CARCINOGENIC POTENTIAL OF *ALOE VERA*: A COMPREHENSIVE REVIEWJayarama Reddy*, Tejas Nanjegowda, Nihal Mandanna, Anurag Kullu, Nishant Tigga, B. Ashish Rahul,
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ABSTRACT

This review paper provides a comprehensive overview of the potential carcinogenic properties of *Aloe vera* (*Aloe barbadensis* Miller), a plant widely used in alternative medicine, cosmetics, and food supplements. While *Aloe vera* is recognized for its diverse health benefits, concerns exist regarding its safety profile, particularly the potential carcinogenic effects of its anthraquinone compounds. This paper synthesizes evidence from scientific studies on the toxicity, genotoxicity, and carcinogenicity of *Aloe vera*, focusing on its chemical composition, mechanisms of carcinogenesis, and regulatory considerations. It aims to provide a balanced assessment of the risks and benefits associated with *Aloe vera* use, informing both consumers and healthcare professionals.

KEYWORDS: This review paper provides a comprehensive overview of the potential carcinogenic properties of *Aloe vera* (*Aloe barbadensis* Miller), a plant widely used in alternative medicine, cosmetics, and food supplements.

INTRODUCTION

Aloe vera Overview

Aloe vera is a succulent plant belonging to the Asphodelaceae family, renowned for its medicinal, cosmetic, and nutritional benefits. Its thick, gel-filled leaves have been a source of therapeutic compounds for millennia. The plant is native to the Arabian Peninsula but is now cultivated globally. *Aloe vera* is rich in polysaccharides, vitamins, enzymes, and amino acids, contributing to its diverse applications. Historically used in traditional medicine for its anti-inflammatory, wound-healing, and digestive benefits, *Aloe vera* is increasingly found in skincare products, beverages, and dietary supplements. The versatility of *Aloe vera* has led to its integration into a wide array of consumer products, reflecting its perceived health benefits.

Fig-1: *Aloe vera* Plant.

Importance of Investigating Carcinogenic Potential

Despite its long-standing use, there is growing concern regarding the safety of *Aloe vera*, especially when consumed in large quantities or applied topically. This concern is fueled by studies suggesting that certain compounds within the plant might pose health risks. The rise in popularity of *Aloe vera*-based products necessitates a thorough evaluation of their safety profile.^[2]

Certain constituents in *Aloe vera*, including aloin, anthraquinones, and other bioactive compounds, have been suggested to have carcinogenic potential. Understanding the risks is crucial to ensure consumer safety. While the gel is often considered safe, the latex, which contains higher concentrations of aloin and anthraquinones, is the primary source of concern. Improper processing or excessive consumption of *Aloe vera* products containing latex could potentially lead to adverse health effects.^[3]



Fig-2: Aloe vera gel oozing out of the leaf.

OBJECTIVE OF THE REVIEW

This paper reviews the evidence surrounding the potential carcinogenic properties of *Aloe vera*, analyzing studies related to both oral and topical usage, and explores the molecular mechanisms implicated in potential carcinogenesis. It's critical to differentiate between the effects of *Aloe vera* gel, latex, and whole-leaf extracts, as their compositions and potential risks vary.

The goal is to provide a balanced assessment of the potential risks and benefits associated with *Aloe vera* use, informing both consumers and healthcare professionals. By synthesizing existing research, this review aims to identify areas of uncertainty and guide future investigations to further elucidate the safety profile of this widely used plant.^[4]

Chemical Composition of *Aloe vera*

Active Compounds in *Aloe vera*

Aloe vera contains a variety of bioactive compounds such as polysaccharides (e.g., acemannan), vitamins (A, C, E), minerals (calcium, magnesium), amino acids, fatty acids, and enzymes (e.g., bradykinase). These compounds contribute to its diverse pharmacological properties. Polysaccharides, particularly acemannan, are

known for their immunomodulatory and wound-healing effects. Vitamins A, C, and E act as antioxidants, protecting cells from damage caused by free radicals. Minerals such as calcium and magnesium are essential for various physiological processes. Amino acids are the building blocks of proteins and contribute to tissue repair and regeneration. Enzymes like bradykinase have anti-inflammatory properties. Fatty acids contribute to the moisturizing effects of *Aloe vera*.

Anthraquinones, including aloin, emodin, and aloemodin, are important compounds of concern due to their potential toxicity and carcinogenicity. These compounds are primarily found in the latex of the plant, the yellowish sap located just beneath the outer rind. The concentration of anthraquinones can vary depending on the *Aloe vera* species, growing conditions, and processing methods. While these compounds have historically been used for their laxative properties, their potential adverse effects have raised concerns about their safety.^[5]



Fig-3: Aloe vera gel extracted.

Table 1: Phytochemical Constituents of *Aloe vera* and Their Applications.

Sl No.	Tentative Identification	Uses
1	Aloesin or aloeresin B	Skin lightening, anti-inflammatory, and antioxidant properties
2	Chlorogenic acid	Antioxidant, weight management, and blood sugar regulation
3	Caffeic acid	Antioxidant, antimicrobial, and anti-inflammatory agent
4	Aloe emodin-diglucoside	Laxative, antimicrobial, and potential anticancer properties
5	Isoquercitrin	Antioxidant, cardiovascular protection, and anti-inflammatory effects
6	Kaempferol-3-O-hexosyl-O-pentoside	Antioxidant, neuroprotective, and anticancer activities
7	6-Methyl-1,3,8-trihydroxyanthraquinone	Laxative, antimicrobial, and anti-inflammatory properties
8	Luteolin-8-C-glucoside (orientin)	Antioxidant, neuroprotective, and anti-inflammatory effects
9	Feruloylquinic acid	Antioxidant, neuroprotective, and skin-protective properties

10	10-Hydroxyaloin A	Laxative, skin healing, and anti-inflammatory properties
11	Isovitexin	Antioxidant, neuroprotective, and anti-inflammatory effects
12	Chrysoeriol-7-O-glucuronide	Antioxidant, anti-inflammatory, and cardiovascular benefits
13	Caffeoyl ester of aloesin	Antioxidant and skin-brightening properties
14	Alain A	Laxative, antimicrobial, and skin-repairing properties
15	Isoaloeresin D	Antioxidant and skin-protective effects
16	2'-p-Methoxycoumaroylaloeresin B	Anti-inflammatory and skin-brightening properties
17	4,5-Dimethyl ether of Aloe emodin	Laxative, antimicrobial, and potential anticancer properties
18	Alain B	Laxative, skin-repairing, and antimicrobial effects
19	6'-Malonylnataloin	Antioxidant and wound-healing properties
20	Naringenin-4'-methoxy-7-O-glucuronide	Anti-inflammatory, cardiovascular benefits, and skin protection
21	7-Methylether of 2'-feruloylaloerin	Antioxidant and skin-brightening properties
22	Aloe emodin-8-O-glucoside	Laxative, antimicrobial, and anticancer potential
23	5,3'-Dihydroxy-6,7,4'-trimethoxyflavone	Antioxidant and anti-inflammatory properties
24	Trihydroxy octadecenoic acid	Skin moisturizing and wound-healing effects
25	3,4-Di-O-caffeoylquinic acid	Antioxidant, neuroprotective, and anti-inflammatory benefits

Focus on Carcinogenic Compounds

Alain: A major anthraquinone compound present in the latex (the yellowish sap) of *Aloe vera*. Studies have shown that alain, when ingested in large amounts, may lead to carcinogenic effects, particularly in rodent models. Alain is a glycoside that is metabolized in the gut to release aloe-emodin, which is believed to be the active compound responsible for its laxative and potentially carcinogenic effects. The mechanism of action involves stimulating intestinal motility and increasing water secretion into the colon. However, chronic exposure to alain has been linked to the development of colorectal tumors in animal studies.^[6]

Emodin and Aloe-Emodin: Other anthraquinones present in the gel and latex, which have been studied for their mutagenic and genotoxic properties. Emodin and aloe-emodin are structurally similar to alain and share some of its biological activities. However, their potency and potential for toxicity may differ. Studies have shown that these compounds can induce DNA damage and mutations in vitro, raising concerns about their potential to contribute to carcinogenesis. Further research is needed to fully understand the role of emodin and aloe-emodin in the carcinogenic process.^[7]

Mechanisms of Carcinogenicity

Genotoxicity and Mutagenicity

Evidence from animal studies suggests that anthraquinones, particularly alain, may cause DNA damage and mutations that could lead to cancer formation. This section explores how alain may interact with DNA and promote tumorigenesis. Alain can undergo metabolic activation to form reactive metabolites that can bind to DNA, forming DNA adducts. These DNA adducts can interfere with DNA replication and repair processes, leading to mutations. If

these mutations occur in genes that control cell growth and differentiation, it can lead to uncontrolled cell proliferation and cancer development.

A study using the mouse lymphoma assay demonstrated that both whole and decolorized *Aloe vera* extracts exhibited concentration-dependent cytotoxicity and mutagenicity, with the whole extract showing a positive response at lower concentrations than the decolorized extract.^[8]

Oxidative Stress

Anthraquinones have been shown to generate reactive oxygen species (ROS) that induce oxidative stress, leading to cellular damage. Chronic oxidative stress can result in mutations, inflammation, and the promotion of cancerous growth. ROS can damage cellular components such as DNA, proteins, and lipids. This damage can disrupt normal cellular function and contribute to the development of various diseases, including cancer. The antioxidant properties of some *Aloe vera* compounds might offer some counteraction, but the pro-oxidant effects of anthraquinones, particularly in high concentrations, remain a concern.^[9]

Hormonal Modulation

Some studies have raised concerns that *Aloe vera* might influence hormonal balance, especially estrogen levels, potentially promoting hormone-related cancers such as breast and ovarian cancer. Certain compounds in *Aloe vera* may interact with estrogen receptors, either mimicking or blocking the effects of estrogen. This can disrupt the normal hormonal balance in the body and potentially promote the growth of hormone-sensitive tumors. More research is needed to fully understand the effects of *Aloe vera* on hormonal regulation and the potential implications for hormone-related cancers.^[10]

Inhibition of Tumor Suppressor Genes

Certain compounds in *Aloe vera* may interfere with tumor suppressor genes, leading to uncontrolled cell division and cancer progression. Tumor suppressor genes play a crucial role in regulating cell growth and preventing the formation of tumors. If these genes are inactivated or suppressed, it can lead to uncontrolled cell proliferation and cancer development. Some studies have suggested that certain *Aloe vera* compounds may

interfere with the expression or function of tumor suppressor genes, contributing to the carcinogenic process.^[11]

Carcinogenicity in Animal Models

Rodent Studies

Numerous animal studies, particularly in rodents, have been conducted to assess the carcinogenic potential of *Aloe vera*. These studies suggest.

Mechanisms of Carcinogenicity in Aloe Vera

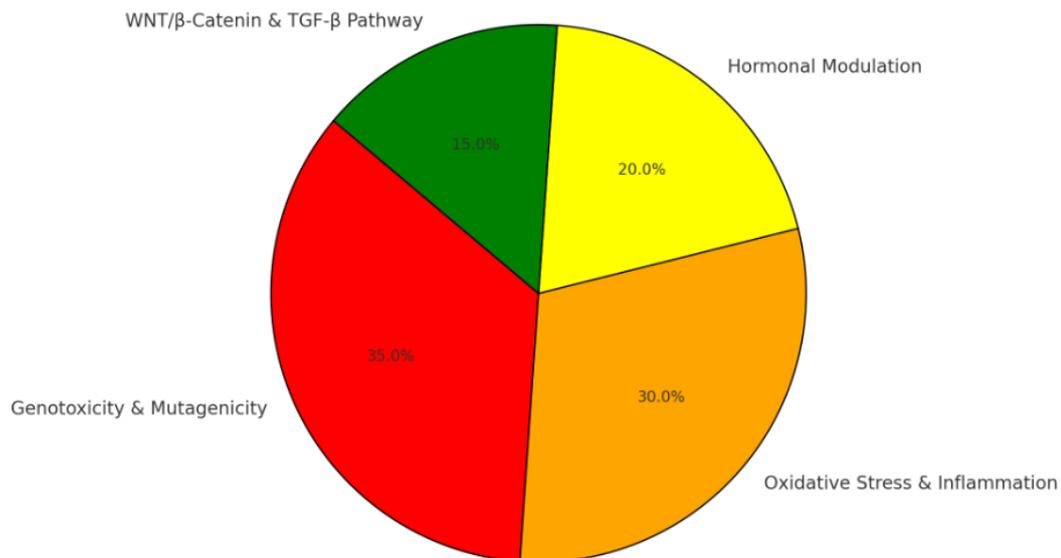


Fig-4: Mechanisms Of Carcinogenicity In *Aloe vera*.

That prolonged exposure to high doses of *Aloe vera* or its compounds, especially aloin, may lead to the development of cancers in the gastrointestinal system, liver, and other organs. Rodents are commonly used in carcinogenicity studies due to their relatively short lifespan and well-characterized physiology. These studies typically involve exposing animals to different doses of the test substance over an extended period and monitoring them for the development of tumors or other adverse health effects.

For example, a study on rats found that long-term consumption of *Aloe vera* latex induced colorectal tumors. This study provided significant evidence for the potential carcinogenic effects of aloin and raised concerns about the safety of consuming *Aloe vera* products containing latex₁. The National Toxicology Program (NTP) Technical Report 577 described clear evidence of carcinogenic activity in F344/N rats after oral administration of *Aloe vera* whole leaf extract.^[12]

Histopathological Findings

Examination of tissues from treated animals has shown signs of inflammation, dysplasia, and cellular atypia,

which are early indicators of carcinogenesis. Histopathological analysis involves examining tissue samples under a microscope to identify any abnormalities or signs of disease. In the context of carcinogenicity studies, histopathological findings can provide valuable information about the mechanisms by which a substance may promote cancer development. Inflammation, dysplasia, and cellular atypia are all signs of abnormal cell growth and can indicate an increased risk of cancer.^[13]

Dose-Response Relationship

A critical aspect of these studies is the dose-response relationship between *Aloe vera* consumption and the development of cancer. While lower doses may not produce observable effects, higher doses or chronic exposure appear to increase the risk of cancer. The dose-response relationship is a fundamental principle in toxicology and pharmacology. It describes the relationship between the dose of a substance and the magnitude of its effect. In the context of carcinogenicity, the dose-response relationship can help determine the threshold dose at which a substance begins to exhibit carcinogenic effects.^[14]

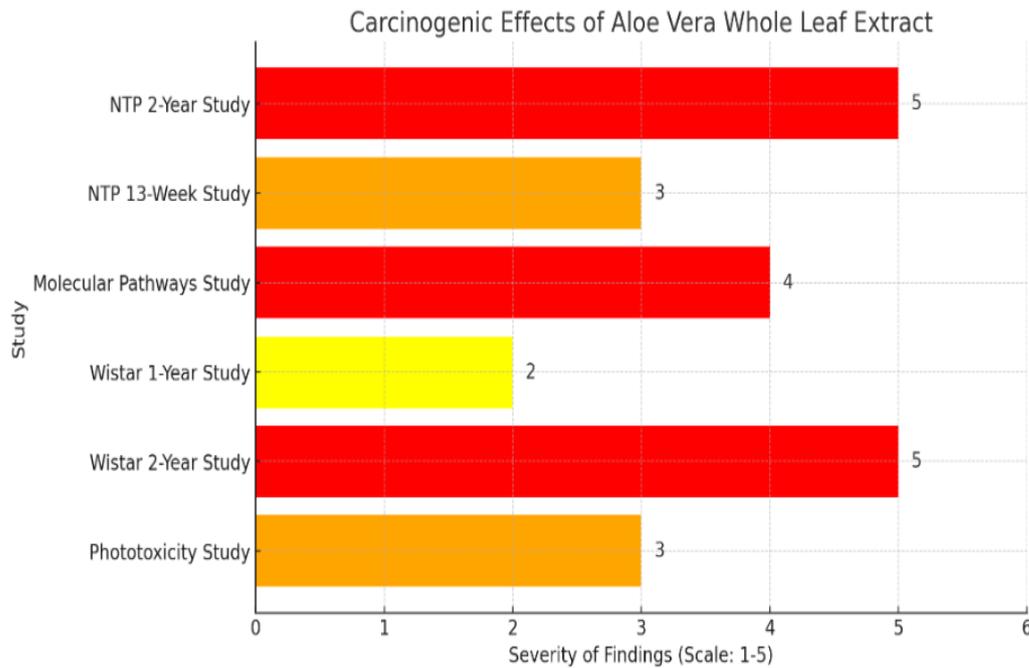


Fig-5: Carcinogenic Effects Of *Aloe Vera* Whole Leaf Extract.

Carcinogenicity in Human Studies

Human Epidemiological Evidence

Although studies in humans are limited, there is evidence that suggests *Aloe vera*, particularly in unprocessed forms or in high concentrations, may have carcinogenic effects. This section discusses the challenges in conducting human studies and the limited data available. Human epidemiological studies are essential for assessing the potential health effects of substances to which humans are exposed. However, conducting such studies can be challenging due to various factors, including the difficulty in controlling for confounding variables, the long latency period for cancer development, and the ethical considerations involved in exposing humans to potentially harmful substances.^[15]

CASE REPORTS

Some case reports have linked the consumption of *Aloe vera* supplements or the use of *Aloe vera* latex in traditional medicine with adverse health effects, including gastrointestinal problems, liver toxicity, and potential links to cancers. Case reports are anecdotal accounts of individual patients who have experienced adverse health effects following exposure to a particular substance. While case reports cannot prove causation, they can provide valuable clues about potential health risks and can prompt further investigation.^[16]

Regulatory Stance on *Aloe vera* Consumption

Organizations such as the U.S. Food and Drug Administration (FDA) and the European Food Safety Authority (EFSA) have raised concerns about the use of *Aloe vera* latex in food products. The FDA has warned against the use of *Aloe vera* as a laxative due to its potential harmful effects. Regulatory agencies play a

crucial role in protecting public health by evaluating the safety of food additives, drugs, and other consumer products. The FDA and EFSA have both raised concerns about the potential health risks associated with the consumption of *Aloe vera* latex and have issued warnings and regulations to limit its use in food products.^[17]

Regulatory and Safety Considerations

FDA and International Regulations

The FDA has issued warnings about the potential carcinogenicity of *Aloe vera* latex in over-the-counter laxatives. *Aloe vera* gel is generally regarded as safe (GRAS) for topical use but not for internal use in large quantities. Regulations regarding the use of *Aloe vera* vary depending on the product and its intended use. Topical products containing *Aloe vera* gel are generally considered safe, while products containing *Aloe vera* latex are subject to stricter regulations due to their potential toxicity.

Aloe vera whole leaf extract has been classified by the International Agency for Research on Cancer (IARC) as a possible human carcinogen.^[18]

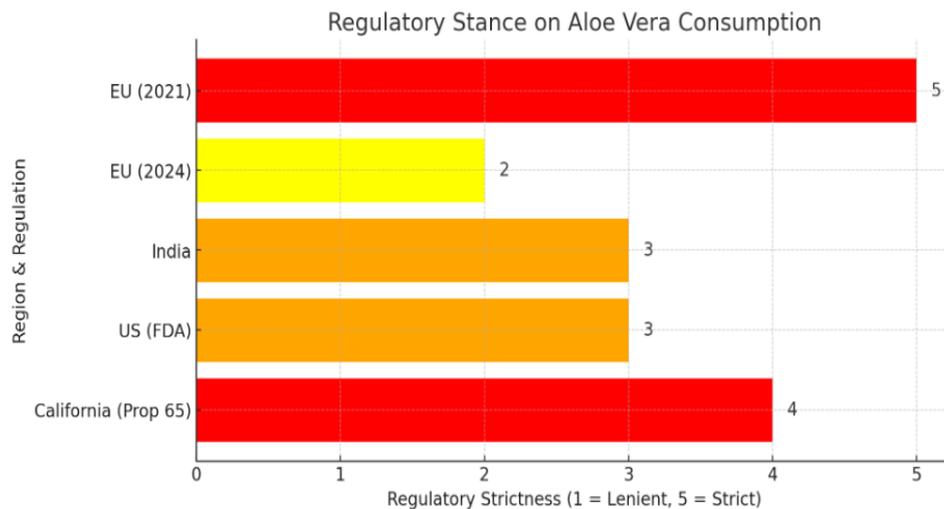


Fig-6: Regulatory Stance on *Aloe vera* Consumption.

Safety Standards for *Aloe vera* Products

The safety of *Aloe vera* products, especially those consumed orally, varies by formulation. *Aloe vera* gel and juices must be processed to remove aloin and other potentially harmful compounds. Processing methods can significantly affect the safety of *Aloe vera* products. Proper processing can remove aloin and other anthraquinones, reducing the risk of adverse health effects. However, improper processing can leave traces of these compounds, potentially increasing the risk of toxicity.^[19]

Recommendations for Consumer Use

This section discusses current recommendations for safe usage, including the need for proper processing to eliminate toxic compounds and the advisability of avoiding high-dose *Aloe vera* products without medical supervision. Consumers should be aware of the potential risks associated with consuming *Aloe vera* products, particularly those containing latex. It is important to choose products that have been properly processed to remove aloin and other potentially harmful compounds. Consumers should also avoid consuming high-dose *Aloe vera* products without medical supervision.^[20]

Potential Benefits of *Aloe vera*

Therapeutic Uses

Despite the concerns about its carcinogenic potential, *Aloe vera* also has many well-documented therapeutic benefits, including its use in wound healing, skin care, anti-inflammatory effects, and digestive health. *Aloe vera* has been used for centuries to treat a wide range of ailments. Its wound-healing properties are attributed to its ability to promote collagen synthesis and accelerate tissue regeneration. Its anti-inflammatory effects are due to the presence of compounds that inhibit the production of inflammatory mediators. Its digestive health benefits are attributed to its ability to soothe the digestive tract and promote the growth of beneficial bacteria.

Balanced Perspective

The review stresses the importance of considering both the beneficial and harmful aspects of *Aloe vera* use. For most individuals, topical application of *Aloe vera* is safe, and the gel may offer relief for skin conditions. However, caution should be exercised when consuming *Aloe vera* orally, particularly unprocessed forms. It is important to weigh the potential benefits of *Aloe vera* against the potential risks. While topical application of *Aloe vera* gel is generally considered safe, oral consumption of *Aloe vera* products should be approached with caution, particularly if the products contain latex or have not been properly processed to remove aloin and other potentially harmful compounds.^[22]

CONCLUSION

This review highlights the complex nature of *Aloe vera*, balancing its therapeutic benefits with the potential risks associated with its anthraquinone compounds. While *Aloe vera* gel is generally safe for topical use, caution is advised when consuming *Aloe vera* products orally, especially those containing latex. Future research should focus on clarifying the safety profile of *Aloe vera* and developing safer products for consumer use. Regulatory bodies must continue to monitor and update guidelines to protect public health.

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