The Effect of Naturally Occurring Dietary Chemicals and Food-Borne Mycotoxins on DNA Methylation and Cancer – A Review

Moniza Nurez Khan [1], Naresh Chandravanshi [1]

Abstract

Food-borne mycotoxins (FBM) can have severe effects, causing sickness or even death shortly after consuming contaminated food. Chronic exposure to mycotoxins is linked to cancer development and immune deficiencies. DNA methylation plays a role in diseases like cancer, influencing the expression of genes that regulate tumor growth. Mycotoxins can lead to crop loss, chemical production, and uncontrolled fungi growth. Aflatoxins, a type of mycotoxin, increase cancer risk and cause severe illnesses. Artificial Light At Night (ALAN) affects melatonin secretion, influencing global DNA methylation in cancer cells. FBM-ALAN shows promise against cancers by restoring normal expression of critical tumor suppressor genes and correcting abnormal DNA methylation. Abnormal DNA methylation can lead to diseases like cancer by silencing tumor suppressors and overexpressing oncogenes. Understanding DNA methylation is crucial for regulating gene expression and preventing illness in eukaryotic cells.

Keywords: Food-Borne Mycotoxins, Artificial Light at Night, Cancer, DNA methylation.

Significance | The critical impact of Food-Borne Mycotoxins (FBM) and Artificial Light At Night (ALAN) on DNA methylation, influencing cancer risk and disease outcomes.

*Correspondence: Moniza Nurez Khan, Department of Pharmacy, Kalinga University, Naya Raipur, Chhattisgarh, India.
Email: ku.pranjaliverma@kalingauniversity.ac.in

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1. Introduction

DNA methylation plays a crucial role in governing gene expression and maintaining genomic stability, ultimately defining the tissue of cells and their lineage. Disruptions in the regulation of DNA methylation have been linked to various illnesses, including cancer (Davoodvandi, A., 2022). The connection between cancer and DNA damage has been well-established, with malignancies developing as a result of DNA repair errors leading to mutations and chromosomal aberrations affecting oncogenes and tumor suppressor genes (Fujii, R., 2022) (Nasir, A., 2022).

The ingestion of mycotoxins present in food poses a potential threat, causing rapid and severe sickness, and even death, when consumed in large quantities. Long-term consequences of mycotoxin exposure include the development of malignancies and weakened immune function (Ghazi, T., 2020) (Kobets, T., 2022). Mycotoxicosis, the toxic reaction resulting from mycotoxin ingestion, manifests through various symptoms, including nephropathy, cancer, alimentary toxic leukemia, hepatitis, hemorrhagic syndromes, and disorders affecting the immune and nervous systems (Yin, S., 2018) (Ruan, H., 2022).

Artificial light at night (ALAN) has been identified as a factor that reduces melatonin production, leading to epigenetic changes and increased breast cancer tumor development. A focused examination has been conducted on the effects of ALAN and exogenous melatonin on the development of breast cancer tumors (Davoodvandi, A., 2022). Prolonged exposure to certain chemicals and environmental hazards, such as asbestos, nickel, cadmium, radon, vinyl chloride, and benzene, poses a significant risk of developing cancer (Jin, J., 2021).

Author Affiliation:
[1] Department of Pharmacy, Kalinga University, Naya Raipur, Chhattisgarh, India.

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Contaminated food can introduce infectious microorganisms, parasites, and toxic chemicals into the body, leading to foodborne diseases. Chemical exposure can result in immediate illness or contribute to chronic conditions like cancer (Shahba, S., 2021). However, exceptions exist, as certain foods naturally contain higher levels of carcinogens than alternatives. Unlike epigenetic carcinogens, DNA-reactive carcinogens exhibit influence at lower doses (Ruan, H., 2022).

The Maillard reaction, which occurs when starchy foods are heated under high temperatures, produces acrylamide from asparagine, a protein. Rodent tests have indicated that acrylamide is carcinogenic, although uncertainty persists regarding the potential harm to humans (Malvandi, A. M., 2022) (Barsouk, A., 2021). Information on exposure led the committee to conclude that the majority of dietary exposure to various natural and artificial chemicals is detectable at concentrations that represent limited to few significant cancer risks. However, it is noted that exceeding these concentrations may result in adverse biological impacts (Patra, S., 2021).

Mycotoxins have lethal risks, causing acute poisoning with long-term consequences. Contaminated foods may lead to vomiting, weight loss, tumors, and death. Critical mycotoxins are found in legumes, roots, tubers, and cereal grains. DNA methylation, in mitosis and meiosis, regulates gene expression, preventing transcription issues. The review provides the role of a DNA Methylation, Mycotoxins, and Environmental Carcinogens in Cancer Development.

2. Literature Review

In recent studies, researchers have shown the intricate connections between mycotoxin contamination in food, epigenetic processes, and the complex landscape of liver diseases.

In their 2022 study, Haonan Ruan and colleagues emphasized the global significance of Mycotoxin contamination in food and feed, identifying it as a pervasive food safety issue and a major health hazard (Ruan, H., 2022). The liver, in particular, is vulnerable to damage from various mycotoxins present in food. Despite this, effective clinical and animal husbandry strategies for preventing and treating Mycotoxin-Induced Liver Injury (MILI) have been limited. Network toxicology has emerged as a valuable tool, predicting potential molecular mechanisms of MILI and suggesting prospective anti-MILI drugs. This lays the groundwork for future research into the toxicity mechanisms of MILI and the development of effective strategies to address MILI-related health risks, thereby advancing food safety.

In a separate study from 2019, Karin Jasek and her team underscored the critical role of DNA Methyl Transferases (DNMTs) in regulating gene expression and DNA repair through epigenetic processes. Mutations in DNMTs were identified as pivotal to cancer development (Jasek, K., 2019). Phytochemicals, synthesized as secondary metabolites in plants, emerged as significant sources of biomolecules with diverse effects and medicinal properties. These phytochemicals impact epigenetic molecular processes, including DNA methylation patterns associated with cancer initiation and progression. Patrick Wellington da Silva dos Santos et al. (2020) proposed that sulforaphane exhibits epigenetic modification effects by suppressing Histone Deacetylases (HDACs), offering potential as a bioactive molecule in epigenetic-focused therapy. However, the exploration of natural chemicals inducing epigenetic modifications continues as an alternative, considering their significant toxicity and unknown mechanisms of action. Sulforaphane is currently under investigation as a potent anticancer medication, exploring its effects on DNA damage, mitotic spindle abnormalities, cell death, and decreased proliferation using high throughput approaches alongside cellular-based testing.

Jeongeun Hyun and colleagues (2020) highlighted the challenges in developing effective medicines and biomarkers for Non-Alcoholic Fatty Liver Disease (NAFLD), attributing the hindrance to a lack of understanding regarding the transition from basic steatosis to NASH. DNA methylation emerged as a key player in the pathophysiology of NAFLD, influenced by climate and lifestyle factors such as nutrition, obesity, and physical exercise. Modifying and reversing DNA methylation patterns in NAFLD offers a foundation for innovative drugs to monitor the disease's development and progression, facilitating the design of effective treatments.

Addressing the drawbacks associated with food-borne mycotoxins, natural chemicals, and their impact on DNA methylation and cancer in contemporary settings (Kobets, T., 2022), Haonan Ruan's work (Ruan, H., 2022) proposes to overcome limitations presented by Jasek (2019) and Dos Santos (2020). Additionally, Ruan suggests a comparison with the proposed method FBM-ALAN, offering a comprehensive approach to address these issues.

3. Food-borne mycotoxins and natural dietary substances affect DNA methylation and cancer.

Foods harbor various compounds, including carcinogens from plants, microbes, contaminants, and processing. DNA reactivity and epigenetics influence cancer development. DNA methylation regulates genomic processes, impacting cell lineages. Dietary micronutrients and bioactive chemicals alter DNA methylation, offering cancer treatment insights. Mycotoxins, like aflatoxin, present in groundnuts and cereals, contribute to cancer risk. Fusaric acid and fumonisin in common fungi impact biological functions, leading to liver and kidney tumors. Zearalenone competes with estrogen, affecting reproductive chemicals.

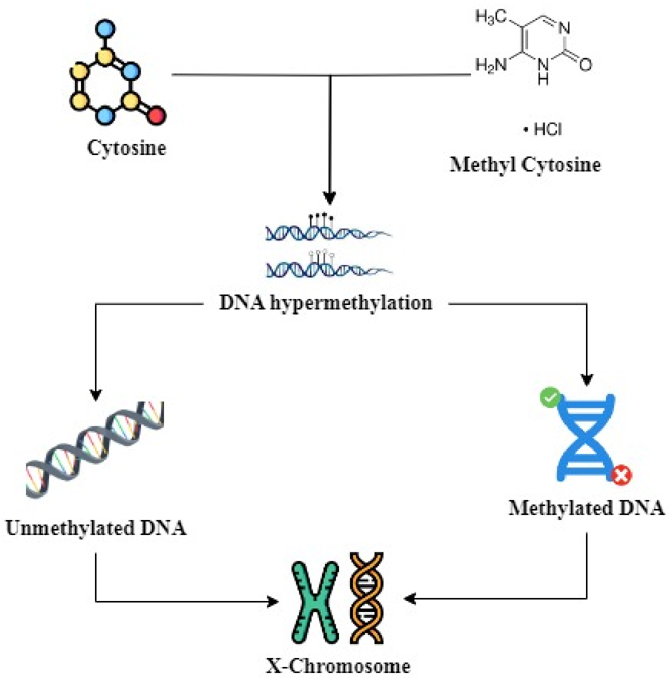

Figure 1. The methylation of DNA process

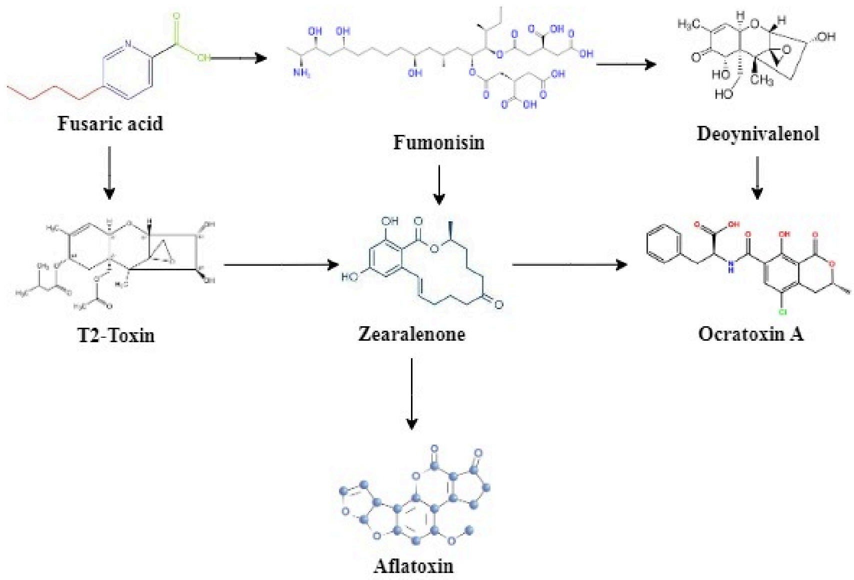

Figure 2. Chemical structures of food-borne mycotoxins

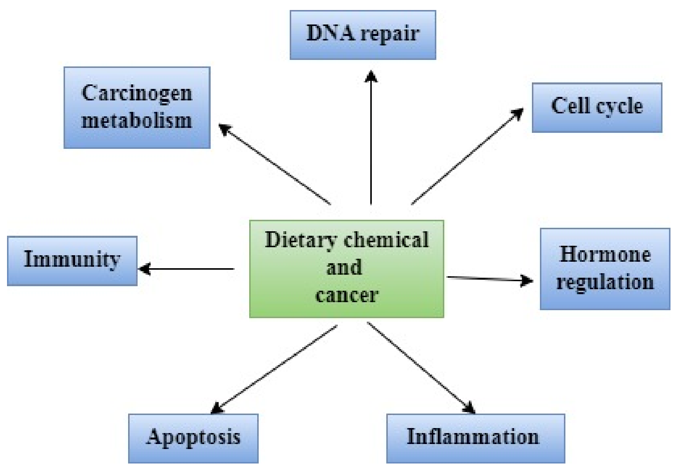

Figure 3. Cancer of naturally occurring dietary chemicals

Nutrition influences cancer progression by altering cell cycle regulation, gene expression, and cellular factors. Long-term dietary interventions may impact cancer prevention, but short-term studies pose challenges in evaluating outcomes. Validating dietary intake through biomarkers is crucial for reliable research in cancer prevention and intervention.

Foods and beverages represent intricate chemical interactions consumed for both nutritional benefits and pleasure. The vast array of compounds in food exhibits diverse qualities. Numerous regularly consumed foods have been identified to contain chemicals with carcinogenic activity in rodent models, stemming from sources such as plants, microbes, contaminants, additives, and reactions during storage, processing, and cooking (Ruan, H., 2022).

DNA reactivity involves covalent contact with nuclear DNA, while epigenetics explores molecular and cellular consequences beyond DNA reactivity. Carcinogens are often detected in food at trace levels, permitting moderate regular consumption exceptions. Figure 1 illustrates that DNA methylation, a biological process safeguarding genomes, is linked to chromatin and gene silencing. Genomic imprinting, transposon silencing, oncogene suppression, X-chromosome inactivation, and pluripotency gene control are influenced by DNA methylation. Occurring predominantly at dinucleotides, DNA methylation requires the addition of a methyl group from the universal donor S-adenosylmethionine (Eskola, 2020). Cancer, characterized by uncontrolled cell multiplication leading to tumor development, involves signaling pathway disruptions and genetic and epigenetic alterations. Recent research suggests that dietary micronutrients and bioactive chemicals altering DNA methylation may offer insights into effective cancer treatment (Erichsen, L., 2022). Utilizing micronutrients, bioactive chemicals, and food-borne mycotoxins affecting DNA methylation patterns may soon contribute to cancer treatment and prevention.

The production of species as a secondary metabolite in Fusaric acid, a metal-chelating agent is shown in Figure 2. This chemical inhibits blood coagulation, bone ossification, hypotension, and notochord development by binding to divalent cations. Fusarium species, common contaminants in maize and other crops, generate fumonisin, leading to sphingoid base accumulation and interference with biological functions. Aflatoxin, found in groundnuts, milk, rice, sorghum, maize, and oils, is a known carcinogen. Zearalenone, structurally similar to estrogen, competes with estradiol for estrogen receptor binding. Deoxynivalenol, a trichothecene present in wheat, maize, oats, and grain, is associated with various health issues (Janik, E., 2020).

Nutrition can influence cancer progression by affecting cell cycle regulation, cell death, differentiation, oncogene and tumor suppressor gene expression, cell signaling, and other factors (Figure 3). Bioactive dietary components can impact gene expression in multiple scenarios, with typical diets providing additive or synergistic effects on cellular processes. It's crucial to consider the short time frames in research results compared to the long latency of most cancers. Implementing interventions at specific times, depending on the suggested mechanism of action, can impact cancer development. Prevention in cancer may be feasible for patients with reversible preneoplastic lesions or high-risk individuals. Linear regression of biomarker readings on intake estimates can calibrate self-reported questionnaire food consumption, and medical indicators in blood and urine authenticate dietary intake reliably.

4. Discussion

Mycotoxins, produced by fungi, pose a serious threat to human and animal health as well as agricultural crops. These toxic secondary metabolites can contaminate various foods, leading to cellular dysfunction and genetic alterations that may contribute to the development of cancer. The production of mycotoxins is influenced by environmental conditions, and different fungus species can produce distinct mycotoxins. Maintaining a good, balanced diet is crucial in reducing the risk of cancer, particularly diet-related cancers affecting the digestive system, such as those in the esophagus, stomach, and colon.

The global issue of mycotoxin contamination in food and animal feed adds complexity to the challenge of ensuring food safety. Mycotoxins not only pose health risks to humans and animals but also result in economic losses in the agricultural sector. Efforts to mitigate mycotoxin contamination involve rigorous monitoring, proper storage practices, and implementing preventive measures in the cultivation and processing of crops.

A significant aspect of understanding cancer development involves exploring the role of DNA methylation, a critical process in regulating gene expression. DNA methylation status has been linked to cancer development, and researchers have constructed methylation-based genetic prognostic signatures by identifying genes with differential expression between methylation high-risk and low-risk groups. This approach helps map the DNA methylation landscape, revealing potential prognostic and therapeutic targets based on gene methylation patterns.

The heritable nature of DNA methylation changes can lead to various diseases, including cancer, atherosclerosis, neurological problems, and cardiovascular disease. Disruptions in DNA methylation regulatory mechanisms can result in a wide range of diseases. Hypermethylation, a common feature in cancer, can be observed even at the early stages of tumor growth, with hundreds to thousands of islands being methylated in certain cancers, such as lung cancer.

The chemical process of DNA methylation, wherein the addition of methyl groups to cytosine bases can block transcriptional factors from binding to DNA. This process induces reduced acetylation of histones and changes in DNA structure. Hypermethylation leads to transcriptional silence and gene inactivation, while hypomethylation is associated with chromosomal instability and lack of imprinting. These epigenetic changes play a crucial role in influencing gene expression and contribute to the development of cancer.

DNA methylation has a critical regulatory mechanism for gene expression. It can serve as a restrictive or activating factor depending on the locations of methylation in a region. Along with histone modifiers, DNA methylation can either hinder transcription machinery binding or create an environment favorable to transcription. This process is implicated in crucial developmental events such as chromosome inactivation, genomic imprinting, and transposable element suppression.

The impact of external environmental factors attributes 80-90% of malignant cancers and cancer development. Lifestyle choices, including dietary habits, play a significant role in cancer risk. Lack of certain food groups, such as fresh produce, fruits, and grains, and excess consumption of processed meats, red meats, and dairy items are associated with an increased risk of cancer. Conversely, exposure to certain substances in the environment can also contribute to an elevated risk of developing cancer.

Currently, the use of melatonin as a potential cancer treatment strategy has shown significant promise and effectiveness. This hormone induces changes in DNA methylation that restore chemoresistance to existing drug regimens, slowing the growth and dissemination of cancer cells by targeting multiple metabolic pathways. While mycotoxins have the potential to infiltrate both human and animal cells, leading to alterations and severe damage, these variations can arise spontaneously during cell division, ultimately impeding healthy cell proliferation.

Before melatonin-induced DNA methylation alterations can be clinically employed as an alternative to chemotherapy regimens, meticulous mechanistic investigations are imperative. Understanding the molecular consequences of melatonin-induced DNA methylation alterations across various malignancies is crucial for ensuring the efficacy of this potential treatment approach.

5. Conclusion

In the realm of diet and its impact on cancer prevention and development, micronutrients, bioactive chemicals, and mycotoxins have garnered attention. These elements have the capacity to modify the epigenome, influencing cancer-related processes. Micronutrients and bioactive chemicals, affecting DNA methylation as a routine epigenetic process, play a role in influencing cancer cell proliferation, invasion, and metastasis. Individuals exposed to certain environmental factors, such as petroleum, pesticides, paint, and other construction chemicals, face an increased risk of developing cancer. Occupational exposure to asbestos, benzene, benzidine, cadmium, nickel, arsenic, radon, and vinyl chloride has been associated with an elevated risk of cancer, as indicated by various research studies. Therefore, a heightened awareness of these occupational exposures is crucial in the context of cancer prevention. The interplay of mycotoxins, DNA methylation, and environmental factors significantly influences cancer development. Understanding these complex interactions is crucial for developing effective preventive measures and targeted therapies to reduce the global burden of cancer.

Author Contributions

M.N.K. and N.C. conceptualized, wrote and reviewed the food-Borne Mycotoxins (FBM), chronic exposure, and DNA methylation's role in cancer development.

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None declared.

Competing financial interests

The authors have no conflict of interest.

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