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Review Article

Aflatoxin: A major risk factor for hepatocellular carcinoma

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Abstract

Hepatocellular carcinoma (HCC) is ranked among the most common leading causes of death from cancers worldwide. Majorly responsible for this is the potent mycotoxin produced by Aspergillus flavus and Aspergillus parasiticus, aflatoxin. The risk factors are included to be hepatitis B and C viruses, HBV and HCV. Molecular mechanisms involved in a flatoxin and HBV/HCV-associated hepatocarcinogenesis include the complex interplay of genetic and epigenetic alterations that help in disrupting normal cellular processes with the action of cancerous traits. As aflatoxin triggers genetic mutations and epigenetic modifications through its activation and production of DNA adducts, while HBV and HCV infections lead to chronic hepatitis, oxidative damage, direct contact with host cellular machinery and favor the development of HCC. Mostly, aflatoxins are ingested through food products contaminated with this toxin, particularly grains and nuts, which are regularly consumed by populations using insanitary agriculture and storage of food. Once inside the body, aflatoxin B1 and similar metabolites have the ability to activate the cellular pathways associated with metabolic activation through cytochrome P450 enzymes that result in the creation of DNA adducts. These adducts lead to mutations within critical tumor suppressor genes like TP53 and activate oncogenes like RAS, causing tumorigenesis. Elucidating the complex molecular crosstalk between aflatoxin exposure and HBV/HCV infections is important for advancing targeted interventions to mitigate the global burden of HCC. This review consolidates the latest findings but sets a course for future research promisingly unravelling the complex interactions between aflatoxin exposure and HBV/HCV infections. It helps pave the way to good clinical outcomes and effective public health strategies as a means of combating hepatocellular carcinoma.

Keywords:
Hepatocellular Carcinoma, Aflatoxin, Genetic Mutations, Molecular Mechanisms.

1. Introduction

Hepatocellular carcinoma (HCC) ranks among the most prevalent and deadly cancers globally. Chronic infections with hepatitis B virus (HBV) and hepatitis C virus (HCV), along with exposure to aflatoxins, are primary etiological factors contributing to HCC [1, 2]. Aflatoxins, mainly produced by the fungi Aspergillus flavus and Aspergillus parasiticus, contaminate crops such as maize, peanuts, and tree nuts, leading to human exposure through the consumption of contaminated food [3]. In the liver, aflatoxin B1 (AFB1) is metabolized by cytochrome P450 enzymes into a highly reactive form, AFB1-8,9-epoxide, which binds to DNA, forming mutagenic adducts [4]. This exposure initiates a biochemical cascade, resulting in DNA adducts that specifically target the third base of codon 249 in the TP53 gene. This mutation causes a characteristic G to T transversion, which disrupts the tumor-suppressing function of p53, allowing cells to proliferate uncontrollably [4, 5]. Additionally, aflatoxins induce oxidative stress and activate inflammatory pathways, further damaging liver tissue and promoting carcinogenesis. HBV DNA integrates into the host genome, disrupting genes and regulatory elements crucial for cell growth and division, thus aiding oncogenesis [5, 6]. The HBV protein interacts with cellular pathways controlling apoptosis, the cell cycle, and DNA repair, and it influences epigenetic modifications such as DNA methylation and histone modification, leading to altered gene expression and tumor progression [6, 7]. HCV infection, on the other hand, causes chronic liver inflammation, leading to fibrosis and cirrhosis, significantly increasing the risk of HCC [8]. HCV proteins can promote cancer by altering signaling pathways related to apoptosis, cell prolif-

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eration, and immune response [9]. HCV also evades immune detection, resulting in continuous liver damage. Moreover, co-infection with HBV and HCV can synergistically exacerbate liver damage and accelerate the development of HCC.

Furthermore, dietary habits, genetic predispositions, and environmental factors also play significant roles in modulating the risk of HCC. Studies have shown that populations with diets high in aflatoxin-contaminated foods and low in essential nutrients such as antioxidants are at increased risk [10]. Genetic factors, including polymorphisms in genes involved in detoxification pathways, can influence individual susceptibility to aflatoxin-induced liver damage. Environmental factors, such as exposure to other hepatotoxins and lifestyle factors like alcohol consumption and smoking, can further compound? the risk [11]. Understanding these multifaceted interactions is crucial for developing targeted prevention and intervention strategies. Public health efforts focusing on improving food safety, increasing vaccination coverage against HBV, and providing antiviral treatments for HBV and HCV infections are essential components in reducing the incidence of HCC. Additionally, advancing research into the molecular mechanisms underlying aflatoxin and viral hepatitis-associated hepatocarcinogenesis will pave the way for novel therapeutic approaches and improve clinical outcomes [12].

1.1. Epidemiological Research Insights

Numerous epidemiological studies have been conducted over the years to thoroughly explore the intricate link between aflatoxin exposure and liver cancer, particularly in regions that exhibit a high incidence of hepatocellular carcinoma (HCC), such as various countries in Asia and Africa [13]. In earlier studies, researchers faced significant limitations, which hindered their ability to accurately measure both aflatoxin exposure and the status of viral hepatitis in the populations they were examining [14]. These limitations often resulted in inconclusive findings and a lack of clear understanding of the relationship between aflatoxin and liver cancer risk. However, recent advances in the field of molecular dosimetry and improved methods for assessing viral infections have led to much clearer insights into this critical relationship [15]. These technological improvements have allowed scientists to better quantify aflatoxin exposure levels and assess the presence of viral hepatitis, resulting in more robust data. Multi-country studies conducted in regions such as China, the Philippines, Mozambique, and Swaziland have provided significant evidence of correlations between aflatoxin exposure and the incidence of liver cancer [5, 15]. These studies frequently highlight the existence of synergistic effects, particularly in conjunction with infections caused by Hepatitis B virus (HBV) and Hepatitis C virus (HCV) [16, 17]. This combination of factors has underscored the heightened risk for individuals exposed to aflatoxin in the presence of these viral infections, reinforcing the need for continued investigation and public health interventions in these affected regions [18].

The development of molecular biomarkers specifically designed to assess aflatoxin exposure has emerged as a significant and critical advancement in the field of toxicology and public health [19]. Among these biomarkers, aflatoxin-DNA adducts and protein adducts have undergone thorough validation in multiple human populations across different geographic regions [20]. These innovative biomarkers serve as a direct and accurate measure of an individual's exposure to aflatoxin and the accompanying biological effects it may produce [3]. By facilitating this measurement, these biomarkers play a vital role in identifying individuals who are at a high risk for health issues related to aflatoxin exposure, thereby enhancing our ability to implement and evaluate preventive interventions effectively [21]. Numerous key studies have provided compelling evidence of the presence of aflatoxin-DNA adducts in biological samples such as urine and serum, with findings that correlate closely with the incidence of liver cancer [22]. This correlation underscores the importance of continued research in this area, as it can provide insights that are essential for designing targeted public health strategies aimed at reducing the prevalence of aflatoxin-related diseases.

1.2. Regional Demographics and Population Trends Analysis

This subsection will primarily concentrate on examining the geographical distributions and patterns associated with aflatoxin exposure and the corresponding incidence rates of liver cancer, specifically hepatocellular carcinoma (HCC). It will delve into several important population-based studies that have been meticulously conducted in regions known for their elevated rates of HCC, notably sub-Saharan Africa and Southeast Asia [23]. The discussion is set to include a comprehensive overview of the various methodologies employed to assess levels of aflatoxin exposure among these populations. This will encompass a detailed exploration of the prevalence rates of co-infections with hepatitis B virus (HBV) and hepatitis C virus (HCV) within these demographics. Furthermore, the analysis will seek to establish and elucidate the statistical correlations that exist between aflatoxin exposure, the prevalence of these viral infections, and the incidence rates of HCC [24]. Significant insights derived from large-scale epidemiological studies will be presented, shedding light on the variations observed in exposure levels and the associated cancer risks experienced among different demographic groups [25]. Through this examination, the aim is to highlight the complex interplay between environmental factors, infectious disease co-morbidities, and cancer outcomes in diverse geographical settings [26].

2. Materials and Methods

To effectively understand and combat hepatocellular carcinoma (HCC) in relation to aflatoxin exposure and HBV/HCV infections, a comprehensive analysis of regional demographics and population trends is essential [27]. This study utilizes a range of innovative methods and materials to gather and analyze demographic and population data, ensuring a thorough understanding of the epidemiological landscape. Data sources include national and international databases such as the Global Burden of Disease (GBD) Database, World Health Organization reports, and Demographic and Health Surveys (DHS), along with local health registries and cancer registries that provide

detailed data on HCC incidence and mortality [28]. Hepatitis surveillance systems track HBV and HCV infection rates, treatment outcomes, and vaccination coverage [29]. Geographical Information Systems (GIS) are employed to visualize and analyze the spatial distribution of aflatoxin exposure, hepatitis virus prevalence, and HCC incidence, incorporating satellite imagery and remote sensing data to assess agricultural practices and environmental factors. The study focuses on targeted recruitment of high-risk regions, such as sub-Saharan Africa and Southeast Asia, ensuring diverse representation through stratified sampling based on age, gender, socio-economic status, and urban/rural residence as shown in Figure 1. Inclusion criteria encompass individuals from high-risk regions with documented aflatoxin exposure and HBV/HCV infection status, while exclusion criteria filter out individuals with other primary liver diseases or insufficient data on exposure and health outcomes [30]. Data collection techniques include structured interviews and standardized questionnaires to gather detailed demographic information, dietary habits, and medical history, along with biological sample collection of blood, urine, and, in some cases, liver biopsy samples for biomarker analysis [31]. Environmental sampling of food, soil, and water is conducted to assess sources of aflatoxincontamination [32]. Analytical methods encompass descriptive statistics to summarize demographic profiles and prevalence of exposure and disease, GIS mapping and hotspot analysis to identify regions with higher rates of exposure and disease [33], and statistical modeling such as multivariate regression and Bayesian hierarchical models to assess relationships between demographic factors, exposure, and HCC risk. Machine learning techniques like cluster analysis and predictive modeling are employed to identify subgroups with similar exposure patterns and predict HCC risk. Data quality and assurance measures include rigorous training for field staff, adherence to standard operating procedures (SOPs), utilization of electronic data capture (EDC) systems, and regular data audits. Ethical considerations ensure informed consent and participant confidentiality [34]. Advanced tools and technologies like remote sensing, satellite imagery, high-throughput sequencing, and wearable technology are integrated to monitor exposure and health parameters in real-time. The study also emphasizes risk communication through community engagement, health literacy materials, policy development for regulatory frameworks and public health guidelines, intervention programs for HBV vaccination and food safety, and enhanced surveillance systems for real-time monitoring [35]. By employing these innovative methods and materials, the analysis of regional demographics and population trends aims to provide a nuanced understanding of the factors contributing to HCC [36], ensuring that public health strategies and clinical interventions are effectively tailored to the specific needs and risks of different populations, ultimately enhancing outcomes and reducing the burden of liver cancer worldwide [37, 38].

Table 1: Key epidemiological studies on aflatoxin exposure and HCC incidence

S. No	Country/Region	Study Population	Methods	HBV/HCV Prevalence	HCC Incidence Rate	Key Findings	References
1	China	Rural cohorts	Dietary surveys, urine biomarker (AFB1)	High (HBV prevalent)	High (30-40 per 100,000)	Significant dose-response relationship between aflatoxin exposure and HCC risk.	[77, 78, 79]
2	Philippines	Urban and rural	Serum aflatoxin-albumin adducts	Moderate (HBV prevalent)	Moderate (20-30 per 100,000)	Synergistic effect of aflatoxin and HBV on HCC development.	[67, 79, 80]
3	Mozambique, Swaziland	Rural cohorts	Dietary surveys, urine biomarker (AFB1)	High (HBV prevalent)	High (30-35 per 100,000)	High aflatoxin exposure linked with increased HCC incidence.	[80, 77, 81]
4	United States (Texas)	Migrant workers	Serum aflatoxin-albumin adducts	Low (HCV more prevalent)	Low (5-10 per 100,000)	Lower aflatoxin exposure but notable in migrant populations with high HCV rates.	[82, 84, 27]

3. Conclusion

In conclusion, analyzing regional demographics and population trends is crucial for understanding hepatocellular car-

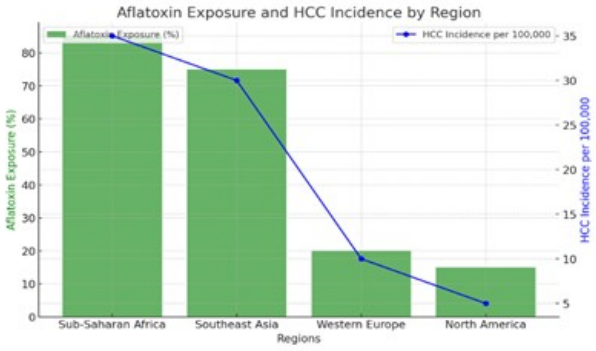

Figure 1: The bar chart above illustrates the percentage of population exposed to aflatoxins and the incidence of hepatocellular carcinoma (HCC) per 100,000 population across different regions. The data highlights the significant correlation between high aflatoxin exposure and increased HCC incidence, particularly in sub-Saharan Africa and Southeast Asia

cinoma (HCC) related to aflatoxin exposure and HBV/HCV infections. This study utilizes various data sources, such as health databases, cancer registries, and GIS tools, to explain the spatial prevalence of these risk factors. Targeted recruitment ensures diverse representation from high-risk areas, while structured interviews and sampling gather solid data on exposure and health effects. Advanced methods, including multivariate regression and machine learning, reveal significant relationships and predict HCC risk. Data integrity is maintained through rigorous quality assurance and ethical practices. Innovative technologies, like remote sensing and wearable devices, enhance monitoring of exposure and health metrics. This holistic approach helps develop targeted public health strategies and clinical interventions aimed at reducing liver cancer burdens in diverse populations, paving the way for better public health outcomes against HCC.

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