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Natural Products as a Carcinogens

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ABSTRACT

Natural products, while a valuable source for therapeutic agents, are also a significant and often overlooked class of carcinogens. This review synthesizes current knowledge on several well-studied naturally occurring carcinogenic compounds, their mechanisms of action, and their public health implications. The review is structured to include a detailed literature review, a discussion of the methodologies used for their study, and an analysis of their results. Mycotoxins, such as Aflatoxin B1 (AFB1) and Ochratoxin A (OTA), produced by fungi like Aspergillus and Penicillium, are highlighted as potent food contaminants that pose a global health threat, particularly through the induction of liver and kidney cancers. Plant-derived carcinogens, including Aristolochic Acids (AAs) from the Aristolochia genus and Pyrrolizidine Alkaloids (PAs), are discussed for their role in causing kidney failure and liver damage, respectively, often via the use of unregulated herbal remedies. The carcinogenic mechanisms of these compounds are diverse, ranging from genotoxicity (direct DNA damage via adduct formation) to non-genotoxic pathways (e.g., chronic inflammation, hormonal disruption, or inhibition of key cellular processes). The investigation of these compounds relies on a combination of epidemiological studies, animal bioassays, and mechanistic molecular analyses, including DNA adduct and proteomics. The diffuse and chronic nature of exposure to these natural carcinogens presents unique challenges for public health interventions. This article emphasizes the critical need for continued research, improved food surveillance, and stricter regulation of traditional medicines to mitigate the significant risks associated with these ubiquitous natural products.

Keywords: *Natural Products, Carcinogens, Mycotoxins, Aflatoxins, Aristolochic Acids, Pyrrolizidine Alkaloids, Genotoxicity, Public Health.*

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1. INTRODUCTION

Natural products have long been a cornerstone of traditional medicine and have provided a rich source for the discovery of novel drugs, including many of the most effective chemotherapy agents used today [1]. The immense structural diversity and biological activity of these compounds make them highly valuable in the pharmaceutical industry. However, the same biological properties that can be exploited for therapeutic purposes can, under different circumstances, lead to adverse health effects, including carcinogenicity. A carcinogen is defined as any substance, radionuclide, or radiation that promotes the formation of cancer, a process known as carcinogenesis [2]. These agents can be genotoxic, meaning they directly damage DNA, or non-genotoxic, causing cancer through other mechanisms, such as chronic inflammation or hormonal disruption.

While the public often associates carcinogens with synthetic chemicals found in industrial settings or processed foods, a significant number of potent carcinogenic compounds are produced naturally by plants, fungi, and bacteria. Exposure to these natural product carcinogens is not a modern phenomenon [2]. Still, it has occurred throughout human history, often through the consumption of contaminated food staples, the use of herbal remedies, or environmental contact. For instance, mycotoxins, like aflatoxins produced by *Aspergillus* fungi, can contaminate crops like peanuts and corn, posing a serious threat to food safety and human health [3-4].

This article aims to provide a comprehensive overview of several well-studied natural product carcinogens. We will explore their origins, the specific mechanisms by which they induce cancer, and the significant public health implications of their exposure. The discussion will highlight the dual nature of natural products—as both potential cures and sources of harm—and underscore the importance of scientific scrutiny and regulation to mitigate the risks associated with these naturally occurring agents. Understanding the specific pathways of carcinogenesis for these compounds, such as the formation of DNA adducts or the induction of cellular mutations, is crucial for developing effective prevention strategies and public health policies [6].

2. LITERATURE REVIEW

The classification of a substance as a carcinogen is a rigorous process that combines epidemiological studies (human data), animal experiments, and mechanistic data [7]. The International Agency for Research on Cancer (IARC), a division of the World Health Organization, systematically evaluates agents for their carcinogenic potential and classifies them based on the strength of the evidence. Group 1 agents are "carcinogenic to humans," while Group 2B agents are "possibly carcinogenic to humans" [8]. Several naturally occurring compounds, or natural products, have been identified and classified within these categories due to their confirmed or suspected carcinogenic properties.

Mycotoxins

Mycotoxins are toxic secondary metabolites produced by fungi, primarily species of *Aspergillus*, *Penicillium*, and *Fusarium* [9]. Among these, aflatoxins are arguably the most potent naturally occurring carcinogens. Produced mainly by *Aspergillus flavus* and *A. parasiticus*, aflatoxins contaminate a wide variety of food crops, including corn, peanuts, and various tree nuts, particularly in warm and humid climates [10].

Table 1: Mycotoxins and Their Carcinogenic

Mycotoxin	Source Fungi	IARC Classification	Carcinogenic Mechanism
Aflatoxin B1 (AFB1)	Aspergillus flavus, A. parasiticus	Group 1 (Carcinogenic to humans)	Genotoxic: Metabolically activated to an epoxide that forms DNA adducts. This can cause a specific G to T mutation in the p53 gene
Ochratoxin A (OTA)	Aspergillus and Penicillium species	Group 2B (Possibly carcinogenic to humans)	Non-genotoxic: Induces oxidative stress, which leads to DNA damage. It also inhibits protein synthesis and disrupts cellular processes
Fumonisin B1 (FB1)	Fusarium verticillioides, F. proliferatum	Group 2B (Possibly carcinogenic to humans)	Non-genotoxic: Inhibits ceramide synthase, disrupting sphingolipid metabolism. This leads to increased cell proliferation and inhibited apoptosis.
Sterigmatocystin (ST)	Aspergillus versicolor, A. nidulans	Not specified, but a potent carcinogen	Genotoxic: Requires metabolic activation by cytochrome P450 enzymes to form a reactive epoxide that binds to DNA.
Phomopsin A (PA)	Diaporthe toxica	Group 2A (Probable	Metabolized into a reactive agent that can

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		human carcinogen)	directly alkylate DNA, leading to mutations.
Aflatoxin M1 (AFM1), Metabolite of AFB1		Group 2B (Possibly carcinogenic to humans)	Genotoxic: Metabolically activated into an epoxide that forms DNA adducts.

Properties

Aflatoxin B1 (AFB1): Aflatoxin B1 (AFB1) is a well-established human liver carcinogen (IARC Group 1) and is a major cause of hepatocellular carcinoma (HCC), especially in regions with high dietary exposure [11]. Its carcinogenicity is linked to its metabolic activation in the liver, where it is converted into a highly reactive epoxide that binds to DNA, forming adducts [12]. This DNA damage can lead to mutations in key genes, such as the tumor suppressor gene *p53*, which is a frequent genetic alteration observed in HCC patients from high-risk areas [13].

Ochratoxin A (OTA): Ochratoxin A is a mycotoxin produced by various species of fungi, primarily *Aspergillus* and *Penicillium* [14]. It is a frequent contaminant of cereals, coffee, wine, and dried fruits, and exposure can also occur through contaminated meat products from livestock fed with contaminated grain [15]. IARC has classified OTA as a Group 2B carcinogen ("possibly carcinogenic to humans"). The evidence for its carcinogenicity comes largely from animal studies where it consistently induces renal (kidney) tumors in a variety of species, including rats and mice [14]. While OTA is not a potent direct DNA-damaging agent like AFB1, its carcinogenic effects are thought to be mediated through a combination of mechanisms. These include the induction of oxidative stress, which leads to DNA damage, as well as the inhibition of protein synthesis and disruption of cellular processes crucial for DNA repair [16]. OTA's strong affinity for the kidneys makes it a primary nephrotoxic agent, and this chronic toxicity is believed to be a key factor in its carcinogenic potential [17].

Fumonisins (e.g., Fumonisin B1): Fumonisins are a family of mycotoxins produced by *Fusarium* species, most notably *Fusarium verticillioides* and *F. proliferatum*, which are common pathogens of corn and other grains [18]. Fumonisin B1 (FB1) is the most prevalent and toxic form. IARC has classified FB1 as a Group 2B carcinogen. Epidemiological studies have suggested a link between high dietary intake of fumonisin-contaminated corn and an increased incidence of esophageal cancer in certain regions of the world, such as parts of China and South Africa [18-19]. In animals, FB1 causes species-specific toxicities, including liver and kidney tumors in rodents. Unlike AFB1, FB1 is considered a non-genotoxic carcinogen [18]. Its primary mechanism of action is the inhibition of ceramide synthase, a key enzyme in the biosynthesis of sphingolipids. This disruption of sphingolipid metabolism leads to an accumulation of sphinganine, which disrupts cell signaling, proliferation, and apoptosis, ultimately contributing to tumor formation [21].

Sterigmatocystin (ST): Sterigmatocystin is a mycotoxin structurally similar to aflatoxins, sharing a common furofuran ring system. It is a precursor in the aflatoxin biosynthetic pathway and is produced by several fungal species, including *Aspergillus versicolor* and *A. nidulans* [22]. ST is a potent carcinogen, although it is generally less potent than AFB1. It has been shown to induce liver and kidney tumors in animal models and is considered to be a genotoxic agent [23]. Like AFB1, ST requires metabolic activation by cytochrome P450 enzymes to form a reactive epoxide that can bind to DNA and form adducts [22]. These DNA adducts disrupt DNA replication and repair, leading to mutations that can initiate cancer.

Patulin: Patulin is a mycotoxin produced by several mould species, including *Penicillium expansum*, which is a common cause of brown rot in apples and other fruits [24]. It is primarily found in apple products such as juices, cider, and compotes. The IARC has classified patulin as a Group 3 carcinogen ("not classifiable as to its carcinogenicity to humans") due to insufficient evidence from human and animal studies [25]. While some animal studies have shown potential for carcinogenicity, the data have been inconclusive. Patulin is known to be genotoxic and can cause DNA damage. Its primary mechanism of toxicity involves its high reactivity with sulfhydryl (-SH) groups in enzymes and other proteins, which leads to the disruption of cellular processes and the induction of oxidative stress [24].

Phomopsins: Phomopsins are mycotoxins produced by the fungus *Diaporthe toxica*, which infects lupin plants [27]. Phomopsin A (PA) is the most well-studied of these toxins and is known to cause a disease in livestock called lupinosis, characterized by severe liver damage. Phomopsin A has been shown to induce liver tumors in rats and is considered a probable human carcinogen (IARC Group 2A) based on the evidence of its hepatotoxicity and its ability to damage DNA indirectly [28]. The primary mechanism of action for phomopsins is the inhibition of microtubule assembly [29]. Microtubules are essential for cell division and maintaining cell structure. By disrupting microtubule function, phomopsins interfere with mitosis (cell division), leading to cell cycle arrest, genomic instability, and ultimately, cell death or uncontrolled proliferation, which can contribute to carcinogenesis [30-31].

Aflatoxin M1 (AFM1): Aflatoxin M1 (AFM1) is a metabolite of AFB1. It is produced in the liver of mammals, including humans, after they consume AFB1-contaminated feed or food. AFM1 is excreted in milk, and as a result, it can be a

contaminant in dairy products [32]. AFM1 is a potent hepatocarcinogen, though it is generally considered to be less potent than AFB1. It is classified as a Group 2B carcinogen by IARC ("possibly carcinogenic to humans") [33]. The presence of AFM1 in milk poses a significant health risk to infants and young children, who are more susceptible to the toxic effects of mycotoxins [30, 34]. Similar to AFB1, AFM1's carcinogenic mechanism involves metabolic activation into an epoxide, which then binds to DNA to form adducts. These adducts can lead to mutations in critical genes, driving the process of liver carcinogenesis [35].

Zearalenone (ZEN): Zearalenone (ZEN) is a non-steroidal estrogenic mycotoxin produced by various species of *Fusarium*, particularly *F. graminearum* and *F. culmorum* [36]. It commonly contaminates corn, wheat, barley, and other cereals. ZEN is not classified as a direct carcinogen by IARC but is noted for its ability to promote the growth of hormone-dependent tumors due to its strong estrogenic activity [37]. It can bind to estrogen receptors, mimicking the effects of the natural hormone estradiol. This can lead to hyperestrogenism in both animals and humans, causing reproductive disorders and potentially promoting the development of breast and other hormone-sensitive cancers [38]. The carcinogenic potential of ZEN is linked to its hormone-mimicking activity. By acting as an endocrine disruptor, it can stimulate the proliferation of cells in hormone-responsive tissues, which increases the likelihood of tumor formation [39]. While it does not directly damage DNA, its non-genotoxic mechanism of action through chronic hormonal stimulation is a significant concern.

Cyclopiazonic Acid (CPA): Cyclopiazonic acid (CPA) is a mycotoxin produced by fungi in the genera *Aspergillus* and *Penicillium*, including *Aspergillus flavus* [40-41]. It is a frequent co-contaminant with aflatoxins in food products like cheese, corn, and peanuts. CPA has shown genotoxic properties in some studies and has been associated with liver tumors in animal models, though it is not classified in a specific IARC group for human carcinogenicity [42]. CPA's main mechanism of toxicity is the potent inhibition of calcium-dependent ATPases in the sarcoplasmic and endoplasmic reticulum. This disrupts calcium homeostasis within the cell, leading to cell death and tissue damage, particularly in the liver and kidneys, which can create an environment conducive to carcinogenesis [43].

Plant-Derived Carcinogens

A diverse array of plants produces secondary metabolites that are carcinogenic to humans and animals (Table 2).

Table 2: Plant-Derived Carcinogens:

Compound	Source Plants	IARC Classification	Carcinogenic Mechanism
Aristolochic Acids (AAs)	Aristolochia genus	Group 1 (Carcinogenic to humans)	Genotoxic: Forms DNA adducts, primarily at adenine residues, creating a unique mutational signature.
Pyrrolizidine Alkaloids (PAs)	Boraginaceae, Asteraceae, Fabaceae families	Not specified, but associated with liver cancer in animals and humans	Non-genotoxic: Chronic hepatotoxicity leads to cell death and regenerative proliferation, which increases the likelihood of mutations and tumor formation.
Safrole	Sassafras, nutmeg, cinnamon	Group 2B (Possibly carcinogenic to humans)	Causes liver tumors in animal models.
Ptaquiloside	Bracken fern (Pteridium aquilinum)	Group 2B (Possibly carcinogenic to humans)	Genotoxic: Causes bladder and intestinal tumors in livestock and experimental animals.
Cycasin	Cycad plants (Cycas revoluta)	Not specified	Metabolized into a reactive agent that can directly alkylate DNA, leading to mutations.
Hydrazines	False morel mushrooms (Gyromitra esculenta)	N-methylhydrazine is Group 2A (Probably carcinogenic to humans)	Genotoxic: Metabolized into reactive intermediates that can alkylate DNA. They can also inhibit DNA repair enzymes.

Aristolochic Acids (AAs): Found in plants of the *Aristolochia* genus, AAs are potent nephrotoxic and carcinogenic compounds [44]. Their exposure, primarily through the consumption of herbal remedies containing these plants, has been linked to a severe form of kidney failure known as Aristolochic Acid Nephropathy (AAN) and a high incidence of upper tract urothelial carcinoma (UTUC) [45]. Due to compelling evidence from human and animal studies, AAs are classified as Group 1 human carcinogens by IARC. The carcinogenic mechanism involves the formation of DNA adducts, which creates a unique mutational signature in affected tumors [46].

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Pyrrolizidine Alkaloids (PAs): These alkaloids are found in over 6,000 plant species worldwide, including those in the *Boraginaceae* (e.g., borage, comfrey), *Asteraceae* (e.g., senecio, ragwort), and *Fabaceae* (e.g., crotalaria) families [47-48]. PAs are well-known for causing hepatotoxicity (liver damage) and have been associated with liver cancer in animals and humans [49]. Human exposure most often occurs through the inadvertent contamination of food crops, such as grains and herbs, as well as through herbal teas, honey, and dietary supplements [50].

Safrole: This compound is a natural component of various plants, including sassafras, nutmeg, and cinnamon. Safrole was historically used as a food additive and flavoring agent, particularly in root beer, before it was banned by the U.S. FDA due to its hepatocarcinogenic potential in animal studies [51]. While there is a lack of conclusive epidemiological evidence linking safrole to human cancer, the strong and consistent findings from animal models, showing it induces liver tumors, have led to its classification as a probable human carcinogen (IARC Group 2B) [52].

Ptaquiloside: Found in bracken fern (*Pteridium aquilinum*), ptaquiloside is considered the primary carcinogen of this plant. It is a potent genotoxic compound that has been shown to cause bladder and intestinal tumors in livestock that graze on it and in experimental animals [53]. Human exposure can occur through the consumption of young bracken fronds, known as fiddleheads, drinking milk from cows that have grazed on the fern, or inhaling airborne spores [54]. Ptaquiloside is classified as a Group 2B carcinogen.

Cycasin: This neurotoxic and carcinogenic glycoside is found in cycad plants (*Cycas revoluta*) [55]. When ingested, it is metabolized by gut bacteria into an unstable compound called methylazoxymethanol (MAM), which then breaks down into a reactive methylating agent [56]. This agent can directly alkylate DNA, leading to mutations that are implicated in the development of cancer, particularly in the liver and colon [57].

Ethylene Thiourea (ETU): Ethylene Thiourea (ETU) is a metabolite of some ethylene bisdithiocarbamate (EBDC) fungicides like maneb, mancozeb, and zineb, which are widely used to protect crops [58]. ETU can also be formed during the processing or cooking of treated foods. ETU is classified as a Group 2B carcinogen by IARC. It is a potent thyroid carcinogen in laboratory animals [59]. The primary mechanism of ETU's carcinogenicity is not direct DNA damage. Instead, it acts as a non-genotoxic carcinogen by disrupting thyroid hormone synthesis [60,61]. This leads to a compensatory increase in thyroid-stimulating hormone (TSH), causing chronic thyroid stimulation and subsequent follicular cell proliferation, which can result in the formation of tumors.

Hydrazines: Hydrazines are naturally occurring compounds found in various mushrooms, particularly the false morel (*Gyromitra esculenta*) [62]. The primary toxic agent in this mushroom is gyromitrin, which is rapidly hydrolyzed in the body to form N-methyl-N-formylhydrazine and subsequently to N-methylhydrazine, a known carcinogen [62]. N-methylhydrazine is classified as a Group 2A carcinogen ("probably carcinogenic to humans") by IARC [64]. Consumption of false morels, especially if improperly prepared, has been linked to liver toxicity and is considered a carcinogenic risk. The carcinogenic effect of hydrazines is due to their ability to be metabolized to highly reactive intermediates that can alkylate DNA, causing direct damage. They can also inhibit key enzymes involved in DNA repair, amplifying their genotoxic effects and increasing the likelihood of mutations that lead to cancer [65].

Gossypol: Gossypol is a polyphenolic aldehyde produced by cotton plants (*Gossypium* species) as a natural defense against pests and diseases [66]. It is found in cottonseed, and human exposure can occur through the consumption of cottonseed oil or flour, particularly in regions where these are dietary staples. Gossypol is not classified by IARC but has been shown in some studies to have mutagenic and pro-oxidative properties that could contribute to carcinogenicity. Its primary concern is its toxicity to various organs, including the liver and reproductive system [67]. While not a direct human carcinogen in the same class as aflatoxins, its potential to induce oxidative stress and DNA damage is a subject of ongoing research. Gossypol's toxicity is believed to be multifaceted. It can generate reactive oxygen species (ROS), leading to oxidative stress and damage to lipids, proteins, and DNA [68]. It also disrupts mitochondrial function and can inhibit several enzymes, which can alter cellular metabolism and increase the risk of malignant transformation.

3. METHODOLOGY

The scientific methodology for investigating the carcinogenic potential of natural products is a multi-faceted and rigorous process, drawing on a combination of epidemiological, in vivo (animal), and in vitro (molecular) studies [69]. This tiered approach allows for a comprehensive evaluation of a substance's risk to human health, from broad population-level associations down to specific molecular mechanisms.

Epidemiological Studies

These studies are the gold standard for establishing a link between exposure and disease in human populations. They are crucial for identifying real-world risks from natural product carcinogens.

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Cohort Studies: In a **prospective cohort study**, researchers follow a large group of people who are initially free of disease. They track dietary habits, environmental exposures, or use of herbal remedies over time. The incidence of cancer in the exposed group is then compared to that in an unexposed control group. This approach can directly measure the risk of developing a disease from a specific exposure.

Case-Control Studies: These are retrospective studies that compare a group of people with a specific cancer (the "cases") to a similar group without the cancer (the "controls"). Researchers then look back in time to assess and compare their past exposures to the natural product. A higher frequency of exposure in the case group suggests an association with the cancer.

Animal Bioassays

Long-term animal studies, typically using rodents, are a cornerstone of carcinogen testing. They provide controlled environments to evaluate a compound's potential to cause cancer and to establish a dose-response relationship.

Chronic Toxicity and Carcinogenicity Studies: Animals are exposed to various doses of the test substance over their lifespan (e.g., two years for rats and mice). The study involves a detailed examination of organs and tissues at the end of the trial to identify and quantify tumors. This method is essential for identifying carcinogens that may act over a long period.

Mechanistic and Molecular Studies

These studies delve into the biological and chemical processes that underlie a substance's carcinogenic activity.

In Vitro Assays: Using cell culture systems and other laboratory tests, scientists can investigate the direct effects of a natural product on cells. A widely used example is the Ames test, a bacterial assay that screens for a substance's mutagenic potential—its ability to cause genetic mutations [10-13].

DNA Adduct Analysis: A key method for genotoxic carcinogens is the analysis of DNA adducts. These are covalent bonds formed between the carcinogen (or its metabolite) and DNA, which can disrupt DNA replication and repair, leading to mutations. Techniques like mass spectrometry are used to detect and quantify these adducts in exposed cells or tissues [5-6, 10-13]. For example, the formation of the AFB1-N7-guanine adduct is a specific and well-known biomarker of aflatoxin B1 exposure, providing direct evidence of DNA damage in the liver [1].

Metabolomic and Proteomic Analysis: These advanced techniques provide a broader view of how a substance affects the body. Metabolomics studies the complete set of small-molecule metabolites, revealing how a compound alters metabolic pathways. Proteomics analyzes the entire set of proteins expressed by a cell or organism, showing changes in protein expression or function that may be linked to carcinogenesis [52, 58]. These 'omic' technologies help researchers understand the systemic and cellular changes that contribute to the initiation and progression of cancer.

4. RESULTS AND DISCUSSION

The findings from decades of research into natural product carcinogens consistently demonstrate that these compounds are potent agents of carcinogenesis. Their diverse chemical structures lead to a variety of mechanisms, but a common theme among many is genotoxicity, the ability to directly damage DNA. This damage, if not repaired, can lead to permanent mutations in crucial regulatory genes, such as tumor suppressor genes and proto-oncogenes, thereby initiating the process of malignant transformation [18] (Figure 1).

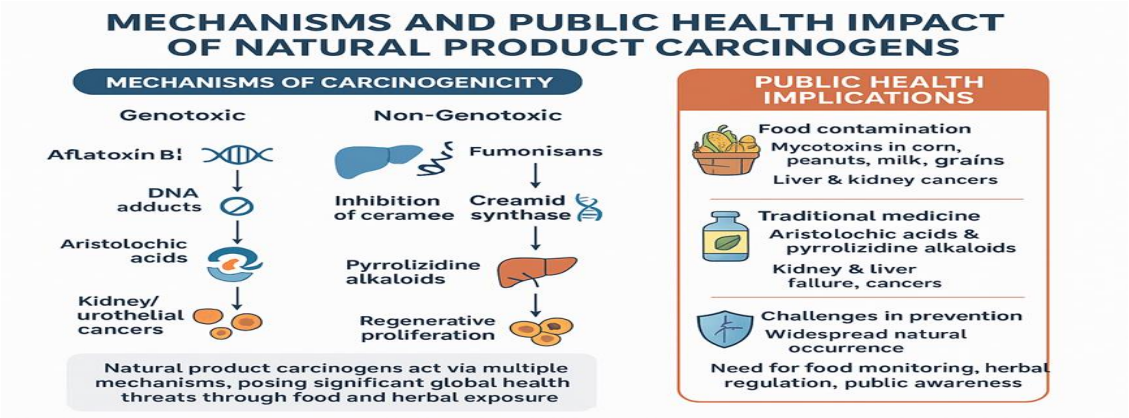

Figure 1: Mechanism and Public Health Impact of Natural Product Carcinogens

5. MECHANISMS OF CARCINOGENICITY

Genotoxic Mechanisms
Many of the most potent natural carcinogens, including aflatoxins and aristolochic acids, exert their effects through direct DNA modification.

Aflatoxin B1 (AFB1): AFB1 is a classic example of a procarcinogen that requires metabolic activation to become an ultimate carcinogen. In the liver, the cytochrome P450 (CYP) enzyme system converts AFB1 into a highly reactive AFB1-8,9-epoxide [19]. This electrophilic epoxide then preferentially binds to the N7 position of guanine residues in DNA, forming DNA adducts [20]. The presence of these adducts can stall DNA replication and, if not repaired, lead to a specific G to T transversion mutation in the third base of codon 249 of the *p53* tumor suppressor gene. This specific mutation is a molecular fingerprint of aflatoxin exposure and is observed in a high percentage of hepatocellular carcinoma (HCC) cases in regions with high AFB1 dietary intake [21].

Aristolochic Acids (AAs): Similar to AFB1, AAs require metabolic activation. They are converted into a reactive intermediate that forms aristolactam-DNA adducts, primarily at adenine residues [16]. These adducts lead to a unique mutational signature characterised by A-to-T transversions in the tumours of patients with Aristolochic Acid Nephropathy (AAN), providing direct evidence of AA-induced DNA damage [22].

Non-Genotoxic Mechanisms
Some natural carcinogens operate through indirect mechanisms that do not involve direct DNA damage.

Fumonisins (e.g., Fumonisin B1): FB1 is a non-genotoxic carcinogen. Its primary mechanism is the inhibition of ceramide synthase, an enzyme crucial for sphingolipid synthesis [23]. This disruption leads to an accumulation of sphinganine, which alters cell signaling, causes an increase in cell proliferation, and inhibits apoptosis (programmed cell death). This chronic disruption of cellular processes creates a fertile ground for tumor development without directly mutating DNA [24, 70].

Pyrrolizidine Alkaloids (PAs): While PAs can form DNA adducts, their primary pathological effect is through sustained hepatotoxicity. Chronic exposure leads to sinusoidal obstruction syndrome and liver cell death. The constant regenerative proliferation of the remaining liver cells to compensate for the damage increases the likelihood of spontaneous mutations and tumor initiation, a classic example of a chronic injury-induced carcinogenesis model [18].

Public Health Implications
The public health impact of natural product carcinogens is substantial and often underestimated.

Food and Agricultural Contamination: Mycotoxins, such as aflatoxins and fumonisins, pose a global threat to food safety, particularly in developing countries where inadequate post-harvest handling and storage practices are common. Chronic dietary exposure is a leading cause of liver cancer and other diseases in these regions [12-14, 25].

Traditional Medicine: The use of unregulated or unmonitored traditional herbal remedies containing compounds like aristolochic acids and pyrrolizidine alkaloids has led to documented epidemics of kidney and liver disease and associated cancers. This underscores the critical need for a more scientific approach to herbal medicine and stricter regulations [12-14, 71-72].

Challenges in Prevention: Unlike synthetic chemical exposures, which can often be traced and regulated at the source, exposure to natural carcinogens is usually diffuse and difficult to control. The compounds are inherent to the natural environment, making complete elimination impossible. Therefore, public health strategies must focus on mitigation, including improved agricultural practices, food monitoring programs, and educating the public about the risks of unregulated herbal products [12-14, 18, 73].

6. CONCLUSION AND FUTURE DIRECTION

Natural products, while a valuable source of therapeutic agents, also represent a significant and often overlooked class of carcinogens. Compounds like aflatoxins, aristolochic acids, and ptaquiloside are well-documented to cause cancer through genotoxic mechanisms, forming DNA adducts that lead to critical mutations. The widespread exposure to these agents through food contamination and traditional medicine poses a serious public health risk globally. Future research in this area should focus on several key directions:

1. **Improved Detection and Surveillance:** Developing more sensitive and rapid methods for detecting natural product carcinogens in food, herbal products, and the environment.

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2. **Mechanistic and Biomarker Research:** Further elucidating the precise molecular mechanisms of less-studied natural carcinogens and identifying reliable biomarkers of exposure to improve risk assessment and early detection.
3. **Public Health Interventions:** Designing and implementing effective public health campaigns and agricultural strategies to minimize exposure, particularly in high-risk regions. This includes better post-harvest handling of crops to prevent fungal contamination and stricter regulation of herbal products.
4. **Chemoprevention:** Investigating natural products with anti-carcinogenic properties to counteract the effects of natural carcinogens and exploring potential interventions to block their metabolic activation in the body.

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