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A review of recent innovative strategies for controlling mycotoxins in foods

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ABSTRACT

Mycotoxin contamination of foods from mycotoxigenic fungi such as *Aspergillus*, *Alternaria*, *Fusarium* and *Penicillium* spp. is a significant threat to food safety and quality. Aflatoxins, ochratoxins, fumonisins, deoxynivalenol, zearalenone, trichothecenes and patulin have been demonstrated to show immune toxicity, carcinogenicity, nephrotoxicity, hepatotoxicity, neurotoxicity and teratogenicity activities in humans and animals. Implementation of the prerequisite programs like the HACCP-based procedures can reduce mycotoxin contamination, while conventional chemical, biological and physical methods can be employed for detoxification after contamination. But the increasing fungal resistance and challenges associated with the conventional systems necessitate the development of innovative strategies for rapid elimination with short processing time and negligible impact on quality. This review evaluated recent innovative strategies of cold atmospheric plasma (CAP), polyphenols and flavonoids, magnetic materials and nanoparticles and natural essential oils (NEOs) for controlling mycotoxin in foods. Although the available studies indicated the promising potential of these strategies, complete decontamination was not achieved. The mechanisms for the reduced bioactivity of mycotoxins included the disruption of fungal cell membrane and structural degradation of complex biochemical molecules by the oxidative effects of reactive species, inhibition of enzymes responsible for breakdown of carbohydrates and adsorption and binding of functional groups of mycotoxins in food substrate. Integrated management systems of combining multiple strategies can be explored for achieving higher efficiency and better adaptability to different food matrices. Additional studies on the toxicity of the food matrices, degraded products and industrial up-scaling are necessary for ensuring widespread adoption and cost-effective commercialisation for sustainable food processing.

1. Introduction

Mycotoxins are of significant global concern and huge challenge to food safety owing to their harmful effects, with their prevalence in food crops suggested to be in the range of 60–80% and over USD 932 million annual financial losses in agricultural commodities contaminated with mycotoxins reported globally (Adebo et al., 2021; Moretti, Pascale, & Logrieco, 2019). These low molecular weight toxic metabolites originate from mycotoxigenic fungi such as *Aspergillus*, *Alternaria*, *Fusarium* and *Penicillium* spp.; and contaminate various categories of foods and feeds

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during the pre-harvest, postharvest and storage management chain of foods (Emmanuel et al., 2020; Gavahian, Sheu, Magnani, & Mousavi Khaneghah, 2021).

Over 400 mycotoxins have been categorized as toxic and the adverse effects of mycotoxicosis from mycotoxin contamination in humans may include necrosis, hepatitis, haemorrhage, gynaecomastia with testicular atrophy, neurological disorders, cancer and death in extreme cases (Adebo et al., 2021; Atanda, 2011; Milicevic, Nesic, & Jaksic, 2015). Likewise, animal feedstuff contaminated with mycotoxins can lead to reductions in available feed nutrients, chronic diseases, damage to animal health, eventual death and reduced production (Luo, Liu, & Li, 2018). The most toxic types of mycotoxins are aflatoxins (AF) and ochratoxins (OT) (Hamad et al., 2022). AFB_1 is a strong hepatocarcinogenic mycotoxin mostly detected in cereals, nuts, grains and feeds, and AFB_1 and AFB_2 can be converted to hydroxylated AFM_1 and AFM_2 in lactating cattle after ingestion via contaminated feedstuff, while OTA with hepatotoxic and nephrotoxic effects is mostly detected in cereals, coffee, wine, grape juice and dried fruits (Bangar et al., 2021; Smith, Madec, Coton, & Hymery, 2016). Therefore, there is an urgent need for appropriate approaches and techniques for reducing and/or eliminating the presence of mycotoxins in foods. The chemical structures of the main mycotoxins in foods are presented in Fig. 1, while the classes of mycotoxins based on symptoms and diseases caused to animals and humans are presented in Table 1.

The risk of food contamination by mycotoxins can be increased from the environmental, agronomic and socioeconomic point of view, but food safety control can be achieved from monitoring at all stages and the implementation of proper processing conditions for reducing mycotoxigenic fungi and by extension control the presence of mycotoxins in food products. The conventional methods i.e., physical, chemical and biological strategies for detoxifying mycotoxins in foods are showed in (Fig. 2), with available literatures reviewing their mechanisms, merits and applicability (Haque et al., 2020; Luo, Zhou, & Yue, 2018; Magan & Aldred, 2007). Although the conventional physical, biological and chemical approaches can reduce fungi and mycotoxin contamination to safe levels, majority of these approaches may lead to significant alterations in the food substrate such as color, flavor, texture and nutritional content like lipid oxidation, breakdown of vitamins and depolymerization and re-polymerization of polysaccharides (Zhang, Wang, Zeng, Han, & Brennan, 2019). Besides, most mycotoxins possess chemical and thermal stability during conventional food processing (Mokhtarian et al., 2020; Okeke et al., 2018). Thus, there is increasing interest in innovative strategies without direct heat application that will lead to notable decline in the concentration of mycotoxin in foods, and at the same time improve organoleptic quality.

Related evaluations and discussions on the trends in applying these innovative strategies are vital for the development of these strategies towards the effective control and reduction of mycotoxins and overall safety of foods. Therefore, this review appraised the statuses of recent

Table 1
Classes of mycotoxins based on symptoms and diseases caused to animals and humans.

Classes	Symptoms and diseases	Representative mycotoxins
Cytotoxins	Cytotoxicity, mutagenic effects and hematological disorders in animals and humans	Alternariol, enniatin B and trichothecenes
Genotoxic	Genotoxic, cytotoxic and DNA damage	Alternariol
Hepatotoxins	Impaired renal function, immuno suppression and liver cancer	Fumonisin B_2 and aflatoxins B_1, B_2, G_1, G_2, M_1 and M_2
Immunosupressant toxins	Carcinogenic, impairment of immune system, nephrotoxicity and ability to cope with infections	Trichothecenes, deoxynivalenol and ochratoxins
Nephrotoxins	Renal failure	Ochratoxins
Neurotoxins	Brain bleeds, nervous system damage and carcinogenic to humans	Patulin, fumonisins and ochratoxin A
Oestrogenic toxins	Degeneration of reproductive cells and cancer	Zeralenone
Respiratory toxicants	Airways damage and toxicity	Fumonisins and trichothecenes
Food rejection and vomiting inducing toxins	Induce apathy, vomiting and food rejection	Deoxynivalenol

Adapted from Pleadin, Frece, and Markov (2019); Alina (2022); Awuchi et al. (2021).

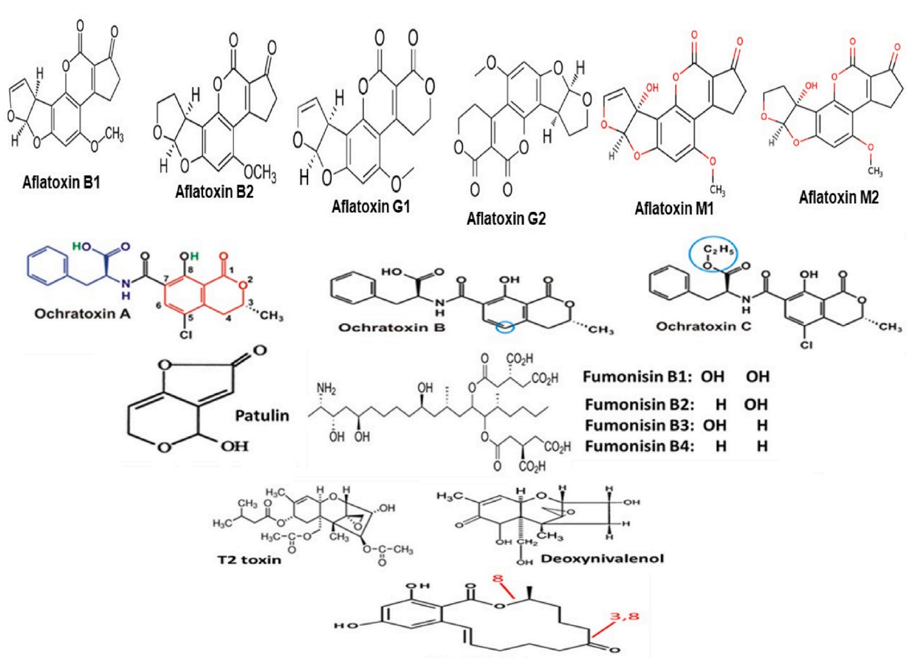

Fig. 1. Chemical structures of the main mycotoxins in foods.

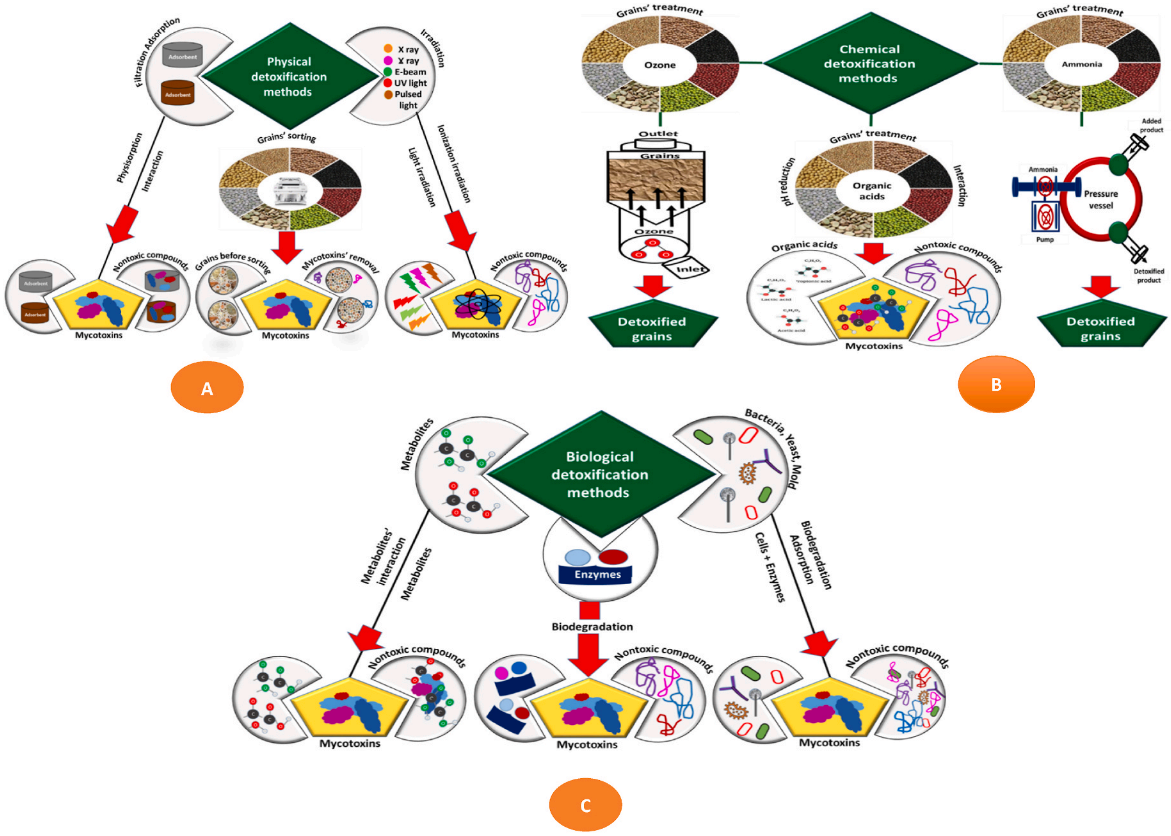

Fig. 2. Conventional methods: (A) physical, (B) chemical, and (C) biological for detoxifying mycotoxins in foods.

innovative strategies like cold atmospheric plasma (CAP) technology, polyphenols and flavonoids, magnetic materials and nanoparticles and natural essential oils (NEOs) for controlling mycotoxins in foods. The factors influencing the mycotoxins production and contamination in foods, the implications and prospects of the recent innovative strategies are also critically discussed.

2. Factors influencing mycotoxin production and contamination in foods

Mycotoxins can grow on a wide range of agricultural and food products and the most common source of exposure to humans are contaminated cereals, cereal-based products and food produced from animals exposed to mycotoxins (Perši, Pleadin, Kovačević, Scortichini, & Milone, 2014). Contamination can occur from pre-harvest to post-harvest stages along the food management chain and the presence of fungi does not necessarily translate to mycotoxin contamination, as mycotoxins production conditions are specific and independent of fungal growth conditions (Kochiieru et al., 2020). The food safety management system (FSMS), which is a system of preparedness, checks and prevention for managing food hygiene and safety in food businesses has been proposed as a possible approach that could influence or prevent mycotoxin production in agricultural products and foods (Nada, Nikola, Bozidar, Ilija, & Andreja, 2022). The FSMS was seen as a practical tool for controlling the food production process and environment for ensuring the safety of the final products for consumption and typically includes procedures and management policies based on good hygiene practices (GHP), good agricultural practices (GAP), good storage practices (GSP), good manufacturing practices (GMP) and hazard analysis and critical control point (HACCP).

For instance, optimal storage practices for foods and feeds including appropriate relative humidity (RH), temperature and moisture could produce undesirable conditions for fungal growth and stop mycotoxins production. Drying corn up to 15.5% moisture content or less before storage reduced the hazard of mold growth and mycotoxins synthesis, while lowering the moisture content on groundnuts to 6.6% ensured the nuts were free of mold and toxins for six months (Awuah & Ellis, 2002). Comparatively high CO_2 and low O_2 (1–5%) in storage systems significantly decreased *Aspergillus* growth and biological aflatoxin production (Magan & Aldred, 2007). Additionally, co-mixing grains during storage can increase their susceptibility to mycotoxins contamination, while prolonged storage time can result in the increase of the fungal biomass at enhanced moisture content as the produce transpire. A significant production of Ochratoxin A with increasing storage period at higher water activity and suitable temperature for fungi growth attributed to *Aspergillus carbonarius* contamination has been reported (Lappa, Kizis, & Panagou, 2017).

Implementing the HACCP system can play a crucial role in mycotoxin inhibition and control, since the system guarantees the achievement of good practices in the field, storage, sorting, monitoring and segregation stages with improvement measures (FAO, 2001). A comprehensive manual on the application of the HACCP system for controlling and preventing mycotoxin production identifies stages for monitoring systems and steps in processing where mycotoxins can be prevented or eradicated (FAO, 2001; Nada et al., 2022). However, a recent study on mycotoxin hazard analysis revealed land preparation (tillage, crop rotation, cover cropping), planting and intercropping, application of botanical extracts and fungal biocontrol agents as the most important pre-harvest practices that can influence/control mycotoxin production (Nada et al., 2022). Intervention treatments, especially cold plasma, ultraviolet light and ozone were also identified as important postharvest operations. But these practices may be influenced by climatic factors and local specificities.

Climatic factors, variations in the micro-ecosystem and moisture of the encompassing surroundings affects the development and intensity of mycotoxins. For example, the ideal temperature for fungal growth and production of mycotoxins ranges from 5 to 40 °C, with an optimal value at 25 °C, and this range is influenced by strains, species, growth conditions and the postharvest temperature (Hassane et al., 2017; Nayak et al., 2017). Higher temperatures hinder fungal growth and the production of mycotoxins from damage to the gene expression profile, although mycotoxins have been reported to survive cooking up to 110 °C for 20 min (Gacem & Ould El Hadj-Khelil, 2016; Zhou, Chen, Kong, Ma, & Liu, 2017). Most fungi are aerobic (Ivarsson, Schnürer, Bengtson, & Neubeck, 2016), on the other hands, a few can be facultative anaerobic organisms such as yeasts; thus, their biomass cannot be affected by higher CO_2 levels (Brzonkalik, Hümmer, Syldatk, & Neumann, 2012). Regarding pH, mycotoxins are synthesized under acidic conditions of 4–4.5 pH, while alkaline conditions reduce the growth of fungi and the secretion of mycotoxins (Moreno-Pedraza et al., 2015). Abundant varieties of mold can grow at water activities of 0.87–0.99, whilst mycotoxin production is inhibited at water activities <0.93 (Leggieri, Decontardi, Bertuzzi, Pietri, & Battilani, 2017). Extreme wet periods and rains prior to harvest were reported to influence the levels of mycotoxins in wheat and eruption of aflatoxin in corn (Centers for Disease Control and Prevention CDC, 2004; Bianchini et al., 2015). Generally, agricultural products in subtropical and temperate regions are easily susceptible to mycotoxin contamination in comparison with tropical regions that are unsuitable for fungal growth and mycotoxin production. Besides, drying of cereals after harvest helps to reduce the moisture content for inhibiting fungal growth and mycotoxins production, and drying at temperatures ≥42 °C have been recommended (Hassane et al., 2017).

The degree of mycotoxin synthesis and contamination is also strongly dependent on local specificities like the substrate type, fungal and nutrient composition. Mold may be found in virtually all kinds of food since the nutrient necessary for the growth of mycotoxigenic fungi is predominantly nitrogen and carbon, present in most food items that are rich in carbohydrates. Tryptophan reduces the growth of fungi, but tyrosine and other nutrients like glucose, lipids and fructose improves mycotoxin production (Gacem & Ould El Hadj-Khelil, 2016). However, numerous factors like composition, temperature, pH and osmotic pressure of the substrate may influence growth, thus the interaction between numerous factors within the substrates are vital (Kokkonen, Jestoi, & Rizzo, 2005). Besides, sugars are naturally major sources of carbon and most filamentous fungi can produce energy for supporting growth from hydrolysing sugars, especially the simple sugars that can be easily

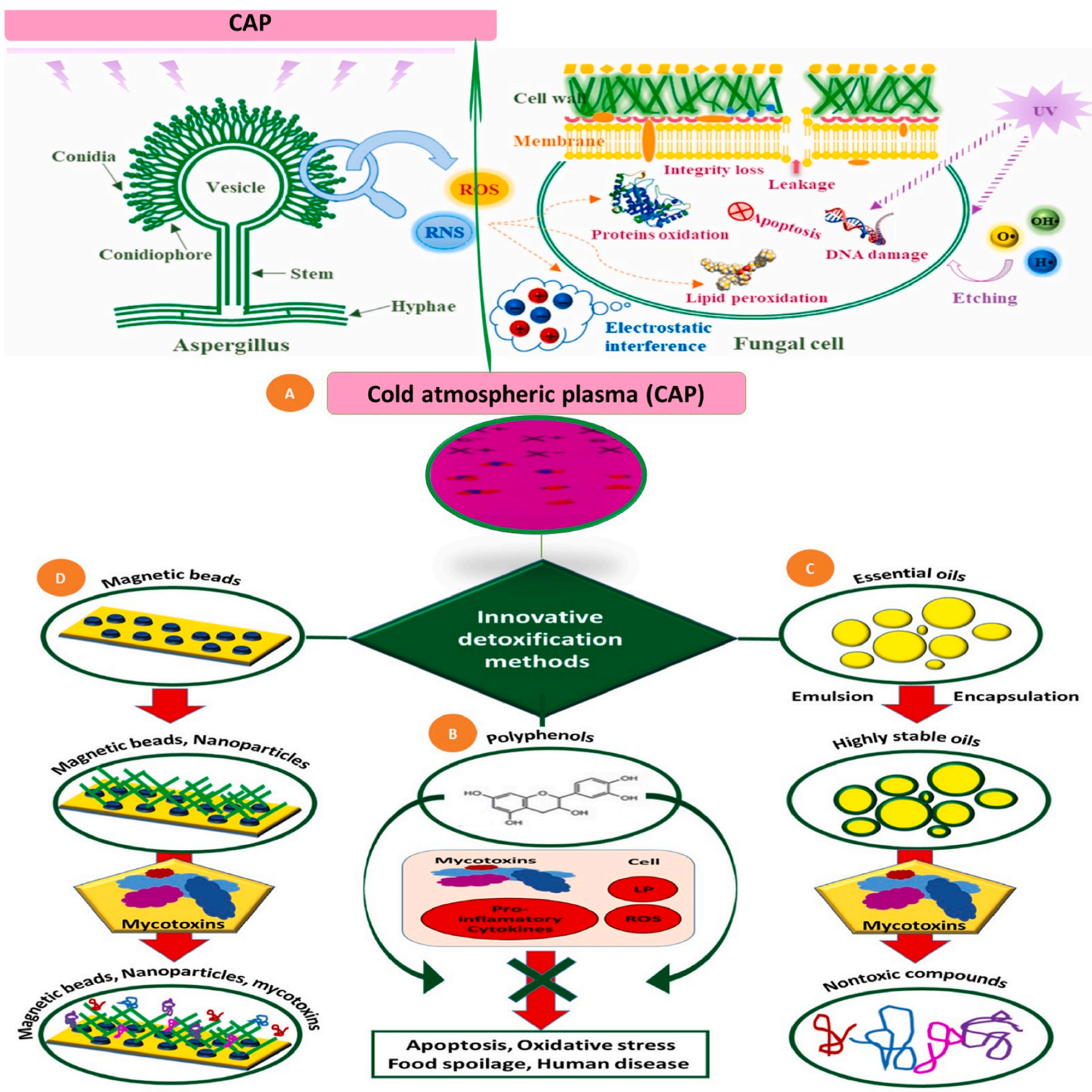

Fig. 3. Innovative strategies for controlling mycotoxin contamination in the foods and their underlying mechanisms i.e., (A) cold plasma (Adapted from Wu et al., 2021), (B) polyphenols, (C) natural essential oils and (D) magnetic and nanoparticles.

induced or readily accessible for breakdown, and increasing the sugar content of media has been linked with more AFB_1 production by *A. flavus* (Liu et al., 2016; Uppala, Bowen, & Woods, 2013). In addition, mycotoxin production may be influenced by the variations, specificity and stability of the fungal strain, since fungal species vary in their level of toxicity and conditions necessary for the growth and promotion of toxins, and mycotoxin production may be limited to particular types of fungi specie or strain (Greeff-Laubscher, Beukes, Marais, & Jacobs, 2020). It was reported that *Aspergillus flavus* and *Aspergillus carbonarius* produced aflatoxin B_1 and ochratoxin at different temperatures of 15–44 °C and 8–40 °C, respectively (Mannaa & Kim, 2017).

3. Recent innovative strategies for controlling mycotoxin contamination in foods

The increasing consumer awareness to food safety and the need for advanced approaches for controlling mycotoxin contaminations, toxicity and accompanying diseases without toxic residuals on foods, with negligible impact on quality has directed research into some innovative strategies of cold atmospheric plasma (CAP), polyphenols and flavonoids, magnetic materials and nanoparticles and natural essential oils (NEOs) (Fig. 3). Besides, Table 2 presents a summary of the recent innovative strategies and their mechanisms and limitations for controlling mycotoxins in foods (Ahmed et al., 2022; Cai et al., 2022; Chtioui, Balmas, Delogu, Migheli, & Oufensou, 2022; Diao et al., 2022; Gavahian, Pallares, Al Khawli, Ferrer, & Barba, 2020; Guimarães & Venâncio, 2022; Nasrollahzadeh, Mokhtari, Khomeiri, & Saris, 2022; Sen, Onal-Ulusoy, & Mutlu, 2019; Jafarzadeh, Hadidi, Forough, Nafchi, & Mousavi Khaneghah, 2022; Wang et al., 2022).

3.1. Cold plasma

Plasma is partially or fully ionized gas generally known as the fourth state of matter, and is generated from the application of electric current through neutral gas that causes the dissociation of the gaseous molecules (Kiš et al., 2020; Wielogorska et al., 2019). Plasma is discharged when the applied voltage exceeds the breakdown voltage to create reactive oxygen and nitrogen species (RONS) and non-thermal cold plasma can be generated at atmospheric pressure under ambient temperature conditions with relatively low energy consumption (Hojnik et al., 2021; Wielogorska et al., 2019). Cold atmospheric plasma (CAP) can be applied directly or indirectly by exposing water, solutions of buffers and acids to plasma discharge to create broad-spectrum washing sanitizers (Ali, Sun, Cheng, & Johnson Esua, 2022; Esua, Cheng, & Sun, 2021). The

Table 2
A summary of recent innovative strategies for controlling mycotoxins in foods and their limitations.

The strategy	The main findings	The limitations	Reference
The use of botanical naturally occurring phenolic compounds extracts	-Inhibition of mycotoxin production through their antioxidant properties, downregulation of the gene's expression and structural modifications of the fungal membrane	-Further studies are required to determine the safety and mechanisms of polyphenols depending on mycotoxin-producing fungi	Ahmed et al. (2022)
Detoxification of hazelnuts by different cold atmospheric plasma (CAP) and gamma irradiation (GMI) treatments	-Great potential to be a substitute to conventional approaches as well as maintains the organoleptic qualities	-Future *in vivo* studies are essential to assess the toxicities of breakdown products of total AFs and AFB_1 by cytotoxicity tests	Sen et al. (2019)
Natural essential oils (NEOs)	-The polyphenols attack and damage of the cell wall or cell membrane of the microorganisms	-NEOs safety is linked to its type, receptor, dosage and action time, as well as more studies is still needed	Cai et al. (2022)
Natural phenolic compounds against *Fusarium*	-Inhibition of trichothecene biosynthesis by the exogenous polyphenols -Phenolic compounds act as an eco-friendly approach to mitigate the issue of food contamination	-Its efficacy depends on the dose and target strain and when applied in the field/or industry, findings were inconsistent -Additional *in vivo* studies are needed on activity, bioavailability and toxicity	Chtioui et al. (2022)
Removal of patulin by thiol-compounds	-Ability to remove patulin efficiently in apple juice with no dramatical effects on the juice's quality -The mechanism of patulin reaction with several functional groups has been shown in –SH, –OH and –NH2 groups on the nucleophiles through forming the hydrogen bonds	-The animal toxicity investigations and epidemiological experiments must be done in the nearest future in order to assess the safety of thiol-compound adsorbents and contaminated juice	Diao et al. (2022)
The use of saturated fatty acids, unsaturated fatty acids and oxylipins, as antifungal agents	-The fatty acids have a wide inhibitory impact to mycotoxins production - Fatty acids' mechanism against the mycotoxin production included the targeted enzymes, cell membrane and interference in metabolic	-Fatty acids act as natural and eco-friendly antifungal, whereas being less likely to indorse fungal resistance - More studies are needed for oxylipins to ensure the free/lack of toxicity	Guimarães and Venâncio (2022)
The control of fungi and its mycotoxins by active food packaging	-Biopolymers like polysaccharides, lipids, proteins and/or their blends are environmentally friendly approach due to its biodegradable properties	-Further research particularly through combination of active packaging with the emergent technologies are recommended	Jafarzadeh et al. (2022)
Mycotoxin detoxification of food by lactic acid bacteria (LAB) as bio preservation and biodetoxification strategy	- LAB has a great potential in detoxification activities against mycotoxins released into foods - LAB reduced of mycotoxins biosynthesis	- Further experiments regarding LAB in the biochemical basis of the detoxification mechanism are required	Nasrollahzadeh et al. (2022)
Reduction of AFB_1 in corn by water-assisted microwave treatment (WMT)	-WMT could diminish AFB_1 effectively and avoid the vast attendance of heat-damaged corn kernels -WMT has a little consequence on the corn color	-The exact processes and mechanisms are not yet fully understood and consequently have a restriction in their application in foods	Zhang, Li, M., Liu, Guan, E., & Bian, (2020).
A combination of *Trichoderma* spp. and selenium nanoparticles	-The proposed mode of action is damage of fungal hyphae. - Mycotoxin production and their genes were meaningfully reduced after the treatment - *Trichoderma* spp.-derived nano-selenium showed greater bio-control impact than single nano-selenium	-Further studies are required to determine the mechanisms of biogenic nanoparticles depending on mycotoxin-producing fungi and the targeted mycotoxins, as well as their potential health concern	Hu et al. (2019)
Alternaria mycotoxin (AM) degradation and quality evaluation of jujube juice by cold plasma treatment (CAP)	-CAP can effectively degrade the AM mycotoxins and has optimistic outcome on brightness, quality and physical stability of jujube juice	-Future studies are recommended in order to investigate their impact on the physicochemical qualities in other food products	Wang et al. (2022)

antimicrobial properties and the ability to degrade complex biochemical molecules is attributed to the unique blend of reactive chemistries like O_2^-, O_3, H_2O_2, •OH, $ONOO^-$, NO_2^-, and NO_3^-, UV photons and electric field, which remain close to ambient temperature to confer the non-thermal characteristics (Esua, Sun, Cheng, Wang, & Chen, 2022; Hojnik et al., 2021; Sen et al., 2019; Wielogorska et al., 2019).

Thus, non-thermal CAP is considered a cheap and fast innovative strategy for decontaminating pathogenic microorganisms in foods and agricultural products, without significant effects on quality (Esua, Cheng, & Sun, 2020).

But the efficiency is dependent on the molecular structure of the mycotoxin and processing conditions. For example, the degradation efficiency of deoxynivalenol (DON) on wheat was demonstrated to be influenced by the plasma voltage, gas type, processing time, matrix characteristics and moisture content of the food. However, 50 kV and 8 min from atmospheric air plasma was enough to cause 25.82% reduction, and high moisture was beneficial as efficiency improved from 9.59 to 36.10% with increasing moisture content from 8 to 20%. Negligible effects were observed in wheat quality except a slight increase in whiteness (Chen et al., 2022). Likewise, the degradation efficiency of T-2 toxin and its major metabolite HT-2 toxin on oat flour were influenced by the flour humidity, exposure time and the gas type used for generating cold plasma. The samples were efficiently oxidized by oxygen atoms from cold plasma to produce CO and N_2 necessary for achieving the highest reductions of 43.25% and 38.54% for T-2 and HT-2 toxins, respectively, when N_2 was employed as the generating gas (Kiš et al., 2020). In another study, increasing the applied voltage from 10 to 30 kV ensured 1.3–56.5% and 8.1–62.8% reductions, respectively in alternariol (AOH) and alternariol monomethyl ether (AME) produced by *Alternaria* that were added to jujube juice, with significant decrease in juice °Brix and increases in reducing sugar, total acids, physical stability and antioxidant activity (Wang et al., 2022).

Furthermore, corona discharge plasma was revealed as the simplest and best reproducible source of multiple oxidants, and optimal degradation of AFB_1 in the range of 45–56% was achieved in spiked rice and wheat after 30 min (Puligundla, Lee, & Mok, 2020). The reduced bioactivity of AFB_1 was attributed to the disappearance of the C8=C9 double bond in the furofuran ring as well as the modification of the lactone ring, cyclopentanone and the methoxyl group from the combined oxidative effects of HO_2, OH•, H_2O_2, O_3, H•, OH•, CHO•, UV photons and electrons. CAP was also demonstrated to be more effective for reducing AFB_1 and AFB_1+AFB_2 (total aflatoxins) spiked on hazel nut at 70–73% when compared with 15–47% for gamma irradiation, with minimal effects on sensory attributes (Sen et al., 2019). The promising potential of CAP for generating harmless products during mycotoxin degradation has also been demonstrated (Wielogorska et al., 2019). In this study, the reduction of AFB_1, fumonisins B_1 (FB_1), OTA, DON and zearalenone (ZEN), enniatin B (ENB) followed first order kinetics with ENB presenting the lowest half-life of 1.1 min in comparison with 74 min for DON. Exposure time of 10 min was enough to ensure 64 and 65% reductions in FB_1 and AFB_1, respectively, from spiked maize values of 259 and 1.25 ng/g. Degradation products were only detected with AFB_1 and ZEN, but showed no increase in cytotoxicity when tested on hepatocarcinoma cells.

Several pathways have been proposed for CAP-induced mycotoxins degradation. Such degradation could be governed by the properties of the plasma employed like the concentration of oxygen, hydroxyl radicals, the presence of photons and ultraviolet radiation (Gavahian & Cullen, 2020). Also, CAP species act on multiple sites of the fungal cell resulting in loss of function and structure, and ultimately cell death. Likewise, the species cause chemical breakdown of mycotoxins through various pathways resulting in degradation products that are known to be less toxic (Misra, Yadav, Roopesh, & Jo, 2019). Gavahian and Cullen (2020) reported that plasma-generated reactive species can alter the cell membrane and cell walls to release the cytoplasm of fungi leading to cell inactivation. A similar mechanism was proposed by Lee et al. (2015) who hypothesized that plasma-generated reactive species inactivated the spores of *Cordyceps bassiana* by altering the morphology of the spores. They observed that the plasma-treated spores were shrunken, flattened and ruptured. In addition, Wu, Cheng, and Sun (2021) summarized the mode of action of CAP and suggested that the mechanisms of detoxifying aflatoxins by CAP involved destroying or oxidizing fungal cell structure, interrupting cell components and cell metabolism, resulting in fungal death (Fig. 3A). Overall, the inactivation mechanism of fungus by non-thermal CAP is linked to induced oxidation that may increase the permeability of the cell membranes by damaging the cell walls, leading to DNA fragmentation and leakage, destruction of cellular proteins, cell apoptosis and the deformation of mycelial spore.

3.2. Polyphenols and flavonoids

Phytonutrients mainly polyphenols and flavonoids have recently been applied in various food systems due to their biological activities, particularly antiviral, antibacterial, antioxidant and anti-inflammatory properties (Mehany et al., 2021). The molecular mechanisms of polyphenols and flavonoids against mycotoxins varies (Fig. 3B) and may be viewed from different perspectives: (I) their antioxidant properties and lipophilicity seem to play a major role in their bioactivity, (II) inhibition of mycotoxin production through structural modifications of the fungal membrane, (III) downregulation of the gene's expression involved in the mycotoxin production and (IV) inhibition of the enzymatic activity (Ahmed et al., 2022). In this regard, Hamad et al. (2021) recommended the use of natural plants extracts and their polyphenols as a vital approach for inhibiting fungal growth and mycotoxin production. For example, polyphenols were demonstrated as having inhibitory effects against the accumulation of patulin such that the genes involved in the biosynthetic pathway of patulin were down-regulated by umbelliferone and quercetin (Sanzani, Schena, Nigro, de Girolamo, & Ippolito, 2009). The inhibitory effects of chlorogenic and gallic acids against the occurrence of AFB_1 in edible beans was also confirmed in a study to determine the inhibitory capacity of phenolic compounds against mycotoxin production (Telles, Kupski, & Furlong, 2017). At least 95% reduction in patulin accumulation was achieved when flavanones such as hesperidin, neohesperidin, hesperetin glycoside and naringin extracted from the byproducts of citrus were tested (Salas, Reynoso, Céliz, Daz, & Resnik, 2012). Makhuvele et al. (2020) revealed that bioactive phenols coupled with β-cyclodextrin-based on nanosponge technique presented promising potential for inhibiting fungal attack and detoxifying mycotoxins. Natural dietary complexes containing numerous nonnutritive active compounds typically display antioxidant potential and other medicinal characteristics, and studies have revealed that these bioactive molecules and natural herbal extracts possess the capacity to reverse the adverse effect of mycotoxins with considerable efficiency (Sharma & Patial, 2021). Together, the few available studies on polyphenols and dietary fiber interventions suggests that they could be promising approaches for countering the harmful effects of fungus and its mycotoxins in the nearest future.

3.3. Natural essential oils

Natural essential oils (NEOs) and their bioactive molecules are considered as green additives against fungal growth and toxins that contaminate food products, as they are eco-friendly with low drug resistance and highly effective (Chaudhari et al., 2019; Mutlu-Ingok, Devecioglu, Dikmetas, Karbancioglu-Guler, & Capanoglu, 2020). The mechanisms of NEOs against fungi and their representative toxins (Fig. 3C) is attributed to the inhibition of the main enzymes responsible for the breakdown of carbohydrates, mycotoxin generation and the disruption of fungal cell and membrane (Tian et al., 2011). These were possible via various pathways: (I) influencing fungal gene expression, (II) disruption of the cell wall or cell membrane of the microorganisms by polyphenols and/or (III) damage to the structure of cell membrane and cell wall (Cai et al., 2022). The *in vitro* and *in situ* antifungal, AFB_1 inhibitory and antioxidant capacity of *Origanum majorana* L. essential oil encapsulated into nanoemulsion was demonstrated, indicating the promising potential as a novel food preservative against mycotoxins for improving food safety (Chaudhari et al., 2020). In other studies, capsaicin inhibited the production of OTA in grapes by *Aspergillus* section *Nigri* and *A. carbonarius* by 78.1 and 61.5%, respectively, while OTA production was completely prevented by garlic and wild oregano essential oils, and bio-synthesis was significantly reduced by sage and mint essential oils (Kollia, Proestos, Zoumpoulakis, & Markaki, 2019; Ozcakmak et al., 2017). It has also been reported that turmeric oil can exhibit high anti-fungal activity against *A. flavus* and aflatoxins contamination in maize (Hu, Zhang, Kong, Zhao, & Yang, 2017), while the capability of *Mentha spicata* essential oil for inhibiting toxin production by *A. flavus* in chickpeas for up to one year was attributed to the plasma membrane (Kedia, Dwivedy, Jha, & Dubey, 2016). NEOs have also shown great potential for inhibiting ZEN, where essential oils from grapefruit, lemon, palmarosa oils and eucalyptus influenced ZEN levels and *Curcuma longa* essential oil completely repressed the growth of *Fusarium graminearum* and zearalenone formation to low levels of 3 and 3.5 mg/L, respectively (Naveen Kumar et al., 2016; Perczak et al., 2016).

3.4. Magnetic materials and nanoparticles

Studies have emerged in recent times to support the eco-friendly, low cost and effective means of controlling mycotoxins through the use of magnetic materials and nanoparticles. For example, magnetic particles (Fe_3O_4) that were coated with chitosan was shown to be effective for the adsorption of patulin from fruit juice, and the conjugation of nanocellulose with retinoic acid could adsorb AFB_1 from a variety of food items without any trace of toxicity, depending on the concentration and pH (Jebali, Yasini Ardakani, Sedighi, & Hekmatimoghaddam, 2015; Luo, Zhou, & Yue, 2017). Magnetic nanoparticles like nano-clay, nano-gel, surface-active maghemite, nanomaterials like zinc oxide nanoparticles (ZON), silver nanoparticles (SLN), copper nanoparticles and selenium nanoparticles (SEN) were effective for removing and binding mycotoxins in agricultural feedstuff and foods (Abd-Elsalam, Hashim, Alghuthaymi, & Said-Galiev, 2017; Magro et al., 2016). FB_1 and DON were reduced by 63 and 76% respectively by SEN produced from *Trichoderma harzianum* JF309 (Hu et al., 2019). SLN prevented the growth of ochratoxigenic and aflatoxigenic fungi and the accumulation of OTA and aflatoxin in a maize-based medium, the use ZON was effective against the growth of *Fusarium* spp., *Aspergillus* spp., and *Penicillium* spp. and the production of FB1, OTA, and AFB_1 in food model systems (Gómez, Tarazona, Mateo, Jiménez, & Mateo, 2019; Hassan, Howayda, & Mahmoud, 2013).

In addition, magnetic carbon nanocomposites synthesized from maize by-products showed great potential for detoxifying AFB_1 in poultry and ensured adsorption of up to 90% at pH 7 within 180 min of application, while a cross-linked chitosan-glutaraldehyde complex was revealed as an effective multi-toxin adsorbent material and presented the highest adsorption of numerous mycotoxins among the different adsorbent materials tested (Zahoor & Ali Khan, 2016; Zhao et al., 2015). The potential of nano-fungicides made from essential oils and phytochemicals like eugenol, caffeic acid, catechols, phloretin, tannins and thymol that showed antifungal and antibacterial activity for inhibiting the growth of toxigenic fungus and mycotoxin contamination without posing any risks to animals and humans were also demonstrated (Thipe, Keyster, & Katti, 2018).

The molecular mechanism of nanoparticles for eliminating the risk of mycotoxins (Fig. 3D) is associated with their role as oxidative stress inductors, inflammatory agents, or their interaction with nucleic acids that contributes to the destruction of microorganisms in both higher plants and animals (Horky, Skalickova, Baholet, & Skladanka, 2018). The interactions with the cell membrane typically results in apoptosis induction, ROS production, inhibition of mitochondrial functions, lipid peroxidation, or autophagy. Accordingly, ZON producing reactive oxide species (ROS) was reported to damage the lipid bilayer cell membrane of fungal hyphae, causing a total breakdown of the affected cell that was evident from the formation of unusual bulges and deformation on the surface of fungal hyphae after treatment with 12 mmol/L ZON, observed from scanning electron microscopy (Pietrzak, Twarużek, Czyżowska, Kosicki, & Gutarowska, 2015). In another study, it was proposed that the relaxed polysaccharide structure of chitosan in a quercetin (Q)-loaded chitosan (CS) nanoparticle was cross-linked with tripolyphosphate (TPP), with the quercetin entrapped in the CS structure to trigger a hepato-protective cascade that leads to antioxidant protection via the stimulation of nuclear factor E2-related factor 2 (Nrf2)-induced heme-oxygenase-1 (HO-1) production (Sun et al., 2015). Quercetin inhibits lipopolysacharide (LPS) induced nitric oxide synthase (iNOS) and NO production via IκB kinase (IKK) and p38 mitogen-activated protein kinases (p38MAPK), and the transcriptional response is mediated by the acting element of antioxidant response element (ARE) found in the genes encoding enzyme detoxication promoters. Horky et al. (2018) had reviewed the key properties of carbon nanoparticles such as fullerenes, carbon nanotubes and graphene (native graphene (G), graphene oxide (GO) and reduced graphene (rGO)) and the possible binding interaction with mycotoxins (Fig. 4). Mycotoxins can be bound to the surface, bundles, grooves, or channels between these nanoparticles through different binding interaction, but so far, the interaction of NPs with the individual components of the fungi cells is still lacking and yet to be investigated.

3.5. Other recent innovative strategies

Pulsed electric fields (PEF) has been applied to food products for the purpose of inactivating fungi and their mycotoxins, especially the removal of aflatoxin B_1 and G_1 produced by *Aspergillus* (Gavahian et al., 2020). In another study, PEF has been categorized amongst the most capable and cost-effective innovative food processing procedures for detoxification of aflatoxins, fumonisins, zearalenone, OTA and trichothecenes in foods, but specific food-target assessment prior to integration in the food industry was recommended (Nunes, Moosavi, Khaneghah, & Oliveira, 2021). The reduction of Aflatoxin B_1 in corn by water-assisted microwaves treatment (WMT) has also been studied (Zhang, Li, M., Liu, Guan, E., & Bian, (2020). The findings indicated that WMT eliminated AFB_1 efficiently and could avoid the immense appearance of heat-damaged corn kernels concurrently, providing the novel idea for AFB_1 decrease by microwave strategy. Likewise, the utilization of high-pressure treatment (HP) for the significant reduction of several mycotoxins in juice samples have been studied (Gavahian et al., 2020). Moreover, the control of fungi and detoxification by active food packaging technology was categorized as an effective way to decontaminate and control fungi and their mycotoxins in several foods including fruits, nuts, bakery products, cereal grains and dairy products (Jafarzadeh, Hadidi, Forough, Nafchi, & Mousavi Khaneghah, 2022). Biopolymers like polysaccharides, lipids, proteins, and/or their blends present cost effective and environmentally friendly approaches, owing to their biodegradable nature.

More recently, food additives mainly calcium bentonite (Ca-bentonite), and sodium bentonite (Na-bentonite) were applied as novel strategies for eliminating OTA from some cheese types, and the detoxification effect of bentonite were determined both *in vitro* and *in vivo* (Hamad et al., 2022). The examined Karish and Roomy cheeses displayed higher OTA concentrations of 3.399 and 4.138 μg/kg, respectively, and Ca-bentonite offered higher adsorption efficiency when compared with Na-bentonite at concentrations of 60 and 100 mg/mL and pH ranges in Phosphate-buffered saline (PBS). *In vivo* studies revealed that the enzymatic activities were close to the control sample in treated rats for both OTA and bentonite in comparison with OTA alone. Furthermore, bentonites were characterized by scanning electron microscopy (SEM) and Fourier transform infrared spectroscopy (FTIR) as

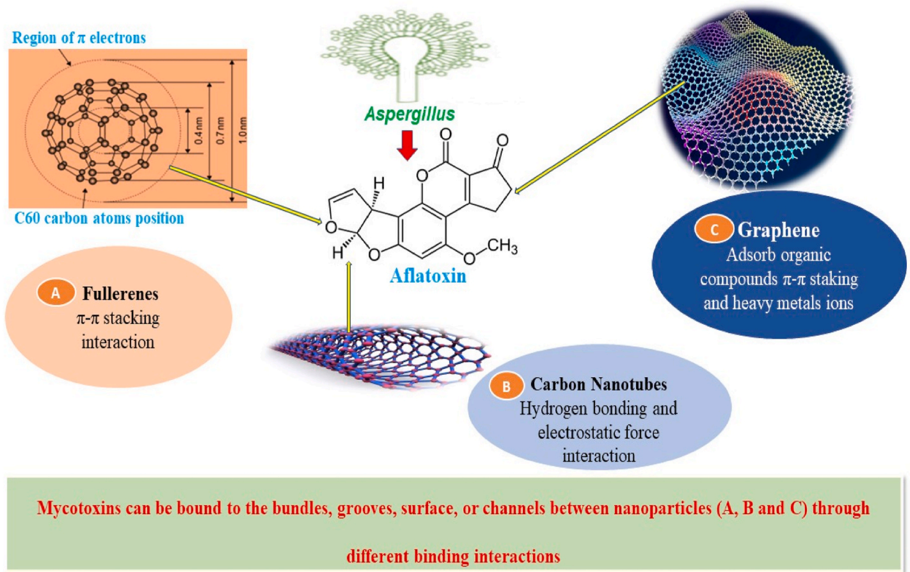

Fig. 4. Binding interactions of carbon nanoparticles with mycotoxins i.e., (A) fullerenes, (B) carbon nanotubes and (C) graphene.

exceptional OTA binder, and the developed Ca-bentonite-supplemented feta cheese presented improved sensory attributes. This method was considered a novel and innovative food grade adsorbent strategy for OTA separation and/or removal in food-stuffs.

4. Conclusions, implications and outlook

Mycotoxin occurrence and contamination along the agricultural produce, food and animal feedstuff management chain is of global concern owing to their toxicity and the danger they pose to both human and animal health, and the associated economic losses. Even with the implementation of the prerequisite programs of the food management systems like GAP, GMP, GSP, GHP and HACCP based procedures at the appropriate stages of pre-harvest, postharvest and processing, mycotoxin contamination is unavoidable (Nada et al., 2022). Early and swift detection is therefore vital for elimination, overall safety of foods, and preventing the related health problems. Increasing consumer awareness to food safety, regulatory issues, potential formation of carcinogenic by-products, limited efficiency and potential alterations in quality have limited the applications of conventional chemical, biological and physical detoxifying methods. Besides, increasing resistance, especially by new strains to the conventional methods has geared research towards innovative strategies for the rapid control, reduction and elimination of mycotoxins in foods with short processing time and negligible impact on morphological, physicochemical, textural, structural properties of food and the environment as well.

The current review revealed the contributions of some recent innovative strategies of CAP technology, polyphenols and flavonoids inhibitors, magnetic materials and nanoparticles and NEOs for inhibiting toxigenic fungal growth, reducing and detoxifying mycotoxin contaminations in foods. The innovative approaches presented considerable efficiency and were suggestively dependent on a range of intrinsic factors like substrate type, degree of contamination, moisture content, chemical constituents and extrinsic factors of decontamination method and processing conditions. CAP technology presented an economic and safe alternative to the conventional thermal methods with promising potential for meeting the demand for sustainable development, but the efficiency is dependent on RONS produced, and by extension the gas type. Besides, the use of CAP may be viewed as adding nitrites to foods which can decrease rapidly over time and be converted to N-nitroso compounds with potential health effects (Esua et al., 2021). This is a challenging issue and appropriate amounts need to be maintained according to the Food and Drug Administration (US FDA) regulations for edible portions of finished products. In addition, longer exposure time is required for complete removal and the alternative of indirect application can be explored.

The NEOs also presented the advantages of being eco-friendly and efficient, but may be limited by low bioavailability, high volatility, instability to oxidation and insolubility (Loi, Paciolla, Logrieco, & Mulè, 2020). Magnetic materials and nanoparticles present great potentials in various aspects of the food, agriculture and livestock industry, and their adsorbent capability on mycotoxins is a great addition, but like the phytochemical inhibitors, application is still at infancy. The antifungal mechanisms of these strategies are still not properly understood and there is no clear perception of their possible side effects, especially the magnetic materials and nanoparticles and this may limit their full potential and applications. The mechanisms of detoxification and their capability to retain nutritional and organoleptic properties, in addition to toxicity studies of the residual components warrants thorough investigation in order to prevent recontamination of foods.

So far, none of the innovative strategies achieved 100% efficiency nor were universal for all matrices, but with the increasing awareness for environmental protection, the innovative strategies reviewed provides critical insights for the accelerated development of promising green technologies for mycotoxin decontamination. Besides, with the multi-dimensional approach to decontamination studies and advances in technology, integrated management systems of combining multiple methods from both the conventional and innovative strategies can be explored for achieving higher detoxifying efficiency and better adaptability to different food matrices. Finally, the studies are still in the laboratory level and underlines the need for multidisciplinary industrial collaboration involving economics and engineering for up-scaling and cost-effective commercialisation for sustainable food processing.

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Gamal M. Hamad: Conceptualization, Writing, Reviewing, Visualization & Supervision; **Taha Mehany:** Investigation, Formal analyses, Data curation, Software, Validation &Writing–Review & Editing; **Jesus Simal-Gandara:** Writing, Reviewing, Editing, Funding acquisition & Project administration; **Sarah Abou-Alella:** Writing &Visualization; **Okon J. Esua:** Writing–Review & Editing; **Mosaad A. Abdel-Wahhab:** Reviewing &Visualization; **Elsayed E. Hafez:** Reviewing & Visualization.

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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