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*Review*

# DNA Damage Induced by Alcoholic Beverages and Repair Mechanism Pathways: A Review

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**Abstract:** Alcoholic beverages contains ethanol as the main component. Ethanol is metabolized into acetaldehyde, a Group 1 carcinogen, and other reactive by-products such as ROS and hydroxyl radicals. These metabolites can interact with DNA to form adducts and interstrand cross-links, leading to mutations and genomic instability, which are key contributors to alcohol-related cancers. Ethanol metabolism is mediated by critical enzymes - Alcohol Dehydrogenase (ADH), Cytochrome P450 2E1 (CYP2E1), Catalase, and Aldehyde Dehydrogenase (ALDH), which regulate both the generation and detoxification of these harmful intermediates. Every cell in our body owns a toolkit with which it can repair different types of DNA lesions. This review highlights the enzymatic pathways of ethanol metabolism, the formation of genotoxic by-products, and the cellular mechanisms that maintain genomic integrity. Understanding these processes provides crucial insights into the molecular basis of alcohol-induced carcinogenesis and may guide strategies for prevention and therapeutic intervention.

**Keywords:** ADH; P450 2E1; Catalase; ALDH; DNA-acetaldehyde adduct; 8-Oxoguanine; DNA repair

## 1. Introduction

DNA is the hereditary material of humans and all living organisms, located mainly in the nucleus of a cell. This essential macromolecule carries genetic information for the functioning and development of an organism. DNA damage is a spontaneous process in organisms; however, cells inherit some specific repair pathways. Almost 169 enzymes are directly or indirectly involved in the DNA repair mechanism [1]. Unrepaired DNA damage of neurons and myocytes of mammalian adults is a leading cause of ageing [2]. DNA lesions are a risk factor for various types of cancer. Before the discovery of the DNA double helix, it was known that exogenous sources like ionizing radiation, UV radiation, X-rays, and chemicals (polycyclic aromatic hydrocarbon, alcohol, vinyl chloride) can damage DNA [3,4]. When the structure of DNA was clear, it was recognized that endogenous DNA damage also occurs, including hydrolysis (deamination & depurination) [5], oxidation (exposure to ROS/RNS) [6], alkylation of bases [7], mismatch of DNA bases, and toxic product formation in cellular metabolism [8]. Besides these factors, DNA damage can occur due to an inherited or acquired defective repair system, which leads to a condition where the rate of DNA damage exceeds the rate of its repair [9].

Recent studies showed that annual consumption of alcoholic beverages increased worldwide. About 23.48 billion (43% of the population) people aged 15 or over consume alcohol in one year [10]. The composition of alcoholic beverages typically includes ethanol,

water, varying amounts of flavorings, sugars, acids, etc. Alcohol intake has been causally linked to over 200 different diseases and conditions [11]. Alcohol drinking is the second important proven cause of cancer after smoking. The carcinogenic effect of alcohol was first published at the beginning of the twentieth century, based on Newsholme's study which reported excess alcohol consumption and cancer mortality. In 1988, the International Agency for Research on Cancer (IARC) categorized alcoholic beverages as a Group 1 human carcinogen [12]. In 2020, more than 740,000 cancer cases worldwide, representing approximately 4% of all cancers, were attributed to alcohol consumption [13]. Chronic alcohol consumption is more dangerous than acute. The World Cancer Research Fund (WCRF) identified strong evidence linking alcohol consumption and increased risk of cancers of the mouth, pharynx and larynx, oesophagus (squamous cell carcinoma), liver, colorectum (men), breast (postmenopausal) and stomach cancer [12,14]. Additionally, there is a possibility of alcohol associated cancer in the skin [15] and gallbladder [16]. The goal of this systematic review is to summarize alcohol metabolism by major enzyme pathways, as well as how toxic ethanol metabolites affect DNA and the associated repair mechanisms.

## 2. Alcohol Metabolism in Body

Alcohol metabolism is a complex process characterized by significant individual variations in absorption, distribution, and elimination rates. After alcohol consumption, a small amount of ethanol is absorbed in the mouth and then the ingested ethanol transits through the esophagus to the stomach and small intestine. Most of the remaining alcohol is absorbed into the small blood vessels of the small intestine, and blood circulation distributes it into different organs. The rate at which alcohol is absorbed depends on various factors such as stomach emptiness, the type of drink, sex, age and body size [17]. Alcohol has the capacity to enter all cells except bone and fat. Since ethanol is BBB-permeable, it can pass into the brain. The liver, having a high level of alcohol metabolizing enzymes, is the pivotal organ responsible for metabolizing most of the ingested alcohol [18]. Nearly 90% of alcohol is metabolized in the liver, while about 2–5% is excreted unchanged through urine, feces, breast milk, sweat, and exhaled air [17]. Non-liver tissues such as brain can also metabolize alcohol by different enzymatic pathways. Multiple enzyme pathways and various biochemical processes are associated with ethanol metabolism (Figure 1). Alcohol dehydrogenase (ADH), CytochromeP450 2E1 and Catalase are involved in the first stage of ethanol breakdown, while Aldehyde dehydrogenase is associated with the second stage.

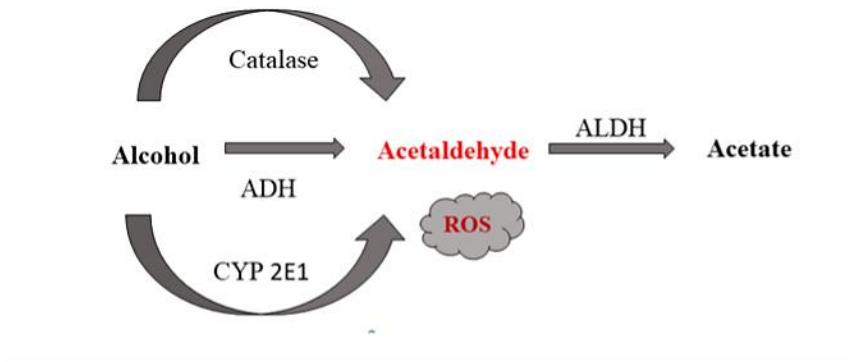


**Figure 1.** Significant pathways of alcohol and acetaldehyde metabolism

## 3. Alcohol Metabolizing Enzymes

### *3.1. Alcohol Dehydrogenase*

Alcohol dehydrogenase (ADH) is the leading enzyme for alcohol metabolism, which is primarily present in the liver and inside the lining of the stomach [19]. Human ADH enzymes are classified into 5 classes, and 7 different ADH genes code as ADH1A, ADH1B, ADH1C, ADH4, ADH5, ADH6 and ADH7 [20]. Class 1 group contains three closely related ADH1A, ADH1B and ADH1C genes responsible for oxidizing most of the ingested ethanol, where nicotinamide adenine dinucleotide ($NAD^+$) acts as a cofactor. ADHs are dimeric zinc metalloenzymes with each subunit binding to two $Zn^{2+}$ ions. In ADH, both the catalytic and structural zinc ions are vital for the catalytic function and the stability of the enzymes, respectively. Catalytic $Zn^{2+}$ has a distorted tetrahedral geometry and within the active site it is coordinated to Cys174, Cys46, His67 and a water molecule [20]. Non-catalytic zinc binds to four cysteine residues, forming a tetrahedral structure. Alcohol oxidation by ADH involves multiple steps, including binding of ADH with $NAD^+$ factor, $H_2O$ molecule displacement of $Zn^{2+}$ by alcohol substrate, formation of zinc alkoxide intermediate through deprotonation of bound alcohol, followed by hydride transfer from alcohol to $NAD^+$ cofactor, forming NADH and finally displacement of aldehyde and NADH occur [21].

### *3.2. Cytochrome P450 2E1*

In hepatic cells, ethanol can also be metabolized by the microsomal ethanol oxidizing system (MEOS) with key enzyme cytochrome P450 2E1 (CYP2E1) [22]. Charles S. Lieber first identified the involvement of cytochrome P450 in alcohol metabolism [23]. CYP1A2 and CYP3A4 are also known to be associated with the ethanol oxidation process [24]. CYP2E1 is a predominant member of the Cytochrome P450 superfamily enzymes containing heme protein as the active site. Chronic alcohol consumption with high blood alcohol concentration activates the microsomal ethanol oxidizing system (MEOS) and expression of CYP2E1. CYP2E1 catalyzes another oxidation pathway of ethanol to acetaldehyde in the liver, brain and other organs [25]. Interestingly, CYP2E1 can further oxidize acetaldehyde to acetate using NADPH and oxygen. However, in the presence of ethanol, this secondary reaction is likely negligible [26]. Ethanol metabolism by CYP2E1 in enterocytes generates significant quantities of reactive oxygen species (ROS), including superoxide and hydrogen peroxide [27].

### *3.3. Catalase*

A tertiary route for the metabolism of ethanol is managed by the catalase enzyme, which is located in peroxisomes. Catalase is a tetramer of four polypeptide chains, each containing 500 amino acids [28]. The active site of catalase holds a heme with catalytic His75 on the distal side and other residues Tyr358, Arg354, His218 and Asp348 on the proximal side. Catalase generally decomposes $H_2O_2$, but it can also use $H_2O_2$ to oxidize ethanol. In the “catalatic” reaction, two $H_2O_2$ molecules are converted into two $H_2O$ and one $O_2$. However, in the presence of ethanol, catalase instead carries out the “peroxidatic” reaction, where $H_2O_2$ oxidizes ethanol to acetaldehyde, yielding $H_2O$ but no $O_2$ [28,29]. Though catalase has a smaller role in alcohol metabolism in comparison to ADH and CYP2E1 it is important in cerebral cells. Studies

showed that it catalyzes approximately 60-70% ethanol in brain cells, where ADH is absent [30,31].

### *3.4. Aldehyde dehydrogenase (ALDH)*

Human aldehyde dehydrogenase (ALDH) is the principal enzyme in the oxidation of highly toxic acetaldehyde into acetate in the second step of alcohol metabolism. Mammalian ALDHs are a family of nicotinamide adenine dinucleotide (phosphate) (NAD(P)) dependent enzymes. They are abundant in the liver and also found in the heart, brain, kidney and uterus. 19 members of the human ALDH superfamily have been identified to date, and among them, the mitochondrial ALDH2 plays a crucial role in maintaining low blood levels of acetaldehyde [32]. ALDH2 is a tetrameric enzyme and contains triple functional domains: coenzyme or NAD+ binding (8-135, 159-270), catalysis (271-470) and oligomerization (140-158, 486-495) (Figure 2) [33,34]. The catalytic mechanism begins with the binding of $NAD^+$ to ALDH2 at multiple sites to activate the key active-site cysteine residue (Cys302). The sulfhydryl group of Cys302 performs a nucleophilic attack on the carbonyl carbon of the aldehyde, forming a tetrahedral thiohemiacetal intermediate [35]. The aldehydic hydride ion is transferred to NAD+, forming NADH and a thioester intermediate. Then, the Glu268 residue activates a water molecule, which performs a nucleophilic attack on the thioester intermediate, resulting in the formation of the carboxylic acid end product. Finally, the reduced coenzyme (NADH) is released from the catalytic pocket, regenerating the enzyme for a new catalytic cycle [36]. ALDH*2 is a mutant form of aldehyde dehydrogenase, where a lysine residue replaces a glutamate in the active site at position 487 of ALDH2. This amino acid change destabilizes the structure at the $NAD^+$ binding site, drastically reducing coenzyme affinity and normal activity of ALDH2 by about 90%. In Asian countries, ~ 40% of the population carries the ALDH*2 genetic variant. The ALDH*2 polymorphism leads to an accumulation of acetaldehyde even in moderate consumption. As a consequence, Asian people are more vulnerable to developing alcohol related cancer, oropharyngeal, laryngeal and esophageal cancer [37,38,39].

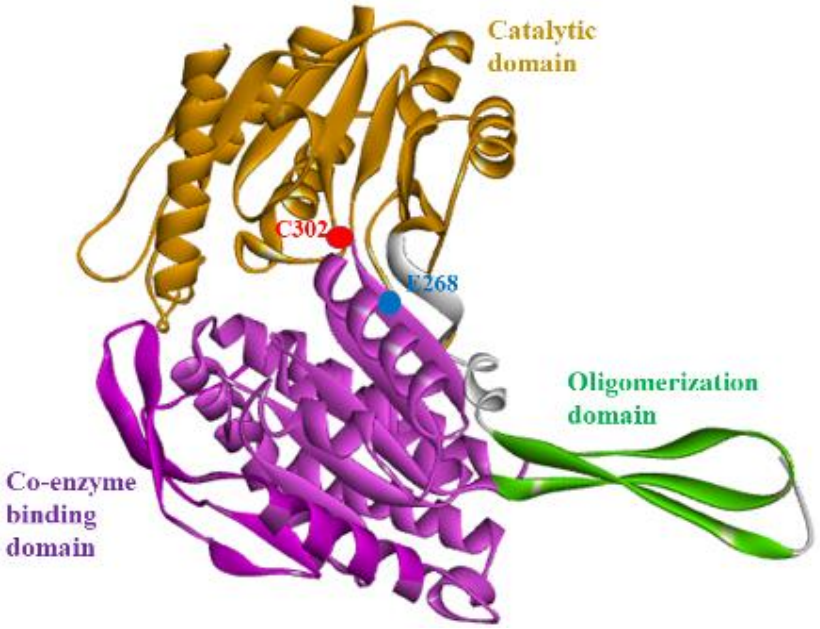


**Figure 2.** ALDH2 enzyme and functional domains. Colored red (Cys 302) and blue (Glu 268) are residues crucial for its catalytic activity

## 4. Oxidative Product of Ethanol

Oxidation of ethanol by major enzymes generates pernicious chemicals like acetaldehyde and ROS. Ethanol is known to enhance the production of superoxide anions and hydroxyl radicals. Acetaldehyde inhibits the activity of superoxide dismutase 2, a key endogenous antioxidant enzyme. ROS are highly unstable and reactive. Accumulation of these by-products are strongly associated with heightened oxidative stress. Excessive oxidative stress can induce damage to various cellular biomolecules including lipids, proteins, and DNA. Damage to DNA can lead to mutations, a predominant step into cancer initiation.

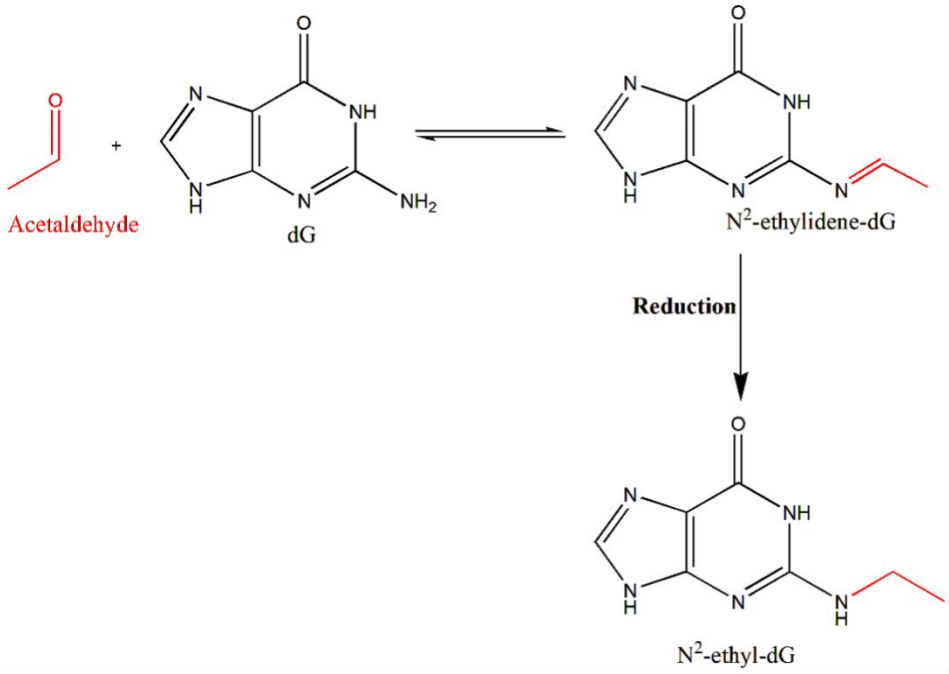


**Figure 3.** Formation N2-Ethyl-dG by toxic effect of acetaldehyde

## 5. Types of Ethanol-induced DNA Damage

### *5.1. Formation of N2-Et-dG Adduct*

Acetaldehyde, the major metabolite of ethanol, is very reactive towards DNA. Numerous studies showed that it can react with DNA to form adducts [40,41]. Acetaldehyde primarily reacts with the N2 exocyclic position of 2′-deoxyguanosine in DNA, forming an unstable Schiff base imine adduct product N2-ethylidene-dG (Figure 3). Vaca et al. (1995) first recognized this type of lesion in their studies on aldehyde-related DNA adduct [42]. Matsuda et al (2007) also revealed its presence in the liver [43]. The accumulation of significantly higher levels of N2-ethylidene-dG is observed in ALDH2-deficient individuals. N2-ethylidene-dG undergoes reduction accomplished by some intracellular molecule or enzyme (vitamin C and glutathione) to stable adduct N2-Ethyl-dG [44]. N2-Ethyl-dG adducts contribute to mutagenesis and carcinogenesis, and their accumulation may interfere with critical biological processes such as DNA replication, repair, and transcription. DNA polymerases, a group of enzymes, catalyse DNA synthesis and work together to generate two identical DNA strands from one original DNA molecule. Direct interaction between the enzyme and the minor groove is significant for enzyme activity. However, the presence of N2-Ethyl-dG adduct in the

incipient base pair hinders the minor groove from interacting with the active sites of polymerase. As a consequence of this, replication catalyzed by DNA polymerase was inhibited. The extent of DNA replication blockage depends on the sizes of the adducts [44]. Other studies demonstrated that N2-Ethyl-dG can potently block the transcription process by interfering with RNA polymerases [45]. Terashima et al explored and found that N2-Ethyl-dG adduct has high miscoding potential leading to production of a unique miscoding spectrum G → C transversions [44]. Moreover, translesion DNA synthesis (TLS), a direct repair pathway for DNA damage, is also hindered by the action of this adduct [46].

### *5.2. DNA Crosslink*

In genetics, DNA crosslinking damage occurs when specific agents covalently connect two nucleotide residues from the same DNA strand (intrastrand crosslink) or from opposite strands (interstrand crosslink). Interstrand crosslink (ICL) is one of the most perilous DNA lesions. ICL hinders transcription and replication by preventing the splitting of the DNA double strand.

Several studies have shown that exposure of DNA to acetaldehyde can result in additional lesions other than N2-Ethyl-dG. When cells are exposed to high concentrations of acetaldehyde, it reacts with DNA base guanine to yield a crosslink precursor N2-propanoguanine (PdG) [47]. The formation of PdG involves a two-step reaction. PdG can exist in ring-opened or closed form depending on the structure and the state of the DNA. In single-stranded DNA, the PdG adduct exists in the cyclic (ring-closed) form while the open form is favored in double-stranded DNA [48]. PdG can induce both interstrand and intrastrand DNA cross-links. In the ring-opened configuration, the free aldehyde group attacks the N2 amino group of an adjoining guanine base in the complementary strand of the CG site to form an acetaldehyde interstrand crosslink (AA-ICL) [49]. ICLs are the most lethal types of lesions because they affect both strands of DNA. Unrepaired or misrepaired DNA ICLs are major sources of genomic instability.

### *5.3. 8-Oxoguanine (8-oxoG)*

Reactive oxygen species like peroxide, superoxide, hydroxide and singlet oxygen are unstable, highly reactive chemicals due to their paramagnetic configuration. They are produced from oxygen. In the human body, ROS are released as byproducts of some cellular metabolism. Oxidation of ethanol also yields ROS. Accumulation of ROS can cause lesions in DNA bases by oxidative stress to form adducts. Guanine is more prone to oxidative stress among the four bases because of its low redox potential and generates the altered base 8-Oxoguanine ((8-oxoG)) (Figure 4) [50]. ROS directly attack the double bond present between C8 and N7 of guanine, resulting in the generation of a reducing neutral radical, which subsequently forms 8-oxoG. Numerous studies have shown that the 5′-G of GG or GGG sequences is more vulnerable to oxidation than free guanines [51]. 8-oxoG was first discovered and reported by Kasai and Nishimura in 1984 in DNA during the characterization of carcinogenic molecules associated with oxidative stress [52].

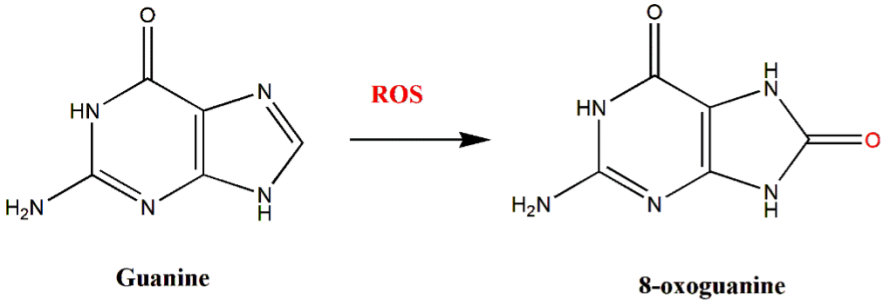


**Figure 4.** Oxidation of guanine base to 8-oxoguanine

It was found that 8-oxoG, present in DNA, makes adjacent DNA bases more susceptible to oxidation and represents a 'hot spot' of oxidative DNA damage [47]. 8-oxoG has a high propensity to adopt the syn conformation because in normal anti conformation 8-oxo group undergoes steric clashes and unfavorable interaction with the O4' position of the DNA sugar. In syn conformation, 8-oxoG has the capacity to functionally mimic thymine (T), and it uses Hoogsteen edge to base pair with adenine [53]. However, in the anti conformation, 8-oxoG can still pair with cytosine, similar to unoxidised guanine [54]. This way, unrepaired 8-oxoG can generate a CG to AT transversion point mutation. These transversions are the second most common somatic mutation found in human cancers. Numerous experimental works on animal and cultured cells also supported this theory [55]. Hence, during replication, various DNA polymerases interpret 8-oxoG as dG or dT, resulting in either correct polymerization or a transversion.

## 6. DNA Damage Repair Pathways

The precise transmission of genetic information from one cell to its daughters is crucial for the survival of organisms, requiring extreme accuracy in DNA replication and chromosome distribution, as well as the capacity to survive spontaneous and induced DNA damage. Therefore, organisms inherit various repair mechanisms to counteract the lethal effects of DNA lesions. DNA repair is a ubiquitous defense mechanism, important to preserve the integrity of the mammalian genome by removing DNA damage. Several repair systems, like base excision, nucleotide excision, and recombination in humans, save the genome by repairing modified bases, DNA adducts, cross-links, and double-strand breaks. In this review, we will discuss the possible DNA repair model for DNA damage occurring due to alcoholic beverages (Table 1).

### *6.1. DNA-acetaldehyde Adduct Repair*

N2-Ethyl-dG is the most common and best studied aldehyde-induced lesion. Researchers attempt to identify a repair route for this adduct, but no specific repair mechanism is yet known [56]. The most likely repair pathway for N2-propanoguanine in its monoadduct form is nucleotide excision repair (NER) [57]. However, N2-propanoguanine is highly reactive and rapidly lead to the formation of DNA interstrand crosslinks (ICLs). Various studies showed that there are two important repair pathways for DNA interstrand crosslink. The first one is Fanconi anemia (FA), a fundamental DNA repair system that functions analogously to the mechanism used for chemotherapeutic crosslinks caused by cisplatin [58]. FA repair pathway starts in S-phase and involves almost 19 genes (FANCA, B, C, D1, D2, E–G, I, J, L–T) [59].

At the site of DNA cross-links, genes FANCA, B, C, E–G, L, and M create a core complex promoting ubiquitination of the FANCD2–FANCI complex. This ubiquitination of FANCD2 engages XPF-ERCC1-SLX4 (XES) complex in incision of the DNA strand adjacent to the ICL [60,61]. This backbone incision leads to the unhooking of the ICL and generates a strand with an adduct and a broken strand. Translesion DNA polymerases hold bulky ICL adducts in their binding pockets, thereby incorporating nucleotides opposite to the ICL and filling the DNA gap. The broken strand is repaired by homologous recombination [49,62]. However, DNA breaks are dangerous, which can lead to chromosomal rearrangement and ultimately cause cancer. Hodskinson et al (2020) uncover a novel, faster repair route that eliminates ICL without creating DNA backbone incisions. It was believed that this mechanism needs replication fork convergence and uniquely unhooks the ICL by internal incision of the crosslink. They suggested that this repair pathway regenerates dG on the top strand and produces dG adduct on the bottom strand. Similar to the FA model, the dG adducts (on the bottom strand) of this repair pathway are bypassed by the REV1, REV7/FANCV and REV3 translesion synthesis complex. In contrast, the top strand extended without any interruption, hence the integrity of DNA is retained [49]. No abasic site formed in the new mechanism.

ICL repair by both routes is prone to risk, which may lead to chromosomal rearrangement and ultimately can cause cancer. However, since the second mechanism works without cutting the phosphodiester backbone of DNA, it has a higher chance of retaining the integrity of DNA.

### *6.2. 8-Oxoguanine Repair*

Repair of 8-Oxoguanine (8-oxoG) DNA lesion is critical since it can pair not only with cytosine but also with adenine during replication, resulting in a G: C to T: A transversion mutation. Since 8-oxoG was reported in 1984, many researchers have tried to identify the repair pathway. 8-Oxoguanine is repaired primarily through the base excision repair (BER) pathway. Miller and Michaels coined the term “GO” (for “Guanine Oxidation”) repair pathway of 8-oxoG in bacteria [63]. Later Hirano (2011) established a similar GO repair system in human cells, which involves three enzymes: 8-Oxoguanine DNA glycosylase 1 (OGG1), MutY homolog (MUTYH and MutT homolog 1 (MTH1). The GO repair system is a base excision repair (BER) pathway. OGG1 is a bifunctional glycosylase that recognizes 8-oxoG opposite to the cytosine base and catalyzes glycosidase activity to cleave N-glycosidic bonds to remove 8-oxoG, resulting in the formation of an abasic site [64,65]. Following lesion removal, OGG1 cuts the DNA phosphate backbone at the abasic site through its AP-lyase activity, yielding a 3’-phospho-α, β-unsaturated aldehyde (3’dRP) and a 5’-phosphate terminus. Since the 3’dRP terminus cannot serve as a primer, apurinic/apyrimidinic endonuclease 1 (APE1) removes it to generate a 3’-OH terminus, producing a single-nucleotide gap [66]. DNA polymerase β then inserts guanine base in the bare site, and DNA ligase completes the repair by sealing the nicks [66]. If 8-oxoG enters into DNA replication step, bypassing the OGG1 enzyme, it pairs with adenine. MUTYH, a mismatch repair enzyme, functions as the second line of defense. It eliminates the mispaired adenine by incision and restores the guanine base [67]. Thus, MUTYH is a unique glycosylase because it removes an undamaged base opposite a DNA lesion, rather than excising the damaged base itself. MutT homolog1 is another line of defense in the GO system and (also known as NUDT1) belongs to the phosphohydrolase superfamily of enzymes. It hydrolyzes 8-oxoG nucleoside triphosphates to monophosphates and removes them from the

nucleotide pool to prevent incorporation of damaged nucleotide into the genome [68]. Thus, the GO system prevents 8-oxoG from taking part in DNA synthesis.

**Table 1.** Types of DNA damage induced by alcohol consumption and their repair mechanisms

| Major cause | DNA damage type | Repair pathway |
|---|---|---|
| Acetaldehyde | N2-Et-dG adduct | No specific mechanism |
| Acetaldehyde | N2-propanoguanine adduct | Nucleotide excision repair (NER) |
| Acetaldehyde | DNA crosslink | Fanconi anemia (FA) pathway and Excision independent novel mechanism (Hodskinson et al) |
| Reactive oxygen species | 8-Oxoguanine | "GO repair" system (Base excision repair) involving OGG1, MUTYH and MTH1 enzymes |

## 7. Conclusions

Consumption of alcoholic beverages has become an inseparable part of modern life, often associated with social events, traditions, and recreational activities. Alcoholism imparts significant health implications, particularly in its capacity to induce DNA lesions and ultimately cancer. This review emphasized the role of four enzymes (ADH, Catalase, CYP2E1, and ALDH2) in alcohol metabolism in humans. Various studies have revealed that the breakdown of ethanol yields carcinogenic products like acetaldehyde, ROS, and RNS, thereby confirming ethanol as a procarcinogen. To understand the evil effect of ethanol byproducts on DNA, we explored alcohol-mediated DNA damage pathways. As a result, the present study describes three remarkable routes through which these toxic byproducts can damage DNA. Studies showed acetaldehyde and ROS generally attack guanine base, hence further studies are needed to understand their effect on adenine, cytosine and thymine bases also.

In addition to DNA damage, we also investigated the repair mechanisms of alcohol associated DNA lesions. Individuals are known to inherit some repair mechanism by which a cell can spontaneously detect and correct DNA lesions. This review discussed multiple repair pathways proposed in the literature, yet the repair of specific adducts such as N2-Ethyl-dG remains unclear. The persistence of such lesions could contribute to mutagenesis and cancer development. In summary, ethanol metabolism, DNA damage, and repair mechanisms interact to create a complex and important factor that determines the health risks associated with alcohol consumption. Further research on ethanol-mediated DNA damage and repair mechanisms would help to recognize an unexplored route.

## Multidisciplinary Domains

This research covers the domains: (a) Cancer Biology, (b) Biophysical Chemistry, and (c) Public health

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## Conflicts of Interest

The authors declare no conflict of interest.

## Declaration on AI Usage

This manuscript has been prepared without the use of AI tools.

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