ONLINE ISSN :3007-309X
PRINT ISSN :3007-3081

Journal of Medical & Health Sciences Review

DIETARY AFLATOXIN AS A SOURCE OF CARCINOGENIC RISK IN HUMANS: A CASE CONTROL STUDY

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ARTICLE INFO:

Keywords: Aflatoxin, Aflatoxin B1 (AFB1), Aspergilli species, Mycotoxins, Unprocessed milk.

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Article History:
Published on 6 July 2025

ABSTRACT

Introduction: Hepatocellular carcinoma (HCC), the most common liver malignancy, is the third leading cause of cancer death worldwide. Chronic liver dysfunction is associated with an increased risk of HCC in 90% of patients. Foods including cereals, dried fruit juice, and spices frequently include aflatoxins, which are secondary metabolites produced by naturally existing Aspergilli species. Aflatoxin is one of the environmental risk factors of hepatocellular cancer (HCC). There is a strong correlation between aflatoxins and HCC that aggravate the severity of disease and have poor prognosis.

Objectives: Objective of our study was to assess the presence of Aflatoxin in HCC patients.

Material and Methods: This analytical case control study was conducted at the Nuclear Institute of Medicine and Radiotherapy (NIMRA) in Jamshoro and the Asian Institute of Medical Sciences (AIMS) in Hyderabad, from January to December 2020.

Results: Our study had 218 subjects in total, 109 patients (77 male, 32 female) were diagnosed with HCC and 109 served as controls (78 male, 31 female), with mean age of 49.5 ± 11.5 year. Majority of the participants were belonging to poor

class 67 (64%) cases and 74 (69%) controls. The frequency of HCC patients on Mycological Culture media positive for aflatoxin were positive in 80 patients (73.4%) and negative in 29 cases (26.6%), according to culture media. The socioeconomic status (SES) and the illness were shown to be significantly associated (p value <0.05). The frequency of Aflatoxin positive in patients with HCC on Mycological Culture media was 80 (73.4%) Patients and 29 (26.6%) were negative with Aflatoxin **(p value 0.002).** Milk drinking causes a statistically significant difference in the patient group's percentage of Aflatoxin B1ng/ml at a level of $\alpha < 0.05$. There is statistically significant difference in the percentage of Aflatoxin B1 in the patient group at the significant level **p value 0.001** due to unprocessed milk. There was statistically significant difference in the percentage of Aflatoxin B1 in the patient group at the significant level with **p value 0.031** due to consumption of Raw uncooked Food**.** There is statistically significant difference in the percentage of Aflatoxin B1 in the patient group at the significant level **p value 0.006** due to Processed Packaging Food.

Conclusion: Our study concluded that HCC patients exposed to AFB1 there is a high risk of Aflatoxin formation in the liver, which leads to a poor prognosis, but this can be avoided by reducing the intake of foods contaminated with AFB1. Therefore, preventive strategies to control these toxins should be used. In particular, it is useful for the appropriate treatment and preparation of general foods for high-risk patients.

INTRODUCTION

Food-borne aflatoxin is a serious public health issue that requires in-depth investigation to fully understand the range of impacts it can have on people. Aflatoxin poisoning prognosis is dependent on immune system function, nutritional condition, length of exposure, and overall health. Long-term exposure to low concentration of aflatoxin can lead to cirrhosis and hepatocellular carcinoma, both of which have high rates of illness and mortality that cannot be reversed. Acute poisoning from a high aflatoxin dosage can cause rhabdomyolysis and fulminant liver failure. Hepatocellular carcinoma can develop from liver cirrhosis brought on by prolonged aflatoxin exposure (Dhakal 2024).

Among people suffering from liver conditions, it represents a significant cause of illness and death; in 2019, it was responsible for 2.4% of all deaths globally.

There have been notable improvements in the management of liver cirrhosis in recent times. Still, the outlook is still dire. Determining and mitigating its avoidable risk factors has to be a top concern (Mekuria, 2023). Together, cirrhosis and liver cancer rank 11th and 16th in the globe respectively, contributing to 3.5% of all fatalities worldwide (Mercado-Irizarry, 2016). This is especially evident in Sub Saharan Africa, where are the consumption of the alcohol and the Hepatitis B, C & HIV viruses are recognized as causal factors in 34%, 17%, and 18% of cases, respectively. However, numerous causal associations have been reported between cirrhosis and hepatocellular carcinoma (HCC), including alcohol abuse, nonalcoholic fatty liver disease/nonalcoholic steatohepatitis, persistent HBV infection, and/or HCV. Eating foods milk consumption, legumes, raw / uncooked food and processed packaging food infected with aflatoxins (AFs) exposes one to new etiologic factors for HCC (Mekuria, 2020).

Because AFs are naturally occurring and structurally stable, environmental factors will unavoidably contaminate herbal medicines in the field or at any point in the supply chain, including collection, processing, transportation, and storage. AFs are more likely to be present in a variety of medicinal parts (seeds, roots, etc.) of medicinal materials that contain higher levels of oils, proteins, starches, and sugars, such as Polygalae Radix,

Nelumbinis Semen, and Platycladi Semen. Examples of animal medications with high protein concentrations that are also more prone to result in AFs infection are Mylabris and Hirudo. Additionally, the addition of AFs to decoctions puts consumers at risk, particularly those who habitually use or take the herbal treatments directly (Raysyan, 2020). Several Aspergillus fungal species naturally produce aflatoxin, a pollutant of agricultural foods that is harmful to human health and significant on a global scale. Aflatoxin B1 is one of the most powerful naturally occurring carcinogens and is harmful to humans (Gachara, 2024). Aflatoxin toxicity and carcinogenicity mostly damage the liver in both humans and animals. Importance in toxicology has been thoroughly examined. Aflatoxin toxicity and carcinogenicity mostly damage the liver in both humans and animals (Hassan, 2024). The metabolic effects of aflatoxin include suppression of DNA, RNA, and protein synthesis, a decrease in the formation of clotting factors, and a decrease in the activity of numerous enzymes. Aflatoxin exposure has been linked to a higher incidence of hepatocellular carcinoma (HCC), particularly when combined with HBV (Jaćevic, 2023). According to a number of epidemiological studies, people with HBV and HCV infections seem to have much higher levels of the toxin's potency (Yang, 2024).

Approximately 80% of instances of liver cancer worldwide are hepatocellular carcinoma (HCC). It is the most common subtype of HCC in the clinical population, accounting for approximately five hundred thousand to six hundred thousand new cases each year. It is the second most frequent type of cancer that kills people worldwide, after lung cancer. Like the majority of cancer types, HCC liver cancer in women is said to be more prevalent in developing nations like China as well as other parts of sub-Saharan Africa and Southeast Asia (Magnussen, 2021). According to multiple sources, like the WHO new liver cancer cases are reported approximately equal to the number of people who die from these new cases, which rests around 600,000 deaths every year. Also, the fatality of liver cancer contributes significantly to a higher number of deaths due to cancer (Lin, 2021).

Numerous investigations have suggested that the pathogenesis of human HCC is complex (Luo, 2024). When aflatoxins are combined with Hepatitis B and C, the risk of liver cancer is a staggering twelve times higher than with Hepatitis B infection alone, according to the World Health Organization's expert committee on aflatoxins and health. This increases the risk of liver cancer by five times, which is concerning in and of itself, according to the WHO expert committee on aflatoxins and health (Benkerroum, 2020).

Numerous other researchers have demonstrated that the risk of dying from liver cancer varies by about 3.5 times depending on the community from which their study populations were drawn. These researches also revealed a fluctuation in the local environment's aflatoxin B1 concentration, which was found to positively correlate with the rate of liver cancer mortality (Mekuria, 2023).

Table 1. List the most common mycotoxins, along with any potential health risks and the commodities they may affect (El-Sayed, 2022)		
Mycotoxin	**Adverse impacts on health**	**Commodities**
Aflatoxins	Hepatotoxic and hepatocarcinogenic liver disorders, teratogenic and carcinogenic consequences, gastrointestinal and renal hemorrhages, and immune suppression	Milk, spices, grains (maize),and groundnuts and nuts.
Ochratoxins	suppressive of immunity, carcinogenic, and nephrotoxic	Wine, grape juice, and cereals (wheat and maize).
Fumonisins	leukoencephalomalacia, pulmonary edema, hepatotoxic and nephrotoxic effects, and immunological suppression	Maize.
Trichothecenes	Reduced weight gain, gastrointestinal issues (diarrhea, vomiting), bleeding (stomach, heart, intestine, lung, bladder), oral lesions, eczema, infertility, bone marrow degeneration, sluggish growth, and immunological suppression	(wheat, barley) Cereals.
Zearalenone	Consequences of oestrogen, vulva edema, vaginal prolapse, uterine hypertrophy, testicular and ovarian atrophy, infertility, Abortion	Wheat Maize
Ergot alkaloids	Hallucinations, convulsions, or gangrene.	Rye**.**
Patulin	carcinogenic, mutagenic, as well as genotoxic.	Apples,pears

METHODOLOGY

This analytical case control study was carried out at the Asian Institute of Medical Sciences (AIMS) and the Nuclear Institute of Medical & Radiological Assessment (NIMRA). Hyderabad, Pakistan. Patients with a diagnosis of hepatocellular carcinoma who were inpatient or outpatients seeking followup care at AIMS and NIMRA comprised the study population. The Cochrane formula was used to get the sample size for the prevalence of liver cancer (7.5%), of all cancers. 109 cases and 109 controls were chosen for statistical convenience fulfilling the criteria. Patients who were already diagnosed cases of HCC due to Viral Hepatitis, willing to participate and were above 18 years of age.

In collaboration with the hospital administrations of ASIAN Hospital and NIMRA, blood samples were taken from patients who had been diagnosed with hepatocellular carcinoma as a result of viral hepatitis. Consent was obtained before samples for the patients and controls were taken. Age, gender, occupation residence, hepatitis B & C antigen status and smoking status were all asked to complete a questionnaire.

The blood samples were analyzed using the broachers' instructions and the reagents included in the kit. MERCK kit was

employed, and the Microlab-300 analyzer with filters was used to conduct the analysis, 546 for the primary filter and 578 for the secondary filter. Protein: 405–450 filter. Human Aflatoxin B1 Aldehyde Reductase Member 4 AKR7L (My BioSource, Catalog Number: MBS7236834) was used to measure the amount of aflatoxin. Every reagent that is supplied is kept between 2 and 8° C.

109 individuals (77 men and 32 women) were diagnosed with HCC, while 109 patients (78 men and 31 women) served as controls.

Statistical analysis: The statistical analysis was conducted using SPSS (Version 26.0) and included the following: mean, median, standard deviation, test of significance (Pearson correlation, student samples t-test, Chi-square, bigraphs, Inferences about the subject population were made, trends were found, and significant conclusions were drawn from the data.

RESULTS:

Nearly majority of the controls were the patients' relatives. The majority of the patients was from low-income families and

Table No. 01 Sociodemographic Information of the Participants (Cases=109, Controls= 109)

Sr. No.	Characteristics	Response	Cases N=109	Controls N=109
1	Participants' Ages	30 to 39 years old	19	16
		40 to 49 years old	28	69
		50 to 59 years old	44	24
		60 and older	18	0
2	Gender	Male	78	79
		Female	32	31
3	Marital Status	Married	103	107
		Unmarried	7	3
4	Economic and Social Status	Lower Social Class	67	74
		Middle Social Class	34	31
		Upper Social Class	9	5
5	Possible Mode of Transmission	Barber	24	-
		Injections	56	-
		Blood Transfusion	18	-
		Surgery	6	-
		Not Known	6	-
6	Family History	Positive	46	-
		Negative	64	-

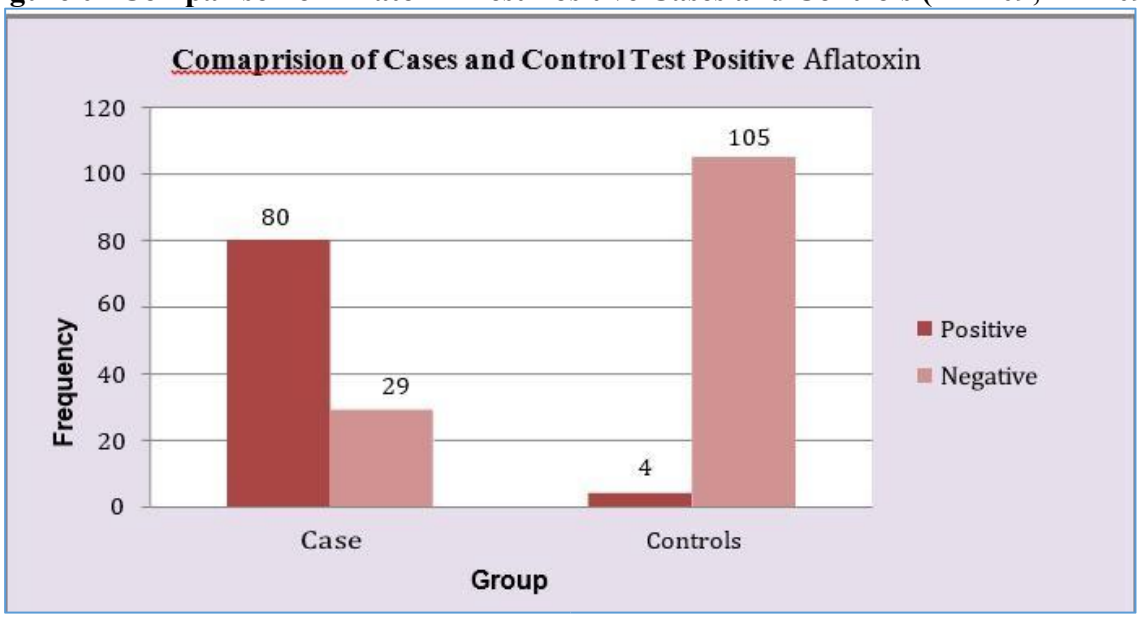
Table No. 02 Correlations between hepatocellular carcinoma and socioeconomic status of the patients (n=109)

		Total Lipids	Liver Enzymes
Hepatocellular Carcinoma	Pearson Correlation	1	0.171*
	Sig. (2-tailed)		0.021
	N 3915	109	109
Socioeconomic status	Pearson Correlation	0.171*	1
	Sig. (2-tailed)	0.021	

	N	109	109
* Correlation is significant at the 0.05 level (2-tailed).			

lived in rural areas. The accompanying figure shows the prevalence of HCC in different socioeconomic classes. Pearson correlation test was appliedto Hepatocellular Carcinoma and socioeconomic patients and it was seen that there were measure the correlation between statistically significant correlation.

Figure 01 Comparison of Aflatoxin Test Positive Cases and Controls (n1=109, n2=109)



The frequency of HCC patients on Mycological Culture media that test positive for aflatoxin is displayed in the above chart. Aflatoxin readings were positive in 80 patients (73.4%) and negative in 29 cases (26.6%), according to culture media.

Table No. 03 Association between consumption of Unprocessed Milk and Alfatoxin B1 Positive in Hepatocellular Carcinoma patients

		Mycological Culture Media		Total	p-value
		Negative Cases	Positive Cases		
Consumption of Unprocessed Milk	No	26	23	49	0.001
	Yes	13	47	60	

Table No. 04 Association between consumption of Raw uncooked Food and Alfatoxin B1 Positive in Hepatocellular Carcinoma patients

		Mycological Culture Media		Total	p-value
		Negative Cases	Positive Cases		
Consumption of Raw	No	26	33	59	0.031

Total	39	70	109	

Milk drinking causes a statistically significant the percentage of Aflatoxin B1 in the patient difference in the patient group's percentage of group at the significant level **p value 0.001** Aflatoxin B1ng/ml at a level of $\alpha < 0.05$. due to unprocessed milk.

There is statistically significant difference in

uncooked Food					
	Yes	13	40	53	
Total		39	70	109	

There is statistically significant difference in **0.031** due to consumption of Raw uncooked the percentage of Aflatoxin B1 in the patient Food**.** group at the significant level with **p value**

Table No. 05 Association between consumption of Processed Packaging Food and Alfatoxin B1 Positive in Hepatocellular Carcinoma patients

		Mycological Culture Media		Total	p-value
		Negative Cases	Positive Cases		
Consumption of Processed Packaging Food	No	29	33	62	0.006
	Yes	10	37	47	
Total		39	70	109	

There is statistically significant change in the percentage of Aflatoxin B1 in the patient group at the significant level **p value 0.006** due to Processed Packaging Food.

DISCUSSION

The primary cause of HCC is a chronic infection with the hepatitis C virus, which causes tumors to form more frequently in livers with cirrhosis than in those without. Similar trends have been observed in regions with high rates of HCV infection, such as the Far East and sub- Saharan Africa (Shiha, 2020). Up to 90 percent of patients with HCC in these areas had liver cirrhosis. In Japan, the yearly risk of hepatocellular carcinoma (HCC) in cirrhotic patients varies from 3% to 11% (Ozakyol, 2017).

Dietary aflatoxins have a wellestablished history of causing cancer, and they work in concert with HCV (Nasir, 2021). their eating profile was used to determine the amount of aflatoxins in their meals; dietary aflatoxins intakes were computed as milligrams per patient body mass based on reports from Pakistan. With the exception of a few who contracted HCV in the late fifth decade, the majority of our HCC patients initially showed up in the late fourth or early fifth decade. Hepatocellular carcinoma (HCC) from areas where HCV is highly common has never been reported before. With a mean age of 49.5±11.5, roughly four out of five patients in our study were in their forties (Asghar, 2018).

Socioeconomic disparities in cancer differed by country and are a growing global concern. As with other malignancies, the survival outcomes of HCC patients will

fluctuate depending on their SES. The findings indicated that low socioeconomic status (SES) is linked to cancer-related symptoms, poor quality of life, and short survival times, even if economic and medical levels differ by nation. In a study conducted by Li Y et al also reported that HCV-related hepatocellular carcinoma (HCC) is highly prevalent in Japan. Compared to HBV-related HCC, HCV-related HCC is more likely to manifest later in life and with more severe cirrhosis. Although their precise role in the pathogenesis of HCC is still unclear, dual infections have been shown to hasten the progression of chronic hepatitis to cirrhosis and to HCC in high- endemic areas (Li, 2007).

Both people and animals can get hepatotoxicity from aflatoxin. This dangerous exposure can cause liver cancer and perhaps death. In order to identify aflatoxin B1 in contaminated food products, they devised a quantitative recombinant AflR gene antiserum ELISA approach [91]. There were either no false negatives or very few false positives in the ELISA data. Furthermore, we used mycological culture media to confirm that aflatoxins were present in HCC patients; 52 (74.28%) of the 70 cases that tested positive for aflatoxins showed positive results (Hafez, 2021).

Aflatoxin-contaminated food has been connected in several clinical reports worldwide to hepatocellular carcinoma, chronic liver damage, and acute aflatoxicosis. In experimental animals, aflatoxins are also known to impact and inhibit immunological responses (Banerjee, 2011). However, as far as we are aware, no prior study has reported aflatoxins found in patients with hepatocarcinoma. Aflatoxin exposure can happen naturally through the consumption of food and through the absorption of contaminated dust through the trachea and bronchi. The full absorption that occurs after oral administration is widely established. The blood, not the lymphatic system, carries AFB1 after absorption. After an hour, Wong discovered that more than half of the radiolabeled toxin had left the duodenum and had instead entered the venous circulation as free toxin, protein adducts, and water-soluble metabolites (Chu, 2017)

In a study conducted by Wenndt at al. revealed that aflatoxin concentration, dietary consumption levels, consumption frequency, and other variables have differing relative contributions to HCC risk across commodities. The quantitative risk assessment estimated that 1.77, 0.44, 0.43, 0.15, and 0.01 HCC cases per year/100,000 population were attributable to aflatoxin exposure through maize, groundnut, rice, cowpea, and soybean, respectively. These findings constitute a novel multi-study risk assessment approach in the Nigerian context and substantiate existing evidence suggesting that there is reason for public health concern regarding aflatoxin exposure in the Nigerian population. Our study also highlighted and there was also association of different food like milk consumption, legumes, raw / uncooked food and processed packaging food were the common sources of aflatoxins in these patients already compromised (Wenndt, 2023).

CONCLUSION

HCC patients exposed to AFB1 there is a high risk of Aflatoxin formation in the liver, which leads to a poor prognosis, but this can be avoided by reducing the intake of foods contaminated with AFB1. The prognosis of patients with hepatocellular HCC and cirrhosis is bad, especially in countries with low income with inadequate medical services. Therefore, preventive strategies to control these toxins should be used. In particular, it is useful for the appropriate treatment and preparation of general foods for high -risk patients, especially for prevention

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