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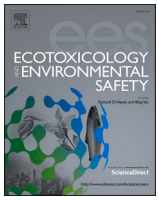

Toxicity, formation, contamination, determination and mitigation of acrylamide in thermally processed plant-based foods and herbal medicines: A review

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ABSTRACT

Thermal processing is one of the important techniques for most of the plant-based food and herb medicines before consumption and application in order to meet the specific requirement. The plant and herbs are rich in amino acids and reducing sugars, and thermal processing may lead to Maillard reaction, resulting as a high risk of acrylamide pollution. Acrylamide, an organic pollutant that can be absorbed by the body through the respiratory tract, digestive tract, skin and mucous membranes, has potential carcinogenicity, neurological, genetic, reproductive and developmental toxicity. Therefore, it is significant to conduct pollution determination and risk assessment for quality assurance and security of medication. This review demonstrates state-of-the-art research of acrylamide focusing on the toxicity, formation, contamination, determination, and mitigation in taking food and herb medicine, to provide reference for scientific processing and ensure the security of consumers.

1. Introduction

Plant based food, such as cereal, vegetables and herbs as well as their processed products, contains a diverse range of bioactive constituents that are beneficial to human health, including dietary fibers, vitamins, minerals, carotenoids, and polyphenols, and sufficient intake of plant based food not only sustain life, but also reduce the risk of diseases, such as cardiovascular diseases and cancer (Liu et al., 2020a). Thermal processing is an important treatment method for preservation and transportation by decreasing the microbial growth and consequently enhancing the shelf life and safety of food (Putnik et al., 2017). Conventional thermal treatments include evaporation, pasteurization, drying, sterilization, steaming, cooking, boiling, roasting, and microwaving, which may induce chemical changes in foods, such as sensory attributes and textures. According to the tradition of the eastern Asia, a series of proper physical and chemical treatments of herbs before application, such as cutting, crushing, torrefying, and stir-frying, could also reinforce efficacy, reduce the toxicity of crude materials, and alter energetic nature and therapeutic direction in individualized treatment (Commission, 2020; Wu et al., 2018a). During the processing of the food and herb medicines, it is inevitable to generate chemical contaminants, including acrylamide, brings potential health risks (Andres et al., 2017; Sirot et al., 2019).

Acrylamide, a well-known chemical compound, is mainly produced industrially for the synthesis of polyacrylamide, which has been used as a dry strength agent and flocculating agent in paper making (Zhu et al., 2015), a filler for human soft tissues in surgery (Itkonen Freitas et al., 2020), a flocculant in wastewater treatment (Hou et al., 2020; Liu et al., 2019), an anti-erosion protective agent for cultivated soil in agriculture (Wiśniewska et al., 2018), and an oil-displacing agent in oilfield development (Yang et al., 2020). However, the health effect of acrylamide had been underemphasized until its wide existence was found in thermally processed starchy food by the researchers from the Swedish National Food Administration (SNFA) and the Stockholm University in 2002, and the mechanism was revealed that the Maillard reaction drives the development of acrylamide at a high temperature (usually in excess of 120 °C) (Mottram et al., 2002a; Stadler et al., 2002a). Since then, there has been a growing awareness of the acrylamide pollution in

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thermally processed food and its potential adverse effects on human health , and the relevant research including the toxicity evaluation of acrylamide to human health, method development of acrylamide determination, production regularity and pollution control in the thermal process have been rapidly attracted great concern of the scientific researchers, organizations and governments (Mottram et al., 2002a; Stadler et al., 2002a; Tareke et al., 2002; Timmermann CaG et al., 2021).

2. Toxicity

Acrylamide is a toxic compound with potential carcinogenicity, neurotoxicity, genetic toxicity, reproductive and developmental toxicity with high permeability. It can enter the body directly through respiratory tract, digestive tract, the skin and other ways, and the potential health risks of acrylamide should not be underestimated (Mesías and Morales, 2016).

2.1. Carcinogenicity

As early as 1994, the International Agency for Research on Cancer (IARC) classified acrylamide as a group 2 A carcinogen for human (Dybing et al., 2005). At the same time, it has been demonstrated that acrylamide can cause cancer in animals. Johnson et al. found that female rats exposed to 2.0 mg/kg/d acrylamide had increased tumor incidence in the mammary glands, thyroid glands, central nervous system, oral tissues and uterus, and there was also a crucial increase in the incidence of thyroid and scrotal mesothelial tumors among male rats (Johnson et al., 1986). Although the acrylamide has not yet been proven to be carcinogenic to humans, the existing epidemiological studies have shown a positive dose response relationship between the exposure of acrylamide and the occurrence of multiple organ cancers, such as female endometrial cancer, ovarian cancer, male cutaneous melanoma, multiple myeloma, follicular lymphoma, and renal cancer (Pelucchi et al., 2015). Studies have revealed that the intake of acrylamide from the diet is associated with an increase in cancer mortality in the elderly in China (Liu et al., 2017). A systematic review revealed that high acrylamide intake was associated with increased risks of ovarian and endometrial cancers in a relatively linear manner, while little association was observed between acrylamide intake and breast cancer risk with the exception of premenopausal women (Adani et al., 2020).

However, insufficient data were obtained to confirm the consistency of the relationship between dietary exposure to acrylamide and cancer. A study conducted by Kotemori proposed irrelevancy between dietary acrylamide intake and the risk of ovarian, endometrial cancer and breast cancer in Japanese woman (Kotemori et al., 2018). Filippini conducted dose-response meta-analysis of epidemiological studies and concluded that dietary acrylamide exposure was not dose associated with the risk of several site-specific cancers (e.g., prostate, gastrointestinal and lung) (Filippini et al., 2022).

Although the animal study confirmed the carcinogenic of the acrylamide, epidemiological studies reported the indeterminate relation between the dietary exposure of acrylamide and increased risk of site-specific cancers. It is notable that the dietary exposure of acrylamide in the general population were 0.5–1.9 μg/kg body weight for infants and children and 0.4–0.9 μg/kg body weight for adolescents, adults, and elderly (Pietropaoli et al., 2022), which were significantly lower than animal studies conducted at 2.0 mg/kg/day or higher, therefore, it may be difficult to induce a significant does-dependency in cohort study. In the other hand, interference from other carcinogenic or antitumor factors and different dietary habits from various countries should be involved in the consideration during study. To date, scant data are available for the carcinogenicity of acrylamide in human study (Filippini et al., 2022).

2.2. Neurotoxicity

One of the main toxic effects of acrylamide on the human body is to nervous system. The mechanism of neurotoxicity is related to the abnormal changes of cytoskeleton protein, oxidative stress, protein binding, axonal lesion of nerve endings and ion reaction (Recio et al., 2017; Faria et al., 2019; Bin-Jumah et al., 2021). Chronic poisoning from long-term low dose exposure to acrylamide can cause limbs fatigue, dizziness, headache, profuse sweating, coldness, anorexia, desquamation and erythema (Faria et al., 2019; Bin-Jumah et al., 2021). After exposure to acrylamide daily at 0.5–50 mg/kg/day, some experimental animals, such as rodents, rabbits, guinea pigs, dogs and cats, showed similar neurological effects to those observed in humans (Busova et al., 2020). When the cerebellum is involved, acrylamide can induce locomotor defects, along with parkinsonian-like movement impairment including bradykinesia and hypokinesia (Li et al., 2016). It may even affect chemotaxis plasticity and reduce learning ability (Liu et al., 2020b).

Faria et al. found that zebrafish showed depression-like phenotype and anxiety behavior by acute acrylamide exposure. The depletion of monoamine neurotransmitters in the brain was found by metabolomics analysis, consistent with the characteristics of depression and anxiety disorders (Faria et al., 2018).

At the same time, in the mechanisms involved in neurotoxicity of acrylamide, the most noteworthy is the neurotoxicity of early life. Lai et al. studied the neurodevelopmental toxicity of acrylamide in the embryonic and lactation stages of rats by observing the histological changes and synapses in the hippocampus. Also, it was found that acrylamide has a dose-dependent effect on the growth and development of hippocampal neurons in weaning rats (Lai et al., 2017). Erdemli et al. performed a caesarean section to analyze fetal brain tissue, showing that acrylamide induces increased oxidative stress and decreases fetal brain tissue brain-derived neurotrophic factor levels (Erdemli et al., 2018).

2.3. Reproductive and developmental toxicity

Acrylamide can cause damage to the human genetic system, although the exact mechanism is not completely clear. Studies have shown that acrylamide plays a role in genetic toxicity through glycidamide (GA), which is one of the acrylamide's main genetic metabolites. About 10% of the absorbed acrylamide can be converted to GA in the liver by the oxidase in mitochondrial cytochrome P450. GA is a substance with strong genotoxicity and cytotoxicity, which can combine directly with nitrogen atoms on DNA bases (G, A) to form DNA-GA adducts even at a low concentration, damaging lung cells and the normal function of liver and kidney (Xiang et al., 2016).

According to the literature, acrylamide can indirectly produce toxicity by destroying the DNA repair function of Sertoli cells in seminiferous tubules, resulting in reduced sperm production, quality, and male fertility (Yilmaz et al., 2017). Moreover, researchers have detected acrylamide in human umbilical cord blood and breast milk, and confirmed that exposure to acrylamide in pregnant women, especially those in the early stage of pregnancy, caused developmental damage to the fetal cardiovascular system, nervous system and motor system based on the results from laboratory animal models, such as zebrafish and Kunming mice. Among them, cardiac toxicity is the direct target of early developmental toxicity, which can lead to abnormal fetal heart shape and function, and directly lead to heart failure in the worst case (Huang et al., 2018a; Yu, 2019). Huang et al. provided the evidence of deficient cardiovascular system with heart malformation and dysfunction of acrylamide in the cardiovascular system (Huang et al., 2018b). In the study, they found that acrylamide could reduce the number of cardiomyocytes through the reduced capacity of cardiomyocyte proliferation.

2.4. Other toxicities

The toxic effect of acrylamide acts on multi-organ and multi-system. In addition to the above toxic effects, acrylamide can also cause damage to the spleen, liver, intestine, thymus, etc. Komoike et al. found that adult zebrafish with intake of acrylamide at the dietary concentration for a consecutive month would not only suffer spleen damage, including hemorrhage and cysts, but also have some immunological reactions, such as activation of macrophages and up-regulation of major inflammatory cytokines in the spleen (Komoike et al., 2020). After continuous exposure to acrylamide at 50 mg/kg, b.w. in adult male rats, Ansar et al. found a significant decrease in the activity of Glutathione S-transferase and an imbalance between oxidative stress and antioxidant activity in the liver (Ansar et al., 2016).

Besides, Aljahdali et al. found that exposure to acrylamide would also have adverse effects on the human intestinal flora and indigestion (Aljahdali and Carbonero, 2019). (Yue et al., 2020) et al. demonstrated that acrylamide disrupted glucose homeostasis and elevated FBG level in female rats possibly by interfering with glucose metabolism and hampering the physiological effect of insulin.

3. Formation of acrylamide

Toxicity caused by acrylamide has attracted extensive attention and considerable researchers have explored the formation mechanism of acrylamide in order to better understand the development of acrylamide and obtain an effective method to mitigate the occurrence of acrylamide.

The formation of acrylamide is a complex process with many pathways and complicated reactions. It has been generally accepted so far that the asparagine pathway of the Maillard reaction is one of the major pathways of acrylamide formation on the basis of current research results (Becalski et al., 2003). As shown in Fig. 1, at high temperatures, free amino groups in asparagine and reducing sugars, such as glucose with carbonyl groups, are dehydrated and condensed to form highly unstable Schiff bases, which subsequently turn into acrylamide by the Strecker degradation pathway or the N-glycoside pathway (Mottram et al., 2002b; Stadler et al., 2002b). Through the Strecker pathway, Amadori rearrangement of Schiff bases occurs in the environment of weak acid, and the rearrangement products degrade to dicarbonyl compounds. In addition, glucose can be directly converted into glyoxal and other dicarbonyl compounds by reverse aldol reaction, and further deaminated with asparagine to form acrylamide. The N-glycoside pathway refers to that N-glycoside or Schiff base, as a direct precursor of acrylamide, is decarboxylated to form decarboxylated Schiff base in different ways under neutral or alkaline environment. The decarboxylated Schiff base and Amadori products can generate acrylamide directly or indirectly by forming the intermediate product of 3-Aminopropanamide (Zhang et al., 2020a).

It has been reported that the asparagine pathway in the Maillard reaction is not the only origin of acrylamide, which can also be formed in the absence of asparagine (Zhang et al., 2009). When heated, fats and carbohydrates give rise to low-molar mass aldehydes such as formaldehyde and acetaldehyde, which can be recombined in suitable conditions and formed into acrylamide after the formation of acrolein (Nan et al., 2020; Trabelsi et al., 2019). Furthermore, the metabolism of proteins and decarboxylation of organic acids including lactic acid, citric acid and malic acid, can also produce acrolein and acrylic acid, leading to the formation of acrylamide. Some studies have shown that α-alanine and β-alanine are generated during the pyrolysis of amino acids, and these two alanine isomers generate acrylamide in the presence of amino groups (Yaylayan et al., 2004). However, the activity of asparagine, as

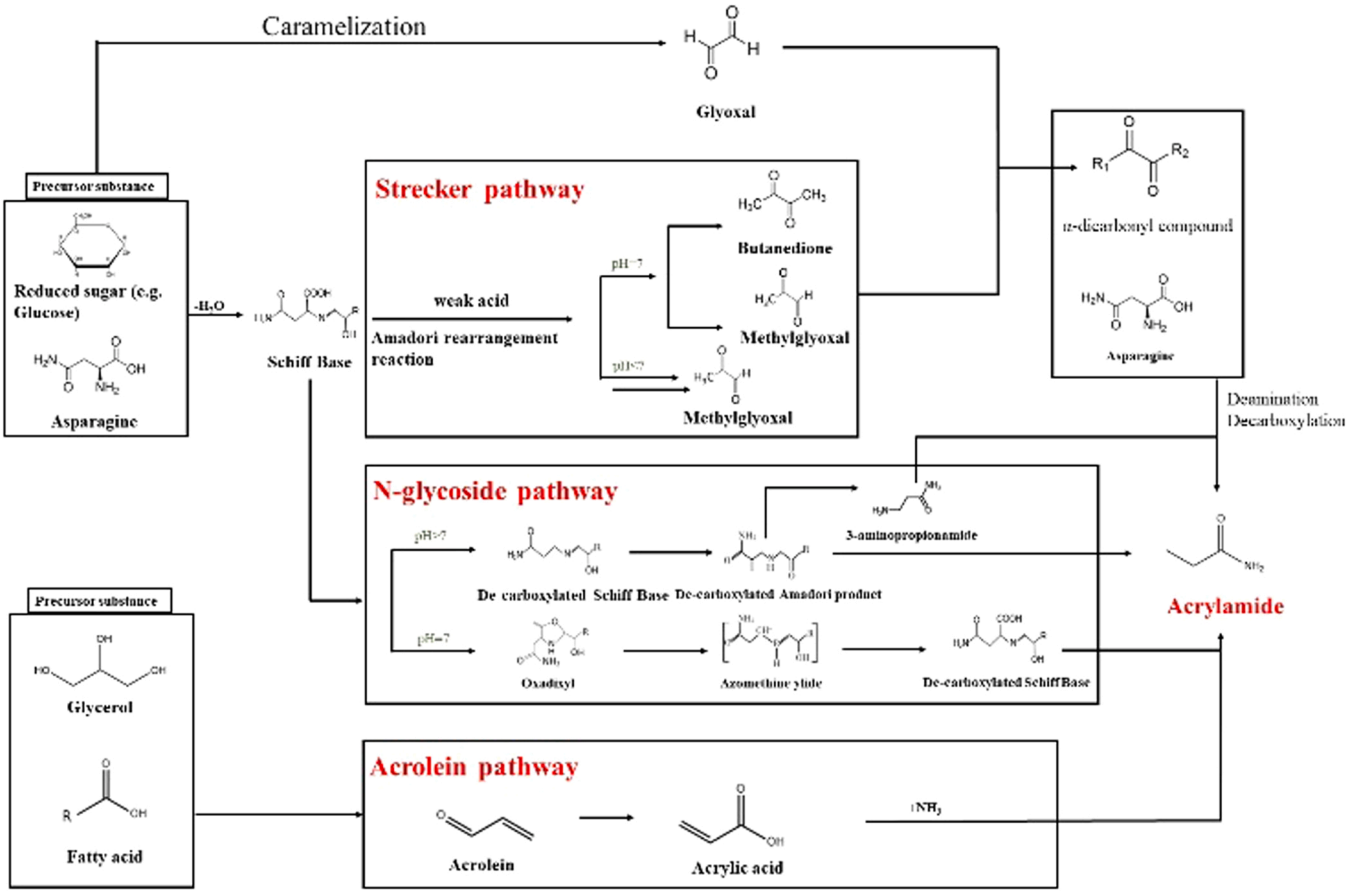

Fig. 1. The formation pathways of acrylamide.

the precursor of acrylamide in the Maillard reaction, is much higher than that of acrolein or acrylic acid in the reactions of above pathways, therefore, the asparagine pathway is the major pathway of acrylamide formation in the Maillard reaction (Xu et al., 2014).

Reactants are the primary factors in the formation of acrylamide. Polysaccharides and proteins are important components of plant composition, and amino acids and reducing sugars, as active monomers, are important ingredients in plant in botanicals and botanical preparations, which are widely used as food, in dietary supplements, and in pharmaceutical products. Carratu et al. reveal that the content of free amino acid varied widely between plants, and the mean values of asparagine in parts of dried plants reached 1195 mg/100 g (Carratù et al., 2008). In a study conducted by Ayvaz, the raw potato tubers were determined to include 7.7 mg glucose, 9.4 mg fructose, 0.4–5.4 mg sucrose, 0.7–2.9 mg asparagine, and 0.3–1.7 mg glutamine per 1 g fresh weight (Ayvaz et al., 2015). The concentrations of reducing sugars and amino acids relate to the species of the plant, cultivars, and planting conditions, resulting as the varying amount of acrylamide after processing (Mollakhalili-Meybodi et al., 2021). It has been demonstrated that the acrylamide was originated from the asparagine molecule, based on the isotope ^{15}N-labeled asparagine and mass spectral analysis (Bertuzzi et al., 2020). Many researchers confirmed that the concentrations of reducing sugar and asparagine are the major determinant of acrylamide forming potential and studies revealed that there is a critical value of the asparagine to reducing sugars ratio, such as 2.257, during the formation of acrylamide (Muttucumaru et al., 2017a). Therefore, the abundant existence of the precursors leads to the formation potential of acrylamide in plant and herbal products.

In addition to above, the processing condition make up another important factor to the formation of acrylamide. Thermal pretreatment of heating, including frying, baking, toasting, and microwaving, are conventional procedures before consumption. In addition, most crude materials of herbal medicines require thermal treatments, such as cutting, crushing, torrefying, and stir-frying, according to the Chinese Pharmacopoeia (Wu et al., 2018a). Models have been established by researchers to investigate the effect of the processing to the acrylamide production. Bertuzzi et al. found the maximum acrylamide content in roaster coffee at 10 min, corresponding to a temperature of 175–177 °C, while a higher temperature or a longer processing time may reduce the acrylamide content (Bertuzzi et al., 2020). Liyanage et al. reported the conditions most conducive to acrylamide formation in all frying potatoes were 190 °C for 7 min, and the acrylamide synthesis was accompanied by significantly decreased levels of reducing sugars and asparagine (Liyanage et al., 2021). The accelerated production of acrylamide possibly resulted from the hydrolysis of the polysaccharides and disaccharides upon heating condition, which released reducing monosaccharides, mainly fructose and glucose, successively converted into their degradation products (Bertuzzi et al., 2020). Pan et al. reported the increment of reducing sugar in *Atractylodis Macrocephalae Rhizoma* during stir frying process along with a decrement of polysaccharide, which was attributed to the transformation and decomposition of the polysaccharide and reducing sugar during the process (Anon, 2016). A further study conducted by Yan et al. revealed that this transformation significantly happened at 140–160 ℃ (Anon, 2020). Tang et al. found high levels of intermediate Maillard reaction products and advanced glycation end-products in the hot air dried goji berries, and the polysaccharides obtained from the processed berries had lower molecular weight, high antioxidant activity and high degrees of Maillard reaction (Tang et al., 2023). Meng investigated parameters of Maillard reaction in the bran stir-fry Chinese yam under 176.3–289.9 ℃ and 10.31 min, and found that pH values and the content of 5-hydroxymethylfurfural were increased ($P < 0.001$), while the content of amino acids was decreased significantly ($P < 0.001$) after processing, indicating the occurrence of Maillard reaction (Meng et al., 2020).

Arousing interests with extensive investigations revealed the production regularity acrylamide in baked cereal products, coffee, potato products, as they have contributed the important part of daily food (Arvanitoyannis and Dionisopoulou, 2014; Zhang and Zhang, 2007). Little attention has been given to the herbal products, including dietary supplementary and herbal medicines, although high production potential of acrylamide exists. The production of acrylamide in herbal products may follow similar mechanism as processed food, further investigation to understand the formation in these products remained valuable.

4. Contamination and risk assessment of acrylamide

4.1. Thermal processing

There is a growing demand for high quality plant based food and herbs, since their beneficial ingredients are investigated and health effects are gradually acknowledged. Nevertheless, high moisture content and rich nutrition impede the maintenance of the quality of the food and herbs. Drying is a common preservation technique in the food industry to increase fruits and vegetables' shelf-life. Meanwhile, cooking is necessary to avoid the foodborne pathogens. Most of the processing techniques involve a series of thermal treatment methods, such as baking, frying, roasting, and boiling. For example, cereals are processed by dietetic product manufacturers in large-scale corporations via toasting and/or boiling, hydrolysis and drying processes to improve their sensory qualities, digestibility, safety and shelf-life.

Especially for herbs, the medicinal value can be fully exerted and the drug toxicity or side effects are reduced or eliminated through reasonable processing before clinical use (Commission, 2020; Zhao et al., 2010; Wu et al., 2018b). For example, *Crataegi Fructus* is a typical herbal medicine that can be stir-fried to different degrees for different therapeutic purpose. The unprocessed material can promote digestion and invigorate blood circulation, the stir-fried product is mainly used for indigestion, and the charred Crataegi Fructus are effective in treating indigestion caused diarrhea and gastrointestinal hemorrhage (Fei et al., 2018). Investigations on the pharmacological effects related to crude and stir-fried *Semen Cassiae* indicated that the stir-fried product was more effective than the crude one in liver protection and decrease of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) (Zhao et al., 2010). In other circumstances, chemical and physical transformations may take place during the thermal processing in order to facilitate the use of the herbal medicine. Therefore, after the long-term practice, the processing turns out to be an indispensable procedure for most of herbal medicines and thermal processing play an important role.

4.2. Contamination

Extensive studies have been conducted to in revealing the contamination of acrylamide in food and French fries, potato chips, coffee beans, cereals are mostly consumed products worldwide contributed to the exposure of the acrylamide.

Fried potatoes exhibited the highest potential of acrylamide pollution in dietary food. Mesias *et. al.* conducted a research by measuring acrylamide in French fries prepared in 31 primary school canteens randomly recruited from different Spanish regions and the mean content was 329 μg/kg (from <20–4000 μg/kg) with 15.7% of samples were above the benchmark levels according to the EU Regulation 2017/2158 (500 μg/kg) (Mesias et al., 2020a). An observational study in 208 volunteers in households from 30 Spanish provinces was carried out in order to evaluate the formation of acrylamide during the preparation of French fries from fresh potatoes following the consumer cooking practices, and the results showed that 36.1% of samples contained acrylamide above the benchmark level of 500 μg/kg with the mean acrylamide content at 550 μg/kg and P95 at 1747 μg/kg. Powder et al. reported a significant reduction in mean acrylamide levels from 763 μg/kg in 2002–358 μg/kg in 2011, however, the downward trend

was not continued in 2016, in which a slight increase to 412 μg/kg was obtained (Powers et al., 2017). A study lasted ten years showed that mean values of acrylamide content in potato crisps marketed in Spain decreased by 55.2% from 2004 to 2019 (1484 μg/kg in 2004, 740 μg/kg in 2008, 629 μg/kg in 2014, and 664 μg/kg in 2019), which showed the efforts that manufacturers make in reducing the acrylamide level to meet the requirement of the benchmark level established in the Regulation (750 μg/kg), however, further work should be continued since 27% of samples still exhibited concentrations above the benchmark level (Mesias et al., 2020b).

Cereals and its related baked good are the main energy source according to the dietary habits in many countries. A study conducted by Kafouris reported that the acrylamide occurrence in the cereals, breads, crackers, and biscuits in Cyprus were ranged in 10 μg/kg − 520 μg/kg, 10 μg/kg − 163 μg/kg, 10 μg/kg − 2542 μg/kg, 10 μg/kg − 1124 μg/kg, with averages of 137 μg/kg, 41 μg/kg, 286 μg/kg, and 353 μg/kg, respectively (Mesias et al., 2020b). A study carried out in Slovenia showed the highest mean acrylamide levels were found in salted snacks at 858.6 μg/kg, biscuits and wafers at 384.5 μg/kg, breakfast cereals at 288.9 μg/kg, and toast and bread at 134.8 μg/kg with exceedance rate of 31%, 57%, 80%, 86% among the analyzed samples according to benchmark levels proposed by the European Commission (Mencin et al., 2020). Between 2018 and 2019, a study conducted in Lebanese, 4 out of 13 biscuit and wafer sample analyzed exceeded the benchmark level (350 μg/kg) (Mihai et al., 2020). In Spain, it was reported that 30% of sample analyzed exceeded the reference level required by EU Regulation 2158/2018 (Mesías et al., 2019). All the results highlight the necessity of the implementation to reduce the acrylamide in cereal and baked food.

Coffee is one of the most widely consumed drink, and roasting is the conventional procedure before distribution of coffee bean. The roasting process is considered as the main responsibility for the formation of acrylamide, because the roasted coffee contains a significant level of acrylamide in the range of 0.1–2.2 ppm, which is undetected in green coffee (Schouten et al., 2020). It was observed that acrylamide content increased to a maximum amount of 151.48 μg/kg in the first few minutes under 250 ℃ the and a decreased trend was obtained with an increased roast level (Rattanarat et al., 2021). In another study conducted by Bertuzzi et al., maximum acrylamide contents were achieved at 1045 μg/kg for Arabica green coffee and 795 μg/kg for Robusta green coffee under the temperature of 136 ℃− 138 ℃ (Bertuzzi et al., 2020), which exceeded the benchmark level of 400 μg/kg. The processing temperature were mainly in the range of 170–260 ℃ and 5–30 min, and dark roasting under a high processing temperature resulted as lower acrylamide content in comparison with those light or medium roasting coffee beans.

Nevertheless, limited studies have been conducted to herbal medicines (Hu et al., 2017). Li et al. analyzed 15 batches of thermally processed herbs, and they found the existence of acrylamide in 14 batches of samples including *Crataegi Fructus*, *Medicated Leaven*, *Astragali* Radix et al. (2010). Zhao selected *Asparagi Radix* rich in asparagine and reducing sugar as the research object, and he found that no acrylamide was detected in the crude *Asparagi Radix*, but acrylamide was generated under different heating conditions (Zhao, 2008a). In the study of dynamic change of active ingredients such as flavone, catechin, ferulic acid and inactive ingredients including acrylamide, 5-hydroxymethylfurfural (5-HMF), reducing sugar and amino acid from *Hordei Fructus Germinatus* during frying process, Tan found insignificant changes on the active ingredients but remarkable changes on inactive ingredients (Tan, 2019). The effects of thermally processed temperature on the reducing sugars and amino acids of Maillard reactants showed that the amounts of D-fructose, D-maltose, D-glucose, etc., decreased with increasing temperature, while the amounts of non-reducing sugar, such as sucrose, increased first and then decreased. The results showed that acrylamide and 5-HMF were not produced when the thermally processed temperature was below 120 ℃. When the temperature was above 140 ℃, acrylamide and 5-HMF start to increase and the production rate rise to maximum at a certain temperature. Similarly, Zhou et al. detected a certain content of acrylamide in the *Hordei Fructus Germinatus* during frying process (Zhou et al., 2007a, 2007a). Zhu et al. designed the orthogonal experiment at processing conditions of 80–210 °C and 5–100 min to evaluate the effect of thermal treatment on the formation of acrylamide in *Atractylodis Macrocephalae* Rhizoma (AMR), and found a significant increase of acrylamide amount in thermally processed AMR with the highest concentration at 9826 μg/kg, implying a high health risk of taking thermally processed AMR (Zhu et al., 2021). The acrylamide content in plant based food and herbal medicines after thermal processing is presented in Table 1.

4.3. Risk assessment

The margins of exposures (MOEs) indicated a concern of acrylamide for neoplastic effects based on animal evidence (Benford et al., 2010; Michael Bolger et al., 2010). The MOE is the ratio between benchmark dose lower confidence limit 10% ($BMDL_{10}$) and estimated daily intake (EDI) (mg/kg). The MOE gives a suggestion about the possible extent of the risk that a higher MOE represents a lower risk of exposure. Researchers have calculated the MOEs for 12 carcinogenic chemicals that can be present in food, and of the 12 case studies, comparison of the calculated MOEs showed that acrylamide could be of relatively higher prioritization for the risk management action (Riboldi et al., 2014). MOE was used to determine the possible risk of exposure to acrylamide calculated based on the $BMDL_{10}$ of 0.31 mg/kg/day for the induction of mammary tumors in female rats and the $BMDL_{10}$ of 0.18 mg/kg/day for Harderian gland tumors in male mice. An MOE of 10,000 or higher would be recognized as low health concern and a low priority for risk management according to the European Food Safety Authority (EFSA) Scientific Committee, while a small value indicated a high potential of health risk. In addition, a non-observed adverse effect level (NOAEL) of 0.2 mg/kg bw per day for neurotoxicity was determined based on morphological changes in the nervous system as endpoint in animal studies and the overall NOAEL was 2 mg/kg bw per day for reproductive and developmental effects. Considering acrylamide as the probable carcinogen (group 2 A) by the IARC, the risk assessment should focus on the evaluation of carcinogenic effects.

In the study conducted by Wyka, intake of acrylamide in a group of teenagers (n = 261) from an urban environment in Poland was estimated to be 0.09 μg/kg bw/day (50th percentile), 0.32 μg/kg bw/day (75th percentile) and 1.04 μg/kg bw/day (95th percentile) for girls, and 0.13, 0.41, and 1.18 μg/kg bw/day for boys based on 7 days record. This result led to the lowest values of MOE at 152–173 for the P95th percentiles of exposure (Wyka et al., 2015). French fries, potato crisps, corn flakes, bread and salty sticks are the main source of acrylamide exposure. In a case study from Belgium consumers, the mean and P95 intake estimated in the 2008–2013 period respectively corresponded to MOE between 515 and 236 and between 155 and 71 based on the endpoint for neoplastic effects ($BMDL_{10}$ = 0.17 mg/kg bw per day) (Claeys et al., 2016). Based on the urine samples of lactating mothers from Spain (n = 114), the exposure to acrylamide was analyzed, showing an average MOE of 349, and the exposure risk was mainly contributed by consumption of coffee, bread and precooked food products (Pardo et al., 2022). In application to diet study, an apparent downtrend occurred in the past decade with MOE values 1653 and 960 from the 3rd Chinese Total Diet Study (TDS), 1069 and 621 from the 4th Chinese TDS, and 973 and 565 from the 5th Chinese TDS, indicating an increased risk on human health (Gao et al., 2016). Acrylamide exposure were mainly contributed by vegetables (35.2%), cereals (34.3%) and potatoes (15.7%). Koszucka summarized average human intake of acrylamide in Korea (1.04 μg/kg bw/day), Mexico (0.68 μg/kg bw/day), Sweden (0.50 μg/kg bw/day), Estonia (0.48 μg/kg bw/day), Italy (0.45 μg/kg bw/day), Netherlands (0.32 μg/kg bw/day), Germany (0.32 μg/kg bw/day), Canada (0.29 μg/kg bw/day), China (0.19 μg/kg bw/day), and Japan (0.10–0.15 μg/kg bw/day), which all led to the MOE far less

Table 1
Acrylamide content in plant based food and herbal medicines after thermal processing.

Category	Concentration (μg/kg)	Reference
Herbal medicines		
Torrefied *Astragali Radi*	3570.9	(Zhao, 2008a)
Stir-fried *Hordei Fructus Germinatus*	43.7	(Zhou et al., 2007a).
Stir-fried *Hordei Fructus Germinatus*	21.46	(Zhou et al., 2007a).
Torrefied *Atractylodis Macrocephalae* Rhizoma	9826	(Zhu et al., 2021).
Stir-fried *Hordei Fructus Germinatus*	3131–5932	(Yang et al., 2016).
Stir-fried *Setariae Fructus Germinatus*	959	(Zhao, 2008b)
Stir-fried *Crataegi Fructus*	1530	(Li, 2010)
Stir-fried *Semen Arecae Praepareta*	2060	
Stir-fried *Massa Medicata Termentata*	1130	
Stir-fried *Massa Medicata Termentata*	420	
Stir-fried *Li Semen Lablab Album*	2200	
Stir-fried *Semen Coicis*	450	
Stir-fried *Semen Ziziphi Spinosae*	1030	
Stir-fried *Fructus Gardeniae*	760	
Stir-fried *Semen Vaccariae*	320	
Stir-fried *Semen Raphani*	710	
Coffee		
Roasted coffee	249	(CONTAM), EFSA ((Contam) E, 2015)
Roasted Coffee	245–251	(CONTAM), EFSA ((Contam) E, 2011)
Roasted Coffee	288	Besaratinia and Pfeifer (Besaratinia and Pfeifer, 2007)
Potato products		
French fries	308	(CONTAM), EFSA ((Contam) E, 2015)
French fries	354–357	(CONTAM), EFSA ((Contam) E, 2011)
French fries	334	Besaratinia and Pfeifer (Besaratinia and Pfeifer, 2007)
Potato crisps	389	(CONTAM), EFSA ((Contam) E, 2015)
Potato crisps	574–576	(CONTAM), EFSA ((Contam) E, 2011)
Potato chips	752	Besaratinia and Pfeifer (Besaratinia and Pfeifer, 2007)
Home cooked potato	344–354	(CONTAM), EFSA ((Contam) E, 2011)
Home cooked potato	380–385	(CONTAM), EFSA ((Contam) E, 2011)
Baked potato	169	Besaratinia and Pfeifer (Besaratinia and Pfeifer, 2007)
Cereals, biscuits, bread and similar		
Breakfast cereals	161	(CONTAM), EFSA ((Contam) E, 2015)
Breakfast cereals	96	Besaratinia and Pfeifer (Besaratinia and Pfeifer, 2007)
Breakfast cereals	130–150	(CONTAM), EFSA ((Contam) E, 2011)
crackers	231	(CONTAM), EFSA ((Contam) E, 2015)
Crackers	291–292	(CONTAM), EFSA ((Contam) E, 2011)
Biscuits and wafers	201	(CONTAM), EFSA ((Contam) E, 2015)
Wafers	206–210	(CONTAM), EFSA ((Contam) E, 2011)
Crisp bread	171	(CONTAM), EFSA ((Contam) E, 2015)
Bread crisp	221–226	(CONTAM), EFSA ((Contam) E, 2011)
Corn snack	226–447	(CONTAM), EFSA ((Contam) E, 2015)
Tortilla chips	164–240	(CONTAM), EFSA ((Contam) E, 2015)
Gingerbread	423–425	(CONTAM), EFSA ((Contam) E, 2011)
Gingerbread	407	(CONTAM), EFSA ((Contam) E, 2015)
Porridge	29	(CONTAM), EFSA ((Contam) E, 2015)
Bread and rolls	446	Besaratinia and Pfeifer (Besaratinia and Pfeifer, 2007)
Pastry and biscuits	350	Besaratinia and Pfeifer (Besaratinia and Pfeifer, 2007)
Others		
Roasted nuts and seeds	93	(CONTAM), EFSA ((Contam) E, 2015)
Vegetables crisps	1846	(CONTAM), EFSA ((Contam) E, 2015)
Roasted Green tea	306	Besaratinia and Pfeifer (Besaratinia and Pfeifer, 2007)
Dried fruits	131	Besaratinia and Pfeifer (Besaratinia and Pfeifer, 2007)
Processed vegetables	59	Besaratinia and Pfeifer (Besaratinia and Pfeifer, 2007)

Mean values were provided unless specified.

than the recommend value of 10000, indicating a high exposure and high health risk (Koszucka et al., 2020). Some researchers have carried out the determination and risk assessment of acrylamide in herbal medicines, which require long term administration and brings risks of durative high exposure. For instance, in a study by Zhu et al., a risk assessment was revealed that the MOEs of thermally processed AMR was calculated to be 90.83–181.7 based on the $BMDL_{10}$ value of carcinogenicity at 0.17 mg/kg/day and 229.7–459.5 based on the $BMDL_{10}$ value of neurotoxicity at 0.43 mg/kg/day (Zhu et al., 2021). Zhao reported the average concentration of 959 μg/kg in taking stir-fried *Setariae Fructus Germinatus*, leading the MOE of 375 (Zhao, 2008b), and the low MOE values were also applicable to the administration of other processed herbal medicines since high concentrations of acrylamide were generated (Zhao, 2008a; Yang et al., 2016; Li, 2010).

Despite the differences of the countries and dietary habits, the MOE values obtained from above studies were all significantly lower than 10000, indicating that high health risk is worthy of attention during the consumption of food and herbal products. Particularly, concerns should be given to the acrylamide exposure by taking thermally processed herbal medicines, which received scant attention. Nevertheless, uncertainties remain by using BMDL data derived from animal studies and population intake assessments in assessing the risk of acrylamide, since differences exist in metabolic performances between humans and animals and solid evidence was unavailable in human clinical studies. Further comprehensive study is needed, and developing reliable analytical methods is also critical in risk monitoring and control.

5. Sample preparation

5.1. Solvent extraction

Extraction appears to be the most critical step in sample preparation due to the complexity and diversity of the thermally processed food and herbal medicines samples as well as food contact materials (Elbashir et al., 2014). Acrylamide can be extracted with water or polar organic solvents such as methanol, ethanol, propanol, ethyl acetate. Hitherto, water is the most commonly used extractant due to the hydrophilia property of acrylamide and the high solubility of acrylamide (215.5 g/100 mL) in water (Mojska et al., 2012). Since most of the food and herbs are rich in proteins, carbohydrate, glycosides and other organic matters, emulsification frequently occurs with co-extraction of unwanted compounds in the matrix, which can be alleviated by using salt solution at a relative high level (Zhang et al., 2005). However, high amount of co-extraction compounds or salts produce interference to the mass detector and column separation. Organic solvents turn out to be a better option since they yield a much clearer extract than water for their low solubility to polysaccharides or proteins, and concentration of the analytes can be easily conducted by evaporation of the solvent (Eslamizad et al., 2020). While acetone, methanol, and ethyl acetate have been investigated in the method development of extracting acrylamide, the acetonitrile has been more extensively used due the adoption of the QuEChERS method and its compatibility to the liquid chromatography (Zhu et al., 2021; Huang et al., 2019; De Paola et al., 2017). A statical interaction between solvent and sample may have limited extraction rate. Pedersen and Olsson applied Soxhlet extraction technique to extract acrylamide from defatted potato chips using methanol for 10 days and a maximum constant level was achieved around 7 days (Pedersen and Olsson, 2003). Therefore, sufficient maceration of sample with appropriate time and temperature are critical factors in sample extraction and grinding sample to fine powder before extraction, vigorous shaking and using homogenizer in the extraction may be beneficial to the extraction efficiency when time is limited (Petersson et al., 2006). Additionally, to facilitate the extraction of the analytes, ultrasonic extraction enables the dissolution of the analytes into the extractant rapidly with simple operation. In the study of determining the content of acrylamide in incense burning, Li et al. used the positive samples to compare ultrasonic extraction and water-bath oscillating extraction, and the results showed that the ultrasonic extraction had a higher extraction rate and was easier to extract the acrylamide in incense burning samples (Li et al., 2018). Another approach in enhancing sample extraction is adding digestive enzymes such as diastase and pepsin to hydrolyze the macromolecules, which also can overcomes the clogging of filters (Jung et al., 2021).

5.2. Sample cleanup

Solid phase extraction (SPE) is a separation technique that analytes or interfering substances can be differently distributed or adsorbed between the liquid and solid adsorbent. Since the introduction in 1970 s, SPE has shown its great potential in the field of environment management, pharmaceutical development, chemical industry and many other fields for its effectiveness and reliability. It has been extensively used in treating different kinds of samples to achieve the goal of sample cleanup by using cartridge containing various materials such as C18, ion exchanger and graphitized carbons (Elbashir et al., 2014; Roszko et al., 2020). In the determination of acrylamide, Zeng and his colleagues found that the average recovery rate was 91.1% after treating by activated carbon solid phase extraction column, which proved the advantage of high recovery rate to some extent (Zeng et al., 2018). Because of the strong polarity of acrylamide, HLB SPE column turns out to be a good option. HLB is a hydrophilic-lipophilic balance and water-wettable reversed-phase sorbent which can meet the general need of the SPE separation and its combination with other types of cartridges can optimized the cleanup performance. Wang et al. combined Oasis HLB and Bond Elut-Accucat cartridges in the determination of acrylamide (Wang et al., 2008). Li achieved a good clean up performance by combining the Oasis HLB and Bond Elut PRS in the determination of Stir-fried *Crataegi Fructus* (Li, 2010).

In order to meet the demands of the rapid analysis, dispersive solid phase extraction (DSPE) have been developed and extensively used in recent years (Huang et al., 2019). In the rapid determination of acrylamide and its metabolites in *Asparagus officinalis* L., DSPE was used as a substitute for the traditional SPE to simplify the extraction process and improve the recovery rate (Ferrer-Aguirre et al., 2016). In the simultaneous determination of acrylamide and 4-hydroxy-2,5-dimethyl-3 (2 H)-furanone (HDMF) caused by the Maillard reaction in baby food, Petrarca et al. took full advantage of the DSPE and SPE in the sample preparation and achieved efficient removal of matrix interferences, without affecting the accuracy and sensitivity of the analytical method (Petrarca et al., 2017). When dealing with sample containing a high amount of fat, hexane and petroleum ether were frequently used to treat the sample prior extraction to reduce the interference of the fat (Elbashir et al., 2014).

DSPE has been gradually optimized to be a relatively fixed and general method in practical application, and the most typical application is QuEChERS (Quick, Easy, Cheap, Effective, Rugged and Safe), which was originated developed for the pesticides analysis in vegetables and fruits (Lehotay et al., 2005). Although the drawbacks of the worse cleanup performance exist comparing with SPE, the assistance of tandem mass spectrometry covers the shortage and enables a good separation and detection (Nachi et al., 2018). Due to its efficiency and conveniency, its application has been extended to various types of samples after modification. De Paola et al. determined the acrylamide in dried fruits and edible seeds using QuEChERS extraction and LC-MS/MS, and contamination was found in dried prunes and peanuts, which required drying or thermally processing (De Paola et al., 2017). Magdalena optimized QuEChERS sample preparation method and determined acrylamide level in coffee and coffee substitutes (Surma et al., 2017). Further studies utilized magnetic material technology and the application scope can be expanded at this stage and the commonly used magnetic materials are mainly iron oxide nanoparticles and graphene oxide (Arabi et al., 2016; Ning et al., 2017; Zhang et al., 2020b). Xian et al. modified QuEChERS method by using Fe_3O_4 nanoparticle as the sorbent and obtained good accuracy of 81.0%− 101.0% with precision less than 9.0% (Xian et al., 2019). In intricate food and herb samples, it might be difficult to achieve ideal separation on account of the non-specificity between traditional adsorbents and acrylamide. Molecular imprinted polymer (MIP), a technique for preparing polymers with specific spatial structure and function toward template molecules and with specific recognition and selection ability for the materials to be measured, aimed to solve the problem. Zhang et al. prepared a novel dummy magnetic molecularly imprinted polymers (dex-MMIPs) using the Fe_3O_4 nanoparticles modified with carboxymethyl dextran as the carrier and propanamide as the dummy template molecule for the selective separation and enrichment of acrylamide, where the satisfactory recoveries of 83.9%− 96.8% were achieved by dex-MMIPs (Zhang et al., 2020b).

Other than SPE and DSPE method, dispersive liquid-liquid microextraction (DLLME), solid phase microextraction (SPME) and many other techniques have been developed in the determination of acrylamide. DLLME requires only a small amount of sample and solvent which is not only efficient but also environmentally friendly. Bellanda Galuch et al. developed a DLLME method and achieved a good recovery of 97%− 106% by employing 300 μL of brewed coffee, 100 μL of dichloromethane, 400 μL of acetonitrile without sodium chloride addition (Galuch et al., 2019). Due to the volatile of the acrylamide, SPME has been another popular method in determination of acrylamide. Wawrzyniak and Jasiewicz developed a fast extraction procedure for the acrylamide from coffee beans by using commercially available SPME

fiber coated with polydimethylsiloxane (PDMS) and followed by silylation reaction before GC-MS analysis (Wawrzyniak and Jasiewicz, 2019). Ghiasvand and Hajipour optimized extraction parameters using a fiber material of carboxen/divinylbenzene/polydimethylsiloxane (CAR/DVB/PDMS) and achieved good validation results (Ghiasvand and Hajipour, 2016). The successful development of the above techniques provided reliable approaches for scientist in understanding the concentration of acrylamide in samples, however, drawbacks remained. The operation of SPE cartridge has been considered laboursome and solvent consuming especially in bulk sample determination. SPME usually required a specific fiber, which may have problems of inconvenient preparation and high cost, and its application frequently limited to GC. DLLME frequently use extraction solvent such as chloroform, which is not environmentally friendly. QuEChERS technique may encounter problem when treating sample with complex matrix due to its limited cleanup performance. Therefore, it is critical to consider the feasibility of the technique and select a validated method according to the property of the sample before analysis. (Fig. 2).

6. Instrumental determination

6.1. Gas chromatography

Gas chromatography (GC) is one of the approaches to determine acrylamide. When GC was coupled with mass spectrometry (GC-MS), stable isotope dilution technique is usually used with the deuterium labelled d_3-acrylamide as an internal standard. Additionally, in order to meet the requirements of thermal stability, volatility and polarity in GC-MS analysis, samples usually need to be derivatized properly before loading into instrument. The common derivatization consists of silylation derivatization (Wawrzyniak and Jasiewicz, 2019), xanthydrol derivatization (Zokaei et al., 2017), and 2-naphthalenethiol derivatization (Faraji et al., 2018). In a study by Wawrzyniak and Jasiewicz, the quantitative detection of acrylamide in coffee beans using GC-MS was realized by means of silylation of acrylamide and the method of internal standards using d_3-acrylamide, which demonstrated the satisfactory repeatability (RSD = 2.6%) with an acceptable precision (RSD = 9.4%) and recovery rate (99%–105%) (Wawrzyniak and Jasiewicz, 2019).

Compared to other detectors, the outstanding feature of MS is its high sensitivity in coupling with GC during the analysis. However, it is notable that MS detector requires high cost, which impeded its popularization. Therefore, other detectors such as nitrogen phosphorus detector (NPD) (Djordjevic, 2015; Kim et al., 2011), electron capture detector (ECD) (Saraji and Javadian, 2019; Zhang et al., 2017; Nasiri Esfahani et al., 2017), flame ionization detector (FID) (Ghiasvand and Hajipour, 2016), are also favored in the determination of acrylamide. NPD is a promising GC detector currently for the determination of nitrogen compounds, and the presence of nitrogen atoms enable acrylamide to be measured by NPD sensitively. Kim et al. developed an analytical method for the detection of acrylamide in fried potato chips using GC-NPD, which showed that the linear response of acrylamide concentrations ranged between 0.5 and 100 μg/mL with a correlation coefficient of 0.999, and the limit of quantification was 0.5 ppm, and the recovery rate was 92–114% (Kim et al., 2011). In addition, changes in the detector are often compatible with respective derivatization method. ECD, for instance, is more often used in conjunction with halogenation derivation such as bromination derivation. In bromination derivation, hydrobromic acid or potassium bromide/potassium bromate is used as a derivative agent to convert acrylamide into 2,3-dibromopropylamide or 2-bromine acrylamide under acidic conditions as to improve sensitivity of the detection and ameliorate chromatographic behavior (Saraji and Javadian, 2019; Zhang et al., 2006a). In the extraction and quantification of acrylamide in water samples, a modified hollow-fiber liquid--phase microextraction and GC-ECD analysis were used after the 2, 3-dibromopropionamide derivatization of acrylamide, which lowered the cost of instrument and was proved to be of satisfactory RSD (2.2%–5.8%) and accuracy with the relative recovery rate (93%–108%) under examined optimal extraction conditions (Sobhi et al., 2017). Zhou et al. achieved the optimum condition in the determination of Stir-fried *Hordei Fructus Germinatus* by using bromination derivation, FFAP GC columns separation and ECD detection (Zhou et al., 2007a).

6.2. Liquid chromatography

The main difference between liquid chromatography (LC) and GC is that LC does not require the derivatization in the sample preparation in

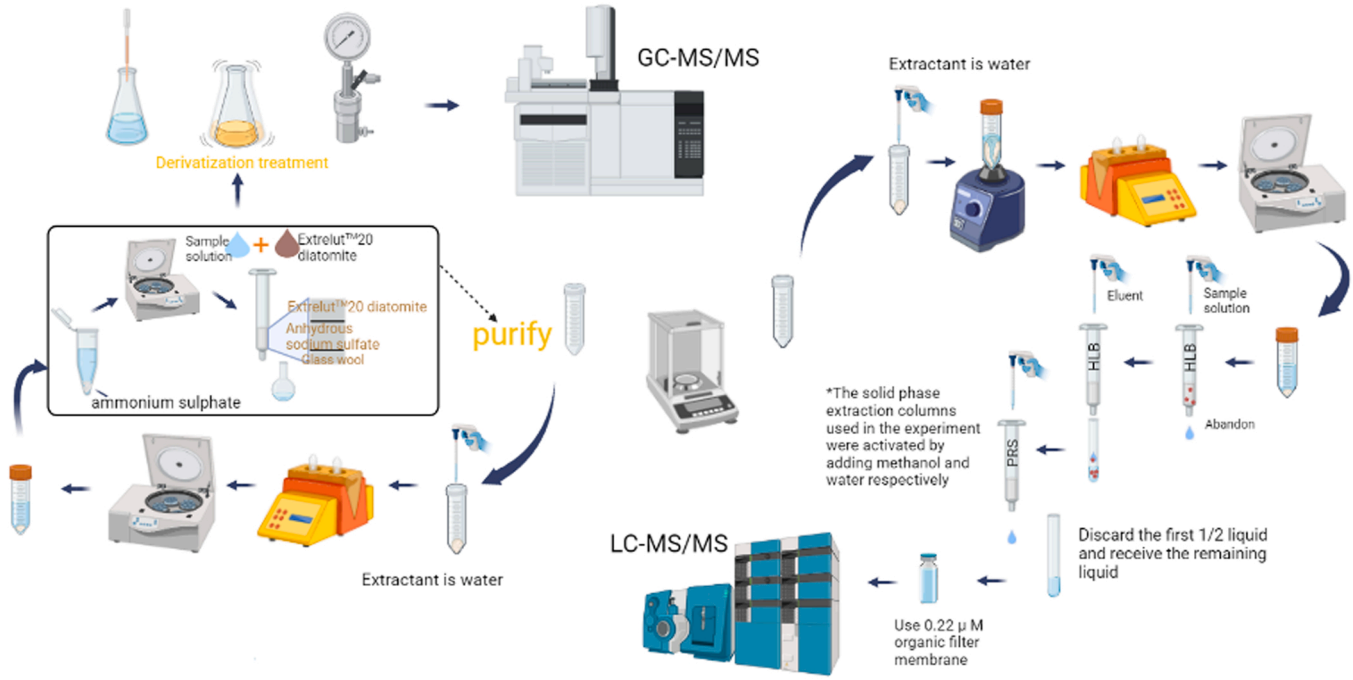

Fig. 2. Pretreatment method for the determination of acrylamide by LC-MS/MS and GC-MS/MS.

general, which avoids the main drawbacks of reducing the accuracy and reproducibility caused by derivatization and improves the experimental efficiency by simplification the experimental operation (Crawford and Wang, 2019). Therefore, LC has advantages in daily practical detection.

Liquid chromatography tandem mass spectrometry (LC–MS/MS) appeared to be acknowledged as useful and authoritative method for acrylamide determination (Zhang et al., 2006b; Eslamizad et al., 2019), in which the sample is usually extracted with water, cleaned up with SPE or DSPE, then detected by LC-MS/MS and quantified by internal standard method. This method is simple, time-saving and can realize the qualitative and quantitative determination in different samples (Yoshioka et al., 2019). However, one of the challenges encountered in the detection of acrylamide by LC-MS/MS is the low molecular weight of acrylamide, which may be interfered by many other compounds with low molar masses. In the determination of acrylamide formed in the heating process of *Asparagi Radix* by Shi et al., it was first found that HPLC with precolumn derivatization, as an alternative to LC-MS/MS, can avoid the interference of the co-extract caused by low-molar mass weight of the acrylamide, and guarantee the precision and accuracy of experimental determination (Shi et al., 2009). Also, Fernandes and others chose Orbitrap LC-MS to improve the selectivity in analysis by virtue of the high resolution, high sensitivity and high precision provided of Orbitrap mass spectrometer (Fernandes et al., 2019). Another great challenge in the detection of acrylamide by LC-MS/MS is its poor retention in reversed phased column due to the high polarity or hydrophilicity nature of the compound. Aiming at the problems caused by the nature of acrylamide, scientists have been studying and seeking for solutions creatively as well as intensively from different perspectives. Ono et al. used Atlantis C_{18} column, a difunctionally bonded, silica-based, reversed-phase column that is designed intelligently to provide complete LC-MS/MS compatibility, and exhibited superior retention and superior peak shapes of acrylamide (Ono et al., 2003). Whereas, Tölgyesiestablished a hydrophilic interaction liquid chromatography tandem mass spectrometry (HILC-MS/MS) on the basis of LC-MS/MS for the determination of acrylamide, in which hydrophilic modified RP (i.e. Luna C-18) or PGC (Hypercarb) HPLC columns were devoted to improve poor retention of acrylamide in conventional reverse column. Acetonitrile-water-formic acid mixture (69/30/1, V/V/V) was chosen as extraction solvent on account of the acrylamide's relatively high solubility in all of three individuals from which acetonitrile was appropriate as HILIC mobile phase organic modifier. The HILIC column retained acrylamide by the use of mobile phase, while mobile phase enhanced the sensitivity of MS detector (Tölgyesi and Sharma, 2020). In the determination of Stir-fried *Setariae Fructus Germinatus*, Zhao optimized the retention time by using C8 column with a low percent of acetonitrile phase at 2% (Zhao, 2008b).

In recent years, a number of optimization and innovation for the chromatographic analysis of acrylamide have been made with continuous development of new techniques. The ultra performance liquid chromatography (UPLC) is usually regarded as an alternative to conventional HPLC. UPLC and HPLC operate in an identical separation principle, but UPLC provides better separation with higher resolution, higher speed and less solvent consumption owing to the presence of small particles and high pressure in the column (Chen and Kord, 2009). In the determination of acrylamide in brewed coffee by Galuch et al., UPLC was arranged in tandem with MS as a detector. And this work proved that ultra performance liquid chromatography tandem mass spectrometry (UPLC-MS/MS) was fast (60 s of each chromatography run) and demanded small solvent consumption with sample solution (300 μL), dispersant (400 μL) and extractant (100 μL) of each extraction (Galuch et al., 2019).

Application of modern methods like supercritical fluid chromatography (SFC) can achieve the determination of sample with trace amount of acrylamide rapidly and accurately. Yoshioka et al. introduced a high-sensitivity and high-throughput method using SFC-MS/MS (Yoshioka et al., 2019). They used supercritical fluid of carbon dioxide as the mobile phase with the advantage of high diffusion coefficient of gas and strong solubility of liquid and the density of carbon dioxide was changed by the adjustment of pressure and temperature to maximize the solubility and achieve high-efficiency separation and detection of the acrylamide. Ion-exclusion liquid chromatography provided another option in the determination. Li established a simple and rapid method using ion-exclusion liquid chromatography to determination the acrylamide in concoction of Chinese herbal medicines, and the method was validated with good recoveries of 95%– 101% and relative standard deviation less than 1.64% (Li, 2010).

6.3. Capillary electrophoresis

The capillary electrophoresis (CE), which uses capillary as the separation channel and high voltage direct current electric field as the driving force to carry out the separation analysis, is another traditional method for the quantitative determination of acrylamide in addition to the above-mentioned GC and LC methods. The CE separation relies on the difference in distribution coefficient and mobility of each component, and this method as the advantage of low sample consumption and rapid and economic detection. According to the way in which the charge is obtained from the acrylamide, CE can be divided into micellar electrokinetic capillary chromatography (MEKC) (Zhou et al., 2007b), non-aqueous capillary electrophoresis (NACE) (Tezcan and Erim, 2008), capillary zone electrophoresis (CZE) (Bermudo et al., 2006) and so on. In practice, the smaller inner diameter of capillary column leads to poor separation effect and low detection sensitivity, and consequently the selection of detector directly determines the sensitivity of CE. The commonly used high-efficiency CE detectors include diode array detector (Yin et al., 2017), capacitively coupled contactless conductivity detector (Yang et al., 2019) and fluorescence detector (Chen et al., 2011).

In trace analysis of acrylamide in the charred *Crataegi Fructus* (CF) by Han et al., the CE method was conducted by combining with diode array detector, and the acrylamide was extracted by water, purified and concentrated with SPE, and then detected by diode array detector (Han et al., 2013). The electrophoresis buffer consisted of potassium dihydrogen phosphate (33 mmol/L)-disodium hydrogen phosphate (33 mmol/L)-SDS (50 mmol/L, pH=6.7). Simultaneously, the separation was carried out at a constant potential of 10 kV and detected at wavelength of 198 nm. Appropriate recovery (93.3%∼98.9%) and precision (RSD<2.57%) were achieved for the quantification of acrylamide in the charred CF, furthermore, adequate linearity (0.50–50.00 mg/L) and correlation coefficient (0.9995) in this method.

6.4. Spectroscopy

For the detection of acrylamide, the commonly used spectroscopic methods include colorimetry (Yang et al., 2015), surface enhanced Raman spectroscopy (SERS) (Cheng et al., 2019), fluorescence spectroscopy (FS) (Liu et al., 2014; Baharinikoo et al., 2020), infrared spectroscopy (IR) (Zhu et al., 2013), ultraviolet-visible spectroscopy (UV–VIS) (Ioannou et al., 2017).

Colorimetry is a method for qualitative and quantitative determination of the analytes by comparing or measuring the color depth of the solution. Although it has the drawbacks of low sensitivity, serious interference and large error, colorimetry has a good prospect of application in analytical chemistry especially in the field of rapid analysis based on simple operation, low cost, and visual results. Yang et al. developed a new method for the visible detection of acrylamide based on PEO-AuNPs, a polymer composite material composed of methoxypoly and AuNPs (Yang et al., 2015). Acrylamide at the concentration of 0.004–0.032 mg/mL can make PEO-AuNPs agglomerate while a higher concentration of acrylamide caused more agglomeration, which led to the color change of AuNPs, and the rapid detection of acrylamide can be achieved with naked eye and UV-ViS spectrophotometer.

SERS uses high-performance SERS substrates such as nanoparticle substrates, metal electrode active substrates and noble metal nanoparticle colloid substrates to enhance Raman scattering signals and realize the analysis based the enhanced and amplified Raman scattering signals, which has advantages of strong fingerprint characteristic, high sensitivity and high speed. Cheng et al. proposed a new kind of SERS by re-oxidized graphene oxide/Au nanoparticle composites for rapid, reliable and quantitative determination of acrylamide. The samples were extracted by a mixture of water and acetonitrile (1/1, V/V) and salted out by sodium chloride and anhydrous magnesium sulfate. Then Au nanoparticle coated with diluted nitric acid was used as SERS substrate for analysis by Raman spectrometer. The result of detection method was always consistent with those obtained by LC-MS/MS, while the measurement time was reduced to 9.5 min per sample, suggesting that this method has great potential for rapid and sensitive detection in the field (Cheng et al., 2019).

FS is known as fluorescence sensing and after the absorption of energy the material molecules can give off the fluorescence in the form of light radiation that reflects the characteristics of the compound. The detection of acrylamide was realized based on the fluorescence determination in a study conducted by Liu et al. (2014). In the fluorescence determination, acrylamide was degraded through Hofmann reaction to generate vinyl amine, and pyrrolidone was produced when the vinyl amine reacted with fluorescamine, which is a fluorescent material, resulting in a strong fluorescence emission at 480 nm. The fluorescence intensity was positively correlated with the acrylamide concentration, by which the acrylamide concentration in the sample was quantified. The fluorescence intensity was linearly proportional (0.05 μg/mL-20 μg/mL) to the square-root of acrylamide concentration with good correlation coefficient (0.9935) and detection limit (0.015 μg/mL). In the quantity detection of the acrylamide in potato chips, Leila used a novel fluorescent reagent called CdTe quantum dot and established a new kind of fluorescence spectroscopy method utilizing CdTe surface functionalized quantum dots (Baharinikoo et al., 2020). CdTe surface functionalized quantum dots can bond with electronegative atoms, such as oxygen and nitrogen, to form hydrogen with acrylamide, causing the change of spacing of CdTe surface functionalized quantum dots and then the change of fluorescence intensity. According to the relationship between the fluorescence intensity and the spacing of quantum dots, the concentration of acrylamide was determined.

6.5. Bioanalytical technique

6.5.1. Enzyme-linked immunosorbent assay

Enzyme-linked immunosorbent assay (ELISA), which analyzed the color reaction of enzyme-catalyzed substrate by the specific binding of antigen and antibody, has been widely used in the field of food hygiene. Because of its low molar mass weight and the lack of immunogenicity, acrylamide need to be linked with high molar mass immune carrier protein to form a complete antigen that stimulates the body to produce the corresponding antibody.

Fu et al. used glutaraldehyde as crosslinker to synthesize complete antigen by forming Schiff alkali covalent bond between bovine serum albumin carrier and acrylamide (Fu et al., 2011). Preston et al. derived acrylamide with 3-Sulfanylbenzoic acid and combined with bovine thyroglobulin to produce complete antigen, which had higher affinity compared with direct glutaraldehyde method (Preston et al., 2008). Quan et al. used N-acryloxysuccinimide (NAS) as incomplete antigen and keyhole limpet hemocyanin (KLH) as carrier protein, and then conjugated them as a complete antigen to obtain a polyclonal antibody for acrylamide by immunization of rabbits (Quan et al., 2011). At the same time, the researchers combined enhanced chemiluminescence detection and the direct ELISA to determine acrylamide, and the results correlated well with those obtained using an HPLC method. Furthermore, Sun et al. formulated biomimetic enzyme-linked immunosorbent assay (BELISA) based on ELISA, a method using a hydrophilic imprinted membrane as biomimetic antibody which exhibits high binding specificity and capacity toward acrylamide (Sun et al., 2014). Under optimal conditions, the method had a high sensitivity (IC50, 8.0 ± 0.4 mg/L) and low limit of detection (IC15, 85.0 ± 4.2 g/L).

6.5.2. Electrochemical biosensor

Electrochemical biosensor (EB) is a qualitative or quantitative method realized by using enzyme, antigen, antibody, cell, tissue and others as a sensitive element, the electrode as the converter and the characteristic signals of capacitance, potential, current, conductivity, potential and other parameters. In recent years, detection based on EB has become a new idea for rapid detection in the field of food hygiene.

Varmira et al. developed an EB to detect acrylamide in samples based on the reaction of acrylamide with α-NH_2 group of N-terminal valine of HG to form admixture, which reduced the peak current of HG-Fe^{+3} reduction (Varmira et al., 2018). The modified acrylamide was characterized by energy dispersive X-ray spectroscopic (EDS), electrochemical impedance spectroscopy (EIS), scanning electron microscopy (SEM) and cyclic voltammetry (CV). The biosensor can selectively determine acrylamide even in the presence of high concentrations of interferers, which confirms the high selectivity of the biosensor. The method has a good prospect in the determination of acrylamide with the characteristics of short response time (less than 8 s), long-term stability, high sensitivity, and high repeatability and even its results were the equal of those obtained by GC-MS as the reference method.

6.6. Computer vision

Computer vision (CV) is a real-time and on-line detection technique based on automatic image processing by computer algorithm, which has been widely used in quality monitoring in the food and drug industry (Hu et al., 2015; Maurya et al., 2021). Dutta et al. proposed a nondestructive CV to identify the presence of acrylamide (Dutta et al., 2015). In order to improve the accuracy and efficiency of recognition for acrylamide, the researchers extracted statistical features and texture features from the segmented sample images and compressed them strategically by means of principal component analysis (PCA). These features are then analyzed using support vector machine (SVM) classifier for identification of acrylamide content. Experimental result indicated that the method provided 94% accuracy and the sensitivity reached more than 96%, which can be considered as an important contribution in image processing for acrylamide identification. Compared with the traditional methods, the greatest advantage of CV is that it does not damage sample in the analysis. However, when the sample matrix is too complex, the accuracy of detection may not be satisfied, which requires further investigation. (Table 2).

7. Mitigation

Since the time that the toxicity of the acrylamide and its health risk were recognized, extensive research has been conducted to mitigate the acrylamide during food processing. Mitigation of the acrylamide formation mostly relies on the critical factors including the precursors reduction, processing parameter control, and acrylamide removal.

Before the formation reaction, reducing the concentration of reactants is one of the approaches such as reducing sugar and asparagine. The commonly used methods include selecting raw materials with low-content of reducing sugar and asparagine (Wang et al., 2017; Muttucumaru et al., 2017b), using biological methods to reduce precursors (Cachumba et al., 2016; Xu et al., 2016; Zhu et al., 2016), and optimizing storage methods (Rosen et al., 2018). Muttucumaru et al. studied the effect of the concentration of reducing sugar and asparagine on acrylamide in thermally processed twenty varieties of potatoes grown near Doncaster in the North of England, UK (Muttucumaru et al., 2017b). A series of data revealed a notably positive correlation ($r = 0.0516$, $p < 0.001$, $n = 240$, F-test) between total reducing sugar

Table 2
Determination methods of acrylamide.

Method	Solvent extraction	Sample cleanup	Instrumental parameters	Reference
HPLC-DAD	Extracted by water	Derivation by thiosalicylic acid. Extraction by ethyl acetate. Redissolved by methanol	Column: Hypersil GOLD column (150 × 4.6 mm, 5 μm). Mobile phase: acetonitrile + 1 g/L acetate solution (20:80, v/v) at 0.7 mL/min. Detector: UV detection 238 nm	(Zhao, 2008a)
GC-ECD	Extracted by water	Derivation by KBr and $KBrO_3$. Extraction by ethyl acetate	Column: HP FFAP (50 m × 0.22 mm × 0.2 μm) Detector: ECD Programmed-temperature: initial 120 °C for 0.5 min, 10 °C/min ramp to 180 °C	(Zhou et al., 2007a)
HPLC-UV	Extracted by water	Clean up using active carbon SPE	Column: Shimadzu SCR-102 H column (300 × 7.8 mm, 7 μm). Mobile phase: acetonitrile + 0.01 mol/L H_2SO_4 solution (30:70, v/v) at 0.6 mL/min. Detector: UV detection 195 nm	(Zhou et al., 2007a)
LC-MS/MS	Extracted by acetonitrile	Clean up using GMWCNTs DSPE method	Column: Cortecs C18 column (100 ×2.1 mm, 2.7 μm) Mobile phase: 0.1% formic acid water solution + methanol (9:1, v/v) at 0.3 mL/min. Detector: ESI MRM. Quantification by isotope internal standard	(Zhu et al., 2021)
LC-MS/MS	Extracted by water	Clean up using Oasis HLB cartridge (500 mg) and Bond Elut LRC-PRS cartridge (500 mg)	Column: Inertsil C8 column (150 ×2.1 mm, 5 μm) Mobile phase: 0.05% formic acid water solution + 0.1 formic acid acetonitrile (98:2, v/v) at 0.2 mL/min. Detector: ESI-MRM. Quantification by isotope internal standard	(Zhao, 2008b)
Ion-exclusion LC	Extracted by water	Clean up using Oasis HLB SPE catridge and Bond Elut PRS SPE catridge	Column: Hamilton HC-75 H^+ column (305 ×7.8 mm, 9 μm) Mobile phase: 0.01 mol/L H_2SO_4 solution +methanol (70:30, v/v) at 0.6 mL/min. Detector: UV at 210 nm.	(Li, 2010)
HPLC-UV	Extracted by water	Pre column derivation by phenyl isocyanate	Column: C18 column (250 ×4.6 mm, 5 μm) Mobile phase: ethyl acetate solution + acetonitrile at 0.9 mL/min. Detector: UV at 254 nm.	(Li, 2010)
GC-MS	Extracted by water	Clean up by adding Carrez I and II solution and using C18 SPE cartridge (500 mg, 6 mL). Derivatization by potassium bromide, concentrated HBr, and bromine water.	Column: HP Innowax (30 m × 0.25 mm × 0.25 μm) Detector: SRM Programmed-temperature: initial 40 °C (hold for 1 min), 15 °C/min ramp to 120 °C (hold for 2 min), 7 ℃/min ramp to 160 ℃, 3 ℃/min ramp to 180 ℃, 20 ℃/min ramp to 230 °C (hold for 5 min). Quantification by isotope internal standard	(Roszko et al., 2020).
LC-MS/MS	Extracted by acetonitrile	Clean up using QuEChERS method (anhydrous $MgSO_4$ + NaCl + PSA)	Column: Luna 3 μm HILIC column (100 × 3.00 mm). Mobile phase: 0.1% formic acid aqueous solution + 0.1% formic acid at 0.3 mL/min. Detector: ESI^++MRM. Quantification by isotope internal standard acrylamide-d_3.	(Nachi et al., 2018).
SPME-GC-FID	Extracted by SPME fiber (CAR/DVB/PDMS)	/	Column: BP20 polar capillary column (polyethylene glycol, 30 m × 0.25 mm × 0.25 μm). Detector: FID Programmed-temperature: initial 45 °C (hold for 2 min), 10 °C/min ramp to 150 °C.	(Ghiasvand and Hajipour, 2016)
LC-MS/MS	sample extracted by methanol	Clean up by adding Carrez I and II solution, and using DSPE method with PSA	Column: ODS-H optimal-C18 column (150 mm × 4.6 mm, 3 μm) Mobile phase: 0.1% acetic acid / formic acid aqueous solution + 3% methanol (97:3, v/v) at 0.5 mL/min. Detector: ESI^+ + MRM. Quantification by isotope internal standard acrylamide-d_3.	(Eslamizad et al., 2019).
LC-MS/MS	Sample extracted by water	Clean-up by adding Carrez I and II, and using OASIS MCX SPE cartridge.	Column: Zorbax column C18 (50 mm × 4.6 mm, 1.8 μm). Mobile phase: 0.3% fomic acid aqueous solution + acetonitrile (90:10,v/v) at 0.8 mL/min. Detector: ESI+MRM Quantification by isotope internal standard acrylamide-d_3.	(Alpozen et al., 2015).
HPLC-UV	Sample extracted by methanol	Clean-up by adding Carrez I and II, and using carbon SPE catridge	Column: Hypersil ODS-C18 column (250 mm × 4.6 mm, 5 mm). Mobile phase: acetonitrile and water (5:95, v/v) at 0.6 mL/min. Detector: UV at 210 nm.	(Wang et al., 2017).
UPLC-MS/MS	sample extracted by 0.1% formic acid water	Clean-up using Oasis HLB SPE cartridge.	Column: UPLC BEH C18 column (2.1 × 50 mm) Mobile phase: water and acetonitrile (90:10, V/V) at 0.2 mL/min. Detector: ESI^++MRM.	(Jesus et al., 2018).
GC-MS	Sample extracted by water	Clean-up by adding Carrez I and II. Derivatization with KBr/HBr (pH 1–3)/ saturated bromine-water solution	Column: TraceGold TG-Wax (30 m × 0.25 mm, 0.25 μm, polyethylene-glycol) at 1.6 mL/min Detector: SRM	(Negoita and Culetu, 2016)

(*continued on next page*)

Table 2 (*continued*)

Method	Solvent extraction	Sample cleanup	Instrumental parameters	Reference
Surface-enhanced Raman spectroscopy	Sample extracted by QuEChERS method using water and acetonitrile (1:1, v/v) solution	Clean up by QuEChERS method (anhydrous MgSO4 + NaCl + PSA).	The supernatant was mixed with rGO/AuNPs. Detector: portable Raman spectrometer (NFQCC-2). Scan data in the range of 500–2500 cm^{-1} was collected. The Raman peak at Δv= 1478 cm^{-1} was used analysis.	(Cheng et al., 2019).
Fluorescence Spectroscopy	Sample extracted by 0.2 mM acetic acid	Clean up by adding Carrez I and II solution	RF-6000 Fluorescence Spectroscopy was used to collected emission spectra in the concentration range within 500–3000 ng/mL at optimal pH and temperature.	(Baharinikoo et al., 2020).
Electrochemical biosensor	Sample extracted by deionized water	Clean up by adding hexane, Carrez I and II, and filtration	Apparatus: Square wave voltammetry (SWV) and cylic voltammetry(CV) measurements used a μstat 400 portable Biopotentiostat/Galvanostat. Detection: SWV was collected using double stranded DNA /Hemoglobin-modified screen printed gold electrode with step potential of 2 mV, a square-wave frequency of 5 Hz, and amplitude of 2.5 mV.	(Asnaashari et al., 2019).

Abbreviations: PSA: primary secondary amine, ESI^+:Electrospray ionization in the positive-ion mode, MRM: Multiple reaction monitoring, SRM: selected reaction monitoring.

concentration and acrylamide formation. On the other hand, free asparagine concentration was significantly correlated with overall formation of acrylamide, albeit weakly, only after 6 months of storage ($r = 0.221$, $p = 0.016$, F-test). Bertuzzi et al. also found similar results that content of reducing sugar has a profound effect on acrylamide formation (Bertuzzi et al., 2018). An increase from 0.15% to 1.0% in content of reducing sugar contributed to a remarkable acryla mide-forming increase of five-to six-fold. Therefore, the selection of raw materials with a low content of acrylamide precursor is a quite effective and fundamental approach of mitigation.

Blanching is a method to leaching out the precursors (reducing sugar and asparagine) by placing the raw material in hot or warm water or steam for a short time before further treatment. Zhang (Zhang et al., 2018) et al. investigated blanching parameters and optimal maximum reductions of reducing sugar, asparagine, and acrylamide were obtained at 64.2%, 49.8%, and 61.3% after blanching 8.8–9.7 min at 68.7–75.0 °C. A significant reduction of acrylamide formation of 60%, 45%, and 23% were obtained in the study conducted by Bakhtiary et al. by blanching potato pieces in hot water at 90 °C, 70 °C, and 50 °C for 3 min before deep-fat fried at 180 °C for 5 min (Jiao et al., 2020). Enzymatic treatment by using L-asparaginase enzyme hydrolyzes L-asparagine into ammonia and aspartic acid, and is an efficient approach to reduce acrylamide formation without significantly changing the taste or bioactive compounds. After treated with 30.0 IU/mL of enzyme, Jiao et al. reported that L-asparagine and acrylamide contents of the potato chip sample reduced by 22.0% and approximately 55.9%, respectively, compared to the control (Jiao et al., 2020). In a research conducted by Meghavarnam and Janakiraman, 300 U/mL L-asparaginase from Fusarium culmorum was used during the fermentation before baking, and the L-asparagine and acrylamide contents in sweet bread samples were reduced to 78% and 86%, respectively, compared to the control (Meghavarnam and Janakiraman, 2018). Corrêa et al. treat coffee beans with L-asparaginase (Acrylaway®) under the conditions of 30% water content, 5000 ASNU/kg enzyme load, and 60 ℃ at 200 rpm for 2 h before roasting, and the acrylamide content was reduced to 59% compared with the control sample (Corrêa et al., 2021). In addition to the blanching and enzymatic treatment, microbial treatment is another effective way of acrylamide mitigation by decreasing the precursors. Various bacterial strains have been applied during the fermentation before thermal treatment, and significant decrement of acrylamide formation were observed (Peivasteh-Roudsari et al., 2022).

During the thermal process, the parameters such as time and temperature (Zhao, 2008b; Mestdagh et al., 2008), water activity (Gómez-Narváez et al., 2019; Miao et al., 2014), and air conditions (Akkurt et al., 2021) of heat processing should be strictly controlled. For instance, Zhao conducted a study about the effect of processing time of stir-frying on the acrylamide content in *Setariae Fructus Germinatus* (Zhao, 2008b). It was found that acrylamide increased most dramatically within 0–30 min in crude *Setariae Fructus Germinatus* at 170 ℃ and reached the maximum at 30 min. Subsequently, acrylamide decreased with the increase of processing time and remained constant in 50–100 min. Then, acrylamide decreased after 100 min of processing and tended to be stable after 130 min. After 100 min of processing, however, the surface of *Setariae Fructus Germinatus* had obvious ustulate. Therefore, in order to maintain the efficacy of herbal medicines and reduce the content of acrylamide, Zhao suggested thermally processing more than 30 min to become fried *Setariae Fructus Germinatus*, or processing more than 130 min to become charred *Setariae Fructus Germinatus*. Bertuzzi et al. found that acrylamide formation increased during the first few minutes and achieved the maximum after 10 min at 175–177 ℃ in the roasting of coffee beans. When the temperatures were above 210 ℃ and time extended, the acrylamide levels tend to decrease (Bertuzzi et al., 2020). Chan mitigated the formation of acrylamide in a potato strip by using a temperature step frying approach based on the heat and mass-transfer model coupled with reaction kinetics, and a 43% decrease of acrylamide content was obtained (Chan, 2020). Air frying is considered as a healthier alternative approach compared to deep oil frying, and Haddarah et al. observed lower level of acrylamide in air frying at 163.1 μg/kg comparing to deep frying at 1384.79 μg/kg in French fries treated with plant extracts of ginger, borage and fennel (Haddarah et al., 2021). In addition, the addition of acrylamide-forming inhibitors during the thermal processing, such as natural extracts (Pantalone et al., 2021; Zhu et al., 2009) and metal cations (Wen et al., 2016), can effectively reduce the content of acrylamide by inhibiting Maillard reaction intermediates.

After the reaction, generated acrylamide in the system could be directly removed to reduce the risk of acrylamide to human health. For instance, microbial fermentation can achieve the purpose. Using 24 filamentous fungi as experimental subjects, Wakaizumi et al. confirmed the degradation ability of fungus to acrylamide produced in thermal treatment, especially *Aspergillus oryzae KBN1010* showed the highest degradation ability (Wakaizumi et al., 2009). Vijayashree et al. also drew a similar conclusion and the acrylamide degradation potential of *Pseudomonas aeruginosa BAC-6* was proved (Chandrashekar et al., 2014). Chemically removal of acrylamide has also been attempted, for example, Banchero et al. used supercritical CO_2 extraction, and a maximum extraction efficiency of 79% was obtained without losing caffeine content (Banchero et al., 2013). However, it needs consideration that the active compounds, textures, and flavors may lose during the removal of acrylamide, which.

In addition to the above, a variety of new techniques, such as vacuum treatment, pulsed electric fields, ultrasound, high-pressure processing, irradiation, genetic engineering, etc., has also been involved to achieve the mitigation of acrylamide (Peivasteh-Roudsari et al., 2022). The mitigation strategies of acrylamide not only stay at the laboratory level, but also gradually adopted by the industrial manufacturing. However,

on the domestic scale, the private habits and preferences of different person affects the acrylamide exposure, causing the difficulty in supervision.

8. Prospect

The authorities have taken corresponding measures to control the production of acrylamide in heat-induced reactions. Code of practice for the reduction of acrylamide (CAC/RCP 67–2009) in foods was published by the Codex Alimentarius Commission (CAC), intending to prevent and reduce formation of acrylamide in dietary food, including potato products, cereal products, coffee products. Food and Drug Administration (FDA) suggested a range of possible approaches to reducing acrylamide levels in certain foods for growers, manufacturers, and food service operators in the Guidance for Industry Acrylamide in Food in March 2016. Subsequently, European Commission issued Commission Regulation (EU) 2017/2158 on November 20th, 2017, providing recommendations for mitigation measures and benchmark levels to reduce of the presence of acrylamide in food. Although there are massive research achievements on the toxicity investigation, analytical methods, risk assessment and mitigation approaches of acrylamide, a high risk of acrylamide exposure remained and exceedance of the bench mark values worth concerning.

In addition to the conventional food products, herbal medicine has been widely used all over the world as one of the important parts of life, especially in Asian countries. From limited references, high risks of acrylamide exposure by taking processed herbal medicines were reported. It worth noting that official regulation is lacking on the acrylamide in processed herbal medicines and study is rare until now. Thus, it is of great significance to introduce modern analytical methods of acrylamide, establish a scientific and reasonable quality inspection system and risk assessment system for maximization the herbal medical application. On one hand, the accumulated studies in food samples afford valuable data and references for the understanding of the generation, analysis, and mitigation of acrylamide in herbal medicines. On the other hand, the complexity of the samples, their specific processing methods before application, and restricted medication dosage and cycle, the existing analytical methods have respective drawbacks and there lacks risk studies of acrylamide in herbal products or generation during thermal processing. In the assessment of the health risk of taking herbal medicines, it requires a more specific evaluation since the application of herbal medicines follows the guidance of the pharmacopeia or the doctor's advice. The durative administration of herbal medicine may inevitably cause health risk, which is important to patient but has rarely been reported.

The standard and traditional analytical methods for acrylamide, including GC-MS, LC-MS/MS and CE, have been providing reliable result in the determination, however, they are restricted to be applied in primary laboratory owing to the proficiency of laboratory technicians, long detection time, high cost, high demand of operation conditions, complicated pretreatment procedure, and potentially toxic exposure especially during the derivatization. In addition to the above methods, rapid detection methods with simplicity and portability have become an increasingly important hit in the world, such as spectroscopy, ELISA, EB, CV, etc. Although these methods are generally simple and time-saving, they still have the drawbacks of low reproducibility, low sensitivity and so on. Therefore, the determination of acrylamide will be developed in the direction of simplified sample pretreatment, low-price and on-site detection in the future to provide data and technical support for the quality and safety of food and herbals products as well as the promotion of industry.

With regard to mitigation, the thermal processing is critical in the generation of acrylamide. The primary method to reduce the acrylamide is optimizing the processing method without altering the original purpose. Besides this, there are various attempts for lowering acrylamide production, but not all of them meet the expectations of practical industrial application or domestic preparation. In addition to reducing the yield of acrylamide, some mitigation methods may also produce possible sensorial alterations or toxic by-products (Nematollahi et al., 2021). Therefore, in-depth studies are needed to explore substantially practical and appropriate solutions for acrylamide mitigation in thermally processed food and herbal medicines.

CRediT authorship contribution statement

Min Fan: Writing – original draft. **Xiaoying Xu:** Writing – review & editing. **Wenjun Lang:** Visualization. **Wenjing Wang:** Writing – review & editing. **Xinyu Wang:** Writing – review & editing. **Angjun Xin:** Writing – review & editing. **Fangmei Zhou:** Writing – review & editing. **Zhishan Ding:** Writing – review & editing. **Xiaoqing Ye:** Writing – review & editing. **Bingqi Zhu:** Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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