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Aloe vera: A review of toxicity and adverse clinical effects

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Abstract

The Aloe plant is employed as a dietary supplement in a variety of foods and as an ingredient in cosmetic products. The widespread human exposure and its potential toxic and carcinogenic activities raise safety concerns. Chemical analysis reveals that the Aloe plant contains various polysaccharides and phenolic chemicals, notably anthraquinones. Ingestion of Aloe preparations is associated with diarrhea, hypokalemia, pseudomelanosis coli, kidney failure, as well as phototoxicity and hypersensitive reactions. Recently, *Aloe vera* whole leaf extract showed clear evidence of carcinogenic activity in rats, and was classified by the International Agency for Research on Cancer as a possible human carcinogen (Group 2B). This review presents updated information on the toxicological effects, including the cytotoxicity, genotoxicity, carcinogenicity, and adverse clinical effects of *Aloe vera* whole leaf extract, gel, and latex.

Keywords

Aloe gel; aloe latex; *Aloe vera*; carcinogenicity; genotoxicity; toxicological effects

1. Introduction

The use of herbal products has been growing rapidly in the general population. In 2007, the National Health Interview Survey reported that approximately 40% of Americans, including adults and children, used complementary and alternative medicine as alternative therapy in the past 12 months.[1] About US $14.8 billion was spent on the purchase of nonvitamin, nonmineral natural products, which accounted for 44% of all out-of-pocket costs for complementary and alternative medicine.[2] Aloe has enjoyed a long history of providing a myriad of health benefits, and is one of the most frequently used herbal remedies employed throughout the world. There are more than 400 species of Aloe, but the most popular and widely used species is *Aloe barbadensis* Miller (also called *Aloe vera* Linne, commonly referred to *Aloe vera). Aloe* is derived from the Arabic word *alloeh* meaning “bitter and shiny substance,” and *vera* from the Latin word for “truth.” Other species used in health and medicine include but are not limited to *Aloe arborescens* Miller (a member of the *asphodelacea* family), *Aloeperryi* Baker, *Aloe andongensis,* and *Aloe ferox*.[3,4]

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Aloe vera, a genus within the Liliaceae family, is a stemless or very short-stemmed perennial succulent or xerophyte with elongated and peaked leaves in which large amounts of water are stored in the tissue.[5] The green fleshy leaves range in height from a few centimeters to 2-3 meters or more and have three identifiable layers. The outer layer is a thick cuticle or rind accounting for about 20%−30% by weight of the whole plant leaf. It consists of upto 18 layers of cells interspersed with chloroplasts where carbohydrates, fats, and proteins are synthesized. The outer leaf pulp, a thin, mucilaginous layer just beneath and adjacent to the thick rind, contains vascular bundles acting as the transport system for the plants. Three types of tubular structures compose the vascular bundles: xylem, which moves water and minerals from the roots to the leaves; phloem, which takes synthesized minerals to the roots; and the pericyclic tubule, which stores and transports bitter yellow latex (often referred to as Aloe sap) along the margin of the leaf. The number of these bundles varies based on the size of leaves.[6] The inner leaf pulp makes up the majority of the plant by volume, and is composed of large thin-walled parenchymal cells containing *Aloe vera* gel, a synonym to inner leaf, inner leaf fillet, or fillet.

Aloe contains pharmacologically active ingredients associated with diverse biological activities including fungicidal, antiviral, antibacterial, anti-inflammatory, antimicrobial, laxative, immunomodulating, and anticancer effects.[3] *Aloe vera,* known as the “plant of immortality” in early Egypt, has been used as a traditional medicine in Arab, Chinese, Egyptian, Greek, Indian, Japanese, Korean, and Roman cultures[7,8] for more than 2000 years to empirically treat a broad list of disorders and ailments, such as skin problems (wounds, x-ray and radium burns, and psoriasis), constipation, external and internal ulcers, hyperlipidemia, diabetes, and lupus erythematosus.[9-12] Due to the numerous purported beneficial effects, *Aloe vera* production has been an emerging industry for making laxative drugs, cosmetics, and functional food, such as face and hand creams, foundations, cleansers, lipsticks, suntan lotions, shampoos and hair tonics, shaving preparations, bath aids, makeup and fragrance preparations, baby lotions and wipes, yogurt, drinks, capsules, and tablets. In order to show current pharmacological and/or toxicological research status on Aloe, we performed a literature search in PubMed using “Aloe” and specific country names as key words (Table 1). A total of 1895 and 975 publications were identified when using “Aloe” as key word in All Fields Not Author and MeSH term databases, respectively. More than half (51%−60%) of these studies were conducted in the top 10 countries (Table 1), and about one third of them are from five Asian countries, including China, India, Japan, Korea, and Iran. However, only about 8% of these articles investigated Aloe-related toxicity in vitro and in vivo (Table 1).

Although *Aloe vera* has long been considered as a safe functional food material that can be used orally and topically,[13] on many occasions it has not been as safe as commonly thought. Recently, the reported adverse effects in humans and toxicity, genotoxicity, and carcinogenicity in both in vitro and in vivo studies raise questions as to whether the components in *Aloe vera* may have tumor-promoting activities in humans. Due to its widespread human exposure and concerns that some components may cause cancer, in 1998 the National Cancer Institute nominated *Aloe vera* as a high-priority candidate for a carcinogenicity study under the National Toxicology Program (NTP). In 2002, the US Food

and Drug Administration (FDA) issued a final rule stating that use of Aloe as a nonprescription laxative drug is no longer generally recognized as safe and effective.[14] Recently, *Aloe vera* whole leaf extract has been classified by the International Agency for Research on Cancer as a possible human carcinogen (Group 2B), along with other natural products such as *Ginkgo biloba* extract and kava extract.[15,16]

The *Aloe vera* whole leaf extract, as well as the two primary components (the gel and the latex or exudates) of the leaf, have been used for various reasons in traditional medicine. Generally, the gel is used topically to soothe wounds, burns, and skin irritations, and the latex is recognized to possess cathartic effects. Nevertheless, there is still some confusion surrounding the whole leaf extract, the gel, and the latex. Given that the beneficial properties of *Aloe vera* have been addressed comprehensively and that the gel and the latex possess distinct components and medical purposes,[5] in this article, the whole leaf extract, the gel, and the latex associated toxicity, genotoxicity, and carcinogenicity both in vitro and in vivo are reviewed, and adverse clinical effects in humans are also summarized.

2. *Aloe vera* whole leaf extract

2.1 Components

Aloe vera whole leaf extract, including the gel and the latex, contains more than 200 chemical substances.[4] The raw Aloe leaf is composed of approximately 98.5% water, the remaining solid material contains a range of compounds including nutrients (e.g., carbohydrates, amino acids, vitamins, and minerals) and non-nutrients (e.g., organic acids, lignins, phenolic compounds, anthraquinones, and phytosterols). The chemical composition and the potency of the various constituents are influenced by many factors, such as species/subspecies, climate, land and irrigation, cultivation methods, harvesting, extraction processing, and storage conditions.[4,5]

To determine whether the presence of the latex alters the physical and chemical properties in whole leaf extract, the decolorized *Aloe vera* whole leaf has been studied for its toxicity and potential carcinogenicity. The decolorized extract was prepared by activated carbon-adsorption of the whole leaf extract (1%, w/w) to remove the latex portion of the plant, mainly anthraquinones, the components giving *Aloe vera* its laxative properties. However, some of the high molecular weight polysaccharides of the inner leaf Aloe gel can also be removed by charcoal absorption. Chemical analysis revealed that the concentrations of aloin, the principle anthraquinone of *Aloe vera* latex, differed by a factor of 100 in unfiltered and filtered extracts (8 mg/g for whole extract and 0.08 mg/g for decolorized extract).[17] The high-performance liquid chromatography (HPLC) analysis showed large differences between the two extracts (Fig. 1), indicating that the activated carbon-filtration eliminated a large number of components from the extract.[18] In addition, *Aloe vera* decolorized leaf extract exhibited a reduction in rheological values and approximately 19%−23% lower content of complex polysaccharides than either the gel or whole extract.[5]

2.2 Toxicity, genotoxicity, and carcinogenicity

2.2.1. Toxicity of the whole leaf extract—Logarto Parra and colleagues[19] investigated the toxicity of *Aloe vera* (L.) Burm. F. (Aloeaceae) extract using both in vitro and in vivo assays. Twenty-four hours following an acute oral exposure to *Aloe vera* dried leaf extract, the medium lethal concentration (LC_{50}) in brine shrimp was estimated as 3.59 μg/ml and the lethal dose (LD_{50}) in Swiss albino mice was 120.65 mg/kg. Another acute toxicity study demonstrated a maximum tolerated dose of 100 mg/kg body weight and LD_{50} of 250 mg/kg, when the whole *Aloe vera* plant powder was extracted with 50% ethanol and administered intraperitoneally to adult albino mice at an initial dose of 400 to 500 mg/kg.[20] In addition, *Aloe vera* whole-leaf material caused a dose-dependent decrease in the viability in HeLa and HepG2 cells with half-maximal cytotoxic concentration (CC_{50}) values of 413.9 and 439.0 mg/ml, respectively, following a 4-h treatment.[21] It also caused a dose-dependent increase of apoptosis in HeLa cells at concentrations up to 1000 mg/ml.

In a subchronic toxicity study, 88 Sprague Dawley rats were fed Aloe whole leaf powder at doses of 2, 4, and 8 g/kg body weight (2.5%, 5%, and 10% Aloe in diet) for 90 days.[22] All dosed rats increased defecation and rats treated with the high doses also showed reduced food efficiency and body weight. Relative kidney weight was significantly increased in males exposed to 8 g/kg body weight and all dosed females. All of the exposed groups displayed a significant increase in the incidences of pigmentation in renal tubular, mesenteric lymph nodes and lamina propria of the colonic mucosa, and proliferation in mesenteric lymph nodes. Reproductive toxicity was observed after a chronic oral ingestion of 100 mg/kg *Aloe vera* extract per day, which is one-fifth of the pharmacologically active dose, for a period of 3 months.[23] This was manifested by significant sperm damage, hematological changes, inflammation, and mortality as compared to control animals.

As part of a 14-day drinking water study conducted by the NTP, *Aloe vera* nondecolorized whole leaf extract and decolorized extract were administered to groups of four male and four female F344/N rats and the same numbers of B6C3F1 mice at 7 weeks of age.[24] The malic acid content of 0.5%−3% *Aloe vera* whole and decolorized extract solutions was 970-5820 *μg/g* and 1240-7440 *μg/g* water, respectively, and aloin A content was 70-422 *μg/g* and 0.8-4.5 *μg/g* water, respectively. After 14 days female rats exposed to 1.5%—3% of decolorized extract displayed significantly decreased blood urea nitrogen levels, whereas rats exposed to 3% whole extract displayed reduced body weight, water consumption, gastrointestinal tract transit times, and liver, heart, spleen, thymus, and kidney weight than those of controls. Leukocyte and erythrocyte counts and hematocrit percentages were significantly elevated in both male and female rats. In contrast, only a significant increase in water consumption was observed in female mice that received 2.0% nondecolorized whole extract.[24]

In comparison to this study, a highly purified decolorized whole leaf *Aloe vera* (L.) Burm. f. juice (total anthraquinones < 0.1 parts per million) was administered to F344/Du rats via drinking water at concentrations up to 2% (w/v).[25] This study was designed to compare the results obtained from other in vivo studies using whole leaf extract, specifically the NTP study reported by Boudreau and colleagues.[24] No significant toxicological findings were

observed after subchronic exposure for 13 weeks. A similar study also showed no toxicity in F344 rats after oral administration of a commercially available *Aloe vera* decolorized extract beverage up to 13 weeks, as evaluated by behavior, stools, weight gain, feed consumption, organ weights, and intestinal mucosal morphologies.[26] These results suggest that anthraquinones may be a major contributor or serve as a marker of other agent(s) for *Aloe* vera-induced adverse effects.[25]

2.2.2. Genotoxicity of the whole leaf extract—The genotoxicity of water extracted *Aloe ferox* was studied using the *Bacillus sub-tilis* rec-assay in the 1980s. *Aloe ferox* is a palm-like succulent with many sharp reddish-brown spines on the margins of the leaves, giving the plant name “ferox” that means “fierce” or “war-like” in Latin. In the absence of metabolic activation, the lengths of inhibition zones formed by 6 mg of Aloe extraction on Rec^+ and Rec^- strains deviated distinctly from those of negative control samples, indicating a positive response in the *Bacillus subtilis* spore rec-assay.[27] However, no genotoxic effects were observed in the histidine reversion Ames test and DNA repair assays using *Aloe vera* decolorized extract beverage at up to 21 × concentrations.[26]

Recently, *Aloe vera* whole extract- and decolorized extract-induced cytotoxicity and genotoxicity were evaluated in our laboratory using the mouse lymphoma assay (MLA).[18] This study used the same test articles that were used for the 14-day studies by the NTP.[24] After a 24-h treatment, both extracts exhibited concentration- dependent cytotoxicity and mutagenicity in the mouse lymphoma cells, with whole extract showing a positive response at lower concentrations than the decolorized extract. Molecular analysis of induced mutant colonies revealed that 77%−92% of the large colonies and 100% of the small colonies from both treatments lost heterozygosity at the *Tk* locus and about half of the mutants lost heterozygosity at both the *Tk* and *D11Mit42* loci, thus affecting approximately 6-30 centimorgans of the chromosome (Fig. 2). These results indicate that the primary type of damage from both treatments was large chromosome mutations (deletions and/or mitotic recombination). In addition, intracellular reactive oxygen species (ROS) levels induced by decolorized extract was about three-fold higher than that of whole extract in treated cells, suggesting that during the process of activated carbon filtration, some mutagenic components were removed from whole extract and other components with pro-oxidative or mutagenic activities, or both, might be enriched. Another important finding in this study was that the mutagenicity of the decolorized extract was detected at doses of about twice that required for whole extract-induced mutagenicity. Since the anthraquinone content was reduced by 99% in the decolorized extract relative to the whole extract, these results indicate that anthraquinones are not the only mutagenic component of these mixtures and Aloe-induced genotoxicity may not be eradicated completely by removing these chemicals from Aloe preparations.[18]

2.2.3. Carcinogenicity of the whole leaf extract—NTP Technical Report 577 described clear evidence of carcinogenic activity in F344/N rats after oral administration of *Aloe vera* whole leaf extract in drinking water for two years.[28] In this study, F344/N rats and B6C3F1 mice were exposed to 0%, 1%, 2%, or 3% (wt/wt) extract for a period of 13 weeks or 2 years. The 13-week exposure caused increased incidences of goblet cell

hyperplasia in the large intestine of both rats and mice when compared to the control. The two-year study demonstrated significant dose-related increases in the incidences of adenomas and/or carcinomas of the ileocecal and cecal-colic junction, cecum, and the ascending and transverse colon in male and female rats in the high-dose groups.[28] Whole extract-induced large intestinal tumors in F344 rats and human colorectal cancers shared similar changes in morphology and in molecular pathways, such as MAPK, WNT, and TGF-β signaling.[29] In a one-year study using Wistar Hannover rats, 4% *Aloe arborescens* (whole leaf powder extract) in the diet resulted in diarrhea, reduced body weight gain, yellowish pigmentation of ileocecal lymph nodes and renal tubules and severe sinus dilatation of the ileocecal lymph nodes.[30] In the subsequent two-year study, adenomas or adenocarcinomas in the cecum, colon, and rectum were observed in the 4% male group, and adenomas were observed in the 4% female group. The irritation of the intestinal tract may contribute to the equivocal carcinogenic potential in the colon.[31] Due to the potential phototoxicity of herbal products,[32] Aloe whole leaf or decolorized whole leaf creams was applied topically in male and female SKH-1 hairless mice for one year.[33] Both products showed a weak enhancing effect on the photocarcinogenic activity of simulated solar light, as manifested by significantly increased histopathologically-determined squamous cell neoplasm in some mice.

2.3. Adverse clinical effects of the whole leaf extract in humans

Topical and oral use of *Aloe vera* can cause skin irritation, hives, cramping, and diarrhea to those who are allergic to other plants in the lily family, for example, onion and tulips. Several case reports on toxicity or hypersensitivity of Aloe products in humans are available, but there are no published controlled toxicology stud- ies.[34] A 35-year-old woman experienced massive intraoperative bleeding after oral consumption of *Aloe vera* tablets for two weeks before the surgery for leg pain. Compounds contained within *Aloe vera* can reduce the synthesis of prostaglandin, thus inhibiting secondary aggregation of platelets. Sevoflurane, a general anesthetic, inhibits thromboxane A(2) formation by suppressing cyclooxygenase activity. Since both sevoflurane and *Aloe vera* have antiplatelet effects, the bleeding could have been due to a possible herb-drug interaction between *Aloe vera* and sevoflurane.[35] A 47-year-old man developed acute oliguric renal failure and liver dysfunction after ingestion of Cape Aloes, a previously described nephrotoxin.[36]

Hepatotoxicity is considered one of the most reported adverse effects caused by herbal dietary supplements.[37] The first case of acute hepatitis due to the ingestion of *Aloe vera* compound was reported in 2005 in Germany.[38] Afterward, cases of Aloe-induced toxic hepatitis were reported in Turkey,[39] United States,[40] Argentina,[41], and Korea.[42] A total of six females and two males were admitted to hospital for acute hepatitis after taking Aloe preparation over 3-260 weeks.[43] Their clinical manifestation, liver biopsy, and laboratory findings supported the diagnosis of toxic hepatitis. All eight patients showed improved conditions after discontinuing this medication. These cases emphasize the importance of considering phytophar- maceutical over-the-counter drugs as causative agents in hepatotoxicity.

3. *Aloe vera* latex or exudate

3.1. Components

Aloe vera latex or exudate is distributed within vascular bundles located between the plant's outer skin (rind) and the pulp. The pericyclic tubules, one of the three types of tubular structures of vascular bundles, store and transport *Aloe vera* latex along the margin of the leaf. The latex is yellow-brownish in color and has a bitter taste. About 80 chemical constituents have been isolated by liquid chromatography in the latex, and most of the compounds are phenolic in nature, mainly anthraquinone C- glycosides, anthrones, and free anthraquinones.[44,45] Barbaloin, also known as aloin A, is identified as the major constituent in the latex.[5,46] The other three main components are isobarbaloin (aloin B), aloesin (aloeresin B), and aloeresin A.[47] The latex also contains several other anthraquinones/anthrones and chromones including aloe-emodin, aloeresin E, aloenin,[44] as well as some aromatic compounds, for example, aldehydes (butanal, pentanal, etc.) and ketones (2-butanone, 2-heptanone, etc.).[47]

3.2. Toxicity, genotoxicity, and carcinogenicity

Aloe vera latex contains a number of biologically active compounds, notably anthraquinones. Various in vitro and in vivo assays have been performed to evaluate the cytotoxicity, genotoxicity, and carcinogenicity of the chemical components contained within the latex, most especially aloe-emodin, aloin, emodin, and dan- thron.

3.2.1. Toxicity of the latex—The cytotoxicity of aloe-emodin has been investigated intensively. Aloe-emodin induced apoptosis through various mechanisms, including a p53-dependent pathway in T24 human bladder cancer cells[48] and G2/M cell cycle arrest in human promyelocytic leukemia HL-60 cells.[49] During the apoptosis process induced by aloe-emodin and emodin in human lung squamous carcinoma cells (CH27) and human lung nonsmall cell carcinoma cells (H460), increases in cytosolic cytochrome c, caspase-3 activation, and changes of protein kinase c (PKC) isozymes were observed.[50] This study also demonstrated that PKC stimulation occurred at a site downstream of caspase-3 in the emodin-mediated apoptotic pathway. Another study demonstrated that aloe-emodine significantly inhibited proliferation and induced apoptosis in adult human keratinocytes.[51] The impairment of ker- atinocyte proliferation could be observed at concentrations far below the industry standards for commercial products containing Aloe extract.

The toxicity of aloin was evaluated in human Jurkat T lymphocytes using flow cytometry and microscopy.[52] Aloin treatment resulted in decreased cell size, increased granularity, a block at the G2/M phase of the cell cycle, and loss of both membrane integrity and mitochondrial membrane potential in a dose-dependent manner, suggesting a mitochondrial-dependent pathway for aloin-induced apoptosis. UP780, a standardized composition of aloe chromone aloesin formulated with an *Aloe vera* inner leaf fillet, showed a no-observed-adverse-effect-level in CD-1 mice with oral administration of UP780 at doses of 2 g/kg/d for 14 days or up to 1 g/kg/d for 90 days.[53]

3.2.2. Genotoxicity of the latex—The genotoxicity of some anthraquinones has been confirmed in a variety of in vitro and in vivo assay systems. A high proportion of anthraquinones was reported to be mutagenic in a number of strains of *Salmonella typhimurium,* for example, TA1537, TA1538, TA102, and TA98.[54-56] These strains are particularly sensitive to frameshift mutagens. Danthron and aloe-emodin were positive in strain TA1357 both with and without metabolic activation.[55] Aloe-emodin also induced increased revertant colonies in strains TA 1537, TA 1538, and TA 98.[57] Muller and colleagues[58] investigated the genotoxicity of three anthraquinones, emodin, danthron, and aloe-emodin using the MLA, micronucleus test, and the Comet assay. At micromolar concentrations, all three compounds induced concentration- dependent increases in micronuclei and moderate increases in mutant frequency in L5178Y cells. Danthron and aloe-emodin also increased DNA breaks at a concentration of 50 μM in the Comet assay. The genotoxicity and mutagenicity induced by these anthraquinones were due to the inhibition of the catalytic activity of topoisomerase II (Topo II), with danthron being the most potent.[58,59] Emodin, the least potent compound among the three anthraqinones, caused DNA doublestrand breaks by stabilizing Topo II-DNA cleavage complexes and by inhibiting ATP hydrolysis of Topo II.[60] Aloe-emodin caused DNA damage in human lung carcinoma cells through the production of ROS,[61] induced micronuclei in TK6 human lymphoblastoid cells,[56] and chromosomal aberration in Chinese hamster ovary cells.[57] Danthron caused DNA damage and caspase cascade-mediated apoptosis in SNU-1 human gastric cancer cells through mitochondrial permeability transition pores and Bax-triggered pathways.[62]

An in vivo mouse Comet assay was performed on isolated kidney and colon cells of male OF1 mice in order to demonstrate the possible organospecific genotoxicity of aloe-emodin.[56] Increases in DNA strand breaks in both the kidney and the colon were observed between 3 h and 6 h after two oral administrations at 500,1000, and 2000 mg/kg body weight, suggesting an in vivo genotoxic mechanism of action.

3.2.3. Carcinogenicity of the latex—Tumor promotion activities, such as stimulation of cell proliferation and enhancement of malignant transformation, have been investigated in mice for 9 hydroxyan- thraquinones (HA) including danthron, aloe-emodin, and emodin.[63] A 2 to 3-fold increase in DNA synthesis was found in primary rat hepatocytes exposed to danthron and aloe-emodin; and danthron also enhanced malignant transformation of C3H/M2 mouse fibroblasts pretreated with N-methyl-N'-nitro-N-nitrosoguanidine or 3-methylcholanthrene, suggesting that HA with hydroxy groups in the 1,8- positions may have tumor-promoting activity. The carcinogenic potential of HA also has been demonstrated in a group of 29 male ACI/N rats.[64] After 480 days feeding with 1% of HA, 25 of 29 rats developed adenomas or adenocarcinomas in the cecum or upper portion of the colon; liver neoplasms (neoplastic nodules and hepatocellular carcinomas) were observed in 12 rats; and benign stomach tumors were observed in five animals. These findings strongly suggest that HA is carcinogenic in rodents.

A two-year feeding study of emodin in male and female F344/N rats and B6C3F1 mice showed equivocal evidence of carcinogenic activity for emodin in female F344/N rats due to

a marginal increase in the incidence of Zymbal's gland carcinoma and in male B6C3F1 mice based on a low incidence of renal tubule neoplasms.[65] In the rat study, diets containing 0, 280, 830, or 2500 ppm emodin (equivalent to average daily doses of approximately 110, 320, or 1000 mg/kg to males and 120, 370, or 1100 mg/kg to females) were administered to 65 male and 65 female rats for 105 weeks. Three Zymbal's gland carcinomas were diagnosed in female rats exposed to 2500 ppm. In the mouse study, 60 male and female mice were fed diets containing 0-625 ppm (equivalent to average daily doses of approximately 15-70 mg/kg) or 0-1250 ppm (equivalent to average daily doses of approximately 30-120 mg/kg) emodin, respectively, for 105 weeks. Low incidences of renal tubule adenoma and one carcinoma each in the 312 and 625 ppm groups were observed in exposed male mice. No evidence of carcinogenic activity of emodin was found in female B6C3F1 mice even at the highest dose of 1250 ppm.

Evidence for aloe-emodin photocarcinogenicity was found in C3H mice after combined treatment with ultraviolet radiation and aloe-emodin in ethanol vehi- cle.[66] C3H/HeN mice were treated with aloe-emodin in 25% ethanol topically three times per week for two weeks and exposed to 15 kJ/m^2 UVB (280-320 nm) radiation. Primary cutaneous melanin-containing tumors were diagnosed in 50%−67% of the UV-irradiated mice given aloe-emodin in ethanol vehicle and in 20%−30% of the mice treated with a combination of UV radiation and ethanol vehicle, whereas no skin tumors were induced by aloe-emodin alone in the absence of UV radiation.

3.3. Adverse clinical effects of the latex in humans

The purgative effect of Aloe latex has long been recognized and has been used empirically to relieve constipation. The earliest medical writer to record the therapeutic use of Aloe is Dioscorides, a Greek physician of the first century A.D.[67] Subsequently, Aloe latex was used widely in herbal laxative preparations in many countries. Thus, a number of adverse effects resulting from ingestion of latex have been reported in clinical studies. Prolonged use was associated with electrolyte imbalance due to diarrhea, abdominal pain, vomiting, hypokalemia, pseudomelanosis coli, and the development of a cathartic colon—the colon becomes atonic and dilated. Longterm use of anthranoid laxatives might be correlated with the risk of developing colon cancer.[68]

A case of Aloe-induced Henoch-Schonlein purpura, an idiopathic vasculitis of the small vessels, was reported. A 52-year-old male patient from Pakistan presented severe arthralgia, palpable purpura, and abdominal pain ten days after taking some juice extracted from four to five leaflets of *Aloe vera.* Twenty-four hours after the juice consumption, the man started to have rash on his legs and a mild arthralgia of the ankle. His symptoms worsened in the following days, and he developed diffuse, colicky, abdominal pain. Marked segmental necrosis and crescent formation were demonstrated by a renal biopsy. The renal dysfunction and nephritis were considered to be a consequence of large doses of Aloe.[69]

A 74-year-old female presented with an impressive deep black pigmentation of the whole colon after chronic use of anthraquinone laxatives over many decades. Various adenomas, which were classified as precancerous lesions, were detected, but no colorectal carcinoma

was found.[70] An 18-year-old Caucasian girl, who was treated with a combination laxative containing 5 ml danthron orally at night to ameliorate constipation from 14 months old to 5-6 years old, presented a small bowel leiomyosarcoma with widespread dissemination.[71] Although one case cannot prove a causative association between danthron and the risk of developing bowel cancer, the authors concluded that prolonged oral exposure to the laxative should be avoided in early childhood. In addition, pregnant women were advised not to take Aloe latex because its cathartic property might result in stimulating uterine contractions, thereby increasing the risk for premature labor or miscarriage. Also, nursing mothers should not take laxatives because of the possibility of anthraquinones causing diarrhea in the infants.[3]

4. *Aloe vera* gel

4.1. Components

Aloe vera gel is a transparent mucilaginous jelly-like substance contained in the parenchymatous cells of fresh *Aloe vera* leaf pulp, with a gel yield of approximately 70% (70 g gel/100 g pulp) from the pulp by mechanical extrusion.[72] The gel has very high water content (99%−99.5%), with the remaining soluble solids making up 0.5%−1%,[73] and a range of gel acidity (pH) of 4.4-4.7.[74] On a dry matter basis, the chemical constituents consist of 35% dietary fibers (nonstarch polysaccharides + lignin), 27% soluble sugars, 24% ash, and a minor fraction of lipids, proteins, enzymes, and mineral elements.[7,72] The alcohol insoluble residues obtained from *Aloe vera* gel lyophilized fractions have a high content of carbohydrates (72%) including mannose, glucose, and uronic acids. Linear chains of β−1-4-linked mannose and glucose molecules compose the primary polysaccharides at a ratio of 1~22:1 in the gel.[6,7,75-77] Most investigators agree that acemannan, an acetylated glucomannan, makes up the major active component of the mucilaginous *Aloe vera* gel,[72] while others report pectic substance as the main polysaccharide.[73] The discrepancies are considered to be a result of differences in the species, seasons of the year, geographical locations, and the gel extraction process.

4.2. Toxicity, genotoxicity, and carcinogenicity

The toxic effects of *Aloe vera* gel have been reported only in a few studies. There is diversity in the results of the observed toxic effects which may be largely due to the differences in the gel contents that are greatly influenced by a variety of factors including seasons, locations, irrigation, harvest time, and, most importantly, the lack of standardization of the gel preparations.

4.2.1. Toxicity of the gel—The cytotoxicity of *Aloe vera* gel has been confirmed in monolayers of chicken fibroblasts based on the observations of disrupted intercellular junctions and the formation of cell-free gaps in the monolayers after treatment.[78] The cell injury assay was conducted using three fractions isolated from the *Aloe barbadensis* leaves, native gel (mucilaginous parenchymous tissue scraped from Aloe leaves), purified gel (the nondialyzable fraction of the native gel), and the low molecular weight fraction (LMWF, the dialyzable material). A 1:10 dilution of native gel and the LMWF promoted similar cell

injuries, while the purified gel behaved like the control at the same dilution. These severe cellular damages were distinct enough to be detected under a microscope. Therefore, it was proposed that the toxicity was mainly caused by the LMWF from the gel since the beneficial characteristics were suggested to result from the high molecular weight components.[78] Following a 4-hour treatment, an *Aloe vera* dehydrated gel material induced dose-dependent cytotoxicity in HeLa cells, with a CC_5o value of 269.3 mg/ml.[21]

Aloe vera gel was administered in drinking water to groups of four male and four female F344/N rats in a 14-day study conducted by the NTP.[28] The gel quality was monitored by the content of malic acid and aloin A (barbaloin). Drinking water solutions of 0.5%−3% *Aloe vera* gel contained 1060-6360 μg malic acid/g water, and 5.6-33.3 μg aloin A/g water. After the 14-day exposure, dose-related increases in urine glucose levels in female rats and dose-related decreasing trends in serum levels of triglycerides, cholesterol, and albumin were observed at concentrations of 1.5% or greater in female rats and of 3.0% in male rats. When adult male Wistar rats were orally administered with *Aloe vera* gel extract solution (150 and 300 mg/kg/day) for 8 weeks, the weight of testes, serum testosterone, sperm count, and sperm fertility were significantly decreased compared to the control rats.[79] In another in vivo study using a commercial stabilized *Aloe vera* gel consumed as a beverage, no changes were found in feed consumption, body weight gain, and serum chemistry tests following a 13-week subchronic exposure in B6C3F1 mice.[80]

After 5.5 months ingestion of crude skinned Aloe filet to male F344 rats, no adverse effect was observed on body weight gain, food intake, gastrointestinal transit time, or gross pathology at dietary concentrations of 1% or 10% (corresponding to doses of *Aloe vera* gel of ~0.33 and 3.3 g/kg bw/day).[16,81] Life-long ingestion of low dose (1%) *Aloe vera* filet caused no obvious harmful effects or deleterious changes in the rat.[82]

4.2.2. Genotoxicity of the gel—Studies on the biological effects of *Aloe vera* pulp extract on *Escherichia* coli-deficient repair mutants and plasmid DNA revealed genotoxic properties of the gel, but not cytotoxicity because of the poor permeability through the cell membrane. The agarose gel electrophoresis assay showed that *Aloe vera* pulp extract produced dose- dependent single-strand breaks in the plasmid DNA.[83] In vitro and in vivo safety studies using a high-purity *Aloe vera* inner leaf fillet preparation demonstrated that the gel was nonmutagenic in the Ames test, the chromosomal aberration test, and the in vivo bone marrow micronucleus test, following oral administration at doses up to 5 g/kg bw/day to rats for 90 days[84] Similarly, a commercial gel juice did not induce a significant increase in SOS DNA repair in *Escherichia coli* or mutagenesis in *Salmonella* TA100[80]

4.2.3. Carcinogenicity of the gel—No carcinogenicity data are available for Aloe gel.

4.3. Adverse clinical effects of the gel in humans

Aloe gels were first used clinically in the 1930s for the treatment of radiation burns.[34] Afterward, several clinical trials of *Aloe vera* gel have been carried out in the treatment of burn wounds,[85] oral lichen planus,[86] hyperlipidemic type 2 diabetic patients,[87] and recurrent aphthous stomatitis.[88] Only some minor adverse effects were reported in these

studies, such as discomfort, pain, and the development of hypersensitive reactions. However, generalized eczematous and papular dermatitis were found in a male patient in response to the oral and topical use of the *Aloe vera* gel.[89] Pruriginous erythema was observed on the legs and eyelids of a 72-year- old woman after applying self-made *Aloe vera* leaf juice over the legs.[90] A very slow recovery from the dermatitis induced by *Aloe vera* preparations was reported in four cases after dermabrasion and chemical peel.[91] No severe adverse effects or carcinogenicity have been reported from using *Aloe vera* gel.

5. Perspectives

More than 300 million people worldwide consume dietary supplements and herbal plants, and about one-half of Americans use them regularly.[92] Dietary or herbal supplement products are expected to be safe, effective, and of appropriate quality. However, the complex chemical nature of dietary supplements makes it difficult to evaluate their efficacy and safety. Herbal products often exhibit great variability in quality because of some issues including authentication, adulteration and substitution, and factors during growth, harvest, and postharvest processing.[93] Authentication of plant species used for preparation of herbal dietary supplements is important for safety assurance. Besides traditional approaches, the use of molecular/genetic profiling in identification of specific molecular changes (fingerprints) and in unveiling signature indicative of exposures remains a promising yet still largely unexplored approach.[94,95]

The reported adverse effects have raised concerns of public health risks regarding the concentration, composition, and individual contaminants of dietary supplements. Herbal dietary supplements and other herbal products have been recognized as the common causes of drug-induced liver injury.[96] A recent report indicates that dietary/herbal supplements are implicated in 19% of drug-induced acute liver failure cases,[97] because consumers often purchase these products online without the supervision of a health care provider and are not aware of drug-herb interactions and appropriate warnings. A total of 1179 English-language, herbal product- related websites (including retail and nonretail websites) were examined and only ~10% of them recommended consultation with a health care professional. In addition, only about 8% of internet retailers provided information on potential adverse effects, drug interactions, and other basic safety precautions; and less than 3% cited scientific references to their claims.[98]

Aloe plant contains multiple constituents with potential beneficial and toxico- logical activities. Three distinct preparations derived from *Aloe vera* (i.e., the whole leaf extract, *Aloe vera* gel, and *Aloe vera* latex) have been used as topical and oral therapeutic remedies. The gel is primarily used topically for wounds and skin problems, as well as taken orally for the treatment of gastrointestinal ulcers and dia- betes.[9] The latex is regulated as a drug by the FDA to relieve constipation and the whole leaf extract may possess antibacterial/viral and anticancer activities.[5] *Aloe vera* appears to be safe when used as a flavoring in foods[16]; and the polysaccharide material derived from the inner gel is noncytotoxic as evaluated by the Cosmetic Ingredient Review Expert Panel.[3] However, due to the cytotoxicity, mutagenicity, and carcinogenicity of anthraquinones, it is crucial to monitor the

content of these phenolic compounds in *Aloe vera* whole leaf extract and latex.[5,24] The International Aloe Science Council standard suggests that the maximum allowable aloin content in Aloe-derived material for oral consumption is less than 10 ppm (parts per million); for nonmedical use the recommended limit is 50 ppm or lower.[3,99]

According to Multinational Integrated Data Analysis conducted by IMS Health (Danbury, CT), the estimated global sales of Aloe products have reached US $351 million.[16] Due to the increased popularity and utilization of Aloe plant, indepth studies are needed to investigate the adverse effects, conventional drug interactions, and the possible toxic and carcinogenic effects of Aloe preparations, especially after long-term use of these products.

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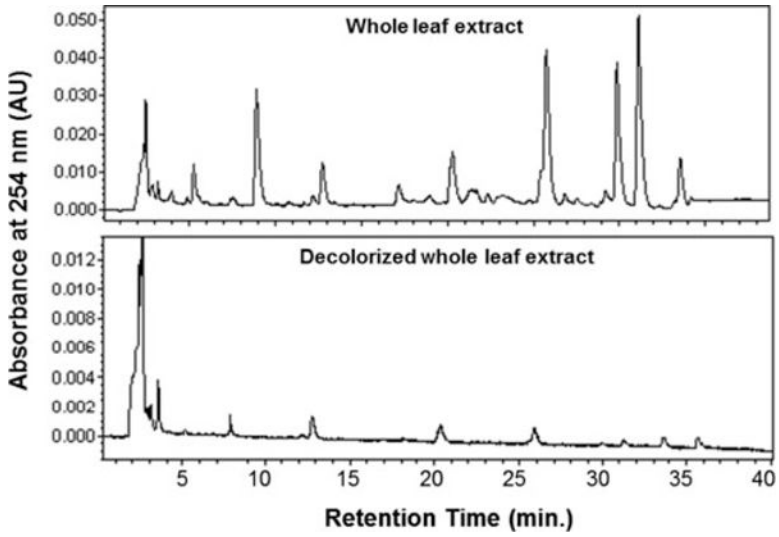

Figure 1.

Representative reversed-phase HPLC profiles of *Aloevera* whole leaf extract and decolorized whole leaf extract. Five mg/ml samples were dissolved in Fischer's medium with pH adjusted to 7.0-7.2. HPLC analysis was performed using a Phenomenex Prodigy 5 μmODS column (4.6 mm x 250 mm) eluted with methanol with a linear gradient of 20%−60% water over 30 min and 60-100% methanol over 30 min at a flow rate of 1 ml/min.

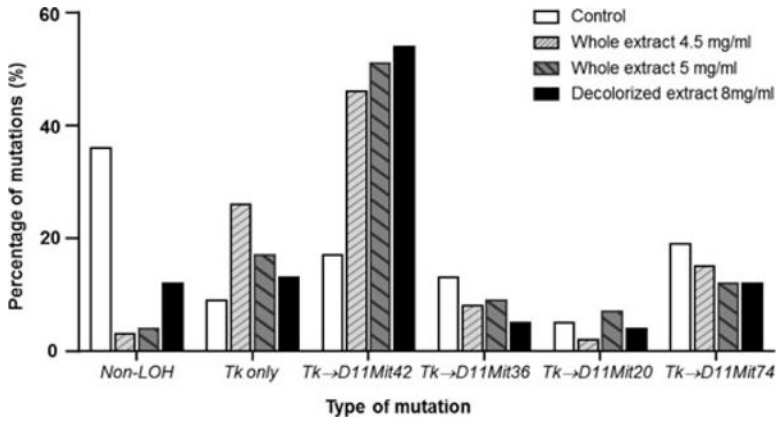

Figure 2.

Comparison of the percentage of mutational types for all (large and small) colonies produced in cells treated with *Aloe vera.* Mouse lymphoma cells were treated for 24 h with 4.5 or 5 mg/ml whole leaf extract, or 8 mg/ml decolorized extract. Whole extract at 4.5 or 5 mg/ml or decolorized extract *vs* control, $p < 0.0001$; 4.5 mg/ml whole extract *vs* decolorized extract, $p = 0.03$; 4.5 mg/ml *vs* 5 mg/ml whole extract, $p = 0.37$; 5 mg/ml whole extract *vs* decolorized extract, $p = 0.26$. Data from Table 3 in [18].

Table 1.

Pharmacological and/or toxicological research on Aloe based on PubMed online search.*

	Country	All fields#	MeSH term
Aloe	All	1895	975
	China	267	76
	India	191	90
	USA	188	95
	Japan	110	61
	South Africa	93	47
	Korea	72	44
	Iran	65	22
	Italy	55	22
	UK	48	21
	Brazil	39	21
Top 10 countries		1128 (60%)	499 (51%)
Toxicity-related		150 (8%)	81 (8%)

*Searched on July 17,2015.

#All fields but not in authors.