

## Potential Genotoxicity of Alkaloids: A Review Article

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### ABSTRACT

Any harm done to genetic material, whether directly interacting with DNA or indirectly through biological systems, is referred to as genotoxicity. Such harm poses major risks to the health of people, animals, and plants as it is a primary source of carcinogenesis, mutagenesis, and teratogenesis. Because of their medicinal qualities, alkaloids—a family of naturally occurring phytochemicals made by plants from amino acids—are frequently utilized to treat ailments such as newborn apnea, gout, and asthma. Recent research has sparked worries about their possible genotoxic consequences despite their therapeutic advantages. Through a variety of processes, including as the creation of DNA adducts, DNA–DNA cross-links, and DNA–protein cross-links, alkaloids have been demonstrated to cause chromosomal abnormalities. These processes can all impede DNA replication, transcription, and repair.

The aims to investigate and compile the most recent scientific findings about the genotoxic potential of alkaloids, emphasizing both the hazards of prolonged exposure and the molecular mechanisms of action. Along with highlighting the pervasive and frequently uncontrolled use of plant-based remedies under the false pretence of safety, it also seeks to distinguish genotoxicity from similar ideas like mutagenicity and teratogenicity.

In conclusion, alkaloids have significant therapeutic potential; however, care is advised due to their potential to harm genetic material. Standardized testing procedures like the Ames, comet, and micronucleus tests are necessary to provide a more thorough knowledge of their genotoxic processes. This knowledge is essential for risk assessment as well as for directing the safe use of treatments containing alkaloids in both conventional and clinical medicine.

**Keywords-** Alkaloids, Genotoxicity, DNA damage, Mutagenicity, Carcinogenicity, Natural products, Toxicology.

## I. INTRODUCTION

Genotoxicity could be defined as any damage to the genetic materials, which is either direct damage or indirect damage. Genotoxic substances are extremely dangerous because they are considered one of the major causes of cancers and/or mutations (1,2).

In general, there is a great deal of confusion between the two concepts (genotoxicity and mutagenicity), whereas mutagenic compounds are a type of genotoxic compound and exert it mutagenicity by one of the genotoxic mechanisms, but not the opposite (3).

On the other hand, substances that cause distortions in the physiological functions and/or development of humans, animals, or plants alike, at any age, are called teratogenic compounds (4).

Continuous exposure to compounds that cause genetic deformities is considered very dangerous, as its danger lies in the high death rate resulting from infection with various types of cancers, and it also leads to the transmission of poor genetic traits to children, not to mention its effect on fertility for both sexes (5).

Genetic toxicity in many cases does not come from direct or indirect exposure to certain chemicals but comes from other cases as a result of infection with certain viruses, nutritional deficiency, continuous exposure to nervous tension or psychological pressure, and other things (6).

Toxic substances affect the genetic material (chromosomes) in several ways, the most important of which is that their effect is either on the shape of the chromosome or on the DNA sequence present in the chromosome. The toxic effect on the chromosome is by forming what are known as DNA adducts, where these adducts are linked between the opposite DNA strands (interstrand cross-linkage) or within a single strand (intrastrand cross-linkage). There is another way for the toxic effect on the chromosome, where some materials turn into what are known as free radicals, like RNS and ROS, where these free radicals break down all the contents of the cell, including the genetic material. The other way is by stopping the process of repairing and maintaining the DNA, which affects its stability. (7,8)

Due to the consequences of exposure to substances that cause chromosomal abnormalities and their negative effects on the lives of humans, animals, and plants alike, very modern and advanced protocols and techniques have been discovered and developed in order to examine the chemicals that the organism is exposed to and measure their safety. Accordingly, many substances entering food and medicines have been examined, and a database has been created that includes all information related to the effect of substances on chromosomes. (9)

Examining the extent of abnormalities that occur in chromosomes because of exposure to various genotoxic compounds is done on two axes. The first axis is studying the abnormalities that occur in the shape of the chromosomes (clastogenicity), and the second axis is the changes that occur in the number of chromosomes (aneugenicity). There are many tests for these two axes, the most important of which is the examination of genotoxicity that occurs in eukaryotic and prokaryotic microorganisms. In bacteria, for example, the Ames test is the best choice for examination of mutagenicity in bacteria, while comet, micronucleus (MN), and chromosomal aberration tests (CA) use in different mammalian cells (10).

Phytochemicals are chemical compounds produced within plants; some of these compounds are formed as final products of the ovaries, and the other part is in the form of intermediate compounds formed during metabolism. In total, the number of these compounds is about 4000. The most important examples of these compounds are polyphenols, flavonoids, and alkaloids, whose primary function for the plant is to protect against bacterial infections and insects. In the past years, many studies have been conducted on many of these compounds, through which some therapeutic properties have been proven, such as anti-inflammatory, antibacterial, anticancer, and others. (11-14)

The therapeutic mechanism of phytochemicals is one of the most important things that has increased their importance in treatment, as many pathological conditions are caused by and/or lead to increased concentrations of free radicals in the body. Phytochemical compounds have the ability and potential to scavenge free radicals and return them to acceptable concentrations. (15)

In recent years, there have been different comparisons between traditional medicine and medicine derived from plants. It has been noticed that there are many advantages to drugs of plant origin, such as high efficacy coupled with low toxicity, low cost, and low interaction with other treatments, so they have attracted much attention in the prevention and treatment of different diseases, and substantial progress has been made in research (16).

The World Health Organization (WHO) reported that between 75% and 85% of people worldwide mostly use traditional medicine, with more than 85% of that medicine derived from plants (17).

The high diversity of plant extracts has played a significant role in the widespread use of these compounds in treatment, as out of every 150 prescriptions, 118 contain medicines from plant sources, and about 1,300 plants are currently used in medicine in Europe alone. Meanwhile, in developed countries, almost 30% of prescribed medication is from plant species (18, 19).

There is a general concept about the high safety of plant medicines; accordingly, many patients use medicinal remedies for a long time. This makes medicinal remedies widespread (20). Additionally, overuse of this type of medication without adequate information on its adverse effects and/or side effects may have a bad impact on health. Nowadays, different studies have shown that many medicinal remedies contain different active ingredients; these ingredients are genotoxic and/or mutagenic (21, 22).

The widespread use of plant-based medicines was mainly due to the prevailing belief at the time that these treatments were safe and had no negative effects on human and animal health alike. However, recently, many of these compounds have been studied, and it has been found that they have toxic effects, the most important of which is on genetic material, which increases the chances of developing cancer (carcinogenesis), genetic mutations (mutagenesis), and birth defects (tetragenesis). (23)

## II. ALKALOIDS

Alkaloids are chemical compounds with complex and diverse structures that plants manufacture from amino acids. More than 20% of the active compounds of plants are alkaloids, which are found in small quantities and have several physiological and protective functions for the plant, as these compounds prevent rodents and also have an effect on regulating plant growth. (24-28)

### III. CLINICAL USES OF ALKALOIDS

Nowadays, many alkaloids have become of therapeutic importance, and scientific studies have proven that alkaloids help treat certain medical conditions. The most important of these alkaloids are caffeine, which is used for neonatal apnea and atopic dermatitis; nicotine, which is used for anti-smoking; colchicine, which is used as amyloidosis treatment and for acute gout; theophylline, which is used for asthma and bronchospasms and others. (29-32)

#### *Alkaloids and genotoxicity*

The prevailing belief about the safety of using plants for treatment has been eliminated due to the emergence of many toxic effects resulting from the use of such types of treatments. The most important toxic effect of these medical tablets is the effect of some of their compounds on chromosomes. Examples of these compounds are alkaloids. Alkaloids have a negative effect directly and indirectly on chromosomes, which causes many diseases, the most important of which are cancers.

#### *DNA adducts*

During lives, humans are exposed to various harmful chemicals, intentionally or unintentionally. Some of these toxic substances are concentrated on the genetic material through the formation of DNA adducts (33). Fortunately, living cells have several enzymes responsible for removing these adducts and repairing the chromosome. Sometimes the DNA repair mechanism fails to remove the adducts, or the adducts are on the genes responsible for manufacturing the enzymes responsible for repairing DNA, like *p53* tumor suppressor gene. (34,35) Different examples of alkaloids forming DNA adducts are heliotrine, lasiocarpine, retrorsine, and senecionine.

#### *DNA cross-linking*

Alkaloids not only act as a toxic effect on DNA but also have the ability to create crosslinks between DNA strands or between different proteins and DNA, which affects the process of replication and cell division as well as the stability of DNA. This effect is due to the presence of active groups on carbon 7 and carbon 9 that are capable of making such an effect (36). Therefore, alkaloids are natural plant substances that can be exposed to or consumed for a long period of time, leading to the occurrence of various cancers. (37)

The pyrrolic alkaloids like dehydrosenecionine, dehydromonocrotaline, dehydroseneciphylline, and dehydroriddelliine had the ability to create DNA-protein crosslinks, which is approximately 50% of all DNA crosslinks. (38,39)

DNA-DNA crosslink is considered the most dangerous type of cross-linking, as this type is considered one of the most cancer-causing types resulting from DNA breakage. The most important examples of alkaloids that lead to this type is dehydromonocrotaline (which is a monocrotaline metabolite that contains piperidine moiety) (40-43). Other examples of alkaloids that cause DNA cross-linkage are seneciphylline, riddelliine, retrorsine, senecionine, heliosupine, latifoline, and retronecine (44,45)

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