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COMPREHENSIVE REVIEW

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Occurrence, toxicity, dietary exposure, and management of *Alternaria* mycotoxins in food and feed: A systematic literature review

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Abstract

Alternaria mycotoxins are emerging contaminants frequently detected in food products and threaten human health. This systematic review aims to provide an up-to-date overview of scientific data and knowledge and gaps therein of natural occurrence, toxicological effects, dietary exposure, and prevention and control management of *Alternaria* mycotoxins in food and feed. A systematic review has been performed, using the databases Scopus and PubMed, retrieving relevant scientific papers published in English from 2011 to 2024. *Alternaria* mycotoxins are widely present in various food and feed products, with tomatoes and cereals being the most contaminated products. From the *Alternaria* mycotoxins, tenuazonic acid (TeA) and alternariol were reported with the highest detection rate and concentrations. Identified toxicological effects vary between the different *Alternaria* mycotoxins and include carcinogenicity, immune toxicity, cytotoxicity, and genotoxicity. Dietary exposure assessments for *Alternaria* mycotoxins have been conducted in several countries but vary in their scope. The calculations and risk values suggest that exposure of children to TeA via their diet is close to their tolerable daily intake. A similar finding has been reported for exposure of adults to alternariol and alternariol monomethyl ether via food consumption. Most *Alternaria* mycotoxins are heat-stable and cannot easily be removed during food processing; therefore, prevention and control measures for *Alternaria* mycotoxin contamination in food and feed are crucial. Fungicide and biocontrol applications have been shown effective in reducing *Alternaria* fungal growth and toxin production, and the development of predictive models may be promising. Collectively, they can contribute to mitigating the impact of *Alternaria* mycotoxins on human health.

KEYWORDS
Alternaria mycotoxins, contamination, incidence, prevention, toxiciological properties

1 | INTRODUCTION

Alternaria species are typically saprophytes, often found in soil or decomposing plant tissues (Thomma, 2003). Most *Alternaria* species can produce over 70 different secondary metabolites, part of which include mycotoxins that are harmful to both humans and animals. In 2011, the European Food Safety Authority (EFSA) proposed several *Alternaria* mycotoxins to be of food safety concern, including alternariol (AOH), alternariol monomethyl ether (AME), altertoxins (ATXs), tentoxin (TEN), tenuazonic acid (TeA), and altenuene (ALT) (EFSA, 2011).

Alternaria mycotoxins have been reported in a variety of food and feed products, such as fruits, grains, vegetables, processed food, coffee, animal feed, and alcoholic beverages (Burkin & Kononenko, 2015; Delgado & Gómez-Cordovés, 1998; Gruber-Dorninger et al., 2017; Zhao et al., 2015). Tomato products are particularly susceptible to being contaminated by *Alternaria* mycotoxins due to their high water content, pH, and nutrient levels that are suitable for the growth of *Alternaria* species and subsequent mycotoxin production. Research on the toxicological effects of *Alternaria* mycotoxins is ongoing, and it is clear that—based on the results—mycotoxins can be divided into two groups. One group consists of genotoxic substances, represented by AOH, AME, and ATXs, which act at the DNA level and have been demonstrated to cause DNA damage in various cell lines, such as Caco-2, HepRG, and HT29 (Aichinger et al., 2018; Fernández-Blanco et al., 2016). The other group consists of non-genotoxic substances represented by TeA and TEN, which have been found to cause cytotoxicity under in vitro conditions. Currently, there are no legal limits for the presence of *Alternaria* mycotoxins in food and feed products worldwide. Only the European Union has published guidelines for the maximum allowable concentration of AOH, AME, and TeA in specific food products (EU, 2022).

Alternaria mycotoxins have a stable chemical structure and, hence, are difficult to reduce or eliminate during food processing. Additionally, *Alternaria* species are plant pathogens commonly found in *Solanaceae* plants, such as tomatoes, potatoes, and peppers. Early blight disease, caused by *Alternaria* species, is one of the most common tomato plant diseases, resulting in production losses from 35% to 78% and decreasing food quality through subsequent mycotoxin production (Barkai-Golan, 2008; Grigolli et al., 2011; Zubrod et al., 2019). Therefore, it is important to effectively control plant infection with *Alternaria* species and the subsequent production of mycotoxins. Traditional management strategies, such as the use of fungicides and biological control, can effectively reduce *Alternaria* species infection and ensure yield (Leiminger et al., 2014; Raymaekers et al., 2020). Additionally, predictive models focusing on fungal infection or mycotoxin production have been introduced as supportive tools for decision-making to control plant diseases and reduce the production of harmful metabolites such as mycotoxins (Casu et al., 2024; Marín et al., 2021). In addition, adhering to good agricultural practices during the cultivation process and applying proper post-harvest control strategies, such as those related to storage conditions, and implementing Hazard Analysis and Critical Control Point systems can also help manage contaminations (Al-Dairi et al., 2023; Schmidt et al., 2018).

Although EFSA raised concerns about *Alternaria* mycotoxins in food back in 2011, to date, there is no comprehensive overview of the state-of-the-art insights into managing such food safety risks. This study aims to provide a comprehensive synthesis of the scientific literature on natural occurrence, toxicological effects, dietary exposure assessments, and prevention and control measures of *Alternaria* mycotoxins in food and feed products. A systematic literature review procedure was applied for each of those four aspects, and a meta-analysis was conducted for two of them, being the reported *Alternaria* mycotoxin concentrations and dietary exposure assessment results in food and feed products.

2 | METHODOLOGY

2.1 | Search strategy

A systematic literature search was conducted to identify peer-reviewed articles published between 2011 and 2024. The search was conducted using the online databases PubMed (National Library of Medicine, NIH, Bethesda, MD, USA) and Scopus (Elsevier B.V.). The search strategy covered four domains relevant to *Alternaria* mycotoxins, including natural occurrence in food and feed products, toxicological effects, dietary exposure assessment, and prevention and control measures. Table S1 provides the search terms and corresponding results for each of these four topics. Only English documents were included, and patents, conference abstracts, conference communications, and letters were excluded.

The procedure for collection of results is outlined in Figure 1. All articles meeting the selection criteria were gathered and organized using Endnote after having removed duplicates. The screening process involved two steps. First, articles were reviewed based on title, keywords, and abstracts, and search outcomes were categorized as relevant, potentially relevant, and non-relevant based on the predefined exclusion criteria. These included: no patents, conference abstracts, conference communication and letters, and non-English written articles. Sub-

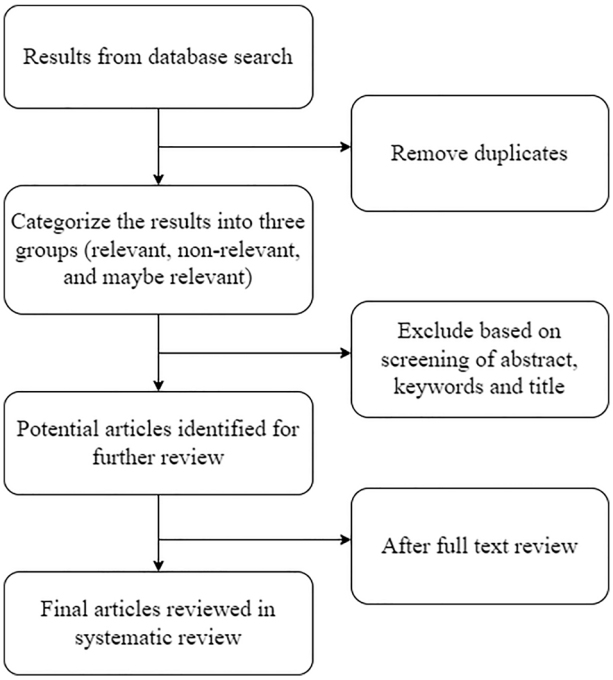

FIGURE 1 Systematic literature review selection process performed in this study.

sequently, the articles falling within the relevant and potentially relevant categories were read in full to identify the final selected articles.

2.2 | Data analysis on *Alternaria* mycotoxin occurrence and dietary exposure assessment in food and feed products

A data analysis was conducted to assess the natural occurrence and dietary exposure associated with *Alternaria* mycotoxins in food and feed products. Data on the natural occurrence were manually extracted from selected articles (listed in Table S2), being concentration data (either specific values, such as average and median values, or ranges) for one or more *Alternaria* mycotoxins in different food and feed products. In order to compare the presence of different *Alternaria* mycotoxins in fresh and processed tomatoes and cereals, the average concentrations of positive samples for each of fresh and processed tomatoes and fresh and processed cereal products are selected and plotted using GraphPad Prism (9.5.0). Regarding the dietary exposure assessment, all estimated probability intake values (probable daily intake [PDI]) and referred safety dose values (threshold of toxicological concern [TTC]) were summarized, and corresponding risk values, hazard quotients in percentage (HQ%), were calculated (Equation 1) to provide an overview of health concerns related to dietary exposure to *Alternaria* mycotoxins via food consumption:

$$\mathrm{HQ\%} = \frac{\mathrm{PDI}}{\mathrm{TTC}} \times 100 \quad (1)$$

When the HQ% is less than 100, the dietary risk is considered acceptable. Otherwise, it indicates a potential public health risk related to the intake of the contaminant (HQ% > 100).

3 | RESULTS

3.1 | Overall results

Applying the search strategy as described in Section 2.1, in total 106, 79, 29, and 108 articles were included for, respectively, natural occurrence, toxicological effects, dietary exposure assessment, and prevention and control measures of *Alternaria* mycotoxins (Table 1).

Selected articles were classified based on the geographical location of the conducted study (Figure 2). This figure also presents the numbers of articles for the different topics (Figure 2). The natural occurrence of *Alternaria* mycotoxins in food and feed products is a global concern, with European countries reporting the highest number of cases. This is probably due to the EFSA designating *Alternaria* mycotoxins as potential food hazards in 2011 and calling for more data to support risk assessment (EFSA, 2011). Subsequently, an increasing number of reports have emerged from Asia, particularly China, regarding the presence of *Alternaria* mycotoxins in tomato and cereal products. This can be explained by China being a major producer of tomatoes and cereals. Given many of these products are exported to Europe, there is a need to meet the requirements of the importing countries, driving monitoring and reporting in China (to ensure compliance with the EU's food safety standards for *Alternaria* mycotoxins), leading to an increase in detected occurrences in Chinese tomato and cereal products (FAOSTAT, 2022). Notably, only a few studies have reported the presence of *Alternaria* mycotoxins in food products from the Americas, with 90% of the data coming from South America. No reports have been found from the United States, likely because the Food and Drug Administration does not consider *Alternaria* mycotoxins a health threat to the United States, resulting in no legislative efforts and thus less frequent monitoring and research targeting these mycotoxins. Additionally, the local growing climates are unsuitable for *Alternaria* species to survive, or the effective control of them through long-term use of fungicides and good agricultural practices. As a result, there have been no large outbreaks within the years covered by the literature review, leading to a

TABLE 1 The number of selected studies (references) for each reviewed topic (natural occurrence, toxicological effects, dietary exposure assessment, and prevention and control measures) based on the search strings listed in Table S1.

Search result	Natural occurrence	Toxicological effects	Dietary exposure assessment	Prevention and control measures
All results	751	229	169	264
After removal duplicates	544	185	144	180
After title and abstract screening	198	111	51	122
Final selection	106	79	29	108

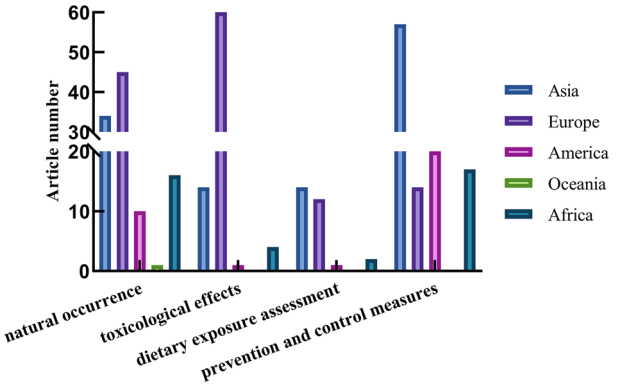

FIGURE 2 Number of selected articles, with region of study, per review topic.

lack of research attention on this topic. Furthermore, only one study detected *Alternaria* mycotoxin concentration in food products in Oceania, likely for reasons similar to those in North America, indicating that *Alternaria* mycotoxins have not yet gained notable attention from local governments or research institutions on this continent.

Regarding the toxicological effects of *Alternaria* mycotoxins, nearly half of the studies originate from Europe, which might be because of EFSA's data call on *Alternaria* mycotoxins to support risk assessment. Sufficient funding and support from the EU for food safety and toxicology studies might be another reason for this focus (Stelzl et al., 2023). In terms of dietary risk assessment, the number of selected articles is lower as compared to the other three review topics. Most of the exposure data comes from Europe and Asia, consistent with the natural occurrence data, which is logical because natural occurrence data are an essential part of dietary exposure assessment.

For the prevention and control measures, most selected articles are from Asia, particularly India, focusing mainly on tomato cultivation. This emphasis likely stems from India's status as a major global tomato producer and the substantial threat posed by *Alternaria* species, which can cause early blight diseases that severely impact crop yield and quality, leading to economic losses (Mugao, 2023). Furthermore, the high humidity in Indian tomato-growing regions fosters an ideal environment for fungal growth, driving extensive research and management strategies to control *Alternaria* species infections and reduce *Alternaria* mycotoxin contamination (Khapte et al., 2022). Interestingly, based on the selected articles, there are no studies from Oceania and North America focusing on the prevention and control of *Alternaria* mycotoxins, which are consistent with the lack of occurrence data from these two continents.

3.2 | Natural occurrence of *Alternaria* mycotoxins

An overview of *Alternaria* mycotoxin occurrence results, based on the selected articles, is presented in Table S2. It summarizes, per *Alternaria* mycotoxin, the reported concentrations, analytical methods used, sample size, and research site of *Alternaria* mycotoxins in various food or feed products. Liquid chromatography with tandem mass spectrometry (LC–MS/MS) is the predominant analytical technique used to quantify *Alternaria* mycotoxin concentrations in food and feed products, even though no inclusion or exclusion criteria were applied to the analytical methods used in our literature search.

Globally, Europe and Asia have the highest number of research articles on the occurrence of *Alternaria* mycotoxins in food and feed products, followed by Africa, the Americas, and Oceania. Among these continents, Italy, China, South Africa, and Argentina are the countries providing the most data on *Alternaria* mycotoxin concentrations. Interestingly, as time progresses, an increasing number of reports on *Alternaria* mycotoxins are emerging, with both the overall sample size and the number of positive samples rising, signifying a growing focus on mycotoxin contamination. Nevertheless, the enhancement of the detection methods may have resulted in a greater sensitivity of the detection limit, thereby causing an increase in the number of concerns. Figure 3 presents the top 10 food products mostly investigated for the presence of *Alternaria* mycotoxins, with the numbers of articles presented with the bars. Among all food and feed groups, fruits and their derived products have been analyzed most, with AOH and TeA being the

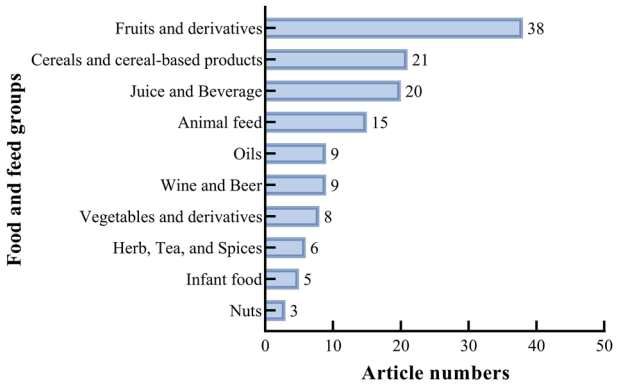

FIGURE 3 The number of articles reporting on the presence of *Alternaria* mycotoxins in various food and feed groups.

most frequently detected *Alternaria* mycotoxins. Next are cereal and cereal-based products, followed by juices and beverages. Notably, 15 studies have investigated and detected *Alternaria* mycotoxins in various animal feeds, including homemade and commercial feed products, indicating potential animal health issues and/or human food safety risks.

Tomatoes and tomato-based products are the primary food items found to contain *Alternaria* mycotoxins in the category of fruits and their derivatives, which are reported as frequently as cereal and cereal-based products, collectively contributing to 50% of all selected studies. We conducted a data analysis on the concentrations (average values) of *Alternaria* mycotoxins, focusing on the positive samples detected in tomato and tomato-based products and cereal and cereal-based products, respectively, and a classified comparison based on different types of products, such as fresh and processed (Figure 4). All selected studies were included. Average concentration data for positive samples alone are insufficient to provide a complete overview of the *Alternaria* mycotoxin contamination. Therefore, the sample size data and percent positive samples, as presented in Table S2, should be taken into consideration when assessing the overall occurrence of *Alternaria* mycotoxins in fresh and processed tomato or cereal products. As can be seen from this table, however, not all included studies reported sample size in fresh and processed tomato or cereal products, making it impossible to estimate average concentrations weighted with sampling size. Despite that, the weighted concentration was also calculated using the available data. Results (data not shown) were comparable with using unweighted concentration data. In tomatoes and tomato-based products, six different *Alternaria* mycotoxins were detected (Figure 4a). For instance, tomato powder sold in China had the highest concentration of TeA (1853.4 μg/kg), likely due to dehydration and concentration during processing (Ji, Deng, et al., 2023). Overall, TeA had the highest reported concentrations among all *Alternaria* mycotoxins, ranging from 9.0 to 1853.4 μg/kg. For AOH, the concentrations were mostly below 100 μg/kg, except for one sample of fresh tomatoes from Spain, in which concentrations reached 1000 μg/kg (Estiarte et al., 2018). For 95% of the analyzed tomato and tomato-based products, AME, TEN, and ALT concentrations averaged below 30 μg/kg. However, in Argentina's tomato puree, ALT was found in an average concentration of 59.8 μg/kg, indicating significant regional variability (Maldonado Haro et al., 2023). Classifying all tomato and tomato-based products into two groups (fresh tomatoes and processed tomato products) and comparing the concentration of *Alternaria* mycotoxins in these two groups, it was found that *Alternaria* mycotoxin concentrations in fresh tomatoes generally are lower than in processed tomato products (Figure 4b). This may be due to the poorer quality of raw materials used in processed products or the processing procedures, which may concentrate mycotoxins. Notably, ATX-I was detected only in processed tomato products, with a concentration of 190.2 μg/kg, whereas it was not found in fresh tomatoes. This could be attributed to the concentration of mycotoxins during processing, which reached the detection limit (Maldonado Haro et al., 2023).

Seven different *Alternaria* mycotoxins were observed in cereal and cereal-based products (Figure 4c). Interestingly, the highest concentration of *Alternaria* mycotoxin was AME in an Argentina barley sample, at 2201 μg/kg, whereas other studies reported average AME concentrations below 200 μg/kg. Most AOH and TEN concentrations were below 150 μg/kg, and the average concentration of TeA varied from 20 to 2000 μg/kg. Only a few studies included ALT, ATX-I, and ALS, with reported concentrations below 50 μg/kg (Hickert et al., 2017; Mašková et al., 2019; Misihairabgwi et al., 2018; Puntscher, Cobankovic, et al., 2019; Ssepuuya et al., 2018; Woo et al., 2022). Through classification comparison, it was found that ALT and ALS were detected only in raw products, and the concentration of *Alternaria* mycotoxins in raw products was higher than in processed products, which is opposite to the results for tomatoes and tomato-based products. This could be due to cereals typically undergoing cleaning, dehulling, and milling during processing, effectively removing surface mycotoxins. Additionally, raw cereals are more susceptible to environmental factors such as temperature and humidity during storage, which benefit fungal growth and mycotoxin production (Hoffmans et al., 2022; Karlovsky et al., 2016).

Specific *Alternaria* mycotoxins are found in co-occurrence with other *Alternaria* mycotoxins or with other mycotoxins, such as deoxynivalenol (DON), aflatoxins, and ZEA (Ji Xiao, Lyu, et al., 2022; Juan et al.,

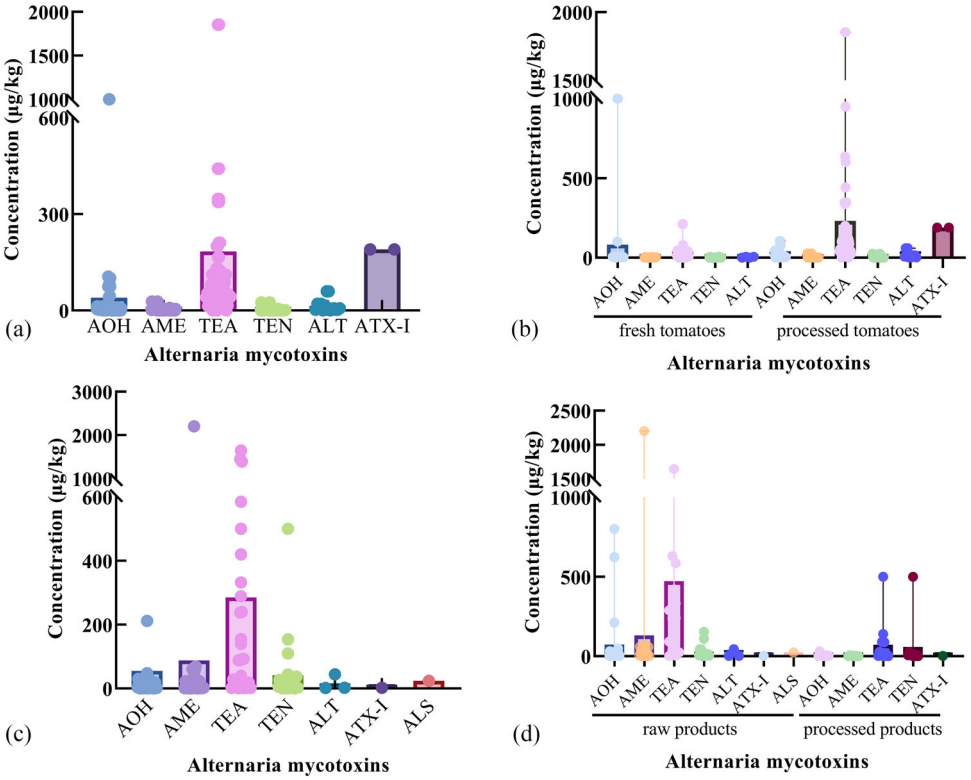

FIGURE 4 Distribution and comparative analysis results for average *Alternaria* mycotoxin concentrations in tomato (a and b) and cereal products (c and d), focusing on positive samples of the included studies.

2017; Narvaez et al., 2020). For instance, Ji, Xiao, Jin, et al. (2022) found that 18.3% (89/486) of food samples from an online supermarket in China were contaminated with two *Alternaria* mycotoxins, 16.5% (80/486) with three toxins, and 2.1% (10/486) with four toxins, indicating the co-occurrence of various *Alternaria* mycotoxins in China is popular. The most common co-detected combinations in food commodities were TeA + TEN (7.8%). Jiang et al. (2021) reported that the combination of TEN + TeA, AME + TeA, and AOH + AME accounted for 97.2%, 91.2%, and 6.1% of the wheat flour samples, respectively. *Alternaria* mycotoxins have also been detected in co-occurrence with other mycotoxins.

Ji, Xiao, Lyu, et al. (2022) reported the simultaneous presence of DON, AME, AOH, and TeA in cereal-based food products in China; overall, 39.9% (348/872) of the analyzed samples were co-contaminated with two or more toxins; particularly, the combination DON + TeA was found in 31.2% of the samples. El Jai, Zinedine, et al. (2021) found that zearalenone (ZEN) and AOH favorably co-occurred in aromatic and medicinal plants in the Moroccan market with a 20% detection rate. Furthermore, Carballo et al. (2021) analyzed 110 beverage samples for mycotoxin concentrations and observed that 45% of beer samples, 20% of beer samples with lemonade, and 25% of alcohol-free beers showed co-occurrence between two or more mycotoxins, with mycotoxin concentrations ranging from 10.86 to 185.15 μg/L.

3.3 | Toxicological effects of *Alternaria* mycotoxins

3.3.1 | Alternariol and alternariol monomethyl ether

Alternariol (AOH) and AME are the most studied *Alternaria* mycotoxins for toxicological effects (55 out of the 79 articles). The toxicological effects of AOH and AME can be divided into six pathways.

First, AOH and AME have the ability to induce cell cytotoxicity, interfere with the cell cycle, and cause cell apoptosis. For example, Bensassi et al. (2012) demonstrated that AOH- and AME-induced cytotoxicity is mediated by the activation of the mitochondrial pathway in human colon carcinoma cells. Specifically, AOH and AME lead to the opening of the mitochondrial permeability transition pore, resulting in the loss of mitochondrial transmembrane potential and the generation of reactive oxygen species, which disrupts cell processes and causes cell apoptosis. Fernández-Blanco et al. (2016) evaluated AOH cytotoxicity using Caco-2 cells and observed that AOH

induced necrosis, apoptosis, and loss of mitochondrial transmembrane potential in a dose- and time-dependent manner.

Second, AOH and AME can trigger mutagenicity in either bacterial cells or mammalian cells. In bacterial cells, the Ames test, used with *Salmonella* strains, has been conducted for AOH and AME, with positive results reported by An et al. (1989). AOH induced weakly positive results in revertant colonies in TA100 and TA104 strains and was clearly positive in TA102 strain. AME clearly showed positive results in *Escherichia coli* ND-106 without metabolic activation (Schrader et al., 2006). In contrast, Davis and Stack (1994) observed negative results for AOH and AME in TA98 and TA100 strains, hypothesizing that the contradictory results in the Ames test were caused by the presence of small amounts of highly mutagenic ATXs in other studies, which could lead to positive results. In mammalian cells, AOH induced a concentration-dependent increase in mutant frequency, starting at 10 μM, whereas AME increased the frequency of hypoxanthine-guanine phosphoribosyltransferase (HPRT) gene mutations, but not in a concentration-dependent manner in Chinese hamster V79 lung fibroblast cells (Fleck et al., 2012).

Third, AOH and AME are known to induce primary DNA damage in vitro and in vivo. AOH has been demonstrated to cause DNA strand breaks in various human cell lines in vitro, such as HT29 cells (Schwarz, Tiessen, et al., 2012), human A431 cells (Fehr et al., 2009), V79 cells (Fleck et al., 2012), human HepG2 cells (Pfeiffer et al., 2007), and in the murine macrophages RAW 264.7 (Solhaug et al., 2012). However, Tiessen et al. (2013) did not observe DNA damage after exposure of HT29 cells to 50 μM AOH for either 3 or 24 h incubation, suggesting that AOH toxicity was decreased by rapid biotransformation reactions such as glucuronidation and glutathione conjugation, which protected the cells from DNA damage. In contrast, AOH has been shown to induce DNA damage after 24 h of exposure in HepG2 cells as well as in RAW 264.7, Caco-2, and HeK239 cells. Nevertheless, it cannot be concluded that the observed DNA damage under a long incubation period is directly and only caused by AOH and/or by the prolonged exposure time. AME-induced DNA strand breaks in HT29 and A431 cells at concentrations lower than 10 and 1 μM, respectively, indicating a substantial genotoxic potential. Notably, AME showed slightly more effectiveness than AOH at low concentrations for increasing DNA strand breaks in V79 cells after 1.5 h exposure. Few studies have investigated AOH and AME genotoxicity in vivo. A study in orally treated NMRI mice showed that AOH did not cause DNA damage in the liver at 2000 mg/kg bodyweight (bw) regardless of sex, neither after a single dose nor with three repeated doses (Solhaug et al., 2014). Miao et al. (2022) observed no DNA damage in peripheral blood and liver cells of male Sprague–Dawley rats after orally feeding them with 22 μg AOH/kg bw for 28 days. In contrast, a single oral dose of 10 mg AOH/kg bw in Wistar rats significantly increased DNA damage in acinar cells (Samak et al., 2019). Tang et al. (2022) found that AME is able to cause DNA damage in the blood and liver of male Sprague–Dawley rats after orally feeding with 7.35 μg/kg bw/day AME for 28 days.

Fourth, AOH and AME are known to exert endocrine-disrupting effects, potentially interacting with the androgen receptor (AR) or acting as synthetic estrogen-mimicking substances, thereby disrupting hormone generation and function (Lehmann et al., 2006; Vejdovszky, Schmidt, et al., 2017). Various studies have observed the interaction between AOH and the AR using androgen-dependent cell systems. Stypula-Trebas et al. (2017) demonstrated an androgenic response at 0.01–400 μM AOH in a yeast bioassay resulting in a remarkably high EC_{50} of 270 μM. Consistently, a possible antagonistic activity of more than 50% was observed with AOH exposure above 4.8 μM to TARM-Luc cells after 48 h incubation (Frizzell et al., 2013). Moreover, AOH was successfully docked into the active pocket of the wild-type AR in a molecular docking study, suggesting possible binding (Agwupuye et al., 2021). Regarding estrogen-mimicking effects, several studies have demonstrated that AOH acts as an estrogen receptor (ER) antagonist with low potency in reporter gene assays and a yeast estrogen-sensitive bioassay (Demaegdt et al., 2016; Frizzell et al., 2013; Stypula-Trebas et al., 2017). Notably, AME was found to fit better than AOH into the binding pocket of ER and had more potential in the alkaline phosphatase assay, indicating that methylation enhanced estrogenicity (Dellafiora et al., 2018).

Fifth, AOH and AME have been shown to influence the NF-κB signaling pathway, leading to increased pro-inflammatory immune responses (Kollarova et al., 2018; Kowalska et al., 2021). Exposure of THP1-Lucia-derived macrophages to AOH resulted in a dose-dependent suppression of the LPS-induced NF-κB pathway activation (Dellafiora et al., 2018). Del Favero et al. (2020) observed that AOH affects the signal transduction of pro-inflammatory stimuli by inducing increased membrane fluidity, suggesting that AOH may inhibit immune responses. Besides AOH, AME demonstrated suppressive effects on IL-8, IL-6, and MCP-1/CCL2 protein secretion in LPS-stimulated BEAS-2B cells at concentrations of 10 μM after 24 h of incubation, suggesting slightly inhibitory effects on immune system (Grover & Lawrence, 2017).

Finally, some studies suggest that AOH and AME accumulate in the gut, disrupting gut pH balance and microbiota diversity, which can further exacerbate their toxic effects (Crudo et al., 2021; Pfeiffer et al., 2009).

3.3.2 | Tenuazonic acid

Chemically, TeA is a tetrameric derivative and an amide metabolite. Regarding its cytotoxicity effects, TeA has been shown to inhibit newly formed proteins from the ribosomes, resulting in reduced cell viability across mammalian cell lines, including 3T3, CHL, and LO2 (Lebrun et al., 1988; Zhou & Qiang, 2008). For example, den Hollander et al. (2022) observed cytotoxic effects of TeA at concentrations between 60 and 90 μM in Caco-2 cells, whereas in HeLa cells, the EC_{50} was 146 μM (Mahmoud et al., 2022). Hessel-Pras et al. (2019) observed a dose-dependent TeA cytotoxicity in HepG2 cells. In contrast, cell viability was not decreased in pig granulosa cells exposed for 24 h to 100 μM TeA (Tiemann et al., 2009). In animal tests, TeA cytotoxicity effects involved liver damage, diarrhea, mortality, cardiovascular collapse, and gastrointestinal hemorrhage in various animal species, including guinea pigs, young mice, rabbits, dogs, and rhesus monkeys (Giambrone et al., 1978; Yekeler et al., 2001; Youngner et al., 1965). Regarding genotoxicity effects, TeA was shown to lead to negative results in the Ames test. No in vivo studies have been carried out to date for TeA (Schrader et al., 2006, 2001). Under the in vitro system, TeA was mutagenic in HPRT/XPRT assays carried out in V79 cells but was negative in HepG2 cells and HT29 cells (Hessel-Pras et al., 2019; Schwarz, Tiessen, et al., 2012). These uncertain genotoxic effects raise concerns about the potential carcinogenicity of TeA and its long-term health implications.

3.3.3 | Altertoxins I, II, and III

ATXs I, II, and III are *Alternaria* mycotoxins categorized within the perylene quinone group (Pinto & Patriarca, 2017). These mycotoxins share a similar chemical structure and can interconvert in vivo (Fleck, Pfeiffer, Podlech, et al., 2014; Puntscher, Marko, et al., 2019; Puntscher, Aichinger, et al., 2019).

Several researchers have shed light on the intricate molecular mechanisms underlying the toxic effects of ATX-II, the most critical mycotoxin within the perylene quinone group (Boutin et al., 1989; Fleck, Pfeiffer, & Metzler, et al., 2014; Stack et al., 1986). Studies have demonstrated ATX-II's ability to induce DNA damage in various mammalian cell lines, including V79, Caco-2, and HT-29, without significantly impacting the cell cycle (Aichinger et al., 2018; Fleck et al., 2012; Schwarz, Kreutzer, et al., 2012; Schwarz, Tiessen, et al., 2012). This DNA damage is of particular concern as it can lead to genomic instability and potentially contribute to the development of cancerous lesions. Investigations into the cellular response to ATX-II exposure have revealed its influence on the regulation of γ-glutamate cysteine ligase expression, suggesting a potential role in disrupting cellular antioxidant defense mechanisms and exacerbating oxidative stress-induced damage (Del Favero et al., 2018; Jarolim et al., 2017). Recent findings by Soukup et al. (2020) have unveiled the formation of covalent adducts between ATX-II and guanine residues within DNA molecules under cell-free conditions. This discovery implicates ATX-II as a potent mutagen, capable of directly modifying DNA bases and inducing genetic mutations. However, the precise molecular mechanisms underlying ATX-II's DNA modification and the subsequent cellular responses remain incompletely understood and warrant further investigation. Compared to ATX-II, ATX-I is less potent but still has considerable DNA strand-breaking potency with about the same genotoxic activity as AOH (Fleck, Pfeiffer, & Metzler, et al., 2014).

Only one study conducted ATX-II genotoxicity under in vivo conditions. The study was performed in rats with single-bolus applications, resulting in enhanced levels of RH2AX in the colon of the animals after 24 h. Besides ATX-II, ATX-I was reported to induce DNA damage in the peripheral blood and liver of male Sprague–Dawley rats after oral exposure for 28 days (Zhu et al., 2022).

3.3.4 | Tentoxin

TEN, a non-host-specific toxin produced by several *Alternaria* species, poses uncertain toxicological effects to human, mammalian, and plant cells. Its toxicological effects include inducing necrosis, reducing cell vitality, and interfering with plant seedlings, as evidenced by several studies (De Bruyne et al., 2016; Delaforge et al., 1997; Hessel-Pras et al., 2019; Liebermann et al., 1996). However, Hessel-Pras et al. (2019) conducted cell viability test with TEN in HepaRG and HepG2 cells after 24 h exposure and observed no significant cytotoxic effects. For the gentoxicity test, TEN was consistently negative in the Ames test with TA98, TA100, TA97, TA102, and TA104 strains, and only one study checked the gentoxicity of TEN for inducing DNA strand breaks in HEK293T cells with negative results (Gruber-Dorninger et al., 2017; Schrader et al., 2006; Tran et al., 2020).

3.3.5 | Altenuene

ALT, as one of the main secondary metabolites from *Alternaria* species, has rarely been investigated for its toxicity. Only four studies focused on the toxicity of ALT, all of which only showed cytotoxicity without investigating the mechanism (Xiao et al., 2014). These studies relied solely on in vitro bioassay observation results. Dong et al.

(2021) tested the influence of ALT on cell toxicity in HaCaT cells and observed no significant effect at a concentration of 80 μM after exposure for 24 h. Similarly, Hou et al. (2021) concluded the same after using the HEK-293T cells to assess cell viability via the MTT assay. Xiao et al. (2014) found that ALT exhibited strong cytotoxicity in the HCT116 cancer cell line, with a median inhibitory concentration value of 3.13 μM. ALT was also tested for mutagenicity using the Ames salmonella strains TA97 under in vitro conditions by Schrader et al. (2006), and the results indicated no significant mutagenicity effects.

3.3.6 | Combination effects of *Alternaria* mycotoxins

The co-occurrence of mycotoxins in food and feed is a well-established phenomenon, and unraveling the potential synergistic or antagonistic interactions among these compounds is crucial for accurately assessing their impact on human health (Abbas, 2019). Research has unveiled the intricate and often unpredictable nature of these interactions, shedding light on the combined toxic effects of *Alternaria* mycotoxins and their interplay with other fungal toxins.

Studies investigating crude extracts of *Alternaria alternata* have revealed complex toxicity profiles that surpass those of individual mycotoxins present in the extract (Dong et al., 1987; Pero et al., 1973; Schrader et al., 2001). Furthermore, low-concentration combinations of *Alternaria* mycotoxins, such as AOH and AME, have been shown to intensify toxicity compared to either compound alone (Bensassi et al., 2015). Similarly, synergistic effects have been observed between AOH and ATX-II, leading to additive toxic effects in various human epithelial and mammalian cell lines (Hohenbichler et al., 2020, 2021; Vejdovszky, Sack, et al., 2017). Moreover, Ismail et al. (2023) tested a combined mixture of *Alternaria* mycotoxins (ALT, AOH, and TeA) on cell viability for human oral epithelial cells using the MTT assay, observing positive cytotoxicity at 125 μM, whereas it is unclear if this is due to one mycotoxin or the combined effects.

In addition to interaction within the *Alternaria* mycotoxins group, studies have explored the combined effects of *Alternaria* mycotoxins with other mycotoxins, such as aflatoxins, DON, and ZEN. Investigations into the cytotoxic and genotoxic effects of these combinations have revealed heightened toxicity and estrogenic activity when AOH is combined with DON and ZEN (Balázs et al., 2021; Juan-García et al., 2016). Interestingly, contrasting effects have been observed when TeA is combined with DON or ZEN, suggesting complex interactions among different mycotoxin groups (Vejdovszky et al., 2016).

3.4 | Dietary exposure assessment about *Alternaria* mycotoxins

A total of 29 articles were found on dietary exposure assessments on *Alternaria* mycotoxins, varying in populations, food sources, and regions of investigation. Nearly half of the studies were conducted for Asian countries, with the majority focusing on China and, in particular, on cereal-related products like wheat, maize, and cereals. This emphasis may be due to cereals being a staple food for the Chinese population, constituting a substantial portion of their dietary intake. Additionally, an increasing number of fungal toxins are being discovered in cereal-related products. To ensure consumer food safety, conducting dietary exposure assessments becomes imperative. On the other hand, because of the different natural occurrence data in food products, the dietary exposure assessment carried out in Europe covered a greater range of food categories, such as fruits, vegetables, infant foods, beverages, and cereals.

Table 2 presents the calculated HQ% for each dietary exposure assessment study included in this literature review, including the focus population, food sources, and estimated daily intake values extracted from the literature. Because tolerable daily intake (TDI) for *Alternaria* mycotoxins has not been defined yet, the TTC established by the EFSA has been used as the reference safe dose. The toxicity of *Alternaria* mycotoxins is varying, and consequently the TTC values are different among the mycotoxins. For example, the TTC value for AOH and AME is set at 2.5 ng/kg bw/day, whereas 1500 ng/kg bw/day has been set as the TTC value for TeA and TEN (Arcella et al., 2016). Hence, assessing the potential human health risks of *Alternaria* mycotoxins via food consumption, it is essential to not only focus on the concentration of the mycotoxins in food products but also execute a thorough assessment based on its TTC value. For instance, according to Liu et al. (2024), the estimated PDI for TeA in coix seeds is 81.4 ng/kg bw/day, which is over 14-fold higher than that of AOH (5.75 ng/kg bw/day). However, the risk assessment results, shown by the HQ% values (5.43% for TeA and 230% for AOH), indicate that dietary exposure to TeA through coix seeds does not pose a health risk to Chinese adults, but AOH does.

Overall, approximately 70% of the dietary exposure assessment studies concluded that one or more *Alternaria* mycotoxins pose a food safety exposure risk. Cereal and tomato products are the primary sources of *Alternaria* mycotoxin intake for both adults and children.

AOH and TeA are the two most included *Alternaria* mycotoxins in dietary exposure assessments. Figure 5 shows the corresponding risk assessment values (HQ%) under upper-bound consumption scenarios for AOH and

TABLE 2 Overview dietary exposure assessment results of *Alternaria* mycotoxins in food products obtained from previous studies around the world over the period 2011–2024.

Food category	Location	*Alternaria* mycotoxin	Population	PDI (ng/kg bw/day)		TTC (ng/kg bw/day)	HQ%		References
				UB	LB		UB	LB	
Wheat flour	China	TeA	Adult—men	3.250	NA	1500	0.22	NA	Wang et al. (2024)
			Adult—women	3.620			0.24		
			Boy (7–18 yrs)	2.980			0.20		
			Girls (7–18 yrs)	3.030			0.20		
Wheat flour	China	AOH	Total	9.640	NA	2.5	385.60	NA	Zhou et al. (2022)
			Adult men	10.300			412.00		
			Adult women	9.000			360.00		
			Boy (7–10 yrs)	17.300			692.00		
			Girls (7–10 yrs)	15.100			604.00		
		TEN	Total	0.769		1500	0.05		
			Adult men	0.818			0.05		
			Adult women	0.718			0.05		
			Boy (7–10 yrs)	1.380			0.09		
			Girls (7–10 yrs)	1.210			0.08		
		TeA	Total	33.100		1500	2.21		
			Adult men	35.200			2.35		
			Adult women	30.800			2.05		
			Boy (7–10 yrs)	59.400			3.96		
			Girls (7–10 yrs)	51.900			3.46		
Coix seed	China	TeA	Adult	81.400	8.880	1500	5.43	0.59	Liu et al. (2024)
		AOH		5.750	0.734	2.5	230.00	29.36	
		AME		1.900	0.207	2.5	76.00	8.28	
Olive oil	China	AME	Adult	0.410	0.350	2.5	16.40	14.00	
		TEN		1.000	0.040	1500	0.07	0.00	
Corn oil		AME		0.030	0.020	2.5	1.20	0.80	
		TEN		0.090	0.080	1500	0.01	0.01	Zhou et al. (2023)
Peanut oil		AME		0.050	0.040	2.5	2.00	1.60	
		TEN		0.130	0.010	1500	0.01	0.00	
Rapeseed oil		AME		0.050	0.040	2.5	2.00	1.60	
		TEN		0.310	0.160	1500	0.02	0.01	

(Continues)

TABLE 2 (Continued)

Food category	Location	*Alternaria* mycotoxin	Population	PDI (ng/kg bw/day)		TTC (ng/kg bw/day)	HQ%		References
				UB	LB		UB	LB	
Camellia oil		AME		0.080	0.070	2.5	3.20	2.80	
		TEN		0.290	0.240	1500	0.02	0.02	
Blended oil		AME		0.480	0.410	2.5	19.20	16.40	
		TEN		1.700	0.080	1500	0.11	0.01	
Rice-bran oil		AME		0.310	0.260	2.5	12.40	10.40	
		TEN		0.850	0.720	1500	0.06	0.05	
Sunflower seed oil		AME		0.290	0.240	2.5	11.60	9.60	
		TEN		0.230	1.200	1500	0.02	0.08	
Soybean oil		AME		0.060	0.050	2.5	2.40	2.00	
		TEN		0.250	0.060	1500	0.02	0.00	
Sesame oil		AME		4.400	3.800	2.5	176.00	152.00	
		TEN		10.500	0.050	1500	0.70	0.00	
Wheat	China	AME	4–7 yrs	4.000	NA	2.5	160.00	NA	Ji, Jin, et al. (2023)
			7–11 yrs	4.000			160.00		
			11–14 yrs	3.000			120.00		
			14–18 yrs	3.000			120.00		
			18–30 yrs	3.000			120.00		
			30–45 yrs	3.000			120.00		
			45–60 yrs	3.000			120.00		
			60–70 yrs	3.000			120.00		
		AOH	4–7 yrs	7.000		2.5	280.00		
			7–11 yrs	6.000			240.00		
			11–14 yrs	5.000			200.00		
			14–18 yrs	5.000			200.00		
			18–30 yrs	4.000			160.00		
			30–45 yrs	4.000			160.00		
			45–60 yrs	4.000			160.00		
			60–70 yrs	4.000			160.00		
		TeA	4–7 yrs	373.000		1500	24.87		

(Continues)

TABLE 2 (Continued)

Food category	Location	*Alternaria* mycotoxin	Population	PDI (ng/kg bw/day) UB	PDI (ng/kg bw/day) LB	TTC (ng/kg bw/day)	HQ% UB	HQ% LB	References
			7-11 yrs	313.000			20.87		
			11–14 yrs	279.000			18.60		
			14–18 yrs	258.000			17.20		
			18–30 yrs	245.000			16.33		
	30–45 yrs	233.000			15.53				
			45–60 yrs	229.000			15.27		
			60–70 yrs	223.000			14.87		
		TEN	4–7 yrs	41.000		1500	2.73		
			7-11 yrs	35.000			2.33		
			11–14 yrs	31.000			2.07		
			14–18 yrs	29.000			1.93		
			18–30 yrs	27.000			1.80		
			30–45 yrs	26.000			1.73		
			45–60 yrs	25.000			1.67		
			60–70 yrs	25.000			1.67		
Wheat	China	AOH	General	24.000	3.560	2.5	960.00	142.40	
		AME		6.090	NA	2.5	243.60	NA	
		TEN		54.500	NA	1500	3.63	NA	Jiang et al. (2021)
		TeA		175.000	NA	1500	11.67	NA	
		AOH	Children	39.100	5.900	2.5	1564.00	236.00	
		AME		10.200	NA	2.5	408.00	NA	
		TEN		90.100	NA	1500	6.01	NA	
		TeA		292.000	NA	1500	19.47	NA	
		AOH	Adolescents	31.000	4.720	2.5	1240.00	188.80	
		AME		8.170	NA	2.5	326.80	NA	
		TEN		469.000	NA	1500	31.27	NA	
		TeA		1537.000	NA	1500	102.47	NA	
		AOH	Adults	21.900	3.240	2.5	876.00	129.60	
		AME		5.520	NA	2.5	220.80	NA	
		TEN		49.700	NA	1500	3.31	NA	

(Continues)

TABLE 2 (Continued)

Food category	Location	*Alternaria* mycotoxin	Population	PDI (ng/kg bw/day)		TTC (ng/kg bw/day)	HQ%		References
				UB	LB		UB	LB	
		TeA		160.000	NA	1500	10.67	NA	
		AOH	Elderly	18.600	2.670	2.5	744.00	106.80	
		AME		4.500	NA	2.5	180.00	NA	
		TEN		41.300	NA	1500	2.75	NA	
		TeA		131.000	NA	1500	8.73	NA	
Tomato and tomato-based product	China	AME	Children	96.000	37.000	2.5	3840.00	1480.00	Ji, Deng, et al. (2023)
		AOH		285.000	100.000	2.5	11,400.00	4000.00	
		TEN		8.000	4.000	1500	0.53	0.27	
		TeA		14,037.000	2979.000	1500	935.80	198.60	
		ALT		22.000	10.000	NA	NA	NA	
		AME	Adults	45.000	17.000	2.5	1800.00	680.00	
		AOH	133.000	46.000	2.5	5320.00	1840.00		
		TEN		2.000	4.000	1500	0.13	0.27	
		TeA		6549.000	1390.000	1500	436.60	92.67	
		ALT		10.000	5.000	NA	NA	NA	
Sweet cherries	China	TeA	Chinese	6857.510	NA	1500	457.17	NA	Qiao et al. (2018)
		AOH		2.360		2.5	94.40		
		AME		41.640		2.5	1665.60		
		ALT		1.010		1500	0.07		
		TEN		20.460		1500	1.36		
Cereal-based food	China	AME	Infant	2.000	NA	2.5	80.00	NA	Ji, Xiao, Wang, et al. (2022)
		AOH		4.000		2.5	160.00		
		TeA		120.000		1500	8.00		
Cereal-based food	China	AME	0–1 yrs	15.000	NA	2.5	600.00	NA	Ji, Xiao, Lyu, et al. (2022)
			1–2 yrs	19.000			760.00		
			2–3 yrs	12.000			480.00		
			Total	19.000			760.00		
		AOH	0–1 yrs	121.000		2.5	4840.00		
			1–2 yrs	151.000			6040.00		

(Continues)

TABLE 2 (Continued)

Food category	Location	*Alternaria* mycotoxin	Population	PDI (ng/kg bw/day) UB	PDI (ng/kg bw/day) LB	TTC (ng/kg bw/day)	HQ% UB	HQ% LB	References
			2–3 yrs	141.000			5640.00		
			Total	151.000			6040.00		
		TeA	0–1 yrs	3205.000		1500	213.67		
			1–2 yrs	3499.000			233.27		
			2–3 yrs	2459.000			163.93		
			Total	3499.000			233.27		
Cereal	China	AME	2–7 yrs	3.700	NA	2.5	148.00	NA	Ji, Xiao, Jin, et al. (2022)
			8–12 yrs	3.000			120.00		
			13–19 yrs	2.300			92.00		
			20–50 yrs	2.200			88.00		
			51–65 yrs	2.100			84.00		
			>65 yrs	2.000			80.00		
Fruit products			2–7 yrs	15.000			600.00		
			8–12 yrs	12.000			480.00		
			13–19 yrs	0.900			36.00		
			20–50 yrs	0.600			24.00		
			51–65 yrs	0.500			20.00		
			>65 yrs	0.500			20.00		
Cereal and fruit products			2–7 yrs	3.200			128.00		
			8–12 yrs	2.600			104.00		
			13–19 yrs	2.000			80.00		
			20–50 yrs	1.800			72.00		
			51–65 yrs	1.700			68.00		
			> 65 yrs	1.500			60.00		
Cereal		AOH	2–7 yrs	17.100	NA	2.5	684.00	NA	
			8–12 yrs	14.200			568.00		
			13–19 yrs	10.900			436.00		
			20–50 yrs	10.100			404.00		

(Continues)

TABLE 2 (Continued)

Food category	Location	*Alternaria* mycotoxin	Population	PDI (ng/kg bw/day)		TTC (ng/kg bw/day)	HQ%		References
				UB	LB		UB	LB	
			51–65 yrs	9.700			388.00		
			>65 yrs	9.100			364.00		
Fruit products			2–7 yrs	4.400			176.00		
			8-12 yrs	3.700			148.00		
			13–19 yrs	2.600			104.00		
			20–50 yrs	1.900			76.00		
			51–65 yrs	1.600			64.00		
			>65 yrs	1.400			56.00		
Cereal and fruit products			2–7 yrs	10.300			412.00		
			8–12 yrs	8.600			344.00		
			13–19 yrs	6.500			260.00		
			20–50 yrs	5.700			228.00		
			51–65 yrs	5.400			216.00		
			>65 yrs	5.000			200.00		
Cereal		TeA	2–7 yrs	472.000	NA	1500	31.47	NA	
			8–12 yrs	393.000			26.20		
			13–19 yrs	302.000			20.13		
			20–50 yrs	281.000			18.73		
			51–65 yrs	268.000			17.87		
			>65 yrs	252.000			16.80		
Fruit products			2–7 yrs	136.000			9.07		
			8–12 yrs	113.000			7.53		
			13–19 yrs	81.000			5.40		
			20–50 yrs	57.000			3.80		
			51–65 yrs	50.000			3.33		
			>65 yrs	43.000			2.87		

(Continues)

TABLE 2 (Continued)

Food category	Location	*Alternaria* mycotoxin	Population	PDI (ng/kg bw/day) UB	PDI (ng/kg bw/day) LB	TTC (ng/kg bw/day)	HQ% UB	HQ% LB	References
Cereal and fruit products			2–7 yrs	302.000			20.13		
			8–12 yrs	251.000			16.73		
			13–19 yrs	190.000			12.67		
			20–50 yrs	167.000			11.13		
			51–65 yrs	157.000			10.47		
			> 65 yrs	146.000			9.73		
Cereal		TEN	2–7 yrs	9.800	NA	1500	0.65	NA	
			8–12 yrs	8.100			0.54		
			13–19 yrs	6.200			0.41		
			20–50 yrs	5.800			0.39		
			51–65 yrs	5.500			0.37		
			>65 yrs	5.200			0.35		
Fruit products			2–7 yrs	0.100			0.01		
			8–12 yrs	0.100			0.01		
			13–19 yrs	0.100			0.01		
			20–50 yrs	0.100			0.01		
			51–65 yrs	0.100			0.01		
			>65 yrs	0.010			0.00		
Cereal and fruit products			2–7 yrs	4.000			0.27		
			8–12 yrs	3.300			0.22		
			13–19 yrs	2.500			0.17		
			20–50 yrs	2.200			0.15		
			51–65 yrs	2.100			0.14		
			>65 yrs	1.900			0.13		
All food	China	AOH	Adult	419.000	3.280	2.5	16,760.00	131.20	Fan et al. (2021)
		AME		36.800	2.330		1472.00	93.20	
		TeA		52.100	0.468	1500	3.47	0.03	
		TEN		107.000	15.200	1500	7.13	1.01	

(Continues)

TABLE 2 (Continued)

Food category	Location	*Alternaria* mycotoxin	Population	PDI (ng/kg bw/day)		TTC (ng/kg bw/day)	HQ%		References
				UB	LB		UB	LB	
All food	China	TeA	Chinese	38.200	NA	1500	2.55	NA	
		AME		12.500	2.5	500.00	NA	Qiao et al. (2022)	
Plant-based beverage	Latvian	AOH	Male	1.090	NA	2.5	43.60	NA	Pavlenko et al. (2024)
			Female	0.740			29.60		
		AME	Male	0.880	2.5	35.20			
	Female	0.600			24.00				
		TEN	Male	0.500	1500	0.03			
			Female	0.340			0.02		
Clear apple juice	Argentina	AOH	6–23 months	NA	NA	2.5	NA	NA	Pavicich et al. (2024)
			2–5 yrs				NA	NA	
		AME	6–23 months	2.5	59.30	0.40			
			2–5 yrs				56.60	0.20	
		TeA	6–23 months			1500	0.00	0.00	
			2–5 yrs				0.00	0.00	
Cloudy apple juice	AOH	6–23 months	NA	NA	2.5	87.30	25.40		
			2–5 yrs				86.30	24.70	
		AME	6–23 months	2.5	56.60	50.20			
			2–5 yrs				75.40	48.80	
		TeA	6–23 months	1500	1.50	0.70			
			2–5 yrs				0.80	0.30	
Apple infant food	AOH	6–23 months	NA	NA	2.5	86.60	28.60		
			2–5 yrs				81.10	24.20	
		AME	6–23 months	2.5	95.80	95.50			
			2–5 yrs				95.80	95.50	
		TeA	6–23 months	1500	0.40	0.20			
			2–5 yrs				0.00	0.00	
Wheat -based meat alternatives	Italy	AOH	Infant	0.031	0.031	2.5	1.24	1.23	Behrens et al. (2024)
		AME		0.010	0.010	2.5	0.42	0.39	

(Continues)

TABLE 2 (Continued)

Food category	Location	*Alternaria* mycotoxin	Population	PDI (ng/kg bw/day) UB	PDI (ng/kg bw/day) LB	TTC (ng/kg bw/day)	HQ% UB	HQ% LB	References
		TEN		0.016	0.015	1500	0.00	0.00	
		AOH	Children	0.036	0.035	2.5	1.43	1.42	
		AME		0.012	0.011	2.5	0.48	0.46	
		TEN		0.018	0.018	1500	0.00	0.00	
		AOH	Toddlers	0.042	0.042	2.5	1.68	1.66	
		AME		0.014	0.013	2.5	0.57	0.53	
		TEN		0.021	0.021	1500	0.00	0.00	
		AOH	Adolescents	0.026	0.026	2.5	1.06	1.05	
		AME	0.009	0.008	2.5	0.36	0.34		
		TEN	0.013	0.013	1500	0.00	0.00		
		AOH	Adults	0.018	0.018	2.5	0.73	0.72	
		AME	0.006	0.006	2.5	0.25	0.23		
		TEN	0.009	0.009	1500	0.00	0.00		
		AOH	Elderly	0.015	0.014	2.5	0.59	0.58	
		AME		0.005	0.005	2.5	0.20	0.19	
		TEN		0.007	0.007	1500	0.00	0.00	
Legume-based meat alternatives	AOH	Infant	0.033	0.033	2.5	1.33	1.31		
		AME		0.009	0.008	2.5	0.37	0.33	
		TEN		0.041	0.040	1500	0.00	0.00	
		AOH	Children	0.038	0.038	2.5	1.54	1.51	
		AME		0.011	0.010	2.5	0.43	0.39	
		TEN		0.048	0.046	1500	0.00	0.00	
		AOH	Toddlers	0.045	0.044	2.5	1.81	1.77	
		AME		0.013	0.011	2.5	0.50	0.45	
		TEN		0.056	0.054	1500	0.00	0.00	
		AOH	Adolescents	0.028	0.028	2.5	1.14	1.12	
		AME		0.008	0.007	2.5	0.32	0.28	
		TEN		0.035	0.034	1500	0.00	0.00	
		AOH	Adults	0.020	0.019	2.5	0.79	0.77	
		AME		0.005	0.005	2.5	0.22	0.20	

(Continues)

TABLE 2 (Continued)

Food category	Location	*Alternaria* mycotoxin	Population	PDI (ng/kg bw/day)		TTC (ng/kg bw/day)	HQ%		References
				UB	LB		UB	LB	
		TEN		0.024	0.024	1500	0.00	0.00	
		AOH	Elderly	0.016	0.015	2.5	0.63	0.62	
		AME		0.004	0.004	2.5	0.17	0.16	
		TEN		0.020	0.019	1500	0.00	0.00	
Vegetable-based meat alternatives		AOH	Infant	0.019	0.018	2.5	0.76	0.73	
		AME		0.009	0.008	2.5	0.37	0.32	
		TEN		0.011	0.010	1500	0.00	0.00	
		AOH	Children	0.022	0.021	2.5	0.88	0.84	
		AME		0.011	0.009	2.5	0.42	0.38	
		TEN		0.013	0.012	1500	0.00	0.00	
		AOH	Toddlers	0.026	0.025	2.5	1.03	0.99	
		AME		0.012	0.011	2.5	0.50	0.44	
		TEN		0.015	0.014	1500	0.00	0.00	
		AOH	Adolescents	0.016	0.016	2.5	0.65	0.62	
		AME		0.008	0.007	2.5	0.31	0.28	
		TEN		0.010	0.009	1500	0.00	0.00	
		AOH	Adults	0.011	0.011	2.5	0.45	0.43	
		AME		0.005	0.005	2.5	0.22	0.19	
		TEN		0.007	0.006	1500	0.00	0.00	
		AOH	Elderly	0.009	0.009	2.5	0.36	0.34	
		AME		0.004	0.004	2.5	0.17	0.15	
		TEN		0.005	0.005	1500	0.00	0.00	
Ready-to-eat nuts	Italy	AOH	Children	NA	NA	2.5	12.40	2.80	Narvaez et al. (2020)
		AME				2.5	21.20	6.40	
		AOH	Teenager			2.5	8.00	1.60	
		AME				2.5	14.00	4.40	
		AOH	Adult			2.5	6.80	1.60	
		AME				2.5	11.60	3.60	

(Continues)

TABLE 2 (Continued)

Food category	Location	*Alternaria* mycotoxin	Population	PDI (ng/kg bw/day) UB	PDI (ng/kg bw/day) LB	TTC (ng/kg bw/day)	HQ% UB	HQ% LB	References
		AOH	Elderly			2.5	8.40	1.60	
		AME	2.5	14.40	4.40				
All food	Austria	AME	Children	15.000	NA	2.5	600.00	NA	Ayeni et al. (2023)
Cereal grains	South Korea	AOH	WHO population	0.201	0.026	2.5	8.02	1.02	Woo et al. (2022)
		AME		0.106	0.011	2.5	4.24	0.44	
		ALT		0.092	0.000	NA	NA	NA	
		ATX-I		0.058	0.008	NA	NA	NA	
		TEN		0.306	0.027	1500	0.02	0.00	
		TeA		2.287	2.254	1500	0.15	0.15	
Pulses		AOH		0.008	0.000	2.5	0.30	0.00	
		AME		0.004	0.000	2.5	0.16	0.00	
		ALT		0.004	0.000	NA	NA	NA	
		ATX-I		0.002	0.000	NA	NA	NA	
		TEN		0.012	0.000	1500	0.00	0.00	
		TeA		0.008	0.100	1500	0.00	0.01	
Nuts and seeds		AOH		0.005	0.004	2.5	0.21	0.16	
		AME		0.045	0.043	2.5	1.78	1.72	
		ALT		0.001	0.001	NA	NA	NA	
		ATX-I		0.001	0.000	NA	NA	NA	
		TEN		0.005	0.001	1500	0.00	0.00	
		TeA		0.206	0.204	1500	0.01	0.01	
Beverages		AOH		0.032	0.017	2.5	1.29	0.67	
		AME		0.045	0.000	2.5	1.78	0.00	
		ALT		0.024	0.000	NA	NA	NA	
		ATX-I		0.025	0.008	NA	NA	NA	
		TEN		0.118	0.000	1500	0.01	0.00	
		TeA		0.502	0.404	1500	0.03	0.03	
Seasoning foods		AOH		0.038	0.036	2.5	1.53	1.45	
		AME		0.011	0.009	2.5	0.44	0.35	
		ALT		0.004	0.000	NA	NA	NA	

(Continues)

TABLE 2 (Continued)

Food category	Location	*Alternaria* mycotoxin	Population	PDI (ng/kg bw/day)		TTC (ng/kg bw/day)	HQ%		References
				UB	LB		UB	LB	
		ATX-I		0.002	0.000	NA	NA	NA	
		TEN		0.014	0.000	1500	0.00	0.00	
		TeA		22.927	22.927	1500	1.53	1.53	
Vegetables		AOH		0.035	0.000	2.5	1.41	0.00	
		AME		0.025	0.000	2.5	0.98	0.00	
		ALT		0.065	0.000	NA	NA	NA	
		ATX-I		0.095	0.000	NA	NA	NA	
		TEN		0.386	0.000	1500	0.03	0.00	
		TeA		0.454	0.000	1500	0.03	0.00	
Fruits		AOH		0.035	0.000	2.5	1.39	0.00	
		AME		0.030	0.008	2.5	1.19	0.32	
		ALT		0.064	0.000	NA	NA	NA	
		ATX-I		0.094	0.000	NA	NA	NA	
		TEN		0.380	0.000	1500	0.03	0.00	
		TeA		0.568	0.176	1500	0.04	0.01	
General food products	The Netherlands	AOH	12–17 months	61.000	21.000	2.5	2440.00	840.00	Pustjens et al. (2022)
			18–23 months	39.000	14.000		1560.00	560.00	
			24–35 months	32.000	11.000		1280.00	440.00	
			1–2 yrs	42.000	14.000		1680.00	560.00	
		AME	12–17 months	41.000	18.000	2.5	1640.00	720.00	
			18–23 months	138.000	19.000		5520.00	760.00	
			24–35 months	127.000	27.000		5080.00	1080.00	
			1–2 yrs	123.000	21.000		4920.00	840.00	
Coffee	Tunisian	AME	Tunisian consumer	2.134	2.035	2.5	85.38	81.40	Oueslati et al. (2022)
		AOH		3.677	3.245	2.5	147.10	129.79	
Plate-ready food	Nigeria	AME	Adult	47.000	19.000	2.5	1880.00	760.00	Braun et al. (2022)

(Continues)

TABLE 2 (Continued)

Food category	Location	*Alternaria* mycotoxin	Population	PDI (ng/kg bw/day)		TTC (ng/kg bw/day)	HQ%		References
				UB	LB		UB	LB	
Breast milk			Infants	56.000	0.600		2240.00	24.00	
Green TeA infusion	Moroccan	AOH	Adult	0.250	0.080	2.5	10.00	3.20	El Jai, Juan, et al. (2021)
		TEN		0.370	0.030	1500	0.02	0.00	
Beer	Spain	AOH	Adult	15.010	NA	2.5	600.40	NA	Carballo et al. (2021)
Alcoholic free beer				3.500			140.00		
Beer with lemonade				0.540			21.60		
Wine		AME		0.890			35.60		
		AOH		0.920			36.80		
Alcoholic free wine		AME		0.800			32.00		
		AOH		0.260			10.40		
Wine with lemonade		AME		0.600			24.00		
		AOH		0.120			4.80		
Cava		AOH		0.500			20.00		
Wheat	Albania-2014	TeA	Adult	94.100	88.600	1500	6.27	5.91	Topi et al. (2019)
Maize				9.000	8.800		0.60	0.59	
Wheat		TEN		34.000	7.800		2.27	0.52	
Maize				0.500	0.200		0.03	0.01	
Wheat	Albania-2015	TeA		155.500	152.700		10.37	10.18	
Maize				0.400	0.000		0.03	0.00	
Wheat		TEN		38.700	10.600		2.58	0.71	
Maize				0.400	0.000		0.03	0.00	
Sorghum	Sub-Saharan	AOH	Adult	400.000	30.000	2.5	16,000.00	1200.00	Ssepuuya et al. (2018)
		AME		60.000	10.000	2.5	2400.00	400.00	
Tomato juice and sauce	Belgium	AOH	Adult	28.500	NA	2.5	1140.00	NA	Walravens et al. (2016)

(Continues)

TABLE 2 (Continued)

Food category	Location	*Alternaria* mycotoxin	Population	PDI (ng/kg bw/day)		TTC (ng/kg bw/day)	HQ%		References
				UB	LB		UB	LB	
		AME		6.890		2.5	275.60		
		TeA		746.000		1500	49.73		
Tomato concentrate		AOH		90.400		2.5	3616.00		
		AME		37.700		2.5	1508.00		
Tomato-based products	Belgium	TeA	Adult	4230.000	NA	1500	282.00	NA	Van de Perre et al. (2014)
Green coffee	NA	AOH	Adult	1.300	NA	2.5	52.00	NA	Mujahid et al. (2020)
		AME		0.600		2.5	24.00		
		TEN		0.200		1500	0.01		
		TeA		6.200		1500	0.41		
		AOH + AME		1.400		2.5	56.00		

Abbreviations: ALT, altenuene; AME, alternariol monomethyl ether; ATXs, altertoxins; HQ, hazard quotient; LB, lower bound; NA, not available; PDI, probable daily intake; TeA, tenuazonic acid; TEN, tentoxin; TTC, threshold of toxicological concern; UB, upper bound; yrs, years.

TeA across different food groups and locations. Health risks associated with AOH intake can be observed in all four general food groups, especially cereals and cereal products (Figure 5a). No exceeding risk values were observed in European studies, indicating that AOH might not pose a threat to European population health through the consumption of cereal and cereal-based products, whereas over 90% of HQ% values calculated for Asian and African populations were higher than 100, suggesting that cereal and cereal-based products may present AOH-related health risks to local consumers.

For TeA dietary exposure assessments, tomato and tomato-based products were the main contributors for both children and adults (Figure 5b). Under lower-bound scenario, the PDI for children was 2979 ng/kg bw/day, and for adults, it was 1390 ng/kg bw/day, exceeding the TTC by 198.60% and 92.67%, respectively. In the upper-bound scenario, the HQ% values for TeA ranged from 0.03 to 935.8, indicating a potential health risk to general consumers (Ji et al., 2023; Topi et al., 2019).

The PDI and HQ% data for AME consumption ranged from 0.0041 to 96 ng/kg bw/day and 0.15% to 3840%, respectively. Particularly, the estimated AME PDI via tomato and tomato-based products consumption for Chinese children exceeded the TTC by 3840% and 1480% under upper- and lower-bound scenarios, respectively, indicating potential health risks for Chinese children (Ji et al., 2023). For adults, sorghum was the main contributor to AME exposure with a PDI of 60 ng/kg bw/day, exceeding the TTC at 2400%. In contrast, South Korea assessed the PDI of cereal grains at 0.0041 ng/kg bw/day, contributing only 0.164% of the TDI, suggesting a large variation of health concerns via cereal products consumption (Ssepuuya et al., 2018; Woo et al., 2022).

The main contributors to TEN dietary exposure of adults were wheat and tomato concentrates, ranging from 7.13% to 32.27% of the TTC (Fan et al., 2021; Jiang et al., 2021), whereas plate-ready food and wheat products were the main contributors to TEN intake for children, ranging from 2.8% to 6.0% of the TTC (Jiang et al., 2021; Pustjens et al., 2022). These results indicate that TEN from dietary consumption does not pose a risk to public health. The PDI values for ALT ranged from 0.001 to 22.0 ng/kg bw/day, with dietary data sourced from the consumption of pulses, cereals, beverages, sweet cherries, and tomato concentrates. However, as there is no defined TTC value for ALT, most studies only calculated the PDI without determining the safety risk. One study, however, defined the TTC value for ALT as 1500 ng/kg bw/day and conducted a risk assessment for sweet cherries, observing no public health risk with an HQ% value of 0.067 (Qiao et al., 2018).

For other *Alternaria* mycotoxins such as ATX-I and ALS, only one study, conducted in South Korea, esti-

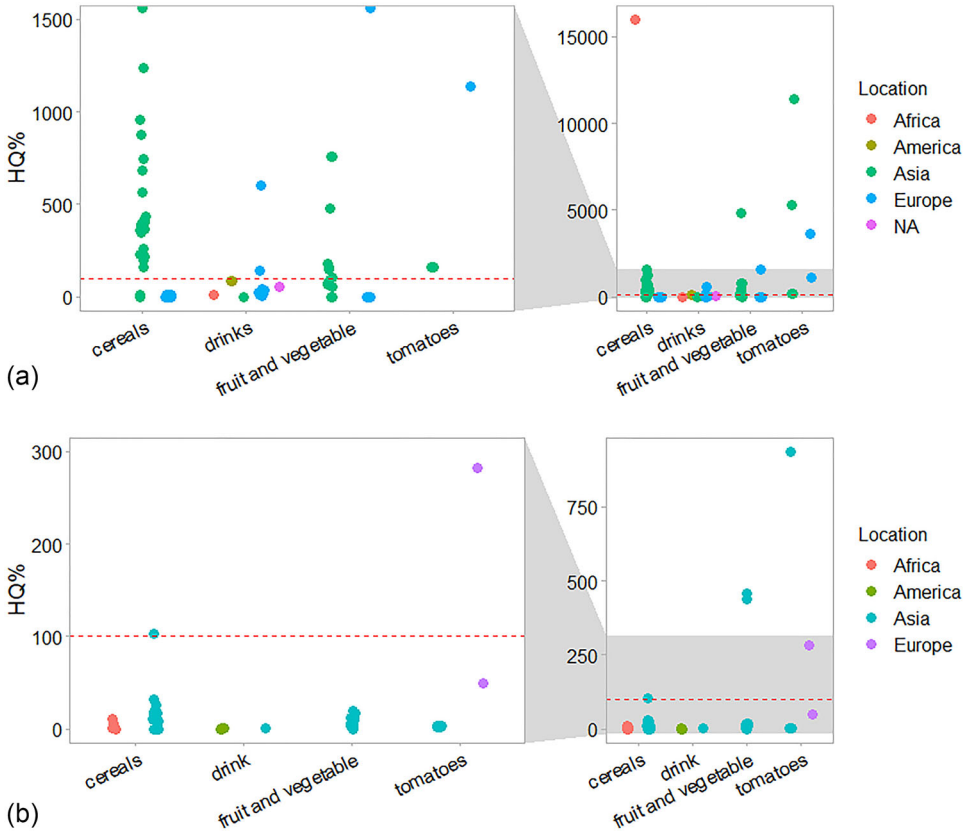

FIGURE 5 Comparative analysis results of hazard quotient (HQ) for dietary exposure focusing on alternariol (AOH) (a) and tenuazonic acid (TeA) (b) in different food categories per continent, as based on 29 exposure assessment studies. The red dashed line represents the maximum safety value (HQ% = 100). HQ%: hazard quotient in percentage (%).

mated the PDI for ATX-I in upper-bound scenarios of 0.0007–0.0951 ng/kg bw/day through consumption of vegetables, seasoning foods, cereal products, and beverages (Woo et al., 2022). The PDI value for ALS from dietary exposure has not been estimated, and TTC values to support the dietary exposure risk assessment for ATX-I or ALS are not defined.

3.5 | Prevention and control measures

The primary strategies for reducing the presence of *Alternaria* mycotoxins in food are to minimize fungal infections and to reduce their mycotoxin production in related commodities. Traditional methods involve using chemicals to combat pathogenic fungal infection of crops during the cultivation stage. However, the extensive use of chemicals often results in toxic residues in soil and food and leads to the emergence of resistant strains (Odilbekov et al., 2016, 2019). Therefore, more environmentally friendly and sustainable ways to control fungal infections and mycotoxin presence are increasingly being investigated.

3.5.1 | Pre-harvest control

Agronomic measures

Using proper agricultural practices related to crop rotation, tillage, planting date, irrigation, and fertilization can reduce the presence of *Alternaria* species and related mycotoxins in crops. Abuley et al. (2019) conducted an open-field experiment to assess the impact of crop rotation on reducing early blight disease in potatoes. Their findings suggest that maintaining at least a 2-year interval among potato crops in the rotation cycle is necessary to delay the onset of early blight in the potato fields. Additionally, rotating *Alternaria* species host crops, such as tomatoes and potatoes, with non-host crops like canola and rapeseed can reduce the presence of early blight disease by breaking the host–pathogen cycle and enhancing soil microbial diversity (Bernard et al., 2014; Larkin et al., 2010, 2012). Olanya et al. (2009) also demonstrated that continuous (year after year) potato production leads to increased presence of early blight disease.

The irrigation method is crucial in reducing the incidence and severity of early blight disease caused by *Alternaria* species in tomatoes and potatoes. Compared to

furrow irrigation, both sprinkler and drip irrigation systems significantly reduce the incidence of *Alternaria solani* and *A. alternata* in potato fields (Nasr-Esfahani, 2022). However, high-frequency sprinkly irrigation can increase the incidence of several diseases, including early blight disease, due to more favorable canopy and soil moisture and temperature conditions for pathogen infection, growth, reproduction, dispersal, and survival (Adams & Stevenson, 1990). Therefore, an appropriate irrigation strategy should be employed to minimize early blight diseases.

Effective planting techniques and seed treatments highly reduced fungal infections and mycotoxin production in crops. Nasr-Esfahani (2022) observed that double- and single-row planting effectively reduced the fungal disease. Early planting also benefits crops to evade early blight infection (Hospers-Brands et al., 2008). Prior to planting, treating seeds with fungicides such as Mancozeb significantly reduces early blight severity and increases yield in tomatoes (Mandal et al., 2019). Additionally, hot water treatment of seeds at 50°C for 30 min can control *Alternaria* disease in cabbages and has been demonstrated to eliminate *Alternaria* species infection in *Brassicaceae* seeds (Sivanesan & Holliday, 1972; Walker, 1952).

Fungicide

Fungicides play a pivotal role in minimizing *Alternaria* species contamination in crops, with both chemical and botanical options demonstrating efficacy in inhibiting fungal growth and reducing mycotoxin production.

Chemical fungicides, particularly Mancozeb and its copper salt formulations, have emerged as prominent choices for controlling *Alternaria* species contamination due to their robust efficacy in inhibiting fungal growth. Several studies have assessed the impact of Mancozeb on reducing *Alternaria* species growth on tomato plants in laboratory and open-field conditions, reporting over 90% inhibition rates (Deshmukh et al., 2020; Gondal et al., 2012; Yang et al., 2019). Research by El-Ganainy et al. (2021) evaluated the effectiveness of Mancozeb copper fungicides in mitigating *A. solani* infections in tomato plants under greenhouse conditions in Egypt, resulting in over 80% reduction. Beyond copper-based fungicides, a diverse array of chemical agents, including demethylation inhibitors, quinone inhibitors, dithiocarbonates, and carboxylic acid amides, have shown potential in reducing *Alternaria* species infections in various crops, such as tomatoes, potatoes, and berries, as demonstrated by Jindo et al. (2021).

Botanical fungicides, derived from plants, possess inherent fungicidal properties, offering a sustainable alternative to chemical fungicides. Extracts from plants have shown significant inhibitory effects on *Alternaria* species growth. For example, crude plant extracts from *Calotropis procera* inhibited *A. solani* growth by 86.3% (Baka & Rashad, 2016). Similarly, clove extracts showed 100% inhibitory effects against *A. solani* growth in vitro, illustrating their strong antifungal properties (Lengai et al., 2021). Furthermore, botanical essential oils, such as those from bergamot oranges and tea trees, have demonstrated notable antifungal activity against *A. solani* with growth inhibition rates of 68.2% and 42.0%, respectively (Hendges et al., 2020, 2021). Additionally, Wang et al. (2019) observed that 222.5 μg/mL of citral essential oil completely suppressed *A. alternata* mycelial growth, and half of this concentration was sufficient to inhibit more than 97% of mycotoxin production, indicating that botanical essential oils are viable alternatives for developing new botanical fungicides. However, the application of plant essential oils in agriculture remains limited due to potential phytotoxic effects (Chang et al., 2021).

Biological control

Biological control, involving the introduction of organisms to inhibit diseases or their causative agents, represents a promising strategy for addressing mycotoxin contamination while minimizing environmental impact (Collinge et al., 2022). Notably, bacterial strains have emerged as prominent agents in limiting the impact of *Alternaria* species both pre- and post-harvest. Extensive research has demonstrated the efficacy of *Bacillus* and *Trichoderma* strains in controlling the proliferation of *Alternaria* species (Dawidziuk et al., 2016; Fontenelle et al., 2011; Shafi et al., 2017; Tekiner et al., 2020). Specifically, *Bacillus velezensis* exhibited significant inhibition of *A. solani* mycelial growth by over 70% in agar plates (Vignesh et al., 2022). Similarly, *Bacillus lechemiformis* strains showed substantial reductions in the incidence of *A. alternata* in tomatoes under laboratory conditions (Ramírez-Cariño et al., 2020; Shoaib et al., 2019). Furthermore, the application of *Trichoderma* species as biocontrol agents has been successful in decreasing *Alternaria* species–induced disease severity by 13.7% under greenhouse conditions (Imran et al., 2022). Additionally, glucose oxidase generated by *Bacillus licheniformis ZOM-1* has demonstrated the capability to degrade AOH and AME in the laboratory, further underscoring the potential of biocontrol agents (Sun et al., 2023).

The exploration of non-pathogenic antagonistic fungi as biological control agents is an expanding field in the management of *Alternaria* species (Thambugala et al., 2020). For instance, *SRNE2BP*, a fungal endophyte derived from *Xylaria feejeensis* and isolated from a mangrove tree, exhibited promising antagonistic effects against *A. solani* infections in tomatoes under experimental conditions, resulting in a notable reduction in mycelium growth and disease severity, with 87.5% and 25.5% inhibition rates, respectively (Brooks et al., 2022). Yeast strains

have also demonstrated efficacy in inhibiting *Alternaria* species growth and mycotoxin accumulation in the laboratory in general. Prendes et al. (2021) evaluated the effects of six different *Metschnikowia* species strains on the growth and production of AME, AOH, and TeA by *A. alternata* in a synthetic medium with a composition similar to grape at various temperatures (15, 25, and 30°C). Their findings indicate that all strains completely prevented *A. alternata* growth and mycotoxin production at all tested temperatures, highlighting antagonistic yeast strains as candidates for combating *A. alternata*.

Plant breeding

In the field of plant breeding, genetic modifications and biosynthetic techniques hold scientific interest as they offer potential methods for preventing and controlling the growth of *Alternaria* species and consequently reducing *Alternaria* mycotoxin contamination risks. These techniques aim to replace or complement traditional prevention and control approaches by employing genome editing strategies such as RNA interference (RNAi) and CRISPR/Cas9. For example, Thakur and Prasad (2020) applied the RNAi technique to silence the *AcCH37* gene in *Cyamopsis tetragonoloba*, associated with *Alternaria* black spot disease, and observed that the mycelium growth rate and disease progression were reduced after the gene modification. Similarly, Lu et al. (2019) reported that silencing the *AbSte7* gene reduced the enzymes involved in host cell wall degradation during *Alternaria brassicicola* infection, further decreasing pathogenicity. CRISPR/Cas9 has also been reported for genome editing in filamentous fungi (Roux et al., 2020). However, few studies have focused on *Alternaria* species, so the possibility for genome editing-mediated plant resistance to these fungi remains relatively unexploited.

Development of resistance cultivars is another approach to handle *Alternaria* species infection from a plant breeding perspective. Nekoval et al. (2022) collected 27 mutant tomato lines to test the resistance to 5 different *A. alternata* strains under open field, greenhouse, and laboratory conditions, finding that only three cultivars exhibited resistance to *A. alternata*. Alizadeh-Moghaddam et al. (2020) conducted genetic diversity analysis on 35 commercial tomato genotypes to evaluate their response to early blight disease at transplanting and maturing stages, suggesting that genetic diversity markers can distinguish between resistant and susceptible tomato genotypes. Multi-omics analysis, including genomics, transcriptomics, metabolomics, and proteomics, provides a novel way to identify plant-resistant genes, aiding in the modification of current crop cultivars to enhance resistance to pathogen attacks. Yang et al. (2020) conducted RNA-sequencing and found that 9 out of 331 pear genotypes were highly resistant to *A. alternata*, identified using 11 simple sequence repeat markers, which could contribute to the future pear breeding. Similarly, Zhu et al. (2017) used RNA-sequence technology to analyze how apples resist *A. alternata* invasion. The results showed a total of 9080 differentially expressed genes (DEGs), with gene ontology (GO) and Kyoto Encyclopedia of Genes and Genomes analyses indicating half of the DEGs were involved in photosynthesis and redox-related pathways. Subsequently, transcription factors and genes involved in cell wall modification and pathogenesis-related (PR) genes were also activated. These findings suggest that the vulnerability of cell wall defenses and the down-regulation of most PR genes in apples might explain their susceptibility to *A. alternata*.

Despite these advancements, crop species that are completely immune to *Alternaria* species have not been identified to date. All resistant cultivars are either partially resistant or highly reliant on fungicide treatments.

3.5.2 | Post-harvest control

Post-harvest strategies are important in controlling *Alternaria* mycotoxin contamination in stored crops or vegetables. These strategies encompass a variety of physical and processing methods aimed at reducing *Alternaria* mycotoxin concentrations in food products, including cold storage. Cold storage at 4°C has been found to reduce *Alternaria* mycotoxin production in fresh tomato fruits, apples, and lettuce (da Cruz Cabral et al., 2019; Mao et al., 2023; Miranda-Apodaca et al., 2023). A proper washing procedure, especially with sodium hypochlorite solutions, and heat treatment (110°C, 30 min) could reduce nearly half of AOH and AME concentrations in tomatoes (Meno et al., 2022). Notably, Bretträger et al. (2023) analyzed the concentrations of *Alternaria* mycotoxin at various phases of the beer brewing process and showed that optical sorting of malt batches can inhibit the concentrations of *Alternaria* mycotoxin, particularly for AOH and AME. Additionally, according to Pavicich et al. (2020), clarifying during the manufacturing of apple concentrates resulted in lowering the concentrations of *Alternaria* mycotoxins, such as AOH, AME, TeA, and TEN, to non-quantifiable levels. Applying UV-C irradiation has been effective in inhibiting *Alternaria* mycotoxin production and penetration in tomatoes during storage, where Jiang et al. (2019) reported reductions of 79.6%, 76.4%, and 51.4% in AOH, AME, and TeA concentrations, respectively, compared to untreated fruits. Moreover, adjustments of processing parameters related to temperature and moisture content have demonstrated efficacy in minimizing *Alternaria* mycotoxin contamination as conducted in whole grain red sorghum flour extrusion processing method (Hajnal et al., 2024).

3.5.3 | Early warning

For *Alternaria* species, several predictive models for the presence of early blight disease in tomato plants have been developed during the 1970s and 1980s (Adhikari et al., 2017), including the FAST (Forecasting *A*. solani on Tomatoes) model (Madden et al., 1978) and the TOMCAST (Tomato Disease Forecast) model (Pitblado, 1992). These models enhance the understanding of disease dynamics and aim to optimize disease management practices. The FAST model, an empirical model for the relationship between weather and early blight disease, offers a fungicide spray plan to manage the disease effectively. Initially applied in Eastern North America in the late 1990s, application of the FAST model has shown to reduce fungicide usage by 30% and to save up to 20% of tomato production (Gleason et al., 1995). Later, Shuman and Christ (2005) extended the FAST model by integrating host resistance factors and applied it to different cultivars with varying levels of resistance to *Alternaria* species infection. They demonstrated that incorporating these factors from different cultivars into the FAST model improved its predictive accuracy and the fungicide spray plan. However, due to geographical and cultivar limitations, this model has not been widely adopted. The TOMCAST model uses temperature and leaf wetness as inputs to estimate daily disease severity, determining optimal fungicide spraying times with adaptable local adjustments (Madden et al., 1978). Field trials in China from 2020 to 2022 using the TOMCAST model and combining different fungicides successfully reduced fungicide application frequency and suppressed the development of early blight disease (Li et al., 2023). Additionally, Abuley and Nielsen (2019) have combined TOMCAST with maturity-based plant growth models to further improve the model's prediction accuracy, reducing fungicide application by over 50% while increasing yield production by 10%.

Other predictive models, such as the physiological days model (P-Days) (Pscheidt & Stevenson, 1986; Sands & Regel, 1983) and growing degree days (Franc et al., 1988), estimate susceptibility periods for early blight infection based on plant development stages. These models predict plant growth stages without considering the pathogen's life cycle, relying on a positive correlation between plant senescence and susceptibility to *Alternaria* species (Landschoot et al., 2017). For example, P-Days uses temperature values to determine the threshold for initial symptom observation and fungicide spraying initiation (Meno et al., 2022). However, due to the limited number of input variables and inherent uncertainties, the accuracy of those models needs improvement.

From a post-harvest perspective, current data indicate that no predictive warning models have yet been developed specifically for *Alternaria* mycotoxins.

4 | CONCLUSIONS AND FUTURE PERSPECTIVES

This systematic review comprehensively synthesizes research findings in the field of *Alternaria* mycotoxins from 2011 to 2024, with a focus on their natural occurrence, toxicological effects, dietary exposure assessment, and prevention and control measures. *Alternaria* mycotoxins are emerging toxins that are increasingly detected in a variety of food and feed products worldwide. They are most frequently found in fruits and their derivatives, particularly in tomatoes and tomato-related products, followed by cereals and cereal-related products. TeA and AOH are the most reported *Alternaria* mycotoxins, with TeA concentrations being higher than those of AOH. Current data indicate that reports of *Alternaria* mycotoxin contamination are primarily from Europe and Asia, followed by Africa and South America, whereas data from North America and Australia are scarce. The underlying reason is not clear. The field of toxicological effects of *Alternaria* mycotoxins is relatively unexplored. Among all *Alternaria* mycotoxins, research on AOH and AME is the most extensive, primarily elucidating their mechanisms of cytotoxicity, teratogenicity, genotoxicity, and immunotoxicity, followed by TeA, mainly for non-genotoxicity-related mechanisms. Additionally, dietary exposure assessment results observed that the cumulative intake of *Alternaria* mycotoxins through various food products may compromise human health risks, particularly among vulnerable populations such as infants and children. Notably, most existing research data on the occurrence and exposure assessment of *Alternaria* mycotoxins in food and feed products originates from European and Asian countries. Information from other regions, such as Oceania and Africa, is scarce. Consequently, future research should prioritize those areas to comprehensively assess the impact of *Alternaria* mycotoxins on human health. Besides, current toxicological and exposure assessment studies focused on several *Alternaria* mycotoxins, such as AOH, AME, and TeA. Other *Alternaria* mycotoxins, like ALT, TEN, and ATXs, have rarely been investigated for at least one of these two aspects. Thus, future research could focus on those *Alternaria* mycotoxins to allow for a comprehensive risk assessment.

Different prevention and control measures at both the pre- and post-harvest stages can be applied to manage the presence of *Alternaria* mycotoxins in foods and their commodities. During the pre-harvest stage, employing good agricultural practices, such as crop rotation, irrigation management, seed treatment, as well as the use of fungicides, applying biological control approaches, and cultivating resistant varieties, can reduce the presence of *Alternaria* species, and thereby *Alternaria* mycotoxins. Fungicide application is the most common approach

to control *Alternaria* mycotoxin contamination currently, which may worsen the environment and lead to an increase in fungal resistance. Biocontrol measurements have primarily been demonstrated in lab settings rather than in the field; hence, their preventative potential is unclear. Therefore, future research should focus on reducing the use of fungicides and accurately analyzing the performance of biocontrol measurements in open-field conditions. At the post-harvest stage, adjusting storage temperature and lighting conditions and parameters during food processing can be applied to manage *Alternaria* mycotoxin presence. For example, cold temperature and UV-C irradiation under storage conditions help to control *Alternaria* mycotoxin concentrations in tomatoes. The application of predictive models can provide early warnings about the potential presence of *Alternaria* mycotoxins and offer stakeholders rapid and accurate information to support decision-making. Despite the potential benefits, challenges persist in predictive modeling, such as data scarcity, model complexity, and validation limitations. Addressing these challenges necessitates interdisciplinary collaboration, data harmonization efforts, and robust validation protocols. Future research should prioritize enhancing model interpretability, scalability, and user-friendliness to facilitate adoption by stakeholders with varying technical intelligence, and blockchain can further enhance mycotoxin control strategies and promote transparency in the food supply chain. Moreover, existing prevention and control measures have primarily been tested in laboratory settings; therefore, scaling experiments to greenhouses or open fields is imperative. Additionally, research is needed to identify plant defense mechanisms that effectively deter *Alternaria* species invasion in crops. A comprehensive understanding of the interplay between fungal infection, host crops, and mycotoxin production is crucial for refining risk management approaches, ensuring food safety, and maintaining the integrity of the food industry.

AUTHOR CONTRIBUTIONS

Yimin Zhang: Data curation; methodology; formal analysis; visualization; writing—original draft. **Cheng Liu**: Methodology; writing—review and editing; supervision. **H. J. van der Fels-Klerx**: Project administration; methodology; writing—review and editing; supervision.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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SUPPORTING INFORMATION

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