Journal of Addiction Research and Treatment
Volume 2 | Issue 1

Review Article Open Access

Psychoactive Drugs Induced DNA Damage: A Review

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Citation: Alabi OA (2022) Psychoactive Drugs Induced DNA Damage: A Review. J Addict Res Treat 2(1):101

Received Date: April 08, 2022 **Accepted Date:** April 27, 2022 **Published Date:** May 05, 2022

Abstract

Psychoactive drugs have been abused by people of different ages and sexes. The dependence on this drug is a public health concern. Reports have shown that psychoactive drugs such as cocaine, morphine, tramadol, alcohol, tobacco, khat, cannabis, etc can interact with the DNA and cause significant damage. In vitro and in vivo studies have been carried out to show the genotoxicity and mutagenicity of these drugs. Cell lines, lymphocytes, microorganisms, mice, and human samples have been used to show the DNA damaging potential of psychoactive drugs. Different types of DNA damage ranging from point mutation to chromosomal damage have been reported and the mechanisms of DNA damage reported vary from oxidative DNA damage to direct drug-DNA adduct formation.

Keywords: Psychoactive Drugs, DNA Damage, Intoxication, Addiction, Genotoxicity

Introduction

Psychoactive substances, also known as psychotropic substances are substances that alter the mental state of a person by affecting the way the nervous system and brain work [1]. Psychoactive substances can cause intoxication and this is generally the major reason why most individuals engage in their use. Individuals who take psychoactive substances experience changes in brain function which alter their mood, consciousness, and/or perceptions. Psychoactive substances are present in different medications, alcohol, plants, and animals [2], many, but not all of which are addictive [1]. The most common psychoactive drugs used by people to alter their mental state are caffeine and alcohol [3]. Although they are available legally, yet, they are harmful both psychologically and physically when used in excess. Usually, the decision of how and when to use these psychoactive drugs is left to the individuals [3], however, in certain situations, the drugs are used for exploitation of others by the alteration of their mental state. For example, Rohypnol has been used as a date-rape [4]. Some of the psychoactive drugs are very unpleasant making the users quit their use. This is the case in certain classic psychedelics (e.g., psilocybin), powerful dissociatives (e.g., Salvia divinorum), and deliriants (e.g., Jimson weed) [5].

Addiction and dependence resulting from the misuse of psychoactive drugs have led to moral debate and legal measures, while governmental controls on prescription, supply, and manufacture have been efforts made to minimize the additive use of these drugs. Also, ethical concerns exist about the marketing of these drugs by manufacturers and their clinical over-use. However, in some countries, there are ongoing popular campaigns geared towards legalizing and decriminalizing the use of some recreational drugs such as cannabis. Many individual, genetic and environmental factors have been reported to work individually or synergistically to decrease or increase the probability that an individual will use a psychoactive drug and to what extent [6]. This review aimed at updating information on the different uses of various psychoactive drugs by humans, the different effects on the biological system, and their reported DNA damaging potential in simulated and real-life scenarios.

Historical Background of Psychoactive Drugs

The use of psychoactive drug can be traced to prehistory. Archaeological evidence of not less than 10,000 years ago exists on the use of psychoactive substances especially plants, while historical evidence of more than 5,000 years exists of their cultural use [7]. For example, in Peruvian society, the chewing of coca leaves dates back over 8,000 years ago. There are postulations that the desire for the alteration of one's consciousness is as basic as the urge to satiate hunger, sexual desire, or thirst [5]. Supporters of this school of thought argue that the history of drug use, and even children's desire for sliding, swinging, or spinning are all indications that it is universal to desire the alteration of one's state of mind [6]. Humans are not the only species with this kind of urge. Evidence exists of some animals consuming various psychoactive plants like berries, fermented fruits, and even animals causing intoxication. For example, cats have been known to get intoxicated after the consumption of catnip. Indeed, animals are the usual reference for human's introduction to the use of psychoactive substances, especially from plants [8]. Psychoactive plants and animals seem to have co-evolved, and might be the reason why the receptors of and some of these chemicals are present in the nervous system [9].

Banning and criminalizing the trade, supply, and use of psychoactive drugs were very common during the 20th century as the initial reaction of many governments worldwide to recreational drug use. Notably among such was the prohibition and criminalization of alcohol for 13 years in the United States. However, many law enforcement agents, governments, and government officials have come to the conclusion that using illicit drugs cannot be effectively regulated through criminalization. Some organizations like the Law Enforcement against Prohibition (LEAP) supported this belief, hence, supporting the move in some countries, where the reduction of harm caused by the use of illicit drugs was planned to be achieved through the establishment of health services without promoting or condoning the use of illicit drugs, but supports and services are provided to ensure that illicit drug users have readily available to them adequate factual information about the negative effects of the use of these drugs so as to minimize the negative public health impact. This was exemplified by the Portuguese drug policy of decriminalization, which significantly reduced the adverse public health impact of drug abuse in Portugal [10].

Uses of Psychoactive Drugs

Humans use psychoactive substances for a variety of reasons in order to achieve a certain end. The use of these drugs widely varies between different cultures. Some psychoactive substances have illegal or controlled uses while others are used for shamanic and medicinal purposes. Psychoactive drugs can be used in various ways including:

Anesthesia

Generally, a class of psychoactive drugs called anesthetics is administered to individuals to negate physical pain and some other sensations. The majority of the anesthetics cause unconsciousness during which the individual undergoes surgery or other medical procedures without emotional trauma or physical pain [11]. The effect of anesthetics on the N-Methyl-D-aspartic acid (NMDA) and gamma-aminobutyric acid (GABA) systems is responsible for the unconsciousness experienced by the individual. Examples of anesthetics include an NMDA receptor antagonist, ketamine [12], and a GABA agonist, propofol [13].

Pain Management

In the management of pain, physicians often prescribe psychoactive drugs. Endogenous opioid peptides primarily regulate the subjective experience of pain. Therefore, management of pain is often achieved by the administration of psychoactive drugs that can operate on the neurotransmitter system called opioid receptor agonists. Examples of these drugs include opiate narcotics such as codeine and morphine which are highly addictive [14]. Other common types of analgesics are ibuprofen and aspirin belonging to the group of non-steroidal anti-inflammatory drugs (NSAIDs). These drugs also inhibit cyclooxygenase thereby reducing eicosanoid-mediated inflammation.

Mental Disorder

Management of emotional and mental disorders or challenging behavior includes the prescription of psychiatric medications that are psychoactive drugs [4]. Medications used for psychiatric treatment belong to at least five major classes: antipsychotics used for the treatment of psychotic symptoms like those associated with severe mania or schizophrenia, or as adjuncts for relief in the case of clinical depression; anxiolytics used for the treatment of anxiety disorders; depressants used as sedatives, anesthetics, and hypnotics depending on the dosage; mood stabilizers used for the treatment of schizoaffective and bipolar disorders; and antidepressants used for the treatment of disorders like borderline personality disorder, clinical depression, eating disorders, anxiety, and dysthymia [15]. Furthermore, different psychoactive substances are at present being deployed in the treatment of various addictions including buprenorphine or methadone maintenance therapy for opioid addiction and naltrexone or acamprosate for alcoholism [16].

Recreation

The ability of most psychoactive substances to alter perception and mood is the main reason for their usage by many including those used in psychiatry and medicine. These include cannabis, caffeine, cocaine, alcohol, Lysergic acid diethylamide (LSD), and nicotine [17]. The psychoactive drugs frequently used for recreation include stimulants capable of activating the central nervous system; those with euphoric effects such as hallucinogens (dissociative, deliriants, and psychedelics) which can induce cognitive and perceptual alterations; depressants and opioid analgesics which are capable of depressing the central nervous system; and inhalants (used in vapor form) which are capable of inducing stupefying effects.

The use of psychoactive drugs is a symbol of high status in certain ancient and modern cultures, thereby promoting their use in such communities. This was the case in ancient Egypt where gods were commonly depicted as holding or drinking from plants with hallucinogenic properties [18]. Psychoactive drug use is also seen as a symbol of status in settings like parties and nightclubs [19].

Spiritual And Ritual Purposes

Since prehistoric times, certain psychoactive drugs especially hallucinogens are used in religious activities. It is documented that, for over 5700 years, the native Americans during their religious festivities have been using peyote cacti (a small spineless cactus) which contains mescaline [20]. Also, in prehistoric Europe, the *Amanita muscaria* mushroom which contains muscimol was frequently used for ritual activities [21]. The 1960s and 70s also witnessed resurfaced use of entheogens in the West for religious purposes during the counterculture movements.

Military

The military usually uses psychoactive drugs as a form of non-lethal weapons. The civilian American intelligence officials and the military make use of psychoactive drugs for interrogation of their captives who were apprehended during its war on terrorism [22]. This has been confirmed by several captives and former captives who reported that medical staff collaborated with interrogators to use powerful psychoactive drugs on captives before their interrogation after the captives were released [23]. Also, the military justice system is known to make use of psychoactive drugs in order to obtain a conviction. Additionally, different psychoactive drugs have been used by the militaries worldwide to enhance soldiers' performance by suppressing fear and hunger, increasing concentration and wakefulness, improving memory recall and reflexes, and reducing empathy [5].

Psychoactive Drugs and their Effects

Psychoactive drugs affect the human body especially the brain depending on the type of chemical properties they have. These include as:

Stimulants

These include substances that can stimulate the mind, prolong wakefulness, induce euphoria and certain physiological responses such as increased blood pressure and heart rate. However, this type of drug does not alter perception. Common examples of this type of drug include modafinil, nicotine, cocaine, caffeine, amphetamine [10].

Depressants

Common psychoactive drugs which serve as depressants are benzodiazepines, sedatives, barbiturates, ethanol (alcoholic beverages), hypnotics, opioids, and cannabis. This category includes all of the sleep-inducing, calmative, anesthetizing, and anxiety-reducing substances, which often evoke euphoria feelings and sometimes alter perception by causing dream images [10].

Hallucinogenic Effects

Psychoactive drugs which are capable of inducing hallucinogenic effects include deliriants, psychedelics, and dissociative. They also include LSD, peyote (mescaline), psilocybin from mushrooms, phencyclidine (PCP) dextromethorphan, and ketamine. They are substances that can produce distinct perception and emotional state alterations as well as the sensation of time and space [10]. Other effects include depersonalization, increased heart rate, and blood pressure, erratic behavior, hallucinations, and paranoia.

Global Use of Psychoactive Substances and Burden to Health

Psychoactive drug use has contributed to the global disease burden in various ways and the level of prevalence is dependent on the type that an individual is dependent on. The consumption of tobacco, alcohol, and other illicit drugs is worldwide growing rapidly thereby significantly contributing to the world's disease burden. In 2019, it was estimated that over 1 billion people smoked tobacco,

and this might increase the economic and health costs of the tobacco epidemic in the coming decades [24]. There is now a rapid spread of smoking among women in developing countries. Currently, in the developing countries, only 9% of women and 50% of men smoke, as compared with the developed countries where 22% of women and 35% of men are smokers. Table 1 shows the age-standardized estimates as of 2019 of the prevalence of tobacco use among people not younger than 15 years in selected countries.

Region	Country	Prevalence of smoking (%)	
		Males	Females
Africa	Algeria	41.8	0.8
	Botswana	31.0	9.0
	Comoros	30.4	12.2
	Lesotho	43.5	5.9
	Madagascar	44.0	13.8
	Nigeria	7.3	0.6
Americas	Argentina	29.8	20.2
	Bahamas	25.2	3.7
	Cuba	26.3	10.7
	Guatemala	25.4	2.0
	USA	29.2	18.0
	Uruguay	27.7	20.7
Eastern Mediterranean	Afghanistan	40.7	7.7
	Egypt	48.6	0.4
	Iraq	40.6	2.5
	Kuwait	40.6	2.9
	Lebanon	48.3	29.7
	Tunisia	48.4	2.1
Europe	Armenia	58.4	1.7
	Azerbaijan	48.8	0.2
	Georgia	58.0	7.0
	Greece	46.1	34.1
	Russia	50.3	21.0
	Turkey	45.9	21.1
South-east Asia	Bangladesh	52.8	18.1
	Indonesia	71.3	3.9
	Myanmar	70.0	21.3
	India	42.6	13.9
	Nepal	49.5	14.0
	Thailand	42.4	3.1
Western Pacific	Cambodia	37.8	6.4
	Malaysia	44.7	1.3
	Mongolia	52.4	7.3
	Samoa	37.3	15.2
	Viet Nam	48.1	2.3
	Marshall Islands	49.0	8.5

Source: WHO (2019)

Table 1: Age-standardized prevalence estimates for current tobacco use among persons aged 15 and above in selected countries, 2019

It is now becoming a tradition to estimate the contribution of the use of an illicit substance, tobacco, and alcohol to the global burden of disease (GBD). This was firstly attempted in the Global burden of disease and injury project of the WHO [25]. The assessment of the burden imposed on the society as a result of years lived with disability and premature death was estimated based on a standard of measurement called disability-adjusted life years (DALYs). The data from this project showed that in the developed countries alcohol and tobacco were major causes of disability and mortality, with a projection of a possible future increase in the impact of tobacco worldwide.

Genetic Basis of Susceptibility Difference of Individuals to Substance Dependence

The possibility of a person to consume a psychoactive drug and to what extent is dependent on different individual or collective factors including biological, environmental, cultural, and social factors. Also, the different genetic makeup among individuals contributes significantly to their use and dependence on psychoactive drugs. There are certain genetic diseases like Huntington's disease caused by mutation of a single gene, however, there exist complex disorders which are possibly caused by the interaction of certain environmental factors with more than one gene. This is the category to which substance dependence belongs [26]. Therefore, having genetic vulnerability to substance dependence can increase the effect of psychoactive substances on an individual in comparison with an individual who does not. There is evidence of significant heritability of tobacco use among different age groups, sex, and populations [26]. Data in the literature further suggest the likelihood of several genes contributing to smoking development and persistence in an individual [27]. Genes which participate in the metabolism of nicotine are likely to be essential risk factors for smoking, while different variations in these genes may be a major determinant of the accumulation and level of nicotine in the brain. A significant heritability of the quantity and frequency of alcohol consumed by an individual has been established, the same as the heritability of alcohol dependence in an individual [28]. The genes that are possibly responsible for this association are those involved with the receptors for neurotransmitters and alcohol metabolism [29]. Variation in the consumption of alcohol may be due to the genetic variations observed in the alcohol metabolizing enzymes in different people [30]. Studies have also shown that the heritability of opioid dependence is as high as about 70% [31]. This is probably a result of inherited differences in opioid metabolizing enzymes and/or opioid receptors. Furthermore, there is a genetic contribution to the dependence on and the use of the combination of tobacco and alcohol together with other substances [31]. Studies estimated about an eight-fold increase in the risk of substance dependence among families of persons with substance dependence in comparison to the controls, when utilized for a wide range of substances especially cannabis, cocaine, sedatives, and opioids [32,33]. Several aspects of substance use like subjective pleasurable effects are influenced by genetic differences, and the toxicity of a particular substance in terms of chronic health effects and overdose may be greatly affected by different genetic factors [34]. The intensity of the effects of psychoactive drugs, cravings, withdrawal, and tolerance development are all also affected by the genetics of the individual [35].

Association between smoking, opioid abuse, schizophrenia, depression, alcoholism, obesity, cocaine abuse, meth-amphetamine abuse, gambling, and the A1 allele of D2R gene has been reported in humans [36,37], although contrary opinions of such associations exist [38,39], thus, the involvement of the A1 allele of the D2R gene in those conditions remains contentious.

Psychoactive Drugs and DNA Damage

The potential of psychoactive drugs to induce DNA damage has been documented in some studies (Table 2). Studies on the genotoxicity of psychoactive drugs are very limited in the literature and most of the available literature are old studies. Hence, there is a need for more wholistic studies on the DNA damaging potential of psychoactive drugs using modern assessment techniques and equipment in different biological models.

S/N	Name of drug	Model organism	Endpoint	DNA damage result
1.	Morphine	Mice	Bone marrow chromosome aberration Bone marrow Micronuclei Comet assay on lymphocytes Apurinic-apyrimidinic site counting assay in CD3+ T cells Phosphorylation of Ser-15 in P53 protein in CD3+ T cells DNA fragmentation in thymocytes Methylation of DNA	+ + + + + +
		Drosophila melanogaster	Sex-linked recessive lethal mutation assay	-
		Non-neuronal cells	Mutation of the hprt gene	+
2.	Codeine	Chinese hamster ovary (CHO) cells	Sister chromatid exchange	+
		Salmonella typhimurium	Mutagenicity	+
		B6C3F1 mice	Carcinogenicity	-
		F344/ N rats	Carcinogenicity	-
3.	Cocaine	Humans	Teratogenicity	+
		Rat	Inhibition of brain's DNA synthesis	+
		Cultured C6 glioma	Inhibition of thymidine incorporation and, to a lesser extent, leucine and uridine.	+
		Cortical glial cells	Inhibition of thymidine incorporation and, to a lesser extent, leucine and uridine.	+
		Mice	Apoptosis and DNA ploidy	+
		Mussels (*Perna perna*)	DNA strand break	+
4.	Marijuana	Alveolar macrophages	DNA single-strand breaks	+
		Human lung cells	Inhibition of RNA and DNA synthesis	+
		Salmonella typhimurium	Mutagenicity	+
		Humans	Tongue cancer	+
		Fetus	leukemia	+
		Human	Bladder carcinoma	+
		Gonadal stem cell	Cancer and cell growth inhibition	+
5.	Tramadol	Mice	DNA fragmentation in comet assay Mouse lymphoma assay Oxidative DNA damage (increased 8-oxo-7,8- dihydro-2'-deoxyguanosine) and apoptosis	+ + +
		Humans	Micronuclei Chromosomal aberrations DNA fragmentation	+ + +
		Rat	DNA fragmentation in comet assay	+
6.	Tobacco	Human	Cancer DNA lesions	+ +

		Mice	Cancer	+
			DNA lesions	+
		Rats	Cancer	+
			DNA lesions	+
7.	Khat	Bacteria	Gene mutation	+
		Mice	Micronuclei	+
			Chromosome aberration	+
			Cancer	+
		Rat	Micronuclei	+
			Chromosome aberration	+
			Cancer	+
8.	Alcohol	Human	Cancer	+
			DNA lesions (7,8-dihydro-8-oxo-2-deoxyguanosine)	+
		Rat	Cancer	+
			DNA double-strand breaks	+
		Mice	Cancer	+
			DNA lesions	+
			DNA double-strand breaks	+
		Cell lines	DNA fragmentation	+

Table 2: DNA damage induced by selected psychoactive drugs in different organisms and the different genetic endpoints

Morphine Induced DNA Damage

Morphine, a metabolite of heroin (diacetylmorphine), has been widely used to manage moderate to severe pain. Limited evidence on the ability of morphine to induce DNA damage is available, however, morphine has been shown to induce a significant increase in the frequency of bone marrow's chromosome aberrations [40], micronuclei, and lymphocytes in mice exposed to 3.2 mg/Kg for 8-168hr [41]. Literature shows that morphine was nonmutagenic in the *Drosophila melanogaster* sex-linked recessive lethal mutation assay. However, it increased micronuclei frequency in both red blood and bone marrow cells in the mouse [42]. A significant increase in micronuclei which was dose-dependent from 5-20 mg/kg was reported in mice exposed to a single treatment of morphine [43]. Also, micronuclei induced in mice by a single dose of 20 mg/Kg morphine were reduced by an opioid antagonist, naloxone, which is an indication that such DNA damage is partly mediated by opioid receptors. Although morphine-3-glucuronide which is the *in vivo* principal metabolite of morphine does not take part in receptor-mediated responses, however, other metabolites might be involved [43]. In an acute study (24hr), 8 mg of morphine was reported to induce significant micronuclei and DNA damage using comet assay in exposed mice through the generation of reactive oxygen species [44]. Morphine has also been shown to be clastogenic in murine lymphocytes [43,45]. DNA damage, quantified by apurinic-apyrimidinic site counting assay and phosphorylation of Ser-15 in P53 protein, was induced in CD3+ T cells by morphine in a naloxone-sensitive manner. This induced DNA damage was through the action on the kappa opioid receptor, which leads to immune suppression by activation of P53-mediated signal transduction [46].

Morphine's potential to induce DNA fragmentation was also confirmed *in vivo* in mice thymocytes, where the induced DNA fragmentation was associated with apoptosis [47]. This morphine-induced apoptosis was believed to involve both glucocorticoid and opiate receptors. Further study showed that a combination of morphine and EMS also induced mutation of the hprt gene which is repairable, thus, suggesting that indirect or direct mutagenesis can be initiated if morphine exposure persisted through several cell cycles. Therefore, morphine can cause long-term inhibition of repair processes or replication, thereby making transient alterations to become permanent mutations. Repairing DNA damage caused by exposure to UV light can also be impaired by exposure to morphine [48]. Report has also shown that rats' exposure to morphine induced a significant increase in the methylation of DNA of the esophagus by N-nitrosodiethylamine, and that morphine can reduce the liver clearance of N-nitrosodiethylamine at high doses [49], therefore, classifying morphine as a co-mutagen.

Some hypothesis of the *in vivo* clastogenic effects reported with morphine in mice may be directly related to increase in glucocorticoid levels produced by morphine in this species [50] or a consequence of hypothermia [45], which is caused in rodents by this drug, but this is worthy of further study.

Codeine Induced DNA Damage

Codeine is a natural constituent of opium that is used in the production of different pharmaceuticals such as sedatives, antitussive agents, hypnotics, analgesics, and antiperistaltic agents [51]. A study by the US National Toxicology Program (NTP) in Chinese hamster ovary (CHO) cells revealed that codeine phosphate (CP) induced a dose-dependent significant increase in sister chromatid exchange, without and with S9 metabolic enzyme activation. Also, CP was shown to induce mutagenicity in four different *Salmonella typhimurium* strains used in the absence or presence of S9 mix. No evidence of carcinogenicity was observed after B6C3F1 mice and F344/N rats were exposed to codeine in 2 year feeding studies. However, after extensive analyses using the multiple computer automated structure evaluation (MULTICASE) and computer automated structure evaluation (CASE) structure-activity relational expert systems to predict carcinogenic activity, it has been suggested that codeine could possibly be a carcinogen in rodents [52].

Cocaine-Induced DNA Damage

Cocaine is the major alkaloid that can be isolated from the coca leaf and it ranks possibly as the most used addictive illicit drug [53,54]. Cocaine has been confirmed as a teratogen and its abuse by humans can also cause a significantly higher malformation rate, reduction in fetus weight, and increase in the rate of stillbirth related to abruption placentae [55]. It has also been documented that in the developing rat brain regions cocaine can inhibit DNA synthesis [56]. Furthermore, a report has shown that 24h exposure to cocaine can cause inhibition of thymidine incorporation and, to a lesser extent, leucine and uridine, in cultured C6 glioma and cortical glial cells [49]. The inhibition of the synthesis of important macromolecules like this in the glial cells could be a possible mechanism of fetal brain growth retardation induced by cocaine. A study in male Swiss albino mice treated with a single dose of cocaine (60 mg/kg) showed induction of liver injury characterized by specific changes in apoptosis and DNA ploidy [57]. The study of Maranho et al. [58] also reported the genotoxicity of cocaine in mussels, while fetal mouse brain treated with cocaine selectively resulted in neural apoptosis, although, major cocaine metabolites showed no detectable effects on neurons, an indication that the observed neural apoptosis was due to the cocaine itself [59]. The carcinogenic effect of cocaine has not been determined, however, using the CASE system, cocaine has been predicted as a probable carcinogen [60].

Marijuana Induced DNA Damage

In vitro and *in vivo* mammalian cell studies have shown that marijuana and its constitutive cannabinoids such as cannabinol (CBN), cannabidiol (CBD), and tetrahydrocannabinol (THC) can induce cytogenetic aberrations [61]. These aberrations include hypoploidy, translocations, chromosomal breaks (either in combination with tobacco smoking or alone), and errors in chromosomal segregation. In an alkaline unwinding assay study, marijuana was shown to induce single-strand breaks in the DNA of alveolar macrophages [62]. These are clear indications that marijuana is a mutagen. A study in cell cultures has shown that THC and other cannabinoids were capable of impairing RNA and DNA synthesis [63], and condensates from marijuana smoke were reported mutagenic using the Ames salmonella assay [64]. Smoking marijuana by 19-30 years old individuals is suspected to be associated with jaw, lung, mouth, and tongue cancers [65,66]. Furthermore, children who were exposed *in utero* to marijuana showed a 10-fold increased risk of leukemia compared to those who are not [67]. The potential genotoxicity of cannabinoids is raising questions as a result of their involvement with at least three enzymes that play important roles in DNA repair, an area that has been less studied. Report has shown that cannabis can alter DNA expression [68] including in the tissues of the germline [13]. Genotoxicity in gonadal stem cell have implications for inheritable defects like cancers, fetal malformations, and cell growth inhibition.

Tramadol Induced DNA Damage

Tramadol is an analgesic synthetically produced from opioids. It binds specifically to the opioid receptors and has been used as a first-

line drug in the treatment of acute pain caused by postoperative injury. It was first used in 1977 in Germany as a therapeutic analgesic and has been in use ever since then [69-71]. The potential DNA damaging ability has been majorly uninvestigated and data are very limited in the literature. However, data from the comet assay showed the genotoxicity of tramadol which was dose-dependent in mice exposed to tramadol [72]. El-Maddah and Mousa [73] also reported the genotoxicity of tramadol with a significant increase in the frequencies of micronuclei, chromosomal aberrations, and SCEs in cultured lymphocytes obtained from tramadol-dependent patients. This observed tramadol genotoxicity was found to correlate with the duration of tramadol dependence. Also, *in vivo* mouse lymphoma assay showed genotoxic activity of tramadol at certain human doses [74]. In another study, tramadol was shown to induce oxidative DNA damage (increased 8-oxo-7,8- dihydro-2'-deoxyguanosine) and apoptosis in mice exposed to 30 and 60 mg/kg of tramadol for 8 weeks [75]. A recent study further showed that mice orally exposed to 25, 50 and 75 mg/kg of tramadol for 15 days had significantly increased DNA damage in the blood lymphocyte comet assay [76]. A similar result was reported by El Kawy [77] where rats exposed to 200 and 400 mg/kg tramadol for 15-45 days showed increased DNA damage using the comet assay.

Tobacco Induced DNA Damage

Globally, lung tumor caused by cigarette smoke (CS) has been recognized as one of the malignancies with the highest incidence and mortality rate [78]. CS also significantly contributes to how other malignancies like pharynx, bladder, larynx, oral, esophagus, kidney, uterine, stomach, cervix, and pancreas cancers develop [79]. There are many reports in the literature indicating the exceedingly complex genotoxicity of CS with more than 60 carcinogens identified in CS which are defined collectively as the "Hoffman list" [80]. Potent carcinogens like tobacco-specific nitrosamines (e.g., N-0-nitrosonornicotine and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone) and polycyclic aromatic hydrocarbons especially benzo(a)pyrene (BaP) are among these 60 carcinogens [81]. There is a need for metabolic activation for most of these carcinogens to bind covalently to the DNA. Chemical constituents of the CS with potential genotoxic activity include tobacco-specific nitrosamines, aldehydes, alkylating agents, lipid peroxidation products, and BaP. The DNA lesions caused by these genotoxins collectively cause genetic defect accumulation on multiple loci [82] which subsequently cause progressive genomic instability and damage [83]. Studies have shown the tumorigenic importance of this genomic instability and damage, indicating that tobacco smokers who have less efficient capacity to repair DNA have a higher risk of developing cancer of the lung [84]. Knowing the temporal sequences of the different molecular responses to the genetic damage induced by CS can lead to the clarification of the specific types of DNA damage that contribute to the observed carcinogenesis and then provides viable cancer risk biomarkers in other individuals exposed to CS [85]. Investigations have been conducted to show if cigarette smoking is a major risk factor for squamous and renal cell carcinoma of the neck and head [86]. Specifically, the interaction of genetic susceptibility and smoking cigarettes is a major influence in the tumorigenesis of cancers related to tobacco [84]. Since CS contains varieties of genotoxins, these can produce different types of DNA alterations which require distinct pathways for these DNA repair. In particular, mutations and cancers induced by smoking are prevented by the genes of the DNA double-strand break, base, and nucleotide excision repair pathways. Therefore, the role of the genetic polymorphisms of genes actively involved in the DNA repair and metabolic activation is very important with respect to the modification of the genotoxicity and cancer risks caused by CS and other environmental carcinogens/mutagens [87].

Khat Induced DNA Damage

Chewing Khat has been a century-long practice of the people of the Arabian Peninsula and the horn of Africa. Khat is the leaf of *Catha edulis* which contains cathinone, a natural amphetamine, with psychoactive and euphoric effects [88]. The genotoxicity of khat has been documented. Crude khat extract has been shown to induce gene mutation in bacteria, as well as bone marrow micronuclei and chromosomal aberrations in exposed mice [89]. It is well established that the genotoxicity of Khat may lead to the development of heritable diseases such as cancer and reduced fertility in consumers [90]. It is also known that polyphenolic constituents of khat like tannins have been shown to induce mutagenicity and carcinogenicity in laboratory animals [91]. The results of Fluorescence *in situ* hybridization analysis also revealed that khat can cause centromere-positive micronuclei. Although micronuclei can result from chromosome breaks lagging behind in the process of cell division, there is a high likelihood that khat is aneuploidogenic. Another

finding has suggested that chewing khat can cause oral and upper digestive tract cancers [92]. Rats exposed to khat have been reported to show increased concentration of free radical and oxidative stress, which could be due to the Khat alkaloid fraction [93]. The long-term effect of the induced oxidative stress by khat could cause neurodegenerative diseases, nephrotoxicity, cardiovascular toxicity, hepatotoxicity, and cancer [94].

Alcohol-Induced DNA Damage

Epidemiological studies have shown an association between cancer risk and chronic ethanol consumption. In 2020, more than 740,000 global cancer cases were caused by the consumption of alcohol which is approximately about 4% of cancers worldwide [95]. The effect of the consumption of alcohol on the development of cancer is different depending on the type of cancer. Globally, cancers of the liver, breast, and esophagus are the cancers most attributable to alcohol. Indeed, studies have shown an increased incidence of women breast cancer [96,97], colorectal cancer [98,99], and esophageal cancer [100] in those who consumed alcohol. The mechanism(s) of alcohol-induced cancer is not well understood even though alcohol has been classified as a human carcinogen. Data have shown that ethanol can increase the generation of hydroxyl radicals and superoxide anions, which can cause oxidative damage in the biological system [101]. Oxidative stress induced by alcohol can cause different DNA damage/alterations such as DNA strand breaks, interstrand DNA crosslinks, and DNA adducts [102-104]. The induction of oxidative DNA adducts and damage is regarded as an important initiating process in the development of alcohol-related cancer [102]. Furthermore, *in vivo* studies have shown that consumption of alcohol induces oxidative stress which produced ultrastructural chromatin damages in the epithelial cells of mammals [105]. This supported the effect of alcohol in the generation of genetic instability which leads to breast carcinogenesis [106].

Acetaldehyde is the first product in the metabolism of ethanol and it is believed to be the main cause of alcohol-induced DNA damage. In the last three decades, genotoxic effects of acetaldehyde derived from alcohol have been studied extensively with the documentation of different evidence supporting the mutagenicity and carcinogenicity of acetaldehyde [107]. Association between consumption of alcohol and generation of genotoxic metabolites which can produce reactive oxygen species (ROS) as well as DNA lesions caused by acetaldehyde have been established. The production of 7,8-dihydro-8-oxo-2-deoxyguanosine is the most common oxidative DNA lesion in such a biological system [107]. N2-ethyl-deoxyguanosine is the primary DNA adduct derived from acetaldehyde [108] and has been reported in human alcoholics [109] and the DNA of mice exposed to ethanol [110]. Indeed, Fowler et al. [111] reported ROS generation and acetaldehyde-derived damage to the DNA in the brain of adult mice exposed to ethanol. Kotova et al. [112] in their study showed that acetaldehyde can effectively block the elongation of DNA replication in the cells of mammals leading to replication-associated DNA double-strand breaks. Acetaldehyde has also been documented to induce genotoxicity majorly through clastogenicity instead of aneugenicity [113]. Lymphocytes *in vitro* studies have shown increased DNA damage induced by chronic consumption of ethanol with acetaldehyde as the major genotoxin [113,114].

Conclusion

All the psychoactive substances have the potential of causing deleterious health effects depending on the quantity and frequency of use. Dependence on these drugs can cause DNA damage and injury to other vital organs in the body. Therefore, there is a need for more wholistic studies on the potential DNA damaging effect of psychoactive drugs and public awareness of such to protect the health of the public.

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