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"The Interplay Between Nutritional Deficiencies and Susceptibility to Mycotoxicosis: Implications for Public Health and Food Safety"

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ABSTRACT

Mycotoxins are pervasive contaminants of staple crops in tropical and subtropical regions and pose a persistent threat to food safety and public health, particularly among nutritionally vulnerable communities. This systematic review synthesizes evidence published between 2020 and 2025 on the bidirectional relationship between nutritional deficiencies and susceptibility to mycotoxicosis, integrating mechanistic, observational, and intervention studies to provide an integrated perspective. We searched PubMed, Scopus, and Web of Science and screened studies that examined nutrient status, absorption, detoxification, immune function, and health outcomes associated with aflatoxins, fumonisins, ochratoxins, trichothecenes, and zearalenone. Results identify several convergent mechanisms by which poor nutritional status amplifies mycotoxin harm. Protein energy deficiency and inadequate micronutrients such as vitamins A, C, E, folate, selenium, zinc, and iron impair hepatic Phase I and Phase II detoxification enzymes, reduce antioxidant defenses, and weaken immune competence. Conversely, common mycotoxins damage intestinal architecture and downregulate nutrient transporters, creating malabsorption syndromes that perpetuate nutrient loss. This reciprocal interaction generates a toxico nutritional spiral that is most evident among children, pregnant women, and immunocompromised adults in low income settings, with documented consequences including stunting, anemia, and adverse birth outcomes. The review highlights the predictive value of nutritional biomarkers such as serum retinol, selenium dependent glutathione peroxidase activity, plasma folate, serum zinc, and urinary oxidative damage markers to stratify vulnerability and monitor interventions. Evidence for mitigation supports integrated approaches combining agricultural measures to reduce contamination, biofortification, targeted micronutrient supplementation, improved post-harvest storage, culturally appropriate food processing, and gut focused strategies such as probiotics. While heterogeneity in study design limited meta-analysis, mechanistic findings from in vitro, animal, and human studies converge to justify context specific trials of combined nutrition and food safety interventions. We conclude that reducing the burden of mycotoxicosis requires coordinated multisectoral policies that link nutrition programs with crop management and surveillance, and research that advances biomarker validation, omics based

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mechanistic discovery, and scalable delivery models. Implementing these strategies can disrupt the toxico nutritional spiral, protect vulnerable populations, and strengthen food system resilience against a changing climate. Policy makers, researchers, and communities must collaborate to translate evidence into action.

Keywords: Mycotoxicosis; Nutritional Deficiency; Detoxification Pathways; Toxico-Nutritional Spiral; Food Safety Interventions; Biofortification; Micronutrient Biomarkers; Intestinal Malabsorption; Vulnerable Populations.

INTRODUCTION

Background on Mycotoxins and Nutritional Vulnerability

Mycotoxins are a diverse group of toxic secondary metabolites produced by fungi such as *Aspergillus*, *Fusarium*, and *Penicillium*. These toxins commonly contaminate staple crops such as cereals, maize, groundnuts, and other nuts, especially under warm and humid conditions typical of tropical and subtropical climates. Such regions often experience both high rates of mycotoxin contamination and widespread nutritional inadequacies, creating an overlapping public health crisis [3].

Among the most studied mycotoxins are aflatoxin B1 and M1, known for their hepatotoxic, immunosuppressive, and carcinogenic effects [3]. The risks are further compounded in settings where dietary diversity is limited and food insecurity is common. Evidence shows that children in rural Tanzania, for example, are frequently exposed to both aflatoxins and fumonisins through contaminated staple foods, increasing their risk for growth impairment [4].

Beyond individual-level health effects, mycotoxins impose significant public health and economic burdens. Interventions such as agricultural control programs and food safety policies have shown varying degrees of cost-effectiveness in reducing exposure, but their implementation remains limited in low-income settings [5]. Importantly, the overlap between areas of high exposure and high rates of Protein-energy malnutrition has drawn attention to a synergistic interaction between mycotoxins and undernutrition that magnifies health risks [6,7].

Nutritional Determinants of Host Defense

Adequate nutrition is foundational for the body's defense against environmental toxins [6]. Key nutrients including protein, vitamins A, C, and E, folate, selenium, and zinc support the immune system and aid in detoxification processes [7]. Deficiencies in these nutrients, prevalent in under-resourced settings, compromise host resilience to toxins, including mycotoxins [8].

While the mechanistic roles of these nutrients in hepatic detoxification, immune modulation, and epithelial protection are acknowledged, detailed discussions are provided in the Results section (3.1–3.2) to avoid redundancy here.

Bidirectional Interaction between Mycotoxins and Nutrition

The relationship between nutrition and mycotoxins is not unidirectional. While undernutrition increases susceptibility to mycotoxicosis, mycotoxins themselves can impair nutrient utilization. Experimental and observational data suggest that aflatoxins and fumonisins disrupt nutrient absorption by damaging the intestinal epithelium and downregulating key nutrient transporters [4,8]. This can exacerbate existing deficiencies in essential micronutrients and contribute to the persistence of malnutrition.

Interestingly, not all studies have shown a direct linear relationship between mycotoxin exposure and anthropometric deficits. In a cohort study of Nepalese children, aflatoxin exposure during the first 36 months of life was not significantly associated with impaired growth, suggesting that the impact of exposure may depend on contextual factors such as baseline nutritional status, dietary diversity, or co-existing infections [9].

The concept of the toxico-nutritional spirals a cycle in which malnutrition and mycotoxin exposure reinforce each other has been proposed as a model to understand these complex interactions. Populations experiencing

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food insecurity, especially children and pregnant women, are particularly vulnerable to this spiral due to their higher metabolic demands and limited access to nutrient-dense foods.

Rationale and Objectives of the Review

Mycotoxins continue to pose a significant challenge to food safety and public health, particularly in nutritionally vulnerable populations. With climate change projected to exacerbate fungal proliferation and extend the growing seasons for mycotoxin-producing crops, the global risk of dietary exposure is expected to increase [10]. At the same time, genomic advances offer promising tools for predicting and mitigating contamination risks at the source [10].

This review aims to systematically evaluate the interplay between nutritional status and susceptibility to mycotoxicosis, with the following specific objectives:

To explore how malnutrition or nutrient deficiencies increase host vulnerability to mycotoxins;

To examine how mycotoxins, impair nutrient absorption and utilization;

To identify high-risk groups and discuss nutritional strategies for mitigation.

By highlighting this bidirectional relationship, the review seeks to support integrated approaches to food safety, nutrition, and public health policy that can reduce the burden of mycotoxin-related diseases in vulnerable communities.

MATERIALS AND METHODS

Overview

This section details the methodology employed to conduct a systematic review on the relationship between nutritional status and susceptibility to mycotoxicosis. A rigorous and structured approach was applied following internationally recognized standards for systematic review conduct and reporting. The process included comprehensive literature searching, transparent inclusion criteria, and critical appraisal using validated tools to ensure methodological integrity. The approach integrates evidence from both randomized and non-randomized studies, ensuring a robust assessment of the interaction between nutrition and dietary mycotoxins.

Search Strategy

A comprehensive search was conducted in PubMed, Scopus, and Web of Science for peer-reviewed studies published between January 2020 and March 2025 [11]. This timeframe was selected to align with the release of the PRISMA 2020 guidelines, as well as to capture emerging data related to mycotoxin exposure in the context of climate variability and recent nutritional surveillance updates [12].

Inclusion and Exclusion Criteria

Eligible studies were selected based on predefined inclusion and exclusion criteria. To be included, studies had to:

- Be published in peer-reviewed journals between 2020 and 2025,

- Be written in English,

- Investigate the relationship between nutritional status and dietary mycotoxins, and

- Report defined endpoints involving nutrient status, absorption, or physiological responses to mycotoxin exposure.

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Studies were excluded if they were editorials, preprints, conference abstracts, animal-only studies without translational relevance, or lacked clear nutritional or toxicological endpoints. These criteria helped streamline the review process and ensure that only studies relevant to the toxico-nutritional interface were analyzed [13].

Data Management and Risk of Bias Assessment

Screening and data extraction were conducted using Rayyan QCRI, a web-based software specifically designed for systematic reviews [14]. The initial screening was done independently by two reviewers based on titles and abstracts, followed by full-text assessment for eligibility. Conflicts were resolved by consensus.

To assess the methodological quality of included studies, multiple tools were applied based on study design. For randomized controlled trials, the RoB 2 tool was used to evaluate the risk of bias across five domains [13]. For scoping and observational studies, the PRISMA-ScR checklist was applied [15], and guidance from the Cochrane Handbook version 6.3 was followed [16]. Literature database combinations were optimized using evidence-based recommendations [17], and academic platform selection followed findings on the retrieval quality of search systems [18]. Reporting fidelity of search methods was ensured using PRISMA-S guidelines [19]. Non-randomized case series were appraised using the JBI tool [20].

Table 1 tabulates the validated tools, guidelines, and software used during literature searching, screening, bias assessment, and reporting for this systematic review. It links each review component (e.g., reporting standard, bias tool, screening software) to the specific instrument applied and its citation, providing transparency for the methods described in Section 2.

Table 1: Tools Used in Literature Screening and Review

Component	**Tool/Guideline Applied**	**Citation**
Review Reporting Standard	PRISMA 2020	[11]
Search String Validation	PRESS 2021 Checklist	[12]
Bias Assessment in RCTs	RoB 2 Tool	[13]
Screening Software	Rayyan QCRI	[14]
Observational Study Evaluation	PRISMA-ScR Checklist	[15]
Eligibility and Method Guidance	Cochrane Handbook v6.3	[16]
Database Search Optimization	Bramer Method for translating and Optimizing Search Strategies	[17]
Academic Search Platform Suitability	Gusenbauer & Haddaway, 2020	[18]
Search Method Reporting	PRISMA-S Statement	[19]
Case Series Appraisal	JBI Critical Appraisal Tool	[20]

Table of components used in the review process with columns showing the review component, the specific tool or guideline applied, and the citation for that tool. Entries include reporting standards (PRISMA 2020), search validation (PRESS 2021), bias tools (RoB 2), and screening software (Rayyan QCRI). Abbreviations: PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PRESS = Peer Review of Electronic Search Strategies; RoB 2 = Risk of Bias 2; JBI = Joanna Briggs Institute; PRISMA-ScR = PRISMA Extension

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for Scoping Reviews; PRISMA-S = PRISMA for Search Reporting; QCRI = Qatar Computing Research Institute.

Study Selection Flowchart

Figure 1 presents the PRISMA 2020 flow diagram summarizing the study selection process detailed in Section 2. It illustrates the sequential stages of Identification, Screening, Eligibility, and Inclusion, showing how records were identified, filtered, and included for final synthesis to ensure transparency and reproducibility.

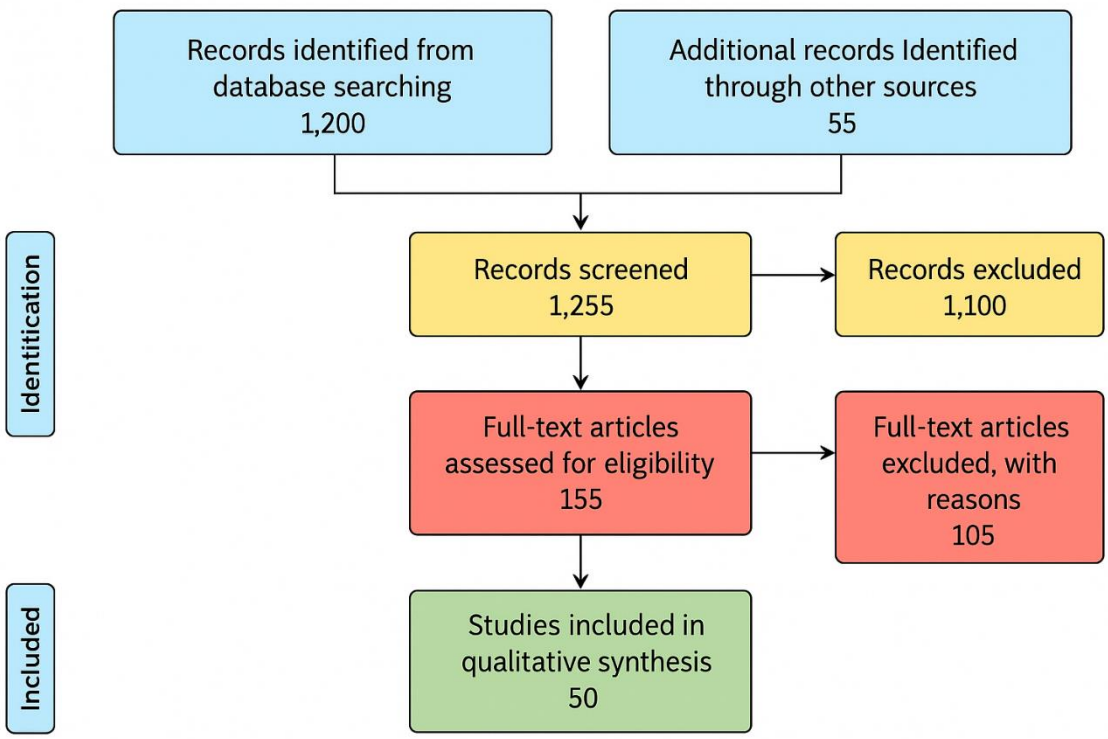

Figure 1: PRISMA 2020 Flow Diagram of Study Selection for the Systematic Review [11-20].

PRISMA 2020 flow diagram showing records identified (n=1,200) from databases and additional sources (n=55), screened (n=1,255), excluded (n=1,100), assessed for eligibility (n=155), excluded with reasons (n=105), and included in the final synthesis (n=50). Color codes: blue = Identification, yellow = Screening, red = Eligibility, green = Inclusion. Abbreviations: PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; n = number.

RESULTS AND DISCUSSION

Overview

This section presents the key findings from the literature and offers an integrative discussion on the interactions between nutritional status and mycotoxicosis susceptibility. The discussion is structured around thematic sub-sections reflecting core mechanisms by which nutrient availability modulates host responses to dietary mycotoxins. These include impaired detoxification capacity, immune dysfunction, intestinal malabsorption, and the perpetuation of a toxico-nutritional spiral. Interventions and future research directions are also considered.

Malnutrition and Impaired Host Detoxification

Nutrient deficiencies particularly of protein, folate, vitamins A, C, E, selenium, iron, and zinc have been consistently shown to impair the liver's capacity to detoxify mycotoxins. The detoxification of xenobiotics, including aflatoxins, primarily involves two critical hepatic enzyme systems: Phase I (cytochrome P450 family) responsible for oxidation, and Phase II (conjugation enzymes like glutathione-S-transferases or GSTs) that facilitate the conversion of toxic intermediates into water-soluble compounds for excretion.

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Protein-energy malnutrition directly compromises hepatic enzyme synthesis. Experimental models show that diets deficient in protein significantly reduce hepatic CYP3A4 activity, a key enzyme in aflatoxin B1 biotransformation [21]. This reduction impairs the oxidation of aflatoxin B1, leading to prolonged circulation of the parent toxin and increased cellular damage.

Selenium, a cofactor of glutathione peroxidases (GPX), plays a crucial antioxidant role in detoxification. Selenium-deficient hepatocytes exposed to fumonisins exhibit heightened oxidative stress and mitochondrial damage, indicating impaired hepatic resilience to mycotoxin insult [22]. Similarly, zinc deficiency has been shown to suppress GST expression, weakening Phase II conjugation and thereby compromising toxin elimination [23].

In populations with vitamin E deficiency, particularly malnourished children, studies report exacerbated aflatoxin-induced damage to CYP450 enzymes, further disrupting Phase I detoxification [24]. These findings align with broader evidence that low-protein diets not only limit enzyme synthesis but also diminish the availability of essential amino acids required for glutathione production and conjugation reactions [25].

Micronutrient imbalances extend beyond selenium and zinc. Deficiencies in multiple trace elements collectively disrupt conjugation pathways, lowering enzymatic defense against multiple mycotoxins [26]. Folate deficiency, for instance, leads to increased DNA adduct formation in the liver when exposed to aflatoxin B1, highlighting the mutagenic risk posed by micronutrient insufficiency [27].

Iron status also modulates detoxification. Iron deficiency anemia has been linked to the downregulation of flavin-containing monooxygenase 3 (FMO3), a lesser-known but critical detoxification enzyme, resulting in slower clearance of mycotoxins from circulation [28]. Meanwhile, vitamin C, through epigenetic modulation of CYP2D6, can influence the metabolism of ochratoxin A, with deficiency reducing enzymatic turnover and increasing toxin burden [29].

Recent studies have added further mechanistic insights. Selenium-dependent suppression of GPX1 during malnutrition was shown to heighten deoxynivalenol toxicity in hepatic cells, pointing to the importance of redox regulation in modulating toxin-induced injury [30].

Figure 2 schematizes how deficiencies in protein and key micronutrients impair Phase I and Phase II hepatic detoxification enzymes.

It highlights the downstream effects (reduced CYP activity, lower GST/GPX function) that increase mycotoxin bioaccumulation and oxidative stress.

The figure links biochemical mechanisms to the subsection's discussion of nutrient-dependent detoxification vulnerability.

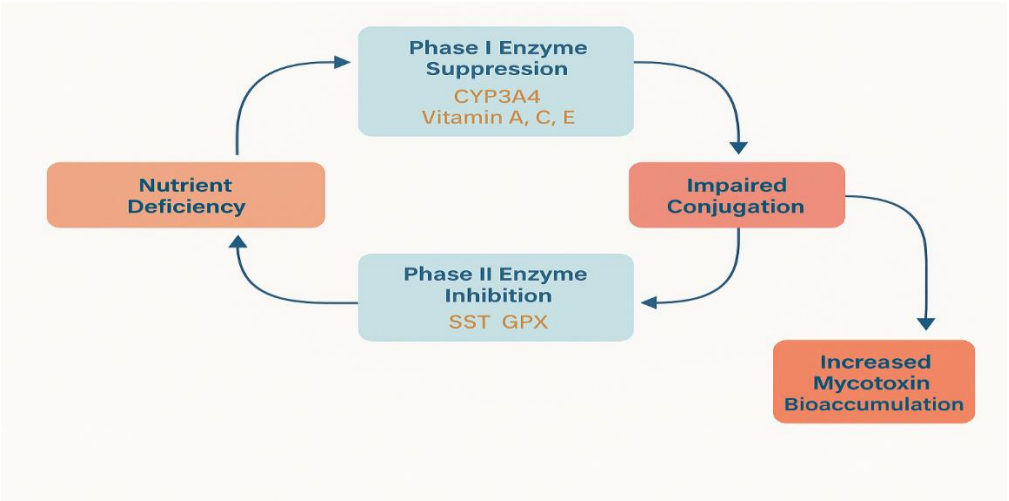

Figure 2. Biochemical Pathway of Hepatic Detoxification Impairment Under Nutrient Deficiency [21-30].

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Schematic of hepatic Phase I (oxidation) and Phase II (conjugation) detoxification illustrating how protein and micronutrient deficiencies reduce enzyme activity and increase toxin persistence. Key labeled enzymes and pathways are shown with inhibitory arrows from nutrient deficits to enzyme groups and resulting increase in oxidative stress. Abbreviations: CYP = Cytochrome P450; GST = Glutathione-S-Transferase; GPX = Glutathione Peroxidase.

Nutrient Deficiencies and Immune Dysfunction in Mycotoxicosis

Nutrient Deficiencies and Immune Dysfunction in Mycotoxicosis

Nutritional deficiencies compromise the immune system's ability to manage mycotoxin exposure. Table 2 summarizes the immunological consequences of deficiencies in vitamins A, C, D, E, folate, selenium, zinc, and iron.

Rather than repeating individual pathways, this section focuses on synthesizing how these micronutrients collectively disrupt mucosal immunity, cytokine regulation, and barrier integrity factors that heighten vulnerability to dietary mycotoxins. Vitamin A plays a pivotal role in mucosal integrity and secretory IgA responses. Its deficiency weakens gut-associated lymphoid tissue (GALT) and increases intestinal permeability, facilitating greater aflatoxin B1 translocation and reducing local immune responses [31]. Zinc deficiency further exacerbates intestinal damage, promoting T-cell apoptosis and reducing lymphocyte viability under fumonisin exposure [32].

Selenium, a trace element vital to glutathione peroxidase activity, also influences immune surveillance. In malnourished children exposed to ochratoxin A, selenium supplementation was found to restore natural killer (NK) cell activity, suggesting its relevance in innate immune defense [33]. Vitamin D3, though not classically associated with antioxidant protection, was shown to modulate T-helper cell differentiation, and its deficiency skewed immune responses toward a pro-inflammatory Th17 phenotype in mycotoxin-exposed individuals [34].

Vitamin E, a lipid-soluble antioxidant, mitigates oxidative damage in immune cells. Its deficiency disrupts macrophage function, suppresses phagocytic activity, and impairs nuclear factor erythroid 2–related factor 2 (Nrf2) signaling, leading to exaggerated responses to aflatoxin B1 [35]. Zinc's role extends beyond T-cell survival to include the regulation of epithelial transporters. Specifically, ZIP1 and ZIP8 downregulation under mycotoxin challenge compromises barrier repair and facilitates antigen penetration into submucosal layers [36].

Iron, essential for neutrophil extracellular trap (NET) formation, also influences innate immunity under toxic stress. Deoxynivalenol (DON) exposure under iron-deficient conditions results in diminished NET release, impairing the host's first-line defense against pathogen-mycotoxin co-exposure [37]. Concurrently, vitamin C deficiency intensifies fumonisin B1 (FB1)-induced pulmonary inflammation by overactivating the NLRP3 inflammasome, suggesting a link between antioxidant balance and inflammasome regulation [38].

Folate, often depleted in malnourished individuals, plays an immunomodulatory role through methylation and nucleotide biosynthesis. Its deficiency has been shown to worsen trichothecene-induced cytokine dysregulation, particularly enhancing pro-inflammatory cytokine release [39]. Lastly, the combined deficiency of vitamin A and zinc was found to exacerbate aflatoxin-associated gut dysbiosis, indicating synergistic nutrient-toxin interactions that disturb microbial homeostasis and immune equilibrium [40].

Table 2 summarizes key nutrients, their primary immune or protective functions, and the major consequences when each is deficient, as discussed in Section 3.2. This table supports the subsection by condensing mechanistic and functional evidence that connects specific micronutrient deficits to increased mycotoxin susceptibility.

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Table 2. Key Nutrients Influencing Susceptibility to Mycotoxins

Nutrient	Primary Immune Function	Deficiency Consequence	Citation
Vitamin A	Maintains mucosal surfaces and IgA production	Increases intestinal permeability and aflatoxin uptake	[31]
Zinc	Supports epithelial repair and T-cell function	Promotes barrier breakdown and lymphocyte apoptosis	[32], [36]
Selenium	Cofactor for GPX, enhances NK cell activity	Reduces oxidative defense and innate immunity	[33]
Vitamin D3	Modulates T-helper cell balance	Favors pro-inflammatory Th17 polarization	[34]
Vitamin E	Protects immune cells via Nrf2-regulated antioxidant signaling	Disrupts macrophage function and increases oxidative stress	[35]
Iron	Enables NET formation	Impairs pathogen defense during DON exposure	[37]
Vitamin C	Neutralizes ROS, regulates inflammasome activation	Exacerbates FB1-induced inflammation via NLRP3 activation	[38]
Folate	Essential for methylation, DNA synthesis, cytokine regulation	Aggravates trichothecene-related cytokine dysregulation	[39]
Vitamin A + Zinc	Maintains gut microbiota balance and mucosal immunity	Amplifies gut dysbiosis under aflatoxin exposure	[40]

Table summarizing selected nutrients, the immune/physiological functions they support, and the observed consequences of deficiency relevant to mycotoxin susceptibility. Each row pairs a nutrient with its principal protective role and the deficit-related outcome (e.g., barrier loss, immune dysregulation, impaired detoxification). Abbreviations: IgA = Immunoglobulin A; NK = Natural Killer (cell); Nrf2 = Nuclear factor erythroid 2–related factor 2.

Mycotoxin-Induced Malabsorption and Nutrient Loss

Despite sufficient dietary intake, nutrient bioavailability can be severely compromised due to the deleterious effects of mycotoxins on the gastrointestinal tract. Several mycotoxins, including aflatoxins, fumonisins, trichothecenes, ochratoxins, and zearalenone, disrupt epithelial integrity, blunt intestinal villi, and impair the function of nutrient transporters. These intestinal insults lead to malabsorption syndromes, resulting in secondary malnutrition and growth impairment, particularly in children and immunocompromised individuals.

Aflatoxin B1 has been shown to impair fatty acid absorption by downregulating intestinal fatty acid-binding protein 2 (FABP2), a key mediator in the uptake and intracellular transport of dietary lipids [41]. In parallel, trichothecene mycotoxins such as deoxynivalenol (DON) inhibit glucose transporters SGLT1 and GLUT2, reducing intestinal glucose absorption and energy availability [42].

Fumonisin B1 (FB1), commonly found in maize-based diets, decreases folate absorption by suppressing the reduced folate carrier (RFC1) in enterocytes. This disrupts one-carbon metabolism and increases the risk of

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neural tube defects and anemia [43]. Zearalenone, another estrogenic mycotoxin, impairs bile acid reabsorption through the farnesoid X receptor (FXR) pathway, further compromising lipid-soluble vitamin uptake [44].

Ochratoxin A disrupts intestinal zinc homeostasis by altering the expression of metallothioneins and zinc transporters in epithelial cells, as demonstrated in Caco-2 cell models [45]. These changes not only impair zinc absorption but also weaken epithelial repair and immune resilience.

Trichothecenes also damage the physical architecture of the intestinal lining. Specifically, they induce villus atrophy and crypt hyperplasia through inhibition of the Wnt/β-catenin signaling pathway, which is essential for intestinal regeneration and nutrient assimilation [46]. This structural disruption translates into impaired absorptive surface area and compromised brush border function.

FB1 has additionally been reported to inhibit vitamin D absorption by disrupting the heterodimerization of vitamin D receptor (VDR) with retinoid X receptor (RXR), a necessary step for genomic activation of calcium and phosphorus uptake mechanisms [47]. In lactose intolerance models, aflatoxin M1 has been observed to reduce lactase enzyme activity, exacerbating gastrointestinal distress and further limiting nutrient availability [48].

T-2 toxin, a potent trichothecene, has been shown to increase hepcidin expression, a hormone that blocks intestinal iron transporters, thereby impairing iron absorption and predisposing to anemia despite adequate intake [49]. Moreover, combinations of mycotoxins have a cumulative effect, with co-exposure shown to impair amino acid transporters such as LAT1, restricting the uptake of essential amino acids required for protein synthesis and immune function [50].

Figure 3 depicts how common mycotoxins target intestinal transporters and signaling (villus blunting, transporter downregulation) to reduce nutrient uptake. It identifies affected transporters (e.g., SGLT1, GLUT2, RFC1, FABP2, LAT1) and signaling nodes (FXR, VDR–RXR) that mediate malabsorption. This visual links directly to the subsection's evidence that mycotoxins produce measurable transporter and structural damage that cause secondary malnutrition.

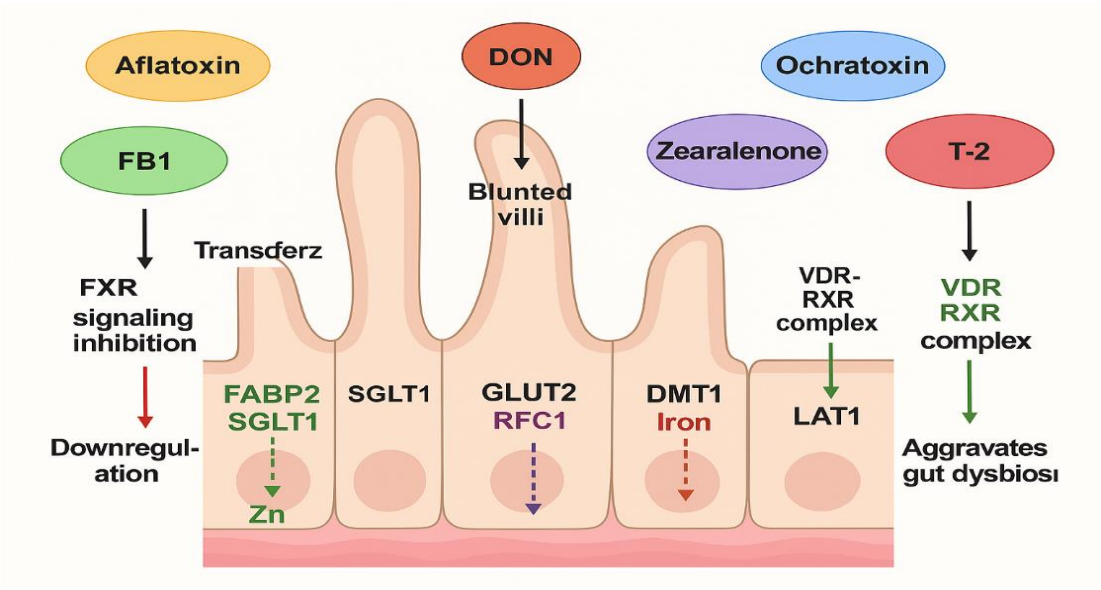

Figure 3. Mycotoxin-Induced Disruption of Intestinal Absorption and Transporter Function [41-50].

Diagram of intestinal epithelial disruption showing villus blunting and downregulation of specific nutrient transporters and nuclear receptors that mediate absorption. Transporters and signaling nodes are annotated where mycotoxins exert inhibitory effects on uptake of glucose, folate, lipids, amino acids, and vitamins. Abbreviations: FABP2 = Fatty Acid-Binding Protein 2; SGLT1 = Sodium-Glucose Co-Transporter 1; GLUT2 = Glucose Transporter 2; RFC1 = Reduced Folate Carrier 1; FXR = Farnesoid X Receptor; VDR = Vitamin D Receptor; RXR = Retinoid X Receptor; LAT1 = L-Type Amino Acid Transporter 1.

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The Toxico-Nutritional Spiral in Undernourished Populations

While many studies documenting the toxico-nutritional spiral originate from sub-Saharan Africa, similar patterns have been observed globally. For example, research in Nepal has linked aflatoxin exposure with stunting among children, while Guatemalan studies show co-occurrence of maize contamination and growth impairment. These findings affirm the global relevance of the interplay between Micronutrient deficiency and mycotoxins, especially in regions dependent on cereal-based diets.

In undernourished children, co-exposure to aflatoxins and stunting has been shown to synergistically impair neurodevelopment, indicating that the nutritional and toxic burdens are not merely additive but multiply detrimental [51]. Chronic aflatoxin exposure has also been implicated in worsening kwashiorkor, an edematous form of Protein-energy malnutrition, through increased albumin oxidation and systemic oxidative stress [52].

A longitudinal study among Tanzanian children highlighted how maize-based diets chronically contaminated with mycotoxins set off a nutritional spiral initiating with malabsorption and ending in growth faltering and stunting [53]. This nutrient depletion can extend to fat-soluble vitamins, such as vitamin A. For example, aflatoxin exposure in Nigerian children was shown to directly deplete vitamin A levels, increasing susceptibility to infection and epithelial damage [54].

Prenatal exposure is equally concerning. Infants exposed to mycotoxins in utero are at elevated risk of postnatal growth faltering, highlighting the multi-generational implications of toxico-nutritional synergy [55]. In Kenyan households that rely on groundnut-based diets a food frequently contaminated with aflatoxins the cycle is magnified, as persistent intake leads to a compounding effect on malnutrition [56].

In pregnant women, exposure to dietary mycotoxins like fumonisins and aflatoxins has been linked to iron metabolism disruption and anemia, which not only affects maternal health but also compromises fetal development [57]. Animal studies have similarly shown that Fusarium toxins reduce dietary energy efficiency, a mechanism translatable to human populations experiencing food insecurity and marginal diets [58].

Moreover, in adults living with HIV, enteric mycotoxin absorption can aggravate wasting syndromes. In such cases, poor mucosal immunity and existing nutritional deficiencies accelerate the downward spiral, undermining both therapeutic and nutritional interventions [59]. Perhaps most alarmingly, fumonisin-induced folate depletion has been implicated in the increased risk of neural tube defects, providing molecular evidence for the transgenerational consequences of the toxico-nutritional cycle [60].

Figure 4 presents a cyclical model showing how malnutrition impairs detoxification and immunity, increasing toxin uptake, which in turn worsens nutritional status. Arrows trace feedback loops (impaired detox → increased absorption → nutrient loss → immune compromise) and identify high-risk groups (children, pregnant women). The model visualizes the subsection's argument that these processes form a self-reinforcing spiral across generations and vulnerable populations.

Figure 4. The Toxico-Nutritional Spiral in Undernourished Populations [51-60].

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Conceptual cyclical model showing interactions between undernutrition, impaired detoxification/immune function, increased mycotoxin absorption, and progressive nutrient loss. Feedback loops are emphasized to show how each node (e.g., gut damage, oxidative stress, immune suppression) amplifies subsequent risk and sustains the spiral.

Nutritional Biomarkers as Predictors of Mycotoxin Risk

Recent advances in nutritional biochemistry and toxicology have highlighted the predictive value of micronutrient biomarkers in identifying populations at risk for mycotoxicosis. These biomarkers, measurable in serum, plasma, or urine, can provide early warning signals of exposure and help guide dietary or clinical interventions. Unlike traditional exposure markers that detect mycotoxins directly, nutritional biomarkers reflect the host's physiological vulnerability and capacity to detoxify these xenobiotics.

One of the most well-established associations is between serum retinol (vitamin A) and aflatoxin-albumin adduct levels. In Gambian children, lower levels of retinol were strongly correlated with higher aflatoxin biomarker concentrations, suggesting that vitamin A status may influence toxin absorption or systemic persistence [61]. Similarly, reduced glutathione peroxidase activity dependent on adequate selenium intake was found to be a reliable indicator of fumonisin-induced oxidative stress, especially in regions where maize is a dietary staple [62].

Plasma folate levels have also been inversely associated with fumonisin B1 (FB1) excretion in pregnant women. This inverse relationship underscores folate's protective role in maintaining methylation balance and preventing teratogenic outcomes linked to fumonisin exposure [63]. Zinc status has emerged as another critical marker; individuals with low serum zinc levels tend to exhibit increased aflatoxin-DNA adduct formation, implicating zinc in the maintenance of epithelial barrier function and DNA repair pathways [64].

Selenium-dependent glutathione peroxidase 3 (GPX3) activity was also validated as a biomarker of ochratoxin A susceptibility in a cohort exposed to high environmental levels of the toxin. Lower GPX3 activity was associated with increased oxidative DNA damage and reduced detoxification capacity [65]. Beyond classical antioxidants, newer markers are emerging. For example, deoxynivalenol (DON) has been shown to form adducts with vitamin D-binding protein, suggesting its potential utility in monitoring DON exposure via proteomic assays [66].

Iron-related biomarkers, such as transferrin saturation, have also demonstrated promise. In aflatoxicosis-endemic settings, altered transferrin saturation reflects disruptions in iron metabolism due to chronic toxin exposure and inflammatory cytokine activity [67]. Similarly, low serum carotenoid levels, particularly β-carotene, have been inversely associated with urinary DON levels, linking oxidative micronutrient depletion to mycotoxin burden [68].

Prealbumin, a marker of protein-energy nutritional status, was found to be significantly reduced in individuals with high zearalenone exposure, indicating its dual utility as both a marker of Micronutrient deficiencies and exposure severity [69]. Finally, urinary 8-hydroxy-2'-deoxyguanosine (8-OHdG), a marker of oxidative DNA damage, has shown consistent elevations in mycotoxin-exposed individuals, providing insight into the genotoxic potential of chronic exposure [70].

Table 3 lists nutritional and protein biomarkers, their biological functions, associated mycotoxins, and the implications of altered biomarker levels for exposure and risk assessment. It links measurable host indicators (e.g., serum retinol, GPX activity, urinary 8-OHdG) to specific mycotoxin associations discussed in Section 3.5, supporting biomarker-based risk stratification.

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Textual Table: Nutritional Biomarkers Linked to Mycotoxin Exposure

Biomarker	Function	Mycotoxin Association	Implication	Citation
Serum Retinol	Regulates epithelial integrity, immune defense	Aflatoxin B1	Low levels increase aflatoxin uptake and DNA damage	[61]
GPX Activity (Selenium)	Detoxification via antioxidant defense	Fumonisin B1, Ochratoxin A	Reduced activity linked to poor oxidative clearance	[62], [65]
Plasma Folate	DNA synthesis and methylation	Fumonisin B1	Inverse correlation with urinary FB1; risk of neural tube defects	[63]
Serum Zinc	Supports mucosal barrier, antioxidant systems	Aflatoxin B1	Low levels enhance toxin-induced genotoxicity	[64]
Vitamin D-Binding Protein	Carrier protein with detox potential	Deoxynivalenol	Potential biomarker for DON-protein adduct formation	[66]
Transferrin Saturation	Iron status indicator	Aflatoxin B1	Disrupted iron metabolism and immune function	[67]
Serum Carotenoids	Antioxidant reserve	DON	Low levels signal increased oxidative stress and exposure	[68]
Prealbumin	Protein-energy malnutrition marker	Zearalenone	Depletion reflects both nutritional status and toxin burden	[69]
Urinary 8-OHdG	Oxidative DNA damage indicator	Multiple mycotoxins	Marker of cumulative genotoxic impact	[70]

Table of nutritional and protein biomarkers showing function, the mycotoxin(s) with which they have been associated, and the practical implication of altered biomarker levels. Biomarkers include serum retinol, GPX activity (selenium-dependent), plasma folate, serum zinc, vitamin D–binding protein, transferrin saturation, serum carotenoids, prealbumin, and urinary 8-OHdG. Abbreviations: GPX = Glutathione Peroxidase; 8-OHdG (8-OHdG / 8-OhdG) = 8-hydroxy-2'-deoxyguanosine (marker of oxidative DNA damage); VDBP = Vitamin D–Binding Protein; FB1 = Fumonisin B1.

Intervention Strategies for Nutritionally Vulnerable Populations

Nutritionally vulnerable populations, particularly those in regions heavily dependent on mycotoxin-prone staples like maize and groundnuts, require integrated strategies that address both toxin exposure and nutritional inadequacy. A multi-sectoral framework combining food safety, nutritional support, and public health education is vital to reduce the cumulative burden of mycotoxicosis.

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Biofortification has shown promising outcomes in reducing mycotoxin susceptibility. In Zambia, the consumption of biofortified maize not only improved nutritional status but also significantly lowered biomarkers of aflatoxin exposure in children, demonstrating the dual benefits of nutrient enrichment and toxin mitigation [71]. This approach can be complemented with micronutrient supplementation. Ayalew and colleagues showed that combined vitamin A and zinc supplementation reduced aflatoxin-albumin adduct formation, indicating improved detoxification capacity and barrier integrity [72].

Additionally, probiotic interventions are gaining traction. *Lactobacilli*-based probiotics have been shown to mitigate fumonisin-induced intestinal damage, enhancing gut resilience and potentially restoring absorption capacity [73]. Similarly, food fortification programs in Ghana demonstrated a reduction in mycotoxin biomarkers following the consumption of nutrient-enhanced foods, highlighting the importance of population-scale interventions [74].

From an agricultural perspective, Aflasafe®, a biocontrol product that outcompetes aflatoxin-producing fungi, has proven effective not only in lowering aflatoxin contamination but also in improving dietary diversity due to improved food safety confidence [75]. Moreover, nutrition education programs targeting school-aged children have successfully reduced risk behaviors associated with mycotoxin exposure. A study in Kenya showed that school-based learning improved awareness and dietary practices, demonstrating the value of early-life education in long-term exposure reduction [76].

Traditional food processing techniques also offer significant benefits. Fermentation, widely practiced in many African and Asian communities, has been shown to degrade various mycotoxins while enhancing nutrient bioavailability, presenting a culturally acceptable, low-cost detoxification method [77].

On a micronutrient-specific level, zinc supplementation has been shown to protect renal function against ochratoxin A nephrotoxicity, further reinforcing the importance of trace mineral adequacy in toxin resistance [78]. Community-level interventions are equally important improved grain storage practices, such as hermetic bagging and elevated platforms, reduce post-harvest contamination and long-term aflatoxin accumulation [79].

Finally, dietary diversification, particularly the inclusion of low-mycotoxin cereals such as millet, has been shown to lower fumonisin exposure while improving micronutrient intake, making it a scalable, sustainable dietary intervention [80].

Figure 5 shows a multi-layered intervention model integrating food-safety, nutritional, agricultural, and community strategies to reduce mycotoxin burden. Layers include pre-harvest biocontrol (e.g., Aflasafe®), post-harvest storage, biofortification/supplementation, probiotics, and education/behavior change. It connects these intervention tiers to the subsection's recommended combined approaches for nutritionally vulnerable communities.

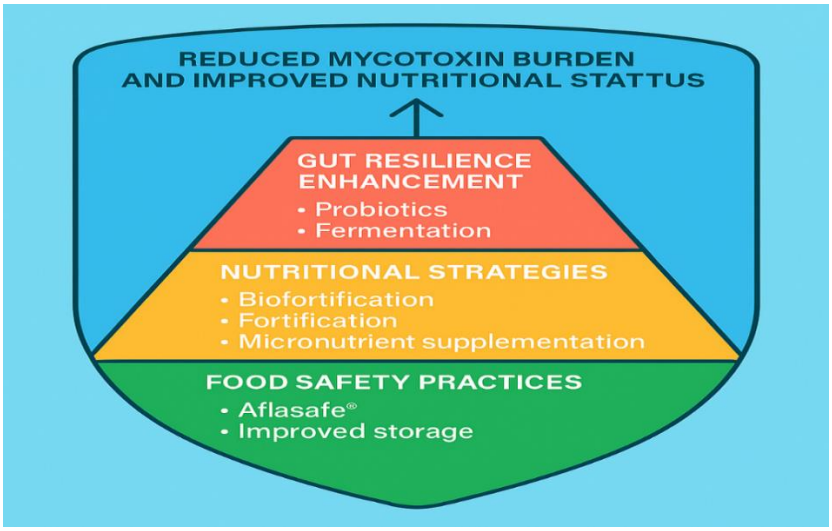

Figure 5. Layered Framework for Mycotoxin Mitigation in Nutritionally Vulnerable Populations [71-80].

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Layered mitigation schematic illustrating integrated interventions at pre-harvest, post-harvest, nutritional, gut-health, and community/education levels to reduce mycotoxin risk. Each layer includes representative tools and programs (e.g., biocontrol, biofortification, supplementation, probiotics, storage improvements). Abbreviations: Aflasafe® = commercial biocontrol product to reduce aflatoxin contamination (Aflasafe® is a registered trade name).

In addition to modern interventions, traditional food processing techniques also play a pivotal role in mycotoxin mitigation. Nixtamalization, a process involving the cooking and soaking of maize in an alkaline lime solution, significantly reduces aflatoxin and fumonisin levels. However, this method may also alter mineral bioavailability, such as reducing zinc and calcium absorption, highlighting the need to balance detoxification with nutrient retention. This approach, widely used in Latin America, offers a culturally adapted, scalable intervention in maize-dependent populations [71-80]

Future Research Directions

The complexity of interactions between nutritional status and mycotoxin exposure underscores the need for a robust, multidisciplinary research agenda. While recent advances have improved our understanding of these interactions, significant gaps remain in identifying effective, scalable interventions tailored to vulnerable populations. Future research must move beyond observational associations to uncover mechanistic pathways and translate these into actionable public health strategies.

One promising area is the application of omics technologies, which offer systems-level insights into nutrient–toxin interactions. Integrative omics spanning metabolomics, transcriptomics, and proteomics has been proposed as a novel approach to decode how dietary components influence the metabolic fate of mycotoxins and host susceptibility to toxicity [81]. Building on this, multi-omics platforms are being explored for biomarker discovery, enabling earlier and more precise detection of mycotoxin effects at subclinical stages [82].

Clinical trials validating the protective effects of micronutrients such as selenium, zinc, and folate are also needed. A framework for testing selenium supplementation against aflatoxin-induced liver damage has already been proposed and offers a template for future nutrient-toxin intervention trials [83]. Moreover, growing interest in the gut microbiome

as a mediator between nutrition and toxicant response has opened a new avenue of inquiry. Microbiome shifts modulate toxin absorption, metabolism, and immune response, suggesting that probiotics or microbiome-targeted diets could modulate risk [84].

Economic feasibility must also guide future strategies. Research has shown that biofortification remains a cost-effective intervention in mitigating mycotoxin exposure, particularly in resource-limited settings [85]. To optimize implementation, machine learning models have been proposed to predict regional mycotoxin burdens based on climatic, dietary, and socioeconomic factors, offering a precision-nutrition framework for at-risk communities [86].

Biotechnological innovations, such as CRISPR-edited crops, hold the potential to reduce fungal contamination at the source by introducing genetic resistance traits in staple crops. These advances may prove transformative in reducing mycotoxin load in the food supply chain [87]. Complementing field-level solutions, in vitro 3D gut models are providing physiologically relevant platforms to study toxin absorption, epithelial disruption, and nutrient competition under controlled conditions [88].

Furthermore, metabolomic studies have begun to identify metabolic signatures of nutrient depletion due to chronic mycotoxin exposure, which may serve as future diagnostic tools or monitoring endpoints in field studies [89]. Finally, climate-resilient agricultural strategies, such as drought-resistant crop varieties and predictive modeling for mycotoxin outbreaks, must be integrated into nutrition and food safety policies to ensure long-term sustainability [90].

Figure 6 is a funnel-style roadmap mapping mechanistic discovery (omics, CRISPR) → biomarker/clinical validation → field deployment (ML, climate-smart agriculture). It identifies priority methodologies (multi-

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omics, microbiome models, clinical trials) and translational stages toward scalable mitigation. The figure links to the subsection's call for interdisciplinary, evidence-driven research to translate mechanistic insights into policy and practice.

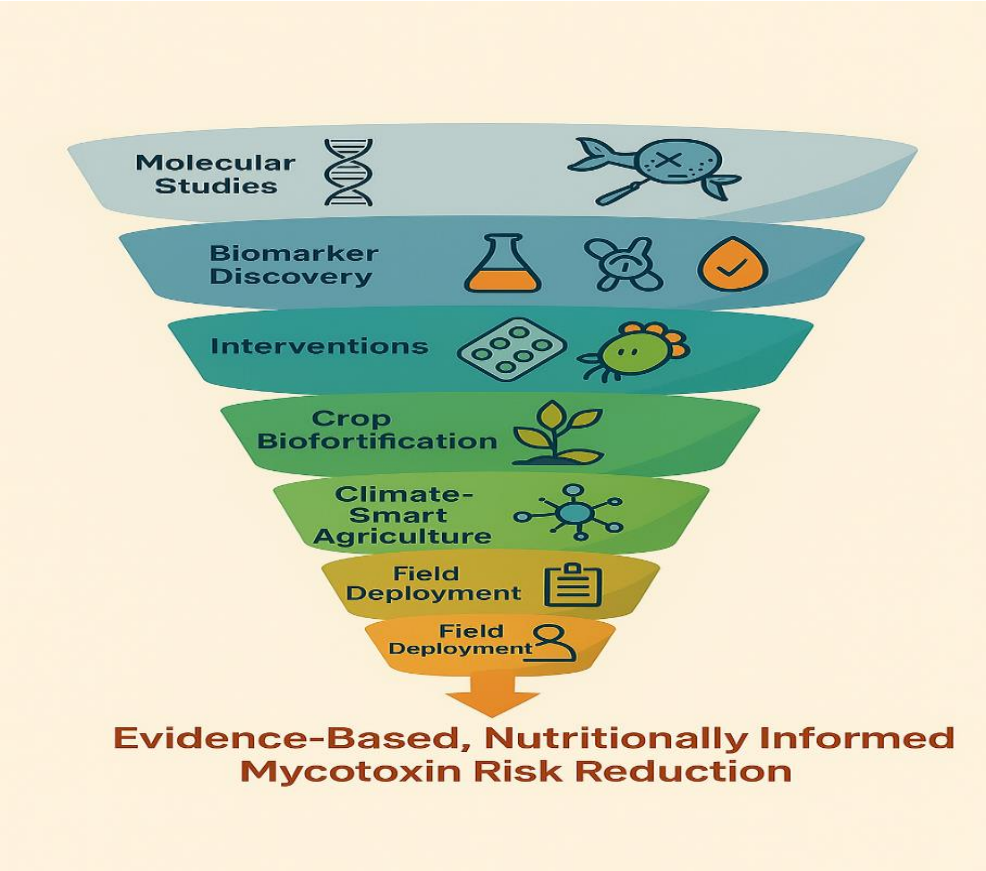

Figure 6. Strategic Research Roadmap for the Toxico-Nutritional Interface [81-90]

Funnel roadmap from mechanistic discovery (omics, gene editing) through biomarker/clinical validation to field implementation using predictive tools and climate-smart strategies. Stages are annotated with representative methods (multi-omics, CRISPR/biotech, clinical trials, machine learning for regional prediction). Abbreviations: OMICS = Integrated omics technologies (e.g., genomics, transcriptomics, metabolomics); CRISPR = Clustered Regularly Interspaced Short Palindromic Repeats (gene-editing technology); ML = Machine Learning.

Although the review integrates mechanistic and observational findings, a meta-analysis was not feasible due to heterogeneity in study designs, endpoints, and exposure measures. Future research should aim to produce standardized effect sizes to enable quantitative synthesis and pooled risk estimation, particularly for associations like aflatoxin exposure and childhood stunting.

CONCLUSION

In conclusion, this review demonstrates that mycotoxin exposure and poor nutrition form a mutually reinforcing cycle that substantially increases health risks for children, pregnant women, and other vulnerable groups. As synthesized here, nutritional deficits impair hepatic detoxification and antioxidant defenses while mycotoxins damage intestinal integrity and reduce nutrient absorption, together driving stunting, anemia, and adverse birth outcomes. Validated biomarkers such as serum retinol, selenium dependent glutathione peroxidase activity, and urinary oxidative damage markers offer practical tools to identify high risk individuals and monitor interventions. Effective mitigation requires coordinated, multisectoral action that links agricultural practices, post-harvest storage, biofortification, targeted supplementation, and gut focused strategies within culturally appropriate delivery models. We recommend prioritizing context specific trials, biomarker validation, and integrated policy initiatives to translate these findings into scalable programs that break the toxico nutritional spiral and strengthen food system resilience.

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Significant Statement

This review reveals how mycotoxin exposure and poor nutrition form a self-reinforcing cycle that magnifies health risks in children, pregnant women, and other vulnerable groups. It synthesizes mechanistic and epidemiological evidence and highlights actionable biomarkers to identify high risk individuals and measure intervention impact. The findings support integrated, context specific strategies linking crop management, nutrition programs, and targeted clinical research to break the cycle and protect food system resilience.

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None

Abbreviations

GPX - Glutathione Peroxidase

CYP - Cytochrome P450

GST - Glutathione-S-Transferase

FABP2 - Fatty Acid-Binding Protein 2

SGLT1 - Sodium-Glucose Co-Transporter 1

GLUT2 - Glucose Transporter 2

RFC1 - Reduced Folate Carrier 1

FXR - Farnesoid X Receptor

VDR - Vitamin D Receptor

RXR - Retinoid X Receptor

T-2 - T-2 Toxin

DMT1 - Divalent Metal Transporter 1

LAT1 - L-Type Amino Acid Transporter 1

NET - Neutrophil Extracellular Trap

NLRP3 - NOD-like Receptor Pyrin Domain Containing 3

PRISMA - Preferred Reporting Items for Systematic Reviews and Meta-Analyses

RoB 2 - Risk of Bias 2 Tool

JBI - Joanna Briggs Institute

SARS-CoV-2 - Severe Acute Respiratory Syndrome Coronavirus 2

WHO - World Health Organization

NCDs - Non-Communicable Diseases

RCT - Randomized Controlled Trials

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OMICS - Integrated Omics Technologies

PRISMA-S - PRISMA Search Strategy

FMO3 - Flavin-Containing Monooxygenase 3

8-OHdG - 8-Hydroxy-2'-Deoxyguanosine

SNP - Single Nucleotide Polymorphism

PRISMA-ScR - PRISMA Extension for Scoping Reviews

AI - Artificial Intelligence

Aflasafe® - Biocontrol Product for Aflatoxin Mitigation

Competing Interests

Authors have declared that they have no known competing financial interests or non-financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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