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# EFFECT OF MYCOTOXIN EXPOSURE ON STUNTING AND GROWTH IMPAIRMENT IN CHILDREN: A SYSTEMATIC LITERATURE REVIEW

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***Abstract***

*Stunting is a critical public health concern in low- and middle-income countries (LMICs), is traditionally attributed to malnutrition and environmental factors. Emerging evidence suggests that mycotoxin exposure is a risk factor. This systematic review, conducted using PRISMA guidelines, investigates the association between mycotoxin exposure and childhood stunting/growth impairment. Twelve relevant studies (predominantly cross-sectional and prospective cohorts) are identified, focusing on children aged 0-5 years in Africa and Asia. Aflatoxins (AFB1, AFM1) and fumonisins (UFB1) are the primary mycotoxins analyzed, measured through biomarkers in biological samples (blood, urine, breast milk). Aflatoxin exposure consistently demonstrates a negative impact on child growth, as evidenced by decreasing anthropometric z-scores (LAZ, WAZ, HAZ). Additionally, it significantly increases the risk of stunting and underweight. Potential mechanisms include disruption of the IGF signaling pathway, oxidative stress, impaired protein synthesis, intestinal barrier dysfunction, and nutrient malabsorption. Fumonisins, both independently and in co-exposure with aflatoxins, are also linked to growth impairment. This review highlights the detrimental effect of mycotoxin exposure on child growth. While aflatoxin exposure appears to be a major contributor, fumonisins warrant further investigation. Elucidating the underlying molecular mechanisms and exploring interactions with other risk factors are crucial next steps. Addressing mycotoxin-related stunting necessitates a multidisciplinary approach.*

***Keywords*****:** *mycotoxin, aflatoxin, stunting*



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## INTRODUCTION

Stunting signifies a hindrance in linear growth among children, which can serve as a marker for underlying chronic health conditions (de Onis & Branca, 2016). The World Health Organization (WHO) describes stunting as a Z-score for height that is less than -2 standard deviations (SD) from the typical growth range of children (de Castro et al., 2023; WHO, 2006). The calculation of HAZ entails subtracting the median height for a child's age and sex from the WHO standard, and then dividing the result by the SD of the reference population (Leroy & Frongillo, 2019). In a typical population, only around 2.5% of children have a HAZ that is below the second décile, this suggests that growth is likely to have been impaired by environmental factors (Leroy & Frongillo, 2019).

A significant public health cost associated with stunting exists in low- and middle-income countries (LMICs). Based on estimates from the World Health Organization (WHO), 148.1 million children under five will be affected by stunting globally in 2022, with a prevalence of 22.3%. Notably, over half of these cases (52%) are concentrated in Asia, while Africa accounts for nearly half (43%) (WHO, 2022). The gravity of this issue is underscored by WHO's designation of stunting as one of six global nutrition targets for 2025, established in 2012. It remains a key indicator for monitoring progress within the post-2015 development agenda (WHO, n.d.). This highlights the growing recognition of stunting as a significant public health challenge (de Onis & Branca, 2016).

The detrimental effects of stunting on children's health and development are not only immediate but also persist into the long term, posing a significant challenge to their overall well-being. During the critical window from conception to two years of age, when 70% of brain cell formation occurs Unicef (2019) stunting can impede this crucial process (Unicef, 2016). This disruption in brain development triggers a decline in the quantity of brain cells, nerve fibers, and critical connections that link them together (Prendergast & Humphrey, 2014; Marsaoly et al., 2021). Beyond the immediate consequences, stunting unleashes a cascade of long-term repercussions, including a heightened risk of morbidity and mortality, compromised physical development, impaired neurodevelopmental and cognitive processes, and an enhanced vulnerability to chronic diseases during adulthood (de Onis & Branca, 2016).

Recent research underscores the critical role of environmental and nutritional factors in the prevalence of stunting. This condition is primarily driven by extrinsic factors, encompassing suboptimal feeding practices, inadequate caregiving, and limitations in infrastructure and healthcare access (WHO, 2017). Low socioeconomic status further exacerbates the challenge of achieving a balanced diet Additionally, poor sanitation, often stemming from limited access to proper latrine facilities, fosters open defecation practices. This behavior increases the risk of diarrhoeal diseases and intestinal parasitic infections, further compromising the effectiveness of nutritional intake in children (WHO, 2019). While a multitude of risk factors contribute to malnutrition in stunting, scientific evidence increasingly highlights the independent or synergistic role of mycotoxin exposure alongside other established risk factors (Abu Al-Rub, 2008; Omotayo et al., 2019; Smith et al., 2015).

Mycotoxins constitute a group of toxic secondary metabolites synthesized by fungi, capable of contaminating a diverse array of agricultural products, encompassing cereals, nuts, spices, fruits, and animal feed (Martindah & Bahri, 2017). Examples of common mycotoxins include aflatoxin, fumonisin, deoxynivalenol, and ochratoxin A (Tola & Kebede, 2016). Aflatoxin B1 (AFB1) poses the most serious carcinogenic threat among mycotoxins, as evidenced by its classification in Group 1 by the International Agency for Research on Cancer (IARC). This classification highlights the substantial risk of AFB1 causing cancer in humans. Ochratoxin A (OTA) and fumonisin B1 (FB1) are categorized as Group 2B carcinogens by IARC, implying a potential for carcinogenicity in humans, but with weaker evidence compared to Group 1. Deoxynivalenol (DON) belongs to Group 3, signifying that current data is inadequate to definitively assess its carcinogenic risk in humans (Ostry et al., 2017).

Mycotoxin exposure in infants and young children can occur via the consumption of food items harboring mycotoxin-producing fungi, posing a potential health risk to this susceptible population (Alshannaq & Yu, 2017). This contamination originates from mold growth on agricultural products, particularly corn, nuts, and seeds. Mycotoxin contamination is not limited to a single stage but rather permeates various phases of the food supply chain, beginning with pre-harvest factors in the field and continuing through post-harvest practices such as drying and storage, and even encompassing food processing steps (Neme & Mohammed, 2017). Environmental factors such as high storage humidity and uncontrolled mold growth significantly elevate the risk of mycotoxin contamination in food (Daou et al., 2021; Ashiq, 2015; Mannaa & Kim, 2017). Additionally, high temperatures, inadequate storage practices, and poor hygiene practices can all contribute to mold proliferation and subsequent mycotoxin contamination (Kyei et al., 2021). The interplay of these factors generates favorable conditions for the flourishing of toxigenic fungi, the group of fungi responsible for mycotoxin synthesis.

Upon ingestion of contaminated food by infants and toddlers, mycotoxins can be absorbed through the digestive tract. Aflatoxin, a prevalent mycotoxin found in corn and beans, readily traverses the intestinal wall and enters the bloodstream, potentially reaching various organs, including the liver, the primary organ responsible for detoxifying harmful substances (Rushing & Selim, 2019). Beyond aflatoxin, other mycotoxins, such as deoxynivalenol (DON) and fumonisin, can also exert detrimental effects on the digestive system and nutrient absorption processes. DON disrupts the integrity of intestinal cells, hindering the effective absorption of essential nutrients. Fumonisin, on the other hand, disrupts amino acid metabolism and

inhibits ceramide synthase, a key enzyme involved in sphingolipid biosynthesis. These combined effects of fumonisin ultimately compromise nutrient absorption and hinder growth (Ahangarkani et al., 2014).

Evidence suggests that mycotoxin exposure can interfere with normal growth and developmental processes in children, raising concerns about their long-term health (Smith et al., 2015). These toxins can inflict damage on vital organs, such as the liver, which plays a crucial role in protein synthesis and growth regulation (Ramalingam et al., 2019). Additionally, the detrimental effects of mycotoxins on the digestive system and nutrient absorption can hinder the achievement of optimal nutritional intake required for growth (Pleadin et al., 2019). Consequently, children exposed to mycotoxins often exhibit compromised weight and height gain, characteristic features of stunting (Smith et al., 2015)

In low- and middle-income countries, stunting, a condition marked by stunted linear growth, continues to pose a major public health challenge. The present review investigates the possible involvement of mycotoxin exposure in the occurrence of stunting among toddlers. To achieve this objective, the review will comprehensively explore the pathways of mycotoxin exposure in young children, including the detrimental effects these toxins exert on the digestive system and nutrient absorption processes. It is anticipated that this review will contribute meaningfully to the advancement of public health policies and the promotion of safer agricultural practices, ultimately mitigating the burden of stunting in this vulnerable population.

## METHOD

This study employed a systematic literature review following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines. The online platform Covidence.org facilitated the review process. Electronic database searches were conducted using Google Scholar, PubMed, and Scopus.

Included studies were observational in nature, encompassing cohort studies, case-control studies, cross-sectional studies, and longitudinal studies investigating the association between mycotoxin exposure and stunting or impaired growth in children. Articles published within the past decade, focusing on children aged 0 to 5 years (with or without the inclusion of mothers), written in English, available as full-text, and reporting human research (excluding animal and plant studies) were eligible for inclusion..

The search strategy involved using the keywords "Mycotoxin AND (Stunt* OR Growth Impair*)" in the electronic databases. The "AND" operator ensured the presence of both concepts (mycotoxin and stunting/growth impairment), while the "OR" operator broadened the search to encompass literature related to either concept. The wildcard symbol "*" facilitated the inclusion of various word forms (e.g., stunted, stunting, growth impairment), maximizing the search's relevance. This keyword combination aimed to capture literature directly relevant to the research question.

Following the Covidence protocol, the screening process commenced with title and abstract screening, followed by a full-text review based on inclusion and exclusion criteria for data extraction. The initial electronic database search yielded 861 articles matching the keywords. After deduplication (111 articles identified as duplicates by both Covidence and manually), and title/abstract screening (370 articles deemed irrelevant), 129 articles remained for a more thorough full-text review based on the research objectives and defined criteria. Ultimately, 12 articles were selected for inclusion in this study and will be discussed further.

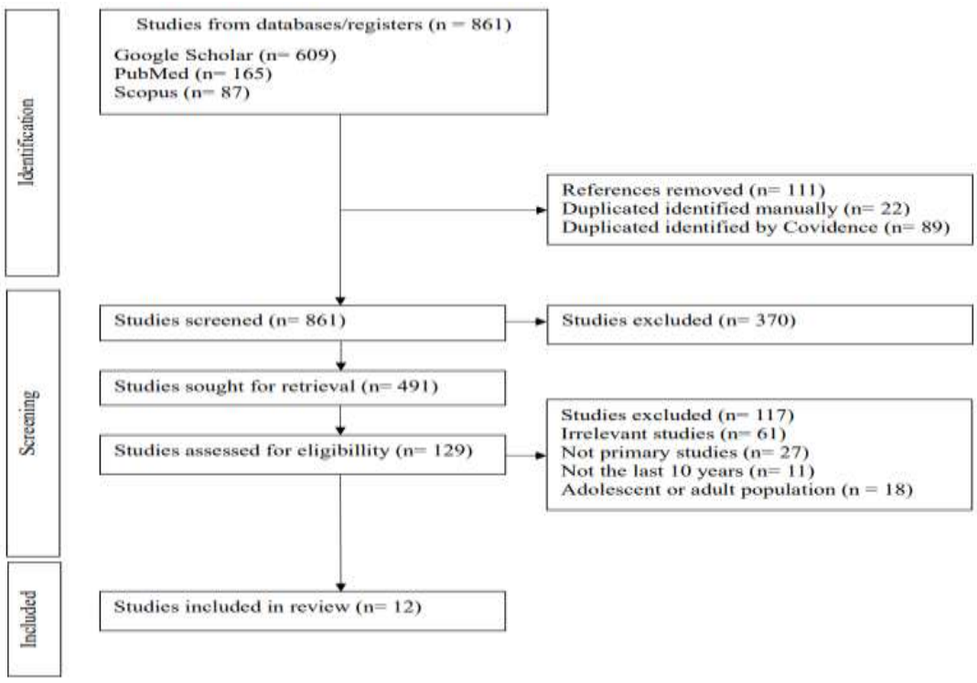


Figure 1. PRISMA flow diagram

## RESULT AND DISCUSSION

Table 1. results of the association between aflatoxin exposure and stunting in children

| Location and Study Design | Total participants and description | Types of Mycotoxin, Variable and measurement instruments | Result | Conclusion | Reference |
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| A cross-sectional study conducted in Zambia | 400 mothers with children aged 6-24 months | Aflatoxin B1-lysine (AFB1-lys) Dietary aflatoxin exposure (AFB1-lys); Outcome: Childhood stunting, Childhood illness, age. Aflatoxin B1-lysine (AFB1-lys) levels; measured using albumin-normalized AFB1-lys, potentially involving SPE Oasis MAX plates and relevant chemicals/solvents. | Significant associations between childhood stunting and: 1) Childhood illness, 2) Dietary aflatoxin exposure (AFB1-lys), 3) Albumin-normalized AFB1-lys levels | Exposure to aflatoxins in food, as indicated by elevated albumin-normalized AFB1-lys levels, may contribute to childhood stunting, potentially alongside other factors like illness. | (Alamu et al., 2020) |
| Cohort study conducted in Banke, Nepal | 1675 mother-child pairs followed longitudinally over the first 1000 days | Aflatoxin B1 (AFB1) exposure was evaluated by measuring AFB1-lysine (AFB1-lysin) levels in maternal and infant blood samples. Anthropometric parameters, including body weight, head circumference, and weight-for-age z-score, were also assessed. | Aflatoxin B1 (AFB1) exposure was found to be inversely associated with multiple growth indicators, encompassing body length, weight, head circumference, as well as both length-for-age z-score (LAZ) and weight-for-age z-score (WAZ) Higher AFB1 exposure linked to increased risk of stunting and underweight. Other mycotoxins (unidentified Fusariotoxins - UFB1 and Deoxynivalenol - DON) also impacted growth: UFB1 associated with underweight risk, DON associated with smaller head circumference. | Mycotoxin exposure, particularly AFB1, is highly prevalent in young children and significantly hinders their growth and development. AFB1 appears to be the dominant mycotoxin impacting child growth. | (Andrews-Trevino et al., 2022) |
| Cross-sectional study conducted in Butajira District, South-Central Ethiopia | 332 children aged 12-59 months | Aflatoxin M1 (AFM1) Dietary intake over the preceding three days was assessed using a validated food frequency questionnaire (FFQ) | The prevalence of aflatoxin exposure was found to be high, with detectable levels ranging between 0.15 ng/ml and 0.4 ng/ml. Aflatoxin exposure demonstrated a strong link with the prevalence of stunting. | The study suggests a link between exposure to high levels of AFM1 and an increased risk of stunting in children. | (Ayele et al., 2022) |
| Cross- | 200 children | Aflatoxin B1-lysine | High prevalence of | While | (Chen et al., |

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| sectional study conducted in Manyara region, Tanzania | aged 1-4 years | (AFB1-lys) and Fumonisin B1 (UFB1)<br>To quantify aflatoxin B1 (AFB1) in plasma, aflatoxin B1-lysine (AFB1-lys) was added as an internal standard. Urinary fumonisin B1 (UFB1) was determined directly from urine samples.<br>Validated LC-MS/MS method for AFB1-lys in plasma; Validated urine biomarker method for UFB1 | mycotoxin exposure: 72% of children with detectable AFB1-lys (mean: 5.1 pg/mg albumin), 80% of children with detectable UFB1 (mean: 1.3 ng/ml)<br>The study revealed a concerningly high stunting rate, with three-quarters of children at 36 months old having a height-for-age z-score (HAZ) of -2 or lower.<br>The study did not find any significant relationship between exposure to aflatoxin B1-lysine (AFB1-lys) at 24 months and subsequent growth faltering in children.<br>Potential association between UFB1 exposure (24-36 months) and growth impairment. | aflatoxin exposure was prevalent, the study suggests fumonisin exposure, as measured by UFB1, may be a more significant contributor to growth impairment in young children from Manyara, Tanzania. | 2018) |
| Prospective cohort study conducted in rural Malawi | Subset of 255 mother-child pairs from the iLiNS-DYAD trial | Aflatoxin B1 (AFB1)<br>Child and maternal AFB1-lysine levels; Outcome: Child growth outcomes<br>Quantification of aflatoxin B1-lysine (AFB1-lys) adduct levels in maternal and child plasma was achieved using isotope dilution mass spectrometry. | longitudinal study demonstrated a robust negative correlation between early aflatoxin B1 (AFB1) exposure and stunted growth in children, characterized by a progressive reduction in height-for-age z-score over 2.5 years.<br>Significant positive association between maternal AFB1 exposure during pregnancy and child growth outcomes. | The study highlights a contrasting effect of AFB1 exposure on child growth. While childhood exposure hinders growth, maternal exposure during pregnancy appears to have a positive influence. Further investigation is needed to understand this unexpected finding. | (Matchado et al., 2023) |
| Randomized cluster longitudinal trial conducted in rural area of Meru of Tharaka-Nithi, Kenya (2013-2016) | A longitudinal study involving 1230 pregnant women commenced between the fifth and ninth months of pregnancy. | Aflatoxin B1 (AFB1)<br>Dietary aflatoxin intake (indirectly measured via intervention); Outcome: Child growth (LAZ) and stunting prevalence, serum aflatoxin levels<br>Serum aflatoxin B1-lysine (AFB1-lys) adduct concentrations | Intervention significantly reduced endline serum aflatoxin levels by approximately 27%.<br>No significant impact of the intervention on children's linear growth (LAZ) or | Increasing access to aflatoxin-free corn effectively reduced final serum aflatoxin levels but did not impact children's long-term | (Hoffmann et al., 2018) |

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| | | were determined using a highly specific and robust high-performance liquid chromatography (HPLC)-fluorescence method. | stunting prevalence at the endline. The study findings failed to demonstrate a significant association between the intervention and changes in children's linear growth (LAZ) or stunting prevalence at the end of the intervention period. Midline analysis suggested a potential effect of aflatoxin exposure on linear growth at younger ages. | linear growth or stunting prevalence. The study suggests a potential window of vulnerability for growth impacts of aflatoxin exposure in early infancy. | |
| The study employed a cross-sectional design, conducted in Korogocho and Dagoretti West, informal settlements within Nairobi County, Kenya. | Data was collected from a total of 204 households. | The study assessed aflatoxin levels in corn, sorghum, and milk, focusing on total aflatoxins (AFB1, AFB2, AFG1, and AFG2) in cereal grains and aflatoxin M1 (AFM1) in milk samples. Dietary intake of children, anthropometric measurements (weight and height), and aflatoxin concentrations in food samples were evaluated. Anthropometric data collection employed electronic digital scales for weight and UNICEF wooden longboards for height/length measurements. Dietary intake was estimated using four 24-hour food recalls. A commercial low matrix enzyme-linked immunoassay (competitive ELISA) was utilized to quantify aflatoxin levels in food samples. | This investigation revealed a statistically significant correlation between exposure to aflatoxin M1 (AFM1) and stunted growth in children, as measured by Height-for-Age Z-score (HAZ). This finding suggests that children with higher AFM1 levels exhibited lower HAZ scores, indicating a potential growth deficit. Notably, no significant associations were observed between total aflatoxin levels (including aflatoxin B1 (AFB) and aflatoxin G1 (AFG)) and various anthropometric parameters, such as HAZ, Weight-for-Age Z-score (WAZ), and Weight-for-Height Z-score (WHZ). | The results of this investigation hint at a potential connection between AFM1 exposure and growth impairment in children. | (GM et al., 2016) |
| The study was conducted in Rombo District, Northern Tanzania, using a research design | Data was collected from 143 infants. | Aflatoxin M1 (AFM1) The study examined Aflatoxin M1 (AFM1) contamination in breast milk samples. Infant anthropometric data (weight, height, and age) was collected alongside maternal dietary information obtained through a 24-hour dietary recall | Analysis of breast milk samples revealed universal contamination with aflatoxin M1 (AFM1), exceeding the stringent safety standards established by the European Union (EU) for both infant food and milk products. A significant negative association | The study suggests that exposure to AFM1 through breast milk may be associated with stunted growth in infants from Northern Tanzania. | (Magoha et al., 2014) |

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| | | questionnaire.<br>High Performance Liquid Chromatography (HPLC) was employed to quantify AFM1 levels in breast milk. | ($p < 0.05$) was observed between AFM1 exposure levels and weight-for-age Z-score (WAZ) and height-for-age Z-score (HAZ). This indicates a potential link between AFM1 exposure and impaired growth in infants. | | |
| A prospective study was conducted in Nyabula village (Iringa region), Kigwa village (Tabora region), and Kikelelwa village (Kilimanjaro region) of Tanzania. | The study included 166 healthy children aged 6-14 months at recruitment. | The study investigated exposure to both aflatoxins and fumonisins.<br>Blood and urine samples were analyzed for: Plasma aflatoxin-albumin (AF-alb) levels using ELISA<br>Urinary fumonisin B1 (UFB1) levels using liquid chromatography-mass spectrometry | The study identified a significant negative association between urinary fumonisin B1 (UFB1) levels and linear growth in children.<br>Specifically, higher UFB1 concentrations at recruitment were linked to lower length-for-age z-scores (LAZ) at both 6 and 12 months of follow-up. Additionally, the mean UFB1 level across all three sampling points was negatively associated with LAZ and length velocity at 12 months.<br>In contrast, No. statistically significant association was found between plasma aflatoxin-albumin (AF-alb) levels and child growth. | The findings suggest that exposure to fumonisin, either alone or co-occurring with aflatoxin, may hinder linear growth in young children. This emphasizes the importance of interventions to reduce mycotoxin exposure, particularly during crucial early childhood development stages. | (Shirima et al., 2015) |
| A birth cohort study was conducted in Mirpur, Dhaka, Bangladesh. | The study followed a cohort of 208 children at birth, with follow-up assessments at 7, 15, 24, and 36 months of age. The number of participants decreased slightly at each follow-up (196 at 15 months, 173 at 24 months, and 167 at 36 months). | Aflatoxin B1-lysine (AFB1-lys)<br>To assess chronic aflatoxin exposure, plasma samples collected at 7, 15, 24, and 36 months of age were analyzed for aflatoxin B1-lysine (AFB1-lys) levels using mass spectrometry (MS).<br>Anthropometric measurements were obtained monthly to track growth patterns.<br>Data on additional factors potentially influencing child health were collected every 6 months. These factors included: water, sanitation, and hygiene (WASH) | The study investigated the relationship between aflatoxin exposure and anthropometric measurements (including stunting) alongside other factors like age, low birth weight, maternal height, and household environment.<br>No significant association was found between aflatoxin exposure (measured by AFB1-lys) and childhood stunting in multivariable analysis.<br>Other factors such as age, low birth | This study suggests that aflatoxin exposure, as measured by AFB1-lys, may not be a major contributor to childhood stunting in the specific slum setting of Mirpur, Dhaka. Other factors appear to play a more prominent role. | (Mahfuz et al., 2021) |

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| | | behaviors, household assets, income levels, food security | weight, maternal height, markers of intestinal inflammation (fecal myeloperoxidase), and overcrowding (number of people sleeping in one room) were identified as having significant associations with childhood stunting. | | |
| A prospective cohort study was conducted in rural Gambia | The study involved a subsample of 374 infants from the Early Nutrition and Immune Development (ENID) trial. | The study investigated the effects of aflatoxin exposure on infant growth. Aflatoxin exposure was measured by analyzing blood samples collected at 6, 12, and 18 months of age for aflatoxin-albumin (AF-alb) concentrations using a competitive ELISA method.<br>Additionally, blood samples collected at 12 and 18 months were analyzed for insulin-like growth factor 1 (IGF-1) and insulin-like growth factor binding protein 3 (IGFBP-3) using the IDS-iSYS IGF-1 and IGFBP-3 assay.<br>Anthropometric measurements (length, weight) were taken at 6, 12, 18, and 24 months using electronic scales and long boards. | The study identified a small but significant inverse relationship between aflatoxin exposure (measured by AF-alb) and infant growth parameters like length-for-age (LAZ), weight-for-age (WAZ), and weight-for-length (WLZ) from 6 to 18 months of age.<br>Furthermore, AF-alb levels at 6 months were associated with changes in growth parameters at later time points: Lower AF-alb at 6 months was linked to reduced weight-for-length gain between 6 and 12 months.<br>Lower AF-alb at 12 months was linked to decreased length-for-age and overall body length gain between 12 and 18 months.<br>Interestingly, AF-alb levels at 6 months were also associated with IGFBP-3 levels at 12 months, although the exact relationship between aflatoxin exposure, IGF-axis, and growth requires further investigation. | The study suggests that aflatoxin exposure can negatively impact infant growth in rural Gambia. While the mechanisms are not fully understood, the findings suggest that aflatoxin exposure may affect growth through pathways not necessarily involving the IGF axis. This highlights the need for further research to elucidate the underlying mechanisms. | (Watson et al., 2018) |
| A cross-sectional study was conducted in ten Woredas (districts) across Amhara and Tigray states in Ethiopia. | The study included 200 children aged 1-4 years. | The study investigated exposure to various aflatoxins by analyzing urine samples for the presence of: Aflatoxin B1 (AFB1), aflatoxin B2 (AFB2), aflatoxin G1 (AFG1), aflatoxin G2 (AFG2), aflatoxin M1 (AFM1)<br>A validated Liquid Chromatography-Tandem Mass | The study identified AFM1 as the most commonly detected aflatoxin in urine samples, with 17% of samples showing contamination by at least one aflatoxin. Notably, AFB1 was not detected in any samples.<br>Importantly, no significant association was | The study revealed that AFM1 was the predominant aflatoxin found in urine samples from children in Amhara and Tigray, Ethiopia. However, no link was | (Ayelign et al., 2017) |

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| | Spectrometry (LC-MS/MS) method was used to quantify aflatoxin levels in urine. | found between aflatoxin exposure (measured through urinary aflatoxin levels) and different forms of malnutrition (stunting, wasting, and underweight) in these children. | observed between aflatoxin exposure and various categories of malnutrition. |

Aflatoxin was the most investigated mycotoxin, particularly AFB1 and its metabolite AFM1. The primary biomarkers used in exposure evaluation were AFB1-lysine adducts in blood or serum or AFM1 in urine or breast milk. ELISA, LC-MS/MS, or HPLC were the analytical techniques used for detection of these biomarkers. Child growth assessment typically involved anthropometric measurements (length/height, weight, head circumference) expressed as z-scores (LAZ, WAZ, WLZ, HAZ).

One noteworthy conclusion from the studies that were analyzed was that, among the twelve, ten of them indicated a statistically significant detrimental relationship between several child growth indicators and mycotoxin exposure, notably aflatoxin. Aflatoxin exposure was consistently associated in these investigations with deficiencies in growth indicators, including head circumference-for-age (HAZ), weight-for-age (WAZ), LAZ (length-for-age), and WLZ (weight-for-length), as well as an increased risk of stunting and underweight. Notably, some studies explored exposure to fumonisins (like UFB1) alongside aflatoxins, suggesting the potential influence of mycotoxin type and co-exposure on growth outcomes.

After twelve appropriate studies were analyzed, strong evidence was found that childhood development problems and mycotoxin exposure, especially aflatoxins, are related. According to Alamu et al. (2019), there is a correlation between a higher risk of stunting and elevated serum aflatoxin concentrations in children from Zambia that result from foodborne aflatoxin exposure. Remarkably, their research revealed that age had no discernible impact on this association (Alamu et al., 2020). Similarly, Andrews-Trevino et al. (2022) observed a negative association between aflatoxin B1 (AFB1) and various growth parameters (length, weight, head circumference) in Nepalese children (Andrews-Trevino et al., 2022). This association translated to an increased likelihood of stunting and underweight. Notably, their study also found that exposure to another mycotoxin, UFB1, elevated the risk of underweight, while deoxynivalenol (DON) negatively impacted head circumference. These results indicate that a variety of mycotoxins, including AFB1, may individually cause growth deficits in children.

Ayele et al. (2022) substantiated these findings by demonstrating a strong correlation between Ethiopian children's stunting and high aflatoxin exposure (Ayele et al., 2022). However, research by Chen et al. (2018) in Tanzania presented a contrasting perspective (Chen et al., 2018). While they found no link between low-level aflatoxin exposure and growth disorders, their study identified fumonisin exposure as a significant contributor to growth impairments. This highlights the potential influence of mycotoxin type and exposure level on growth outcomes. In Malawi, Matchado et al. (2023) underlined the detrimental relationship between aflatoxin exposure and child growth, which is especially noticeable in head circumference deficiencies (Matchado et al., 2023). Remarkably, their research also revealed a positive correlation between a mother's exposure to aflatoxin during her pregnancy and the growth of her child, indicating a possible intricate interaction of variables.

Intriguingly, Hoffmann et al. (2018) observed successful reductions in serum aflatoxin levels in Kenyan children following interventions, but these reductions did not translate to improvements in linear growth or stunting prevalence (Hoffmann et al., 2018). These findings warrant further investigation into the potential mechanisms by which aflatoxin exposure disrupts growth, independent of serum levels.

Further nuances emerged from studies examining specific aflatoxin metabolites. Kiarie et al. (2016) in Kenya demonstrated a negative relationship between AFM1 exposure and head circumference-for-age Z-scores (HAZ), suggestinga link to stunting (GM et al., 2016). Nevertheless, they discovered no meaningful correlations between total aflatoxins and other growth markers. In a comparable direction, Magoha et al. (2014) in Tanzania found a strong correlation between development deficits and breast milk exposure to AFM1(Magoha et al., 2014). These findings highlight the potential differential effects of various aflatoxin metabolites on child growth.

Shirima et al. (2015) investigated the possible synergistic effects of mycotoxins in Tanzania (Shirima et al., 2015). Their findings suggested that growth deficits may be caused by fumonisin exposure, either on its own or in conjunction with aflatoxin. Aflatoxin exposure and stunting, however, did not significantly correlate, according to Mahfuz et al. (2021) in Bangladesh (Mahfuz et al., 2021). Their research focused on the possible effects of additional variables on child growth, including age, low birth weight, mother height, and environmental circumstances. Lastly, an inverse connection between AF-albumin adducts (AF-alb) and many growth indices was shown by Watson et al. (2018) in the Gambia (Watson et al., 2018). Ayelign et al. (2017) in Ethiopia confirmed aflatoxin exposure in the studied population, although not finding a

significant correlation between aflatoxin exposure and malnutrition categories (Ayelign et al., 2017).

Expanding beyond aflatoxins, several studies have identified fumonisin exposure, both in isolation and co-occurring with aflatoxins, as a contributing factor to impaired growth in children. Andrews-Trevino et al. (2022) further suggest that various mycotoxins may independently impact distinct aspects of growth, with AFB1 exerting the most dominant effect (Andrews-Trevino et al., 2022). This emphasizes how co-exposure and mycotoxin type may affect the results of growth. Generally, there is strong scientific evidence that mycotoxin exposure—specifically aflatoxins—is a major risk factor for stunting and impaired growth in children, especially in low- and middle-income nations.

Even while there is a clear correlation between mycotoxin exposure and stunted growth in children, the underlying mechanisms are still unknown. Numerous theories have been put out to explain how these toxic substances interfere with the process of growth and development. However, the current evidence supporting these mechanisms is limited and necessitates further investigation.

Interference with the Insulin-like Growth Factor (IGF) system is one possible method. A set of proteins known as the IGF system are essential for controlling the growth, development, and metabolism of cells (Clemmons, 2016). The two main ligands, IGF-1 and IGF-2, two cell surface receptors, IGF-1R and IGF-2R, and a variety of IGF-binding proteins, or IGFBPs, that regulate IGF bioavailability and activity make up this complex (Li et al., 2022).

Watson et al. (2018) found an inverse association between blood levels of aflatoxin-albumin adduct (AF-alb) and IGFBP-3 in Gambian infants at 12 months of age, supporting the possible involvement of the IGF system. IGFBP-3, the primary circulating IGF-binding protein, modulates IGF action on target cells(Watson et al., 2018). The study suggests that aflatoxin exposure may decrease IGFBP-3 levels, potentially disrupting the IGF axis and contributing to growth disorders. However, no significant association was found between AF-alb and IGF-1 levels or other growth parameters, highlighting the need for further investigation into the specific mechanisms at play.

Beyond the IGF system, mycotoxins are postulated to impede growth through a multitude of mechanisms, including oxidative stress, mitochondrial dysfunction, impaired protein synthesis, and compromised intestinal barrier function leading to nutrient malabsorption(Watson et al., 2018; Liew & Mohd-Redzwan, 2018). For instance, aflatoxin forms adducts with DNA and proteins, potentially causing genetic mutations and disrupting cellular function, which can have negative consequences for growth (Rushing & Selim, 2019). Similarly, fumonisin disrupts sphingolipid metabolism by inhibiting ceramide synthase. Sphingolipids are crucial for cell membrane integrity and signaling, and their disruption can lead to changes in intestinal permeability, damage to the intestinal lining, and ultimately, impaired nutrient absorption (Abdel Hadi et al., 2016).

The multifaceted nature of mycotoxins and their effects on growth highlights their pleiotropic nature, influencing various cellular and physiological processes directly or indirectly. To elucidate the underlying molecular mechanisms and pathophysiological pathways, a multidisciplinary approach is necessary. This approach should integrate in vitro, in vivo, and epidemiological studies to comprehensively understand how mycotoxins exert their detrimental effects on child growth and development. Furthermore, investigating potential interactions between mycotoxin exposure and other risk factors such as malnutrition, infection, and poor environmental conditions is crucial. These factors can exacerbate the negative impact of mycotoxins on growth. A holistic approach that considers these multiple risk factors and growth determinants is essential to effectively address stunting and mycotoxin-related growth disorders.

## CONCLUSION

This systematic review of twelve relevant studies provides compelling evidence that mycotoxin exposure, particularly aflatoxins, constitutes a significant risk factor for stunting and growth disorders in children, especially in low- and middle-income countries. The majority (10/12) of the reviewed studies demonstrated an association between aflatoxin exposure, assessed through biomarkers like AFB1-lysine adduct in blood/serum or AFM1 in urine/breast milk, and various child growth parameters including length/height, weight, and z-scores (LAZ, WAZ, WLZ, HAZ). Aflatoxin exposure consistently correlated with negative growth outcomes and increased risks of stunting and underweight.

While the precise mechanisms underlying the detrimental effects of mycotoxins on growth remain elusive, several potential pathways have been proposed, including disruption of the IGF system, oxidative stress, mitochondrial dysfunction, impaired protein synthesis, and compromised intestinal barrier function leading to nutrient malabsorption. Beyond aflatoxins, some studies identified fumonisin exposure, either alone or co-occurring with aflatoxins, as contributing to impaired growth. However, further research is necessary to elucidate the molecular mechanisms and pathophysiological pathways involved. Additionally, investigating potential interactions between mycotoxin exposure and other risk factors such as malnutrition, infection, and poor environmental conditions is crucial for a comprehensive understanding. A multidisciplinary and holistic approach that integrates in vitro, in vivo, and epidemiological studies is essential to effectively address the public health challenge of mycotoxin-related stunting.

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