

**Mini-Review****Open Access****The synergism of hepatitis B and aflatoxicosis in hepatocellular carcinoma development: A mini-review**¹Alao, J. O., ¹Oni, M. O., ^{*2}Bello, O. O., ³Bejide, I. O., ⁴Alao, O. J., and ³Komolafe O. I.¹Departmental of Microbiology, Adeleke University, Ede, Nigeria²Department of Biological Sciences, University of Medical Sciences, Ondo, Nigeria³Department of Biological Sciences, Redeemer's University, Ede, Nigeria⁴Department of Otorhinolaryngology, Babcock University Teaching Hospital, Ilisan-Remo, Nigeria*Correspondence to: obello@unimed.edu.ng; +2348057892661**Abstract:**

Hepatocellular carcinoma (HCC) is the twelfth most common cancer and the fifth leading cause of worldwide cancer-related death. Chronic hepatitis B infection, caused by the hepatitis B virus (HBV) and exposure to aflatoxins is fundamental in the formation of HCC in developing countries. This review of scientific publications aims to establish the detrimental effects of aflatoxin-contaminated foods and highlights the correlation between aflatoxin and hepatitis B viral-associated hepatocellular carcinoma. Research has shown a significant increase in the occurrence of HCC in HBV-infected individuals exposed to fungal toxins. HBV demonstrates the ability to integrate and bind to p53 protein in the host DNA and propagate hepatocyte vulnerability through carcinogenic aflatoxin B₁ (AFB₁) damage. Although there has been clear evidence about the synergistic interaction of exposure to AFB₁ and HBV infection in the induction of HCC, other literature has shown otherwise, mainly because incomplete and vague findings and hypotheses were made in regions where AFB₁ and HBV pose a public health risk. Vaccination against hepatitis B and measures such as robust food safety systems to avoid hepatotoxicity and hepatocellular carcinogenesis induced by AFB₁ is the most effective methods in the prevention of HCC induced by HBV and AFB₁.

Keywords: aflatoxin B₁; hepatitis B; hepatocellular carcinoma; synergy

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La synergie de l'hépatite B et de l'aflatoxicose dans le développement du carcinome hépatocellulaire: une mini-revue¹Alao, J. O., ¹Oni, M. O., ^{*2}Bello, O. O., ³Bejide, I. O., ⁴Alao, O. J., et ³Komolafe, O. I.¹Département de Microbiologie, Université Adeleke, Ede, Nigeria²Département des Sciences Biologiques, Université des Sciences Médicales, Ondo, Nigeria³Département des sciences biologiques, Université Redeemer, Ede, Nigeria⁴Département d'Oto-Rhino-Laryngologie, Hôpital Universitaire de Babcock, Ilisan-Remo, Nigéria*Correspondance à: obello@unimed.edu.ng; +2348057892661**Résumé:**

Le carcinome hépatocellulaire (CHC) est le douzième cancer le plus fréquent et la cinquième cause de décès par cancer dans le monde. L'infection chronique par l'hépatite B, causée par le virus de l'hépatite B (VHB) et l'exposition aux aflatoxines est fondamentale dans la formation du CHC dans les pays en développement. Cette revue de publications scientifiques vise à établir les effets néfastes des aliments contaminés par l'aflatoxine et met en évidence la corrélation entre l'aflatoxine et le carcinome hépatocellulaire associé au virus de l'hépatite B. La recherche a montré une augmentation significative de la survenue de CHC chez les personnes infectées par le VHB exposées à des toxines fongiques. Le VHB démontre sa capacité à s'intégrer et à se lier à la protéine p53 dans l'ADN de l'hôte et à propager la vulnérabilité des hépatocytes par le biais de dommages cancérogènes à l'aflatoxine B₁ (AFB₁). Bien qu'il existe des preuves claires de l'interaction synergique de l'exposition à l'AFB₁ et à l'infection par le VHB dans l'induction du CHC,

d'autres publications ont montré le contraire, principalement parce que des conclusions et des hypothèses incomplètes et vagues ont été formulées dans des régions où l'AFB₁ et le VHB posent un risque pour la santé publique. La vaccination contre l'hépatite B et des mesures telles que des systèmes de sécurité alimentaire robustes pour éviter l'hépatotoxicité et la carcinogénèse hépatocellulaire induites par l'AFB₁ sont les méthodes les plus efficaces dans la prévention du CHC induit par le VHB et l'AFB₁.

Mots clés: aflatoxine B₁; hépatite B; carcinome hépatocellulaire; synergie

Introduction:

Hepatocellular carcinoma (HCC) is most frequent type of primary liver cancer in adults. Based on the number of cases reported each year, HCC (Plate 1) is the twelfth most common cancer and the fifth leading cause of all cancer-related deaths worldwide (1).

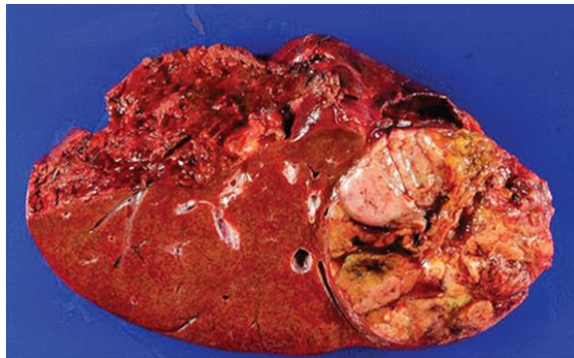
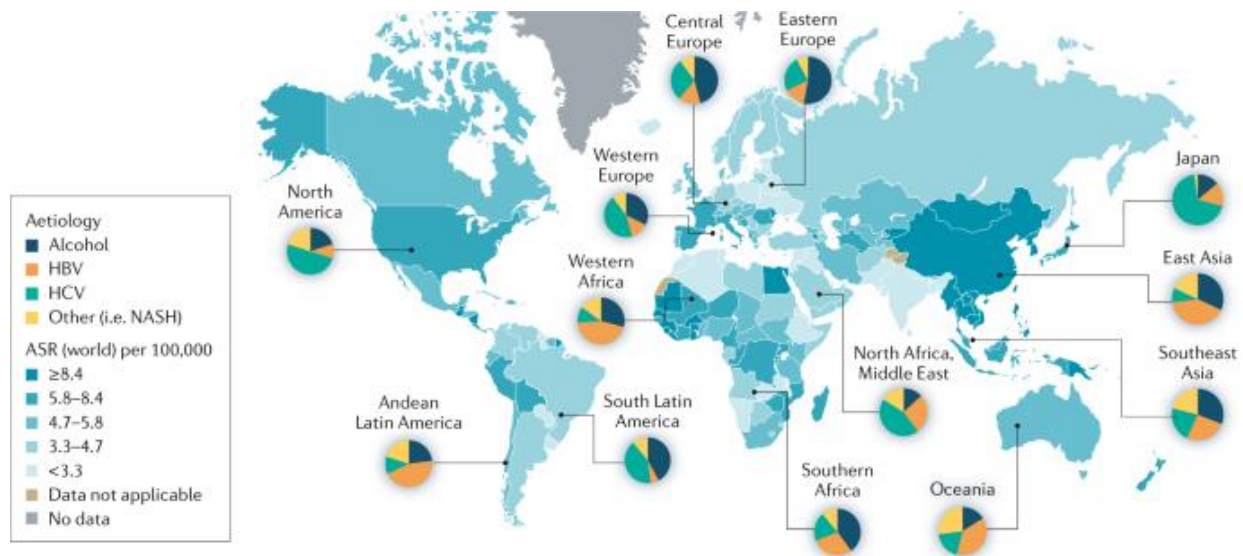


Plate 1: Macroscopic morphology of a large HCC from a patient with a co-infection of hepatitis B and aflatoxicosis (20)

HCC is an exigent disease that leads to the mortalities of greater than 600,000 people every year. In a recent study, 841,080 new cases of tumor were reported, accounting for up to 9.2% of all new cancers (3). Although HCC does not have a uniform geographical distribution as shown in Fig 1 (4), its overall incidence in developing countries at 513,000 new cases is five times that of the developed nations at 110,000 new cases (5). These rates have been apparent, especially in sub-Saharan Africa and the Asia Pacific (3). Chronic hepatitis B and C infection and aflatoxin (AFT) exposure are decisive in the manifestation of HCC in developing countries (6). However, excessive alcohol intake is also a major predisposing factor.

Viral hepatitis is the inflammation of the liver, which is caused by a viral infection (7). The infection may be manifested as acute (recent infection, relatively rapid onset) or chronic (persistent). Viral hepatitis may be caused by infection by one of the five currently known viruses,



This figure shows that the highest prevalence of HCC occurred in East Asia, while the highest worldwide was observed in Mongolia. The major aetiological factor in many parts Africa, South America and Asia (excluding Japan) is the Hepatitis B virus (HBV) while Hepatitis C virus (HCV) is the chief aetiological factor in Japan, North America and Western Europe. Alcohol intake is indicted in Central and Eastern Europe. Non-alcoholic steatohepatitis (NASH) is the major aetiological factor of the category tagged 'Other'; it is a fast-rising risk factor that could become the predominant aetiology of HCC. ASR is the age-standardized incidence rate.

Fig 1: Global map showing the prevalence and major aetiological factors of HCC (4)

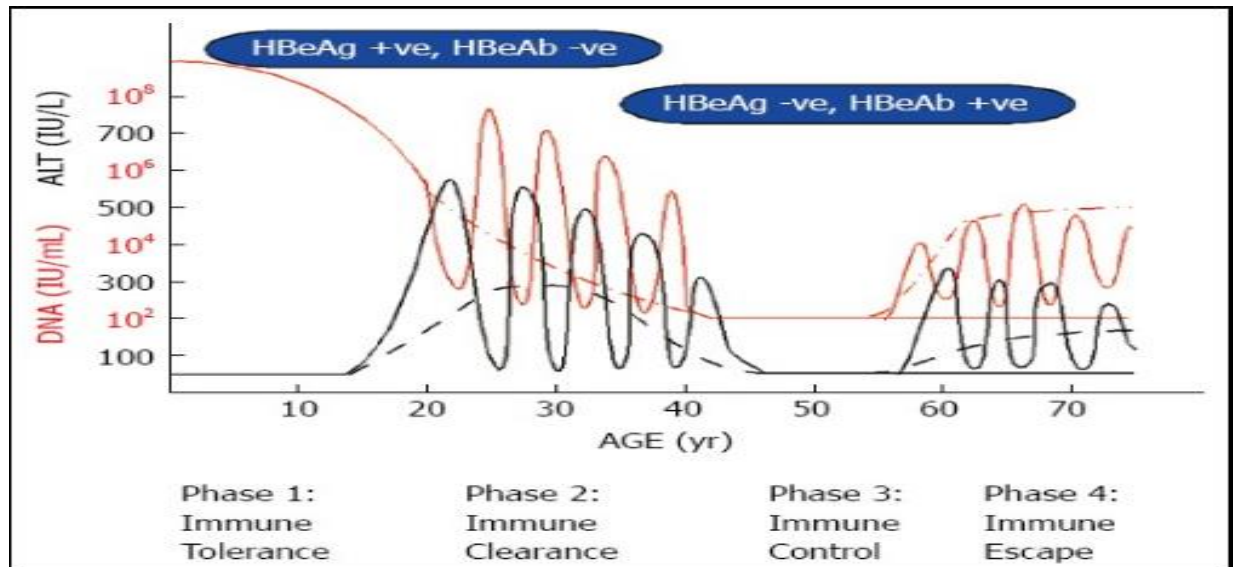


Fig 2: The natural history of CHB, demonstrating the interaction of serology, biochemistry and molecular virology (10)

which principally affect the liver; hepatitis A, B, C, D and E viruses (HAV, HBV, HCV, HDV and HEV) (8). Although there are certain similarities in the clinical manifestations caused by them, the hepatitis viruses differ widely in their morphology, genomic organization, taxonomic classification, and replication modes. The epidemiology of viral hepatitis infection is substantial. About 2 billion people exposed and 350 million people with chronic infection are at risk for developing liver disease and are responsible for nearly 1 million deaths annually (9).

Chronic HBV infection (Fig 2) associated with cirrhotic liver was categorized as the essential factor linked with the HCC development (10), which has been reported as one of the principal causes of death among men (11,12). In Africa, more than 65 million people are estimated to be chronic carriers of hepatitis B virus (10), which accounts for up to a quarter of the world's chronic HBV population and may be an understatement because of the lack of surveillance and underreporting in many African countries. Studies outside Africa cannot be extrapolated to Africa because HBV strains circulating in Africa differ from those found outside Africa and have unique characteristics.

Aflatoxins (AFTs) are extremely hazardous secondary metabolites obtained from polyketides associated with fungal species such as *Aspergillus flavus*, *A. parasiticus*, and *A. nomius* (13). These fungi typically affect cereal crops, including wheat, walnut, corn (Plate 2), cotton, peanuts, and tree nuts, during favorable tempe-

ratures and humidity (3). They can cause toxic damage to humans and animals, such as hepatotoxicity, teratogenicity, and immunotoxicity (14). AFTs are classified as group 1 carcinogenic agents to humans by the International Agency for Research on Cancer (IARC) (5). Even at minute concentrations, aflatoxins still pose serious health threats to humans. Liver necrosis could occur as a result of the consumption of high concentrations of aflatoxins and this is usually accompanied by rapid death (15).

Aflatoxins exist in four primary forms; B1, B2, G1, and G2. These forms occur in synergy, varying in proportions in foods. Since ambient humidity and plant moisture content are important factors in determining the growth and toxin output of these moulds, seed exposure occurs primarily in tropical and subtropical environments with high humidity and high temperatures. These atmospheric conditions are characteristic in parts of sub-Saharan Africa, the Asia Pacific region, and parts of South America. The probability for exposure is high in subsistence farming communities situated in these regions which experience these conditions, where regulations to control toxin exposure are either non-existent or impracticable (16). Aflatoxin B₁ (AFB₁) has a similar geographical distribution to chronic HBV infection, colonizing various food products in the same Far Eastern and sub-Saharan African countries. Therefore, synergistic interactions of the hepatocarcinogenic effects of HBV and AFB₁ would possibly explain or elucidate the prevalence of HCC in these regions of the world.



Plate 2. Maize infested with *Aspergillus flavus* (17)

Probable modes of interaction between AFB₁ and HBV in hepatocarcinogenesis:

Some studies (as shown in Table 1) have been conducted to identify the possible mechanisms of synergism of AFB₁ and hepatitis B in the development of HCC. However, most of the studies were carried out decades ago, and there is currently inadequate information on the mecha-

nisms of interaction between the primary causative factors. Some potential mechanisms have been suggested for the interaction of HBV and AFB₁ in the cause of HCC. A mechanism in which this is achieved is through specific cytochrome P450s that metabolize AFB₁ to AFB₁-8,9-epoxide, which may be caused either by chronic hepatitis by HBV infection or by the presence of the virus itself (Fig 3).

Induction of these phase I enzymes have been described in HBV transgenic mice (18). The hepatocyte damage caused by the virus seemed to result from this effect instead of the virus itself. The discovery that Gambian and Taiwanese children and adolescents chronically infected with HBV have lower AFB₁ adduct concentrations than non-infected people (19) correlate with this mechanism. The aflatoxin-8,9-epoxide generated has been shown to bind to proteins that cause acute toxicity or DNA changes that increase the probability of malignant transformation over time (20).

Table 1: Studies on hepatocarcinogenic synergy of aflatoxicosis and hepatitis B virus

Findings	Location	Reference
AFB ₁ and HBV coinfection hastens the development of HCC	Swaziland, Africa	(21)
HCC prevalence is 10 times more in HBV-positive individuals with high aflatoxin consumption	Guangxi, China	(22)
HBsAg carriers with detectable aflatoxin-albumin adduct are likely to develop HCC	Taiwan, Asia	(23)
AFB ₁ and HBV bind and integrate to P53 protein, cause P53 mutations and induce carcinogenesis	Ejura-sekyedumase District, Ghana	(24)
Exposure of AFB ₁ can increase the risk of HCC through a dose-response among chronic HBV carriers.	Taiwan, Asia	(25)

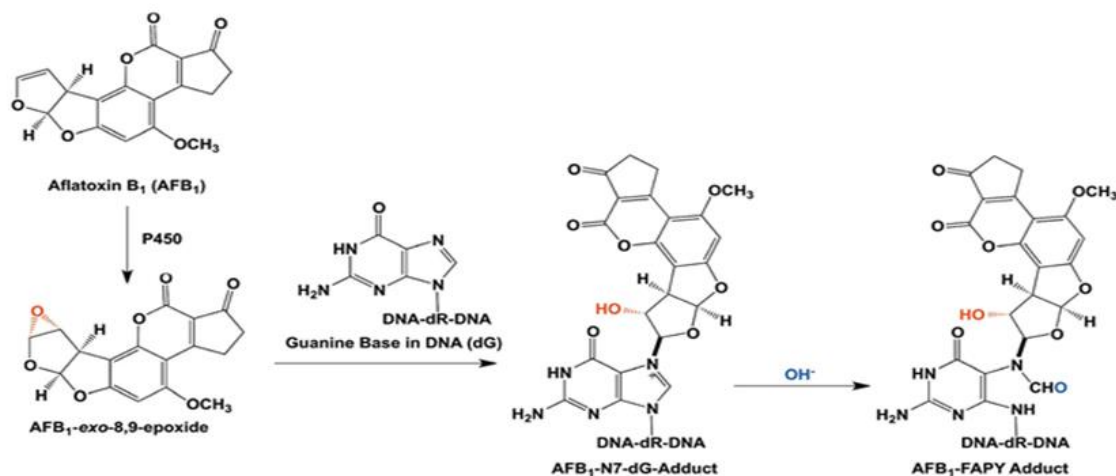


Fig 3: Diagrammatic illustration showing the metabolism of AFB₁ to AFB₁-8,9-epoxide to induce Guanine Base changes (26)

Another suggested hypothesis is that the development of phase II detoxification enzymes [glutathione S transferase (GST) and epoxy hydrolase (EPHX)] contribute to the proliferation of AFB₁ and HBV-induced HCC (23). There was a multiplicative association in the development of HCC in West African and Chinese patients between HBV infection and EPHX mutations (27); patients with chronic HBV infection but with healthy EPHX alleles were 15 times at higher risk, and those with both HBV infection and at least one EPHX mutant were at 77 times higher risk. Subsequent reports on these patients indicated a positive relationship between HBV and AFB₁ and which seemed to rely on the existence of a polymorphism of the genes GST T1, GST M1, and EPHX. These genes are normally responsible for transforming carcinogenic AFB₁-8,9-epoxide into non-reactive metabolites (23).

The carcinogenic association between AFB₁ and HBV may also be mediated through elevated hepatocyte necrosis, and proliferation due to chronic HBV infection, which increases the probability of both AFB₁ mutations, like 249^{ser}, and eventual clonal expansion of cells carrying these mutations (28). Chronic necro-inflammatory hepatic conditions, like HBV infection contribute to generation of oxygen and nitrogen reactive species (29).

Prevention of HCC associated with AFB₁ and hepatitis B viral infection:

Genetics account for only 5–10% of all HCC cases, while environmental and lifestyle factors account for 90–95% of cancer cases (30).

This suggests that the cancer can be prevented when risk factors that contribute to the development of cancer are avoided or reduced (31,32). A central concern of the public health sectors in developing countries is the HCC correlated with AFB₁. However, it remains a limiting factor in countries with weak public health and agricultural safety and food regulation systems. In countries with low capital, practical methods that have ensured minimal contamination of AFB₁ in industrialized countries cannot be applied realistically (33). Thus, efficient and effective approaches should be developed for developing countries to mitigate the AFB₁ contamination of human and animal foods. A variety of approaches have been tried (Fig 4) in order to reduce patient and population exposure to aflatoxins (34), also referred to as primary methods of prevention, as well as secondary forms of prevention using chemo-preventive agents to treat individuals at high risk of AFB₁ exposure (35).

It is necessary to implement long-term measures such as robust food safety systems to avoid hepatotoxicity and hepatocellular carcinogenesis induced by AFB₁. Steps should be at the level of individuals and communities. Such efforts must be directed at both market vendors and local farmers to avoid or reduce long-term exposure to aflatoxins, thereby increasing the incidence of HCC (36). Pre-harvesting measures include development of fungal-resistant crops and crops which have been genetically modified to inhibit the biosynthesis of aflatoxins and the application of insecticides and fungicides (35).

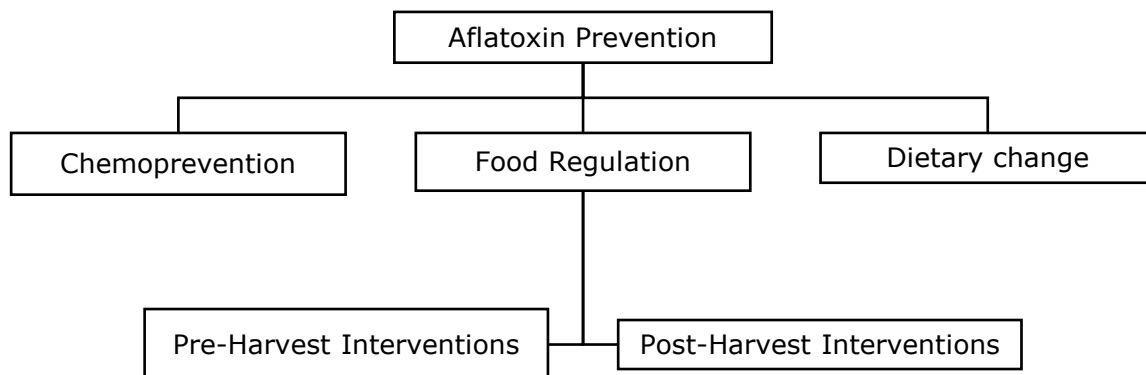


Fig 4: Proposed scheme for aflatoxin prevention (34)

To effectively prevent HBV infection, it is essential to understand its transmission route. Infection age and the origin of the disease are significant determinants in HBV infection outcome (37). The most important transmission route in endemic areas is perinatal mother-to-infant transmission; HBV infection occurs primarily during infancy and early childhood. In the absence of prophylaxis, 90% of babies develop chronic condition from highly infectious (HBeAg-positive) hepatitis B carrier mothers. HBV immunization can be categorized into passive and active immunization. Passive immunization with hepatitis B immunoglobulin (HBIG) provides temporary immunity, while effective vaccination provides long-term immunity. Since the primary infection route in endemic areas comes from the maternal transmission and the perinatal transmission results in a very high rate of chronic infection (90%), the best timing for initial HBV immunization should therefore be within 24 hrs of conception, accompanied by subsequent doses of HBV vaccine during infancy (38).

Other preventive measures, such as blood screening, proper sterilization of injection syringes, and avoidance of risky behaviors such as intravenous drug abuse, unprotected sex, skin piercing or tattooing can prevent horizontal transmission of HBV. Additionally, awareness should be provided to avoid high-risk behaviors such as encouraging condoms use during sexual intercourse. Most of the countries with low prevalence of HBV infection normally have adolescent HBV vaccinations to prevent exposure to sexual encounters or other threatening behaviors related to exposure to HBV.

Assessing further synergistic roles of AFB₁ and HBV in the development of HCC:

Although the etiological function of AFB₁ exposure to HCC has been researched for 50 years, there is limited information on the interaction of HBV infection (5). Hepatitis B virus is a significant risk factor in the development of primary liver cancer, and many of the studies are affected by this viral infection. In a study carried out by Lereau et al., (39), which sought to investigate the relationship between short-term exposure to AFB₁ (dose-dependent) and HBV on the *P53* gene in *HepaRG* cells, AFB₁ was evaluated as a natural antiviral agent. However, it was noted that there was no clear correlation between the doses applied to the cells in the study and the concentrations of AFB₁ liver after human dietary exposure.

AFB₁ research programs lack adequate resources in developing countries with high levels of aflatoxin food contamination in terms of qualified personnel, capital investment, and ana-

lytical and technical facilities. Besides, funding support for systematic assessments in these regions is essential in following all these factors. The truth is that much of society suffers from food shortages, so contaminated food products are likely consumed. For this reason, hepatitis B vaccine services have been proposed as a more practical and cost-effective plan to decrease the occurrence of liver cancer than to eliminate aflatoxin from the diet (40).

Incomplete and vague findings and hypotheses were made in regions where AFB₁ and HBV are widely at risk for public health. For the prospective aspects of the research, a significant number of methodological optimizations and brand-new approaches are required, sustaining an apt opportunity to depict the profound effect of AFB₁. Researchers regarding this subject still face some issues. The primary problem is that most experiments have been redirected to endemic areas, showing high HBV rates, and the codon 249 mutation of the *p53* gene has not been tested to demonstrate any relation to the sensitivity to AFB₁. Another issue is that the accuracy of HCC clinical data and the prevalence of HBV are reduced. Also, the determination of AFB₁ intake was not scrutinized for each patient and was restricted only to certain types of food (5).

From the findings of this mini-review, it is hoped that necessary action would be taken to monitor the aflatoxin levels and decrease the occurrence of aflatoxins in foods to benign levels. This is expected to increase the efforts by government and non-governmental organizations to support the course that would reduce the incidence of hepatitis B virus and aflatoxins-induced liver conditions.

Contribution of authors:

JOA, MOO, and OOB conceptualized the research; JOA, MOO, OOB, IOB, OJA, and OIK contributed to the development and writing of the manuscript; and JOA, MOO, and OOB contributed in validating and reviewing the manuscript. All authors approved submitted version.

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