

The Carcinogenicity of Acetaldehyde: A Systematic Review of Current Evidence, Mechanisms, and Experimental studies

Pragya ¹, Sindhu R^{2*}, M.S. Philomin Elgiva³, Prabu D⁴, Rajmohan M⁵, Dinesh Dhamodhar⁶, Lubna Fathima⁷.

¹Undergraduate (Bachelor of Dental Surgery), SRM Dental College, Ramapuram, Bharathi Salai, Chennai, TN, India

^{2,7}Master of Dental Surgery, Senior lecturer, Department of Public Health Dentistry, SRM Dental college, Bharathi salai, Chennai

³Postgraduate, Department of Public Health Dentistry, SRM Dental college, Ramapuram, Bharathi Salai, Chennai, TN, India.

⁴MDS, PhD Professor and head, Department of Public Health Dentistry, SRM Dental college, Ramapuram, Bharathi Salai, Chennai, TN, India.

^{4,5}Master of Dental Surgery, Reader, Department of Public Health Dentistry, SRM Dental college, Bharathi salai, Chennai

Corresponding Author: Sindhu R, Master of Dental Surgery, Senior lecturer, Department of Public Health Dentistry, SRM Dental college, Ramapuram, Bharathi Salai, Chennai, TN, India (researchphdsrm@gmail.com)

ABSTRACT

Background: Acetaldehyde (AA) is a highly reactive, low-molecular-weight compound and an established carcinogen that is generated as the first metabolite of ethanol metabolism. It is generated systemically during alcohol metabolism and locally by oral and gastrointestinal microorganisms and encountered through various environmental exposures.

Aim: To systematically review the available evidence regarding the carcinogenic potential of acetaldehyde, along with its mechanisms of carcinogenesis, sources of exposure and genetic susceptibility.

Methods: Relevant experimental, animal, and human studies investigating acetaldehyde exposure and carcinogenicity were identified and evaluated. Evidence concerning DNA damage, oxidative stress, mitochondrial injury, genetic polymorphisms, and alcohol- and tobacco-related exposure was synthesized.

Result: Experimental studies showed that Acetaldehyde induces DNA damage, oxidative stress, mitochondrial injury, and chromosomal abnormalities, with chronic exposure causing dose-dependent tumours in animals and humans. *ALDH22*, *ADH1B*, and *ADH1C* variants were associated with altered AA metabolism and increased cancer risk.

Conclusion: The evidence synthesized in this systematic review from findings from both in vitro and animal studies demonstrates that AA is a potent genotoxic and carcinogenic agent with well-established biological mechanisms underlying its carcinogenicity. It can be used in alcohol dependence therapy as AA reacts with disulfiram to produce a characteristic aversive disulfiram-ethanol reaction such as flushing, headache, nausea, vomiting, tachycardia, and hypotension that acts as a deterrent to drinking.

Key words: Acetaldehyde, carcinogen, group 1 carcinogen, alcohol metabolite, DNA adducts, genetic pleomorphism, alcohol dehydrogenase

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INTRODUCTION

Acetaldehyde (AA) is a highly reactive, low-molecular-weight compound generated through endogenous metabolism and encountered through various environmental exposures. Over 90% of alcohol consumed is metabolized in the liver, where alcohol dehydrogenase (ADH), cytochrome P450 2E1 (CYP2E1), and catalase are the main enzymes that convert ethanol to acetaldehyde. AA is then oxidized by aldehyde dehydrogenase (ALDH) to acetate, which enters the circulation and undergoes further metabolism in peripheral tissues, including skeletal muscle and the heart. ^(1,2)

Beyond systemic metabolism, acetaldehyde (AA) is also produced locally by microorganisms in the oral cavity and gastrointestinal tract, potentially prolonging mucosal exposure. ⁽³⁾ Although various oral microbes can convert ethanol to AA, their

ability to further degrade it is limited, leading to its accumulation in saliva after alcohol consumption. ⁽⁴⁾ Poor oral hygiene, heavy alcohol use, and chronic smoking may increase microbial AA production. Salivary AA can then be swallowed, exposing the pharynx, oesophagus, and stomach to this carcinogen. ⁽⁵⁾ Exogenous sources include tobacco smoke, industrial pollutants, and fermented food, resulting in widespread and continuous human exposure. ⁽⁶⁾

The carcinogenicity of AA has been extensively studied and is well established by major health organizations. The “International Agency for Research on Cancer (IARC)” classifies AA associated with alcohol consumption as a “**Group 1 carcinogen.**” ⁽⁷⁾ Epidemiological, genetic, biochemical and microbiological evidence has consistently supported this classification system

especially among individuals who consume alcohol and carry ADH and ALDH2 gene variants. In the presence of ethanol, these genetic alterations can increase AA exposure of the upper gastrointestinal mucosa. ⁽⁸⁾ Similarly, the National Toxicology Program has listed AA as “reasonably anticipated to be a human carcinogen.” ⁽⁹⁾

Nearly every tissue has ADH activity and there are seven isoenzymes for ADH of which ADH2 is found only in the liver and ADH4 in the upper gastrointestinal mucosa ⁽¹⁰⁾. Genetic polymorphisms in *ADH1B* and *ALDH2* provide evidence of AA’s carcinogenic potential. It has been reported that inactive *ALDH2* and less-active *ADH1B* genotypes increased the risk of oesophageal squamous cell carcinoma among East Asian drinkers. ⁽¹¹⁾ Similarly, it was found that impaired AA metabolism, particularly in *ALDH2* carriers, increased the risk of metachronous oesophageal carcinoma, whereas alcohol abstinence or reduction lowered this risk. ⁽¹²⁾ The *ALDH2* allele, present in approximately 40% of East Asians, reduces acetaldehyde detoxification, leading to higher salivary AA levels and a markedly increased risk of oesophageal cancer among drinkers. Similarly, the Caucasian *ADH1C1* allele enhances AA production and has 2–4-fold higher risk of upper aerodigestive tract, liver, and breast cancers among heavy alcohol consumers (>60 g/day ethanol) ⁽¹³⁾.

Experimental evidence strongly supports the carcinogenic potential of acetaldehyde (AA). In vitro studies have shown that AA can cause DNA damage by inducing DNA adduct formation, DNA–protein crosslinks, and chromosomal abnormalities. ^(14,15) Its genotoxicity is mediated partly through the formation of stable DNA adducts, including N²-ethyl-2'-deoxyguanosine (N²-Et-dG) and 1, N²-propanodeoxyguanosine (PdG), which may result in point mutations, sister chromatid exchanges, and chromosomal aberrations. ⁽¹⁶⁾

AA promotes carcinogenesis through multiple mechanisms, including DNA adduct formation, replication errors, and mutations ⁽¹⁴⁾, as well as oxidative stress and cellular injury. ⁽¹⁷⁾ It has been reported that AA induces oxidative stress in gastric epithelial cells through mitochondrial damage. ⁽¹⁸⁾ Impaired DNA repair and cell-cycle regulation may further promote genomic instability ⁽¹⁵⁾, while synergistic interactions with tobacco carcinogens can enhance cancer risk. ⁽⁶⁾ Additionally, *ADH1B* and *ALDH2* polymorphisms, combined with alcohol and tobacco exposure, may increase susceptibility to earlier-onset oesophageal squamous cell carcinoma (ESCC). ⁽¹⁹⁾

Animal studies further support the carcinogenicity of acetaldehyde, demonstrating dose-dependent tumour development, particularly in the respiratory and upper aerodigestive tract epithelium after prolonged exposure. ^(20,21)

Epidemiological data link AA to upper aerodigestive tract (UADT), oesophageal, colorectal, liver, and breast cancers, accounting for ~3.6% of global malignancies. Furthermore, AA is considered one of the major carcinogenic constituents of tobacco smoke. The gastrointestinal mucosa appears to be more exposed to numerous known risk factors including locally produced AA. In this process, oral and gastrointestinal microorganisms, salivary glands, and mucosal epithelial cells may play important roles in AA production and exposure. ⁽²²⁾

Genetic studies in alcohol users provide direct evidence linking acetaldehyde (AA) to alcohol-related carcinogenesis. Approximately 40% of Japanese, Korean, and Chinese individuals carry the heterozygous *ALDH2* allele, which encodes a poorly active ALDH2 enzyme and results in elevated AA levels even after consuming small amounts of alcohol. ⁽²³⁾

Despite extensive research there remains a gap in understanding the relationship between AA exposure and carcinogenicity due to variability in experimental modalities, difference in routes of exposure and concentration and inconsistencies in reported outcomes.

This systematic review aims to evaluate and integrate findings from multiple sources into one article to better elucidate the carcinogenic properties of AA.

Materials and method

This systematic review was carried out to evaluate the carcinogenic properties of AA, a ubiquitous ethanol metabolite that was established as a Group 1 human carcinogen per IARC criteria.

Search Strategy

A systematic search of the electronic database was conducted with the following search terms: (a) AA or CH₃COOH (b) neoplasm or cancer or DNA adduct (c) human or animal or in vitro.

Eligibility Criteria

Inclusion Criteria

Original articles

In vitro and in vivo studies

Studies evaluating carcinogenic properties of AA

Articles published in English

Exclusion Criteria

Review articles

Articles published in other languages

Duplicate publications

Unrelated articles

Databases and Search Engines used:

PubMed

Scopus

Google Scholar

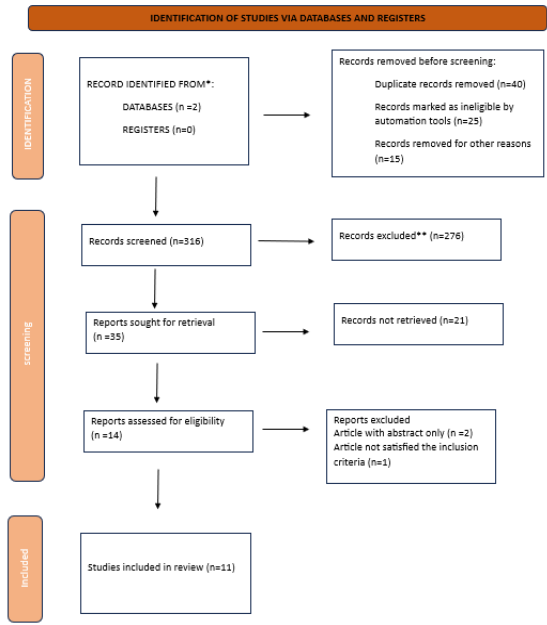
Research Gate

Wiley Online Library

science Direct

Figure: 1 Prisma Flowchart

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Result

The included studies comprise both in vitro and animal experimental investigations evaluating and assessing the various outcomes regarding the carcinogenic properties of AA.

Table 1: Characteristics of the study

S n o .	Auth or Name	Y ea r	Stud y Desi gn	Sample	Technique
1	N Homa nn et al ⁽²⁴⁾	19 97	Ani mal stud y	20 Wistar rats	Mean epithelial thickness was assessed using light microscop y with a calibrated eyepiece grid
2	M Muto ⁽²⁵⁾	20 00	Hum an stud y	31 head and neck cancer patients	Multiple oesophage al dysplasia was identified endoscopic ally as multiple LVL using the Lugol dye staining method. ADH3 and ALDH2 genotypes were determined using PCR- restriction fragment length polymorph ism.
3	Akira Yoko yama et al ⁽²⁶⁾	20 05	Hum an stud y	1535 Japanes e men of age 40-79 years with a history of alcohol consum ption	Endoscopi c examinatio n was performed along with iodine staining of the oesophagu s
4	Dirk W Lache nmeie r ⁽²⁷⁾	20 09	Hum an stud y	Human dietary exposur e to AA through alcoholi c beverag es	Lifetime cancer risk was estimated using T25 dose descriptor.
5	Ri Cu i et al ⁽²⁸⁾	20 09	Hum an stud y	1070 Japanes e patients with ESCC and 2836 controls	A two- stage genome- wide association study followed by replication analysis was

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HeLa; Henrietta Lacks cell line, EPC2-hTERT cells; Esophageal primary cells 2- human telomerase reverse transcriptase, Msh2-LS; MutS Homologue 2- Lynch Syndrome, PCR; Polymerase Chain Reaction

Table 1 summarizes the author's name, year of study, the sample used, biological sample applied and the experimental technique used, consisting of 3 animal studies, 5 human studies and 3 laboratory studies.

Table 2: Summary of intervention and outcome

S n o.	Author	Ye ar	Interventio n	Outcome
	N Homann et al ⁽²⁴⁾	1997	Rats were provided either drinking water supplemented with 120mM AA (or) Untreated tap water	AA exposure resulted in a statistically significant increase in epithelial thickness compared with controls at all three anatomical sites (p < 0.05).
	M Muto ⁽²⁵⁾	2000	ALDH2 genetic pleomorphism with ADH3 pleomorphism assessed as a comparator with alcohol exposure as a prerequisite	Multiple oesophageal dysplastic lesions were identified as multiple Lugol-voiding lesions during endoscopy. Genotyping demonstrated variations in the ADH3 and ALDH2 genes.
	Akira Yokoyama et al ⁽²⁶⁾	2005	1535 alcoholic Japanese men of age	Individuals carrying the inactive

			40-79 years with oesophageal melanosis	ALDH2*1 /2*2 genotype showed an approx. 2.66-fold increased risk of oesophageal melanosis and an elevated risk of dysplasia/intraepithelial lesions and squamous cell carcinoma
	Dirk W Lachenmeier ⁽²⁷⁾	2009	Life-time cancer risk was calculated using the T25 dose descriptor.	Alcoholic beverages were identified as an important source of human exposure to acetaldehyde
	Ri Cui et al ⁽²⁸⁾	2009	Identification of epidemiologic factors that influence the development of ESCC	Two established functional genetic variants involved in the metabolism of alcohol- and tobacco-derived compounds emerged as significant determinants of ESCC risk.
	Jessy Abraham et al ⁽²⁹⁾	2011	Ethanol 20 mM incubation with 4-methyl	Intracellular metabolism of ethanol to

			pyrazole (4-MP)	AA results was associated with DNA damage
	Bagnardi V et al. ⁽³⁰⁾	2014	572 studies, including 486 538 cancer cases	Alcohol consumption was associated with increased risk of cancer of oral cavity and pharynx, oesophagus, colorectum, liver, larynx and female breast
	Yusuke Amanuma et al. ⁽³¹⁾	2015	EPC2-hTERT cells	Acetaldehyde exposure produced DNA adduct formation in a dose-dependent manner
	Hatanaka R, et al. ⁽³²⁾	2021	incubated with 0.01, 0.05, 0.1% of AA	The extent of malignant transformation showed a tendency to increase progressively with both acetaldehyde concentration and duration of exposure.
	Guia Cerretelli, Et al. ⁽³³⁾	2023	Treated with either 20% ethanol or water. Conditional or constitutive	Aldh1b1 inactivation in the ethanol-exposed model was associated with approxima

			inactivation of <i>Aldh1b1</i>	tely a 2.5-fold increase in the occurrence of clonal tumours.
	Chen Y, et al. ⁽³⁴⁾	2025	Human melanoma xenografts in immunodeficient mice	ALDH2 deficiency altered acetaldehyde-related cellular responses and was associated with changes in tumour-related outcomes in the xenograft mode

ESCC; Oesophageal Squamous Cell Carcinoma, EPC2-hTERT cells; Esophageal primary cells 2-human telomerase reverse transcriptase, ALDH; Aldehyde Dehydrogenase

Table 2 Outlines the key intervention and the outcome thus drawn from each study. Overall, the findings suggest that AA exposure and genetic polymorphisms in alcohol-metabolizing enzymes may contribute to epithelial alterations.

Table 3: Risk of Bias

Abraham et al., 2011	 Unclear	 Low	 Low	 Unclear	 Unclear	 Mode rate
Lachenmeier et al., 2009	 Unclear	 Mode rate	 Mode rate	 Mode rate	 Unclear	 Mode rate
Cerretelli et al., 2023	 Unclear	 Low	 Low–moderate	 Unclear	 Unclear	 Mode rate
Amanuma et al., 2015	 Unclear	 Low	 Low	 Unclear	 Unclear	 Low–moderate
Hatanaka et al., 2021	 Unclear	 Low–moderate	 Low	 Unclear	 Unclear	 Mode rate

Chen et al., 2025	 Unclear	 Low-moderate	 Low	 Unclear	 Unclear	 Mode rate
Bagnardi et al., 2014/2015	 Mode rate	 Mode rate	 Low-moderate	 Mode rate	 Unclear	 Mode rate
Homann et al., 1997	 Unclear	 Mode rate	 Low	 Unclear	 Unclear	 Mode rate
Yokoyama et al., 2005	 Mode rate	 Mode rate	 Low-moderate	 Mode rate	 Unclear	 Mode rate
Cui et al., 2009	 Mode rate	 Mode rate	 Low-moderate	 Mode rate	 Unclear	 Mode rate
Muto et al., 2000	 Mode rate	 Mode rate	 Low-moderate	 Mode rate	 Unclear	 Mode rate

Risk of bias was systematically assessed across the included studies using the OHAT, considering study selection, randomization, blinding, outcome measurement, and reporting bias. [Table 3]

 **Low**
 **Moderate** / **some concerns**
 **High risk**
 **Unclear risk**

Discussion

This systematic review evaluated the available in vitro and animal evidence regarding the carcinogenic properties of AA. The findings consistently demonstrate that AA possesses significant genotoxic and carcinogenic potential due to DNA adduct formation, chromosomal damage, oxidative stress, and impairment of DNA repair mechanisms.

One of the most consistent findings was the ability of AA to induce DNA damage. Brooks and Theruvathu (2005) reported that AA forms stable DNA adducts, particularly N2-ethylidene-deoxyguanosine adducts, which can lead to replication errors and mutations if left unrepaired, highlighting that DNA adduct formation is crucial in initiating AA-mediated carcinogenesis.^[23] Its mutagenic property was furtherer stated by Kayani and Parry (2010) who demonstrated that AA induces

chromosomal aberrations, micronucleus formation, and other genotoxic effects in vitro.⁽¹⁵⁾

The carcinogenicity observed in cellular studies is reinforced by evidence from animal experiments. In a landmark inhalation study, Woutersen et al. (1986) exposed rats to varying concentrations of AA and observed a dose-dependent increase in nasal epithelial tumour.⁽²⁰⁾ Proving that chronic AA exposure can induce malignant transformation in vivo. Furthermore, Morris (1997) evaluated the dosimetry and carcinogenicity of inhaled AA and demonstrated a clear relationship between exposure levels and tumour incidence, strengthening the evidence for a dose-response association.⁽³⁵⁾

The mechanisms underlying AA-induced carcinogenesis appear to be multifactorial. According to Seitz and Stickel (2007), AA is the principal carcinogenic metabolite of ethanol and contributes to carcinogenesis through direct DNA damage, disruption of DNA methylation, interference with DNA repair pathways, and induction of oxidative stress. Their review emphasized that AA acts at multiple stages of carcinogenesis, increasing the likelihood of malignant transformation.^[1] Ohashi et al. (2017) described how AA promotes genomic instability through DNA crosslink formation and impaired cellular repair mechanisms, particularly in squamous epithelial tissues.⁽³⁶⁾

Another important aspect highlighted by this article is the role of endogenous AA production. Homann et al. (2000) demonstrated that oral microorganisms can produce substantial amounts of AA from ethanol, resulting in elevated salivary AA concentrations among smokers and heavy alcohol consumers. The synergistic interaction between AA and tobacco-derived carcinogens may further enhance cancer risk in susceptible individuals.⁽³⁷⁾

Public health implications of AA exposure have also been discussed. Lachenmeier, Kanteres, and Rehm (2009) emphasized that AA is not only formed metabolically but is also present in alcoholic beverages. Hence highlighted the importance of considering both endogenous and exogenous AA exposure when evaluating alcohol-related cancer risk.⁽³⁸⁾

This study by Keisuke Hori et al (2023) demonstrates that alcohol-associated field cancerization may be reversible, suggesting that cessation or reduction of alcohol consumption can help prevent the development of multiple squamous dysplastic lesions, as well as metachronous “oesophageal squamous cell carcinoma (ESCC)” and “head and neck squamous cell carcinoma (HNSCC)”.⁽³⁹⁾

Priyadarshini et al stated Skeleton with diverse associated biological activities, including anti-inflammatory, antidiabetic, hepatoprotective, immunomodulatory, and, most importantly,

anticancer properties. Its remarkable bioavailability, minimal toxicity, and capability to influence diverse molecular processes render it a compelling subject for research in cancer studies. ⁽⁴⁰⁾

Acetaldehyde is not used as a therapeutic drug, because of its toxicity and reactivity, but it has pharmacological relevance in the treatment of alcohol dependence. Disulfiram inhibits aldehyde dehydrogenase, leading to accumulation of acetaldehyde after ethanol ingestion and the characteristic aversive disulfiram–ethanol reaction such as flushing, headache, nausea, vomiting, tachycardia, and hypotension that acts as a deterrent to drinking. ⁽⁴¹⁾

Despite substantial evidence that AA is carcinogenic, there exists a gap within the existing literature. Considerable heterogeneity exists among studies regarding exposure concentrations, duration of exposure, experimental models, and outcome measures. Many in vitro studies employed concentrations higher than those typically encountered in human tissues.

Investigations should focus on establishing standardized experimental protocols and physiologically relevant exposure models. In addition, species-specific differences in metabolism and detoxification pathways may influence the applicability of animal findings to human populations. Research is needed to identify reliable biomarkers of AA exposure, clarify low-dose dose-response relationships, and investigate the influence of genetic factors on individual susceptibility. Understanding these factors may lead to better risk assessment and targeted preventive strategies.

Conclusion

In conclusion, the evidence synthesized in this systematic review from both in vitro and animal studies demonstrates that AA is a potent genotoxic and carcinogenic agent with well-established biological mechanisms underlying its carcinogenicity. It also highlights that exposure to AA may also arise from tobacco smoke, environmental sources and endogenous production by oral and gastrointestinal microorganisms. Future research should focus on standardized experimental protocols, clinically relevant exposure models, identification of reliable biomarkers of AA-induced DNA damage, and evaluation of genetic susceptibility factors.

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