
29.	Crocin	Albino Wister rats, 25 mg/kg/ day, (p.o.) for 21 day	50 mg/kg, (p.o.) for 21 days	↓ AST, ALT, ALP MDA and TOS levels, ↓Inflammatory cell infiltration and vascular congestion ↓ Intracytoplasmic vacuolization, ↑ CAT and SOD levels	Gedik et al. [44]
30	Rutin	Albino Wister rats, 20 mg/kg/ day, (p.o.) for 21 day	100 mg/kg, (p.o.) for 21 days	↓ NO, MDA, TNF-α, IL−6, cyt-c, Bax and 8-OHdG, ↑ GSH, GPx levels	Ahmed, Ibrahim Laila [9]
31	Ammodaucus leucotrichus Coss. & Dur. seed extract	Male Wistar albino rats, 25 mg/ kg/day, for 7 days (from 4th day onward)	200 mg/kg/day, (p.o.) for 10 days	↓MDA, CHOP, ATF6,BAX, Beclin−1, LC3, ↑GSH, Bcl2	Annaz et al. [15]

DNA damage in various tissues. A study found that, acrylamide "20 mg/kg for 14 days" resulted in a considerable degree of DNA damage to the kidney and liver, as evidenced by an increase in the DNA damage biomarker 8-OHdG [23]. Another investigation founds similar results in which acrylamide increase the ROS production and increases the oxidative stress along with induction of the DNA oxidation and damage [37]. In a recent study, when acrylamide given "3 mg/kg five times per week" for two weeks, it caused a significant amount of damage to renal genomic DNA, shown by the fragmented pattern of smeared DNA on the agarose gel. Additionally, copies of mitochondrial DNA were also reduced significantly along with the elevated p53 and reduced β-Catenin gene levels in renal cells after oral administration of AA [88]. Similarly, another study conducted employing cat fish (*Clarias gariepinus*) found that AA caused marked DNA fragmentation in brain, liver and kidney [63]. The results of this research reveal that when exposed to acrylamide it increases the oxidative stress and damages the DNA causing the toxicity in the kidney and liver. DNA damage induced cell death is widely reported in several experimental models. Thus, it is imperative to inhibit the DNA damage for the alleviation of AA-induced renal and hepatotoxicity.

6.4. Mitochondrial damage and dysfunction

In eukaryotic cells, mitochondria are organelles which convert energy and produces the ATP for survival and biological processes via oxidative phosphorylation and tricarboxylic acid cycle (TCA cycle) [79]. It also has a vital role in modulation of cell signals, cytoplasmic Ca^{2+} homeostasis lipid metabolism, apoptosis cascade signals, and several other essential biological processes [10]. Both, the primary source of reactive oxygen species generation and the primary target of their attack are mitochondria. ROS exposure can alter the morphology and functioning of the mitochondria by damaging proteins, lipids, and nucleic acids [129]. Substation amount of experimental evidences suggested that detrimental role of AA on mitochondria [125]. Studies has found that AA altered mitochondrial biogenesis and dynamics occurs due to alteration of several mitochondrial genes including PGC-1α, Mfn2 etc. and reduced expression of mitochondrial complexes thereby triggering cell death pathway including apoptosis and mitophagy [129,29]. In kidney, AA treatment in rats leads to significant mitochondrial damage and triggered mitochondrial dependent cell death through P53 acetylation. Further, the study found that Allicin markedly protected the kidney from AA through the inhibition of P53 acetylation mediated through upregulation of SIRT-1, thereby inhibited apoptotic cell death [129]. Another research was conducted to assess the effect of AA and titanium dioxide nanoparticles found that mitochondrial impairment by altering the mitochondrial membrane potential and reduced mitochondrial DNA copies, and upregulation of P53 expression in kidney [88]. A transcriptional profiling study reveals that AA altered several genes related to mitochondria in mice liver [72]. Recently, the relevance of miRNAs in Acrylamide-induced mitochondrial dysfunction was discovered. Study discovered that AA elevates miR-27a-5p expression in the liver cell lines. miR-27a-5p upregulation triggered mitochondrial depended apoptosis and mitochondrial function impairment in rats via Bft-ATM-p53 pathway [131]. Another study found that AA triggered mitochondrial dysfunction mediated by alteration circadian gene expression (cry1 and Bmal1) in liver cells [117]. Thus, AA triggered mitochondrial dysfunction in kidney and liver cells through multifaceted pathways.

6.5. Autophagy

Cellular degradation system called autophagy is activated in response to the stress signals such OS and inadequate nutritional energy by recycling cytosolic proteins and organelles that are damaged, misfolded, or superfluous [94]. Macroautophagy is the process by which the autophagy system is activated and encloses the identified damaged proteins and organelles in cytoplasm inside a double-membrane structure called autophagosomes. Moreover, one kind of selective autophagy that breaks down mitochondria is called mitophagy, which remove aberrant mitochondria while managing the number of mitochondria in the cell. Autophagosomes combine free lysosomes in the cytoplasm to form autolysosomes, which are then degraded to create new autophagosomes [99]. Autophagy-associated proteins, including autophagy-related 5 (ATG5), P62, Bellin-1 and 1 A/1B-light chain 3 (LC3) are mainly responsible for the control of the mitochondrial autophagy process. The most well-known signalling pathway associated with autophagy is PI3K/Akt/mTOR pathway [58]. In a previous study when acrylamide was administrated at "38.27 mg/kg/day dose for 10 days" to induce nephrotoxicity and hepatotoxicity, AA increases the mitochondrial damage by inhibits the mitochondrial autophagy by decreasing the levels of PI3K, mTOR and AKT, in kidney and liver. Additionally, it has been seen that AA can inhibits the autophagy and can induce apoptosis causing cellular toxicity [68]. According to a recent study, oxidative stress caused by AA-induced hepatic damage

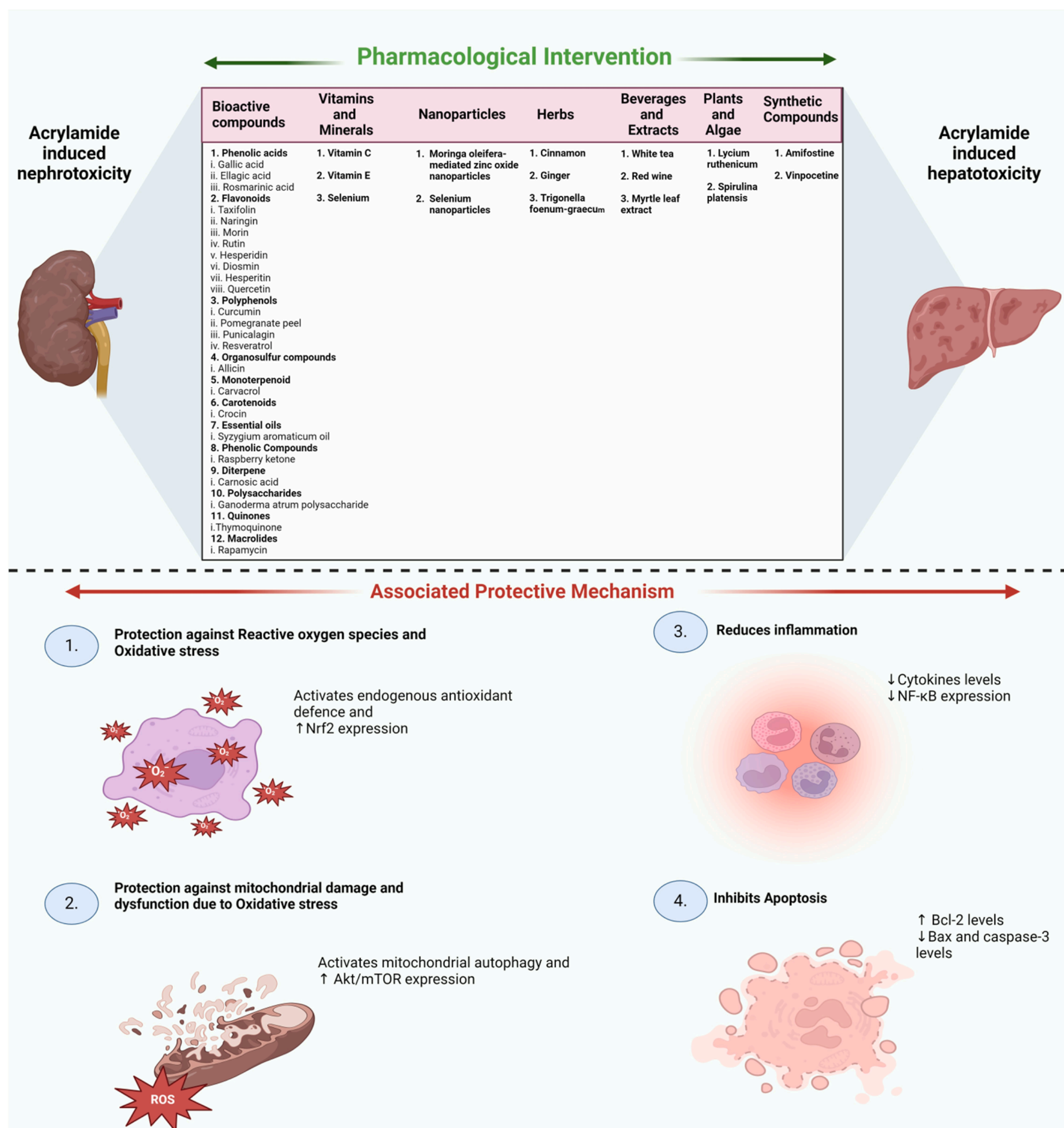

Fig. 5. Various Pharmacological intervention against acrylamide induced nephrotoxicity and hepatotoxicity along with the associated protective mechanism.

prompted ferroptosis and autophagy [60]. Furthermore, autophagy indicators such as LC-3 and Beclin-1 were also found increased in kidney as well as liver of AA treated rats [68]. Although there are not many studies reported that has demonstrated the relationship between autophagy and AA-induced nephrotoxicity and hepatotoxicity, further investigation is required to validate these findings more correctly.

7. Pharmacological intervention for counteracting the acrylamide induced nephrotoxicity and hepatotoxicity

Numerous animal studies have been done recently to evaluate the impact of AA on nephrotoxicity and investigate the potential of different pharmacological interventions to mitigate acrylamide-induced hepatotoxicity and nephrotoxicity. These interventions include a variety of natural products or bioactive compounds including (phenolic acids, flavonoids, polyphenols, Organosulfur compound, Monoterpenoids etc.), vitamins and minerals, nanoparticles, herbs, extracts, plants, algae, and synthetic compounds [109,20,116,77,51,18,43,70]. Researchers are actively investigating these compounds to explore their underlying mechanism. Table 2 and Table 3 discuss various pharmacological interventions with their therapeutic effect against AA-induced nephrotoxicity and hepatotoxicity, respectively via inhibition of inflammation, OS and other pathways. Moreover, Fig. 5 illustrates different pharmacological interventions along with the molecular

mechanism associate with them.

7.1. Anti-oxidant effect

Various pharmacological interventions discussed in Table 1 and Table 2 has shown the anti-oxidant effect by reducing the NO and MDA levels while up-regulating SOD, GPx, GSH and CAT levels. When Morin, which is a flavonoid was administrated “100 mg/kg, (p.o.) for 10 days” in an AA-induced nephrotoxicity and hepatotoxicity rat model it reduced the levels of NO and MDA and elevates levels of CAT, GSH, SOD and GPx [68]. In another study, of acrylamide induced hepatotoxicity when Allicin, which is an organosulfur compound was administrated at “50 mg/kg, (p.o.) dose for 28 days” it also reduces the MDA and increases the level of SOD, GPx GSH and CAT and inhibiting the oxidative stress [91].

7.2. Anti-inflammatory effect

Additionally, various pharmacological interventions mentioned in Table 2 and Table 3 has also reduced the inflammation by down regulating the levels of various proinflammatory cytokines like IL-6, COX-2 and IL-1β and When Naringin, which is a flavonoid was administrated, “100 mg/kg, (i.g) for 10 days” in an AA-induced nephrotoxicity rat model it significantly decreases the IL-33, COX-2, IL-6 and IL-1 levels in treatment group when compared to toxic group [45]. Similarly, when Resveratrol, which a polyphenol when administrated at “60 mg/kg, (i.g.) dose for 10 days” in a acrylamide induced hepatotoxicity rat model it also downregulated the IL-1β, TNF-α and IL-6 levels significantly in treatment group [117]

7.3. Other protective effect

Furthermore many of these interventions also inhibit the mitochondrial damage [43], restore the autophagy [73], prevent DNA damage [4] and inhibit the apoptosis [52,73], preventing the liver and kidney damages. Along with this, they also restore the normal liver and kidney functioning by reducing the elevated level of ALT, AST and ALP which are biomarkers to determine the normal liver functioning and creatinine, urea, blood urea nitrogen and uric and which are biomarkers to determine the normal kidney functioning [91,47]. In an another study, when Allicin was administrated at “50 mg/kg, (p.o.) dose for 28 days” in an AA-induced hepatotoxicity rat model it reduces the ALP, AST, BUN, ALT levels along with this it reduces the 8-OHdG level which an important biomarker for the OS to the DNA and reduced the level of NF-κB which is an essential protein to trigger the apoptosis and inflammation. [91] Hamdey et al., demostrated that, when cinnamon is given at a dose of “50 mg/kg, (p.o.) for 28 days mg/kg and 400 mg/kg, (p.o.) for next 7 days” it reduces the elevated levels of creatinine and urea [51].

All of these pharmacological interventions have shown therapeutic effect against AA-induced nephrotoxicity and hepatotoxicity but finding most efficient among them is hard as all of them have shown positive therapeutic effect on different animal models under different experimental conditions so it is not easy to choose the best one. Moreover, these all are finding on animal models but to determine their potential on human further investigation is required on these pharmacological interventions.

8. Summary and conclusion

Acrylamide is an environmental toxicant which can be found in various food items from coffee to various bakery products and humans are exposed to it every day as these food items is generally consumed worldwide. In coming years, toxicity caused by the acrylamide can become a major public health problem due to the negligence to its toxic effect by the population. Cooking food at low temperature, low pH and adding acidic content to food can lower the amount of AA in food, reducing the chances of acrylamide induced toxicity. The molecular mechanism behind the acrylamide induced nephrotoxicity and hepatotoxicity is mainly the OS caused by AA and its metabolites in the kidney and liver tissues, ROS intern causing DNA damage, mitochondrial dysfunction, autophagy inhibition apoptotic cell death in liver and kidney. However, there is a need of further investigations to deepen the knowledge about acrylamide induced nephrotoxicity and hepatotoxicity. Moreover, pharmacological interventions including, bioactive compound, minerals, vitamin, synthetic compound etc. listed in this article has shown a positive result in various animal models of acrylamide induced nephrotoxicity and hepatotoxicity. However, studies that depicted effect of these pharmacological interventions on human are warranted. Although many animal studies have shown the adverse effect of acrylamide in renal and hepatic health, various research gaps still lies within and need to be address. The role and regulatory mechanism of miRNAs and IncRNAs are still unexplored in AA-induced nephrotoxicity and hepatotoxicity. Furthermore, there is a notable lack of clinical studies investigating the toxic effects of acrylamide on hepatic and renal health, highlighting the need for further research in this area. These future strategies will bring new insights into the mechanism and treatment strategy for AA-induced nephrotoxicity and hepatotoxicity.

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Data availability

No data was used for the research described in the article.

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