

1. Exposure Data

The first record of human use of *Aloe vera* is in Sumerian hieroglyphics engraved on clay tablets during the Mesopotamia civilization circa 2200 BC, in which it is described as a laxative. Use of aloe in ancient times is also documented in Egypt, Greece, and China. *Aloe vera* was cultivated on the islands of Barbados and Curacao in the Caribbean by Spain and the Netherlands, and was sold in various parts of Europe during the 17th century ([Park & Jo, 2006](#)). Commercial cultivation of *Aloe vera* in the USA began in the 1920s in Florida ([Grindlay & Reynolds, 1986](#)). Although *Aloe vera* originated in the warm, dry climates of Africa, the plant is readily adaptable and grows worldwide ([Steenkamp & Stewart, 2007](#)).

Use of *Aloe vera* gel extracts in health foods and beverages, and moisturizing cosmetics, began during the 1970s, starting in the USA and parts of Europe ([Park & Jo, 2006](#)). Historically, *Aloe vera* was used topically to heal wounds and for various skin conditions, and orally as a laxative ([Steenkamp & Stewart, 2007](#)). The dried latex of other *Aloe* species, such as *Aloe ferox* Miller (Cape aloe or bitter aloe) has also been used as a laxative ([EMA, 2006](#)). Today, *Aloe vera* is also used as a folk or traditional remedy for a variety of conditions and is found in some dietary supplements and food products. *Aloe vera* gel can be found in hundreds of skin products, including lotions and sunblocks ([NCCAM, 2012](#)).

A glossary of commonly used terms for *Aloe vera* products is provided in [Table 1.1](#).

1.1 Identification of the agent

1.1.1 Botanical data

(a) Nomenclature

For details on botanical nomenclature, see [Newton \(2004\)](#).

Chem. Abstr. Serv. Reg. No.: 8001-97-6

Chem. Abstr. Name: *Aloe barbadensis*

Botanical name: *Aloe vera* (L.) Burm. f. (synonym, *Aloe barbadensis*, *Aloe humilis* Blanco, *Aloe indica* Royle, nomen nudum, *Aloe perfoliata* var. *vera* L., *Aloe vulgaris* Lam.) ([GRIN, 2013](#)).

Family: Xanthorrhoeaceae

Genus: *Aloe*

Plant part: Leaf

Common names: *Aloe vera*; *Aloe vera* Linné; True aloe; *Aloe barbadensis*; Barbados aloe; Curaçao aloe; Mediterranean aloe; Ghritakumari; Lu Hui; Luhui, etc.

From [WHO \(1999\)](#), [Eur Ph \(2008\)](#), [O'Neil et al. \(2006\)](#), [SciFinder \(2013\)](#), [IASC \(2013a\)](#), [Boudreau et al. \(2013a\)](#).

Table 1.1 Definition of terms commonly used in the Aloe industry

Term	Definition
Leaf	The part of the <i>Aloe vera</i> plant used in commerce, where processing is begun without stripping off the rind.
Whole leaf	Historically used to describe products derived from the entire leaf that were filtered/purified. However, use of this terminology without adequate additional descriptors is not recommended. This terminology is now seen on products or in reference to raw material where the entire leaf is used as a starting ingredient to create <i>Aloe vera</i> juice.
Decolorized whole leaf	A process, usually involving filtration with activated charcoal, that clarifies the liquid aloe mass.
Inner leaf	Plant part used to describe the clear, central parenchymatous tissues of the aloe leaf.
Aloe latex	Brown, yellow-brown, or occasionally red exudate found between the rind and inner leaf. Also called “sap,” it contains several constituents, but most notably anthraquinones.
Anthraquinone	An organic compound primarily found in the aloe latex, whose structure serves as the basic building block for several naturally occurring plant pigments. The substance is commonly used for laxative purposes.
Gel	Liquid product typically derived from the inner leaf.
Juice	Liquid product derived from <i>Aloe vera</i> leaf [the Working Group noted that the term “juice” is used arbitrarily and may either apply to products from the latex or from the gel].

Adapted from [IASC \(2009\)](#)

(b) Description

Aloes are perennial succulents or xerophytes; they can adapt to habitats with low or erratic water availability, are characterized by the capacity to store large volumes of water in their tissue, and are able to use crassulacean acid metabolism, an adaptation to the photosynthetic pathway that involves the formation of malic acid ([Boudreau et al., 2013a](#)). Aloe plants, such as *Aloe vera* ([Fig. 1.1](#)), all have green fleshy leaves covered by a thick cuticle or rind, under which is a thin vascular layer covering an inner clear pulp ([Boudreau et al., 2013a](#); [Fig. 1.2](#)) The leaves are 30–50 cm in length and 10 cm in width at the base, pea-green in colour (when young spotted with white), and with bright yellow tubular flowers 25–35 cm in length arranged in a slender loose spike ([WHO, 1999](#)).

The vascular bundles, located within the leaf pulp, transport (i) water and minerals from the roots to the leaves; (ii) synthesized materials to the roots; and (iii) latex along the margins of the leaf for storage ([Ni et al., 2004](#); [Fig. 1.2](#)). The number of vascular bundles varies depending on the size of the leaves and the age of the plant ([Ni et al., 2004](#)).

Aloe vera plants contain two major liquid materials ([Fig. 1.2](#)): first, a bitter yellow latex located under the strongly cutinized epidermis of the leaves in the vascular layer and containing a high concentration of anthraquinone compounds, which has been used throughout the centuries as a cathartic and for medicinal purges; and, second, a clear mucilaginous gel produced by the thin-walled tubular cells in the inner central zone (parenchyma) that has been used since ancient times to treat burns and other wounds, where it is thought to increase the rate of healing and reduce the risk of infection ([Joseph & Raj, 2010](#)). A third liquid may also be obtained by macerating the whole leaf.

[Both the scientific and the lay literature (e.g. on internet sites) are extremely inconsistent when referring to products obtained from *Aloe vera*. The problem starts with the fact that the three types of liquids that are obtained from *Aloe vera* leaves are interchangeably referred to as “Aloe juice,” which has caused confusion in the literature. For disambiguation reasons, the term “Aloe juice” should be restricted – if used at all – to the latex material of the pericycle, which is in accordance with the pharmacopoeial definitions

Fig. 1.1 *Aloe vera* (L.) Burm. F, plant and flower

From [Spohn \(2013\)](#)
© Roland Spohn

([WHO, 1999](#); [Eur Ph, 2008](#); [JP XVI, 2011](#)); and the inner leaf liquid material should be referred to as “gel” ([WHO, 1999](#)). Interchangeable terms found in the literature for the “gel” are inner pulp, mucilage tissue, mucilaginous gel, mucilaginous jelly, inner gel, and leaf parenchyma tissue ([Hamman, 2008](#).)

1.1.2 Chemical constituents and their properties

A review of the chemistry of *Aloe vera* was provided by [Reynolds \(2004\)](#), and a summary of the chemical constituents of *Aloe vera* is provided in [Table 1.2](#).

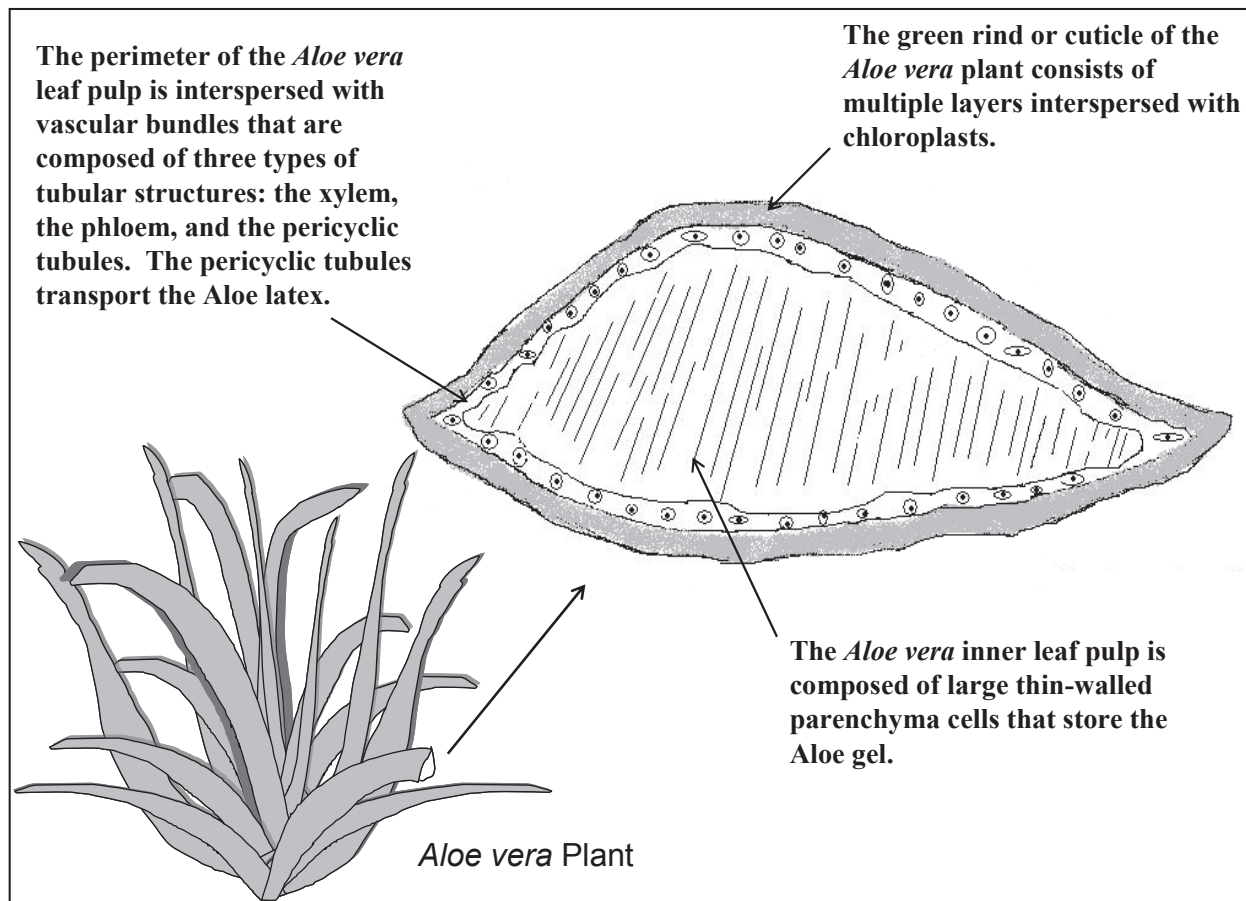
The main feature of the *Aloe vera* plant is its high water content, ranging from 99% to 99.5%, while the remaining 0.5–1.0% solid material is reported to contain over 200 different potentially active compounds, including vitamins, minerals, enzymes, simple and complex polysaccharides, phenolic compounds, and organic acids ([Boudreau et al., 2013a](#); [Rodríguez et al., 2010](#)).

In compositional studies on the structural components of leaf portions of the *Aloe vera* plant, the rind was found to compose 20–30% and the pulp 70–80% of the whole leaf weight. On a dry-weight basis, the rind and pulp contain 2.7% and 4.2% lipids, and 6.3% and 7.3% proteins, respectively ([Femenia et al., 1999](#)). The percentages of soluble sugars (11.2% and 16.5%), primarily as glucose, and the percentages of ash (13.5% and 15.4%), in particular calcium, were relatively high in the rind and pulp, respectively. Non-starch polysaccharides and lignin represented the bulk of each leaf fraction and were found to be 62.3% and 57.6% of the dry weight of the rind and pulp, respectively ([Boudreau et al., 2013a](#)). Acetylated mannan is the primary polysaccharide in *Aloe vera* gel ([Ni et al., 2004](#)). Other chemical constituents of *Aloe vera* include lectins such as aloctins A and B ([Kuzuya et al., 2004](#)).

The physical and chemical constituents of the products derived from *Aloe vera* plants differ depending on the source (e.g. part of the plant), the species of the plant, the climate conditions, seasonal and grower influences ([Boudreau et al., 2013a](#)), and processing techniques ([Waller et al., 2004](#)).

1.1.3 Technical and commercial products

Three types of *Aloe vera* extracts can be distinguished –gel extract, whole leaf extract, and decolorized whole leaf extract ([Boudreau et al., 2013a](#)), and a fourth type of commercial material is available as dried latex, which has

Fig. 1.2 Schematic representation of the *Aloe vera* plant, showing a cross-section through a leaf

From [Boudreau et al. \(2013a\)](#)

been traditionally used as the laxative ([Eur Ph, 2008](#)).

(a) *Aloe vera gel extract*

The inner leaf pulp of the *Aloe vera* plant contains large, thin-walled cells that produce gel, the clear, mucilaginous, and aqueous extract of the inner central area of the leaf pulp ([Fig. 1.2](#)). *Aloe vera* gel serves as the water and energy storage component of the plant. The mechanical extrusion of the mucilaginous gel from the inner leaf pulp gives a 70% yield with a water content of 99–99.5% ([Femenia et al., 1999](#)).

Polysaccharides in *Aloe vera* gel consist of linear chains of glucose and mannose molecules,

and, because there is considerably more mannose present than glucose, the molecules are referred to as polymannans. These linear chains range in size from a few to several thousand monosaccharide molecules. The major polysaccharide, acetylated mannan, is composed of one or more polymers of various chain lengths with molecular weights ranging from 30 to 40 kDa or greater, and consisting of repeating units of glucose and mannose in a 1:3 ratio ([Channe Gowda et al., 1979](#); [Mandal & Das, 1980](#); [Yaron, 1993](#); [Femenia et al., 1999](#); [Boudreau et al., 2013a](#); [Fig. 1.3](#)). Chemically preserved fresh *Aloe vera* gel stored at room temperature or incubated at 40 °C for 48 hours exhibited degradation in its

Table 1.2 Summary of chemical constituents of *Aloe vera* products

Class	Compounds
Anthraquinones/ anthrones	Aloe-emodin, aloetic acid, anthranol, aloin A and B (or collectively known as barbaloin), isobarbaloin, emodin, ester of cinnamic acid
Carbohydrates	Pure mannan, acetylated mannan, acetylated glucomannan, glucogalactomannan, galactan, galactogalacturan, arabinogalactan, galactoglucoarabinomannan, pectic substance, xylan, cellulose
Chromones	8- <i>C</i> -Glucosyl-(2'- <i>O</i> -cinnamoyl)-7- <i>O</i> -methylaloediol A, 8- <i>C</i> -glucosyl-(<i>S</i>)-aloesol, 8- <i>C</i> -glucosyl-7- <i>O</i> -methyl-(<i>S</i>)-aloesol, 8- <i>C</i> -glucosyl-7- <i>O</i> -methylaloediol, 8- <i>C</i> -glucosyl-noreugenin, isoaloesin D, isorabaichromone, neoaloesin A
Enzymes	Alkaline phosphatase, amylase, carboxypeptidase, catalase, cyclooxygenase, cyclooxygenase, lipase, oxidase, phosphoenolpyruvate carboxylase, superoxide dismutase
Minerals	Calcium, chlorine, chromium, copper, iron, magnesium, manganese, potassium, phosphorous, sodium, zinc
Lipids and miscellaneous organic compounds	Arachidonic acid, γ -linolenic acid, steroids (campesterol, cholesterol, β -sitosterol), triglycerides, triterpenoid, gibberillin, lignins, potassium sorbate, salicylic acid, uric acid
Amino acids	Alanine, arginine, aspartic acid, glutamic acid, glycine, histidine, hydroxyproline, isoleucine, leucine, lysine, methionine, phenylalanine, proline, threonine, tyrosine, valine
Proteins	Lectins, lectin-like substance
Saccharides	Mannose, glucose, <i>L</i> -rhamnose, aldopentose
Vitamins	B1, B2, B6, C, β -carotene, choline, folic acid, α -tocopherol

Adapted from [Hamman \(2008\)](#)

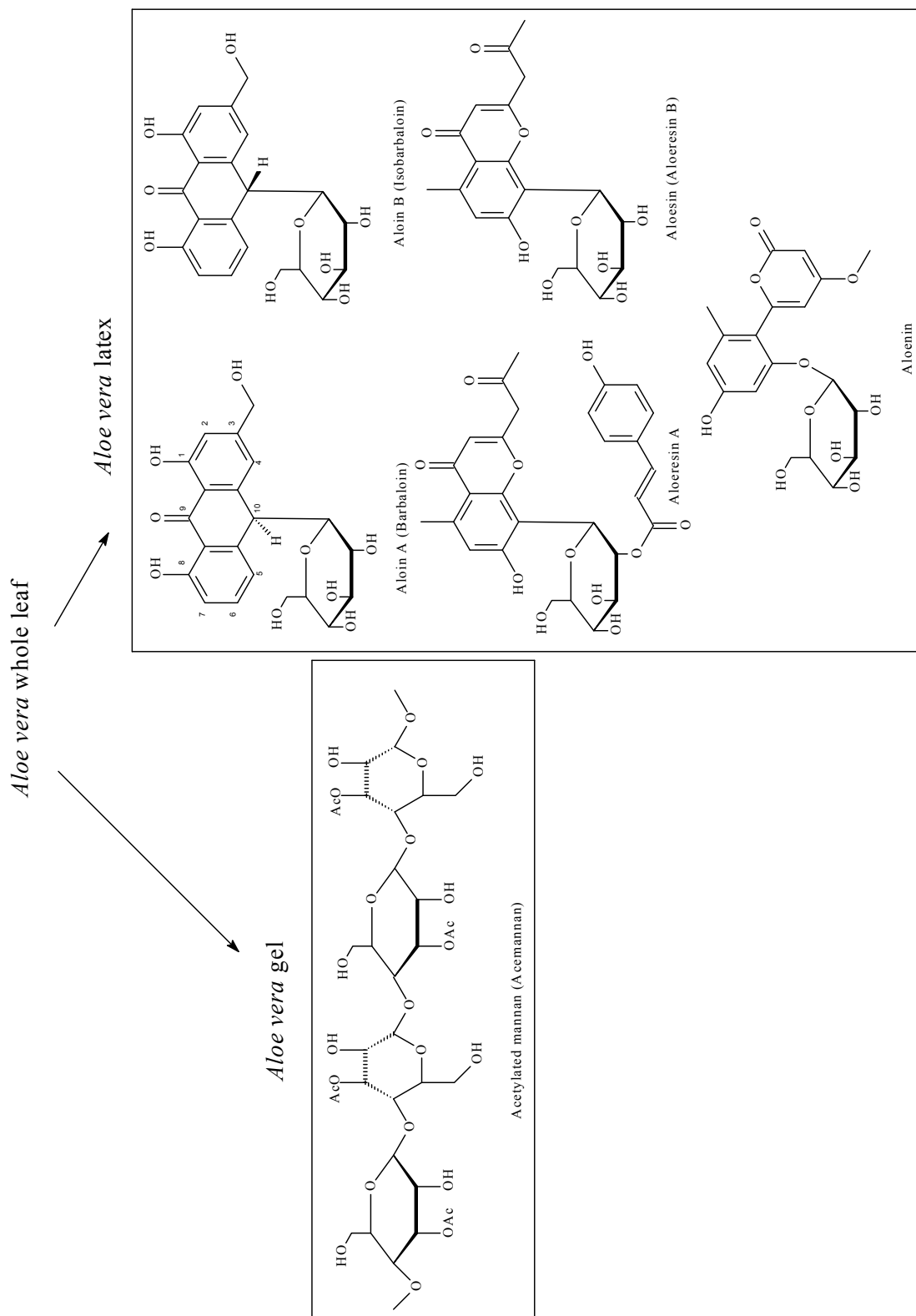
rheological properties, a decrease in the content and composition of polysaccharides, and a substantial increase in the mannose:glucose ratio, from 2.9 in the fresh gel to 13.4 in the incubated gel ([Yaron, 1993](#)).

(b) *Aloe vera* whole leaf extract

The *Aloe vera* whole leaf extract (sometimes referred to as whole leaf *Aloe vera* juice, Aloe juice or nondecolorized whole leaf extract), is the aqueous extract of the whole leaf with lignified fibres removed. The whole leaf extract contains both the gel from the inner parenchyma leaf pulp and the latex. The restricted distribution of the bitter latex within the margins of the leaves of the *Aloe vera* plant suggests that this thin layer is the primary site of secondary metabolites biosynthesis: compounds that do not function directly in plant growth and development and serve as a plant defence strategy ([Boudreau et al., 2013a](#)). A wide variety of secondary compounds have been isolated from the *Aloe vera* latex ([Reynolds, 2004](#)). The isolated compounds are

largely phenolic in nature, and many are anthraquinone *C*-glycosides, anthrones, and free anthraquinones ([Park et al., 1998](#)). The levels of anthraquinone *C*-glycosides in *Aloe vera* latex are quite variable; however, they may constitute up to 30% of the dry weight of the latex ([Groom & Reynolds, 1987](#)). *Aloe vera* latex contains four major *C*-glycosyl constituents: aloin A, aloin B, aloesin, and aloeresin A ([Fig. 1.3](#); [Saccù et al., 2001](#)). Aloin A, a *C*-glycosyl anthrone, also referred to as barbaloin, is the major component of aloe latex. Aloin A and its epimer, aloin B, also referred to as isobarbaloin, have a 9-anthrone skeleton and a β -D-glucopyranosyl substituent. Aloesin, also known as aloeresin B, is a 5-methyl chromone with an 8- β -D-glucopyranosyl substituent, and aloeresin A is a 5-methyl chromone with an 8- β -D-glucopyranosyl-2-*O*-*trans*-*p*-coumarol substituent. Several other *C*-glycosyl-chromones and anthrones have been isolated from *Aloe vera*, including aloe-emodin, the anthraquinone of barbaloin and isobarbaloin ([Boudreau et al., 2013a](#)).

Fig. 1.3 Chemicals present in gel and latex prepared from *Aloe vera*



Ac, acetyl group
From [Boudreau et al. \(2013a\)](#)

The occurrence in *Aloe vera* latex of endogenous free anthraquinones and anthrones results from oxidative processes acting on the glycosides rather than from metabolic synthesis (Boudreau *et al.*, 2013a). In addition, the latex from *Aloe vera* contains several aromatic compounds, such as aldehydes and ketones (Saccù *et al.*, 2001). The sugar moiety in aloins is D-glucose, and studies indicate that carbon atom 1 of the D-glucose moiety is linked directly to carbon atom 10 of the anthracene ring in a β -configuration (Fig. 1.3). The carbon-carbon bond is quite resistant to acid and alkaline conditions; however, the intestinal microflora of humans and animals have been shown to cleave the β -C-glucosyl bond, although considerable variation in response among animal species occurs. Cleavage of the β -C-glucosyl bond results in the formation of aloe-emodin, the cathartic principle of the latex, and other free anthraquinones and anthrones (Boudreau *et al.*, 2013a; see Section 4.1.1b). In commercial products containing whole leaf extract, a rapid deterioration of aloin was detected during storage, especially at higher temperatures (Pellizzoni *et al.*, 2011).

(c) *Aloe vera* decolorized whole leaf extract

Activated carbon treatment of the *Aloe vera* whole leaf extract is used to remove bitterness and colour caused by the anthraquinone components of the latex. This results in a product termed “decolorized whole leaf extract” that has quite different properties from the whole leaf extract. *Aloe vera* decolorized whole leaf extract is also referred to as “whole leaf *Aloe vera* gel” (Boudreau *et al.*, 2013a). Dentali (2013) noted that an industry standard for aloin content of decolorized *Aloe vera* whole leaf extract is < 10 ppm. Sehgal *et al.* (2013) reported results of toxicological assessment of a commercial decolorized whole leaf extract that contained approximately Aloin A at 0.9 ppm, Aloin B at 1.3 ppm, and aloe-emodin at 0.2 ppm. A decolorized *Aloe vera* whole leaf extract assessed for safety by Shao

et al. (2013) was reported to contain combined Aloin A and Aloin B at < 0.1 ppm.

Although *Aloe vera* gel and the decolorized whole leaf extract are similar in that each contain little or no latex anthraquinones, carbon adsorption changes the physical and chemical properties of the whole leaf extract. *Aloe vera* decolorized whole leaf extract differs from the gel in that it exhibits a degradation in rheological properties and a loss of approximately 19–23% of the complex polysaccharide content (Pelley *et al.*, 1998).

(d) *Dried Aloe vera latex (pharmaceutical material)*

The dried *Aloe vera* latex is the solidified liquid originating in the cells of the pericycle and adjacent leaf parenchyma, and flowing spontaneously from the cut leaf, allowed to dry with or without the aid of heat (WHO, 1999). The material is used for medicinal purposes and its composition is specified in several official pharmacopoeias (see Section 1.6).

1.2 Analysis

For *Aloe vera* sold for medicinal purposes, analyses are defined in pharmacopoeial monographs (see Section 1.6). Most of the published analytical methods (Table 1.3) deal with the determination of the anthraquinone compounds in the latex, and fewer and mostly qualitative methods are available for authentication.

To carry out an exhaustive quality control of commercial *Aloe vera* gel products (e.g. for food or cosmetic uses), the following analyses should be carried out: (i) investigation of authenticity; (ii) test for identification of additives (to control the labelling or regulatory limits); and (iii) determination of the aloin content (Lachenmeier *et al.*, 2005; Rodríguez *et al.*, 2010). The investigation of authenticity aims at confirming the amount of *Aloe vera* in the preparation; adulteration

Table 1.3 Selected methods of analysis of *Aloe vera* constituents in various matrices

Sample matrix	Analyte/purpose of analysis	Sample preparation	Assay method	Detection limit	Reference
Urine	Aloin/detection of laxative abuse	Glucuronidase, SPE	HPTLC	10–20 mg/L	Perkins & Livesey (1993)
Urine	Aloe-emodin/detection of laxative abuse	Glucuronidase, Extraction with chloroform/isopropanol 9+1	HPLC/UV	0.015 mg/L	Stolk & Hoogtanders (1999)
Serum	Aloin/pharmacokinetic study	Extraction with ethyl acetate	TLC	0.033 mg/L	Ishii et al. (1987)
Plasma	Aloe-emodin/pharmacokinetic study	Dichloromethane extraction	HPLC/FD	4.5 µg/L	Zaffaroni et al. (2003)
Aloe leave exudates	Aloin/taxonomy	Methanolic solution	HPLC/UV	NA	Groom & Reynolds (1987)
<i>Aloe vera</i> gel	13 phenolic compounds/quality control and standardization	Liquid–liquid extraction	HPLC/UV	NA	Kim & Park (2006)
<i>Aloe vera</i> products	Acetylated polysaccharides, glucose, malic acid, lactic acid, and acetic acid/quality control	None (dissolve in D ₂ O)	NMR	< 0.05 µg/L	Jiao et al. (2010)
Aloe extracts and commercial formulations	Aloe-emodin/identity confirmation	Preparative TLC	HPLC/UV and FD	UV: 3 µg/L FD: 0.8 µg/L	Mandrioli et al. (2011)
<i>Aloe vera</i> plants	Metabolite profiling/metabolomics	Extraction with methanol. Derivatization with MSTFA for GC-IT-MS analysis	GC-IT-MS and UPLC-Q-TOF-MS	NA	Lee et al. (2012)
<i>Aloe vera</i> leaves	Aloin derivatives/regulatory control	Ultrasound-assisted extraction in methanol	HPLC-DAD, HPLC-MS, UPLC	3–10 mg/L	Azaroual et al. (2012)
Pharmaceutical formulations	<i>Aloe vera</i> polysaccharides/control for adulteration or degradation	None (dissolve in D ₂ O)	NMR	2 g/L	Davis & Goux (2009)
Cosmetics	Mannose/determination of quantity of <i>Aloe</i> in product	Extraction with diethyl ether and hydrolysis with sulfuric acid	HPTLC	3% of <i>Aloe vera</i> in cosmetic product	Geisser & Kratz (2010)
<i>Aloe</i> species	Aloin derivatives/authenticity control	Methanolic extraction	HPLC/UV	< 0.05 mg/L	Okamura et al. (1996)
<i>Aloe</i> exudate	Volatiles/flavour characterization for beverage industry	Ethanol 40% for HPLC, HS sampling for GC	HPLC, HS-GC/MS	NA	Saccù et al. (2001)

Table 1.3 (continued)

Sample matrix	Analyte/purpose of analysis	Sample preparation	Assay method	Detection limit	Reference
<i>Aloe vera</i> beverages	Profiling for identity, adulteration, dilution	None	HPTLC, HS-SPME-GC/MS	NA	Lachenmeier et al. (2005)
<i>Aloe</i> species	13 Phenolic compounds/seasonal variation	Extraction with ethanol	HPLC/UV	NA	Park et al. (1998)
Commercial aloe products	High molecular-weight polysaccharides	Dilution with water and 0.2 M NaCl	SEC	NA	Turner et al. (2004)
Commercial aloe products	Aloe-emodin, aloin A	Extraction with ethyl acetate/methanol 9+1	HPLC/MS	Aloin-A, 1 µg/L; Aloe emodin, 2.5 µg/L	Elsohly et al. (2007)
Commercial aloe products	Aloin A, aloin B	Extraction with ethanol/water (90+10)	HPLC	0.06 mg/L	Ramírez Durón et al. (2008)

DAD, diode array detector; FD, fluorescence detection; GC, gas chromatography; HPLC, high-performance liquid chromatography; HPTLC, high-performance thin-layer chromatography; HS, headspace; IT, ion trap; MS, mass spectrometry; MSTFA, *N*-methyl-*N*-(trimethylsilyl)trifluoroacetamide; NA, not applicable; NMR, nuclear magnetic resonance spectroscopy; Q-TOF, quadrupole-time of flight; SEC, size-exclusion chromatography; SPE, solid-phase extraction; SPME, solid-phase microextraction; TLC, thin-layer chromatography; UPLC, ultra-performance liquid chromatography; UV, ultraviolet

has been a major concern as a consequence of the high cost of the raw materials. Common adulterants have included maltodextrin in *Aloe vera* gel, powder or water in the liquid preparations ([Pelley et al., 1998](#)). Many authors have reviewed the considerable available amount of literature for analysis and authenticity control of *Aloe vera*. Besides various chromatographic approaches, nuclear magnetic resonance spectroscopy appears to be the method of choice for this purpose ([Table 1.3](#)). Common additives found in *Aloe vera* gel preparations, which can be detected by chromatographic methods, include preservatives such as benzoic acid and sorbic acid, or antioxidants such as ascorbic acid ([Lachenmeier et al., 2005](#)). Several methods to control the gel material for contamination with aloin are available (see review by [Rodríguez et al. \(2010\)](#) and [Table 1.3](#)).

1.3 Use

1.3.1 Indications

(a) Medicinal use

The *Aloe vera* plant has been used in folk medicine for more than 2000 years, and it remains an important component of traditional medicine in many contemporary cultures, such as China, India, the Caribbean, and Japan ([Grindlay & Reynolds, 1986](#)). *Aloe vera* first gained popularity in the USA in the 1930s with reports of successful use of freshly cut leaves in treating X-ray burns ([Ulbricht et al., 2007](#)). Both classes of *Aloe vera* leaf products, gel and latex, are reported to possess a wide range of pharmaceutical activities.

WHO lists the short-term treatment of occasional constipation as a use for *Aloe vera* latex that is supported by clinical data ([WHO, 1999](#)). The well established cathartic properties of anthraquinone glycosides provide strong evidence in support of the laxative properties of *Aloe vera* ([Ulbricht et al., 2007](#)). The European Medicines

Agency also found that the therapeutic indication as an “herbal product for short-term use in cases of occasional constipation” is a well established use of *Aloe vera* latex ([EMA, 2006](#)).

For the gel, WHO identified no uses supported by clinical data. Traditional uses include the external treatment of minor wounds and inflammatory skin disorders. The gel may be used in the treatment of minor skin irritations, including burns, bruises, and abrasions ([WHO, 1999](#)).

In recent times, the oral consumption of *Aloe vera* has been promoted as prophylaxis and therapy for a variety of unrelated systemic conditions. The scientific literature yields little to substantiate claims of usefulness for systemic conditions by the ingestion of *Aloe vera* ([Boudreau et al., 2013a](#)).

Aloe vera may be used in veterinary medicine as laxative or in topical applications, e.g. in udder disinfectants ([Leon, 2003](#)).

(b) Food use

Aloe vera extracts may be used in beverages as bitter flavouring agent ([O’Neil et al., 2006](#)). Food products include health and soft drinks, yoghurts, jams, instant tea granules, candies, alcoholic beverages, and ice cream ([Ahlawat & Khatkar, 2011](#)). *Aloe vera* may also be used in food supplements ([Steenkamp & Stewart, 2007](#)). The Dietary Supplements Label Database lists 43 products that contain *Aloe vera* as an active ingredient in amounts of 0.33 to 750 mg per capsule ([NLM, 2012](#)). *Aloe vera* whole leaf extract (which combines both the gel and latex) and *Aloe vera* decolorized whole leaf extract (from which most of the latex components have been removed) are popular as dietary supplements for various systemic ailments. The anthraquinone components of these products appear to vary significantly in their content of aloe-emodin and aloin A, the major anthraquinone constituent of *Aloe vera* latex. ([Elsohly et al., 2007](#)) evaluated 53 liquid and 30 semisolid and solid aloe-based commercial products. The liquid samples all

contained either aloe-emodin or aloin A at ≤ 10 ppm, with many having no detectable levels of either of the two compounds. Unlike liquid products, many solid and semisolid products (11 out of 30) contained one or both of the compounds, aloe-emodin and aloin A, at ≥ 10 ppm.

(c) Cosmetic use

The gel may be used as emollient and moisturizer in cosmetics and personal care products (O'Neil *et al.*, 2006). The gel is used in the cosmetics industry as a hydrating ingredient in liquids, creams, sun lotions, shaving creams, lip balms, healing ointments, and face packs (WHO, 1999). Other products containing *Aloe vera* include after-shave gel, mouthwash, hair tonic, shampoo, and skin-moistening gel (Newton, 2004).

Aloe vera may be used in cosmetics for marketing reasons (i.e. to impart a touch of "nature" to the product) rather than for actual effects, and the content may be normally kept at a low level (Committee of Experts on Cosmetic Products, 2008).

A study on skin hydration found that a single application of a cosmetic formulation containing $> 0.25\%$ of a commercial freeze-dried *Aloe vera* gel 200:1 concentrate improved the water content of the stratum corneum (Dal'Belo *et al.*, 2006). However, the concentrations of *Aloe vera* raw materials in cosmetics vary widely from 0.1% or less up to 20% (Cosmetic Ingredient Review Expert Panel, 2007).

Anthraquinone-rich *Aloe vera* extracts may function as absorbers of ultraviolet radiation in sunscreens, because anthraquinones absorb ultraviolet radiation (Committee of Experts on Cosmetic Products, 2008). Regulatory authorities in Germany have proposed that cosmetic products for which claims are made regarding *Aloe vera* should contain at least 5 g of *Aloe vera* per 100 g of product (Kratz, 2009).

1.3.2 Dosage

For medicinal use as a laxative, the correct individual dose is the smallest amount required to produce a soft-formed stool. For adults and children aged more than 10 years, the dose is 40–110 mg of the dried latex, corresponding to 10–30 mg of hydroxyanthraquinones per day, or 100 mg as a single dose in the evening (WHO, 1999). The European Medicines Agency suggests a maximum daily dose of hydroxyanthracene glycosides of 30 mg, and that the correct individual dose is the smallest required to produce a comfortable soft-formed motion (EMA, 2006). As for other laxatives, there is potential for abuse of *Aloe vera* latex (Perkins & Livesey, 1993; Stolk & Hoogtanders, 1999). It is difficult to estimate rates of laxative abuse, and more so for cases of abuse attributable to *Aloe vera* alone.

For medicinal use of *Aloe vera* gel, 25 to 100 mL per day of a 4.5:1 gel concentrate was suggested as typical oral dose range in adults (Morgan *et al.*, 2005). The International Aloe Science Council recommended a total daily consumption of *Aloe vera* of 2–8 fluid ounces (59–237 mL) of single-strength leaf gel (IASC, 2013b). For topical use, pure *Aloe vera* gel is often used liberally on the skin. Hydrophilic cream of 0.5% (by weight) of a 50% ethanol extract of *Aloe vera*, three times per day for five consecutive days per week has been used for treatment of genital herpes and psoriasis vulgaris (Ulbricht *et al.*, 2007).

1.4 Production, sales, and consumption

1.4.1 Production

(a) Production process

Aloe vera grows best in dry chalky soil or in a sandy loam (Grindlay & Reynolds, 1986). While the plant needs warm semi-tropical conditions, overexposure to sun results in stunted plants with low gel yield. Therefore, *Aloe vera* is commonly

interplanted with other crops, such as fruit trees. The quality of *Aloe vera* plant products varies considerably due to differences in growing, harvesting, processing, and storage techniques (Boudreau *et al.*, 2013a), and may also depend on the regulatory regime under which the product is sold (see Section 1.6).

Mexico, followed by the rest of Latin America, China, Thailand, and the USA were described as main producing countries (Rodríguez *et al.*, 2010). *Aloe vera* has become an important plant crop in Arizona and in the Rio Grande valley of southern Texas (Boudreau *et al.*, 2013a).

The production processes for *Aloe vera* products include various steps such as crushing, grinding or pressing, filtration, decolorization, stabilization, heat processing, and may be followed by addition of preservatives and stabilizers. A complete overview of production was provided by Ahlawat & Khatkar (2011). The technology for processing of *Aloe vera* gel was reviewed by Ramachandra & Rao (2008).

Harvesting of the leaves of the *Aloe vera* plant is generally performed by hand, with the leaves cut from the base of the plant (Grindlay & Reynolds, 1986). Individual leaves are wrapped, crated, and transported to processing plants. Ideally, the leaves are processed within a few hours after harvesting, as temperature, light, air, and humidity can affect the stability of the plant components (Paez *et al.*, 2000). At the processing step, the leaves may be cleaned with water and a mild chlorine solution (Grindlay & Reynolds, 1986).

Aloe vera gel from the fillet of the inner leaf pulp is obtained either by manual removal of the outer layers of the leaf with a knife or by machine. Either method can be flawed and has the potential to contaminate the gel with latex (Grindlay & Reynolds, 1986). This process yields crude *Aloe vera* gel. High quality gel appears opaque, slightly off-white in colour, and is viscous (Vogler & Ernst, 1999).

Aloe vera whole leaf extract is obtained by grinding the whole fresh leaves, without removal of the rind. Extraneous material and lignified fibres are then removed by homogenizing and filtering the crude gel or whole leaf extracts (Yaron, 1993). Since various amounts of latex and rind may be present in the whole leaf extracts, the extracts may appear yellow to yellow-green in colour.

Activated carbon adsorption to produce *Aloe vera* decolorized whole leaf extract is the first processing step where an extract is intentionally subjected to chemical alteration. *Aloe vera* decolorized whole leaf has lower rheological values than the gel and has a lower content of complex carbohydrates than either gel or whole leaf extracts (Pelley *et al.*, 1998).

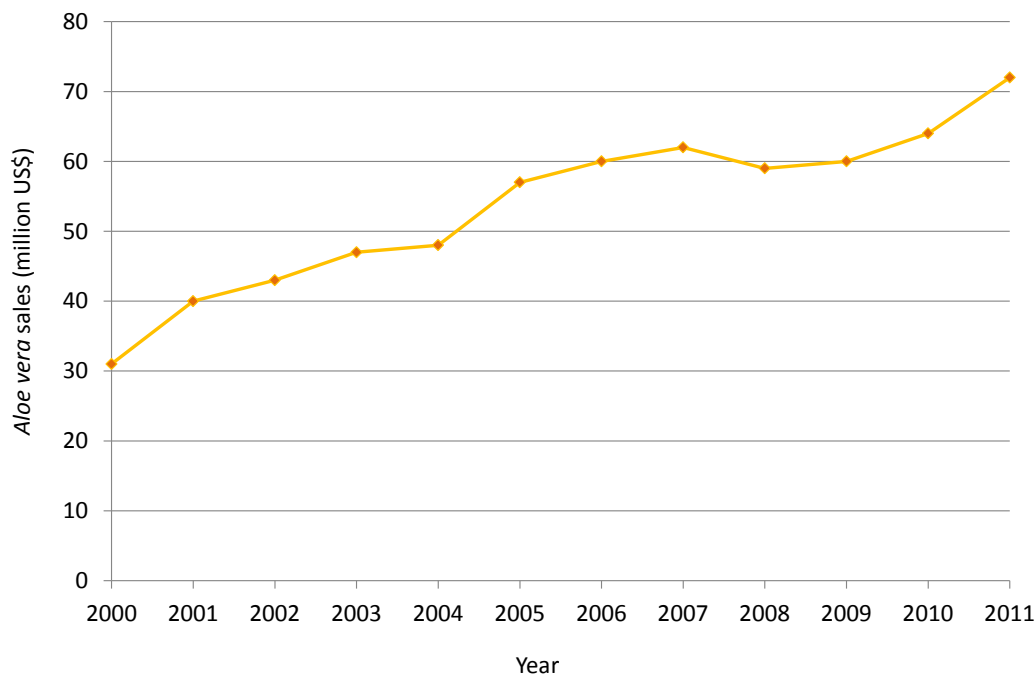
The processed extracts are difficult to keep stable, a problem that may cause differences in product potency; therefore, the gel or whole leaf extracts can undergo a stabilization process before being bottled. This process may involve pasteurization, ultraviolet stabilization, chemical oxidation with hydrogen peroxide, addition of chemical preservatives and additives, or concentration, and/or drying (Boudreau *et al.*, 2013a).

(b) Production volume

In the cosmetic industry, *Aloe vera* ingredients hold a prominent position at the top of the list showing the relative frequency of use of plant ingredients within formulations filed with the United States Food and Drug Administration (FDA) (Committee of Experts on Cosmetic Products, 2008).

1.4.2 Sales

According to the 2012 Nutrition Business Journal Annual Report, *Aloe vera* was 20th among best-selling dietary supplements in the USA. There has been a general upward trend in sales from US\$ 31 million in 2000 to US\$

Fig. 1.4 Sales of dietary supplements containing *Aloe vera* in the USA

Compiled by the Working Group from data in [Nutrition Business Journal \(2010, 2012\)](#).

72 million in 2011 ([Fig. 1.4](#); [Nutrition Business Journal, 2010, 2012](#)).

In 2006, the industry size for *Aloe* species raw material was estimated to be about US\$ 125 million worldwide, while the industry for finished products containing *Aloe vera* was around US\$ 110 billion ([Ahlawat & Khatkar, 2011](#)).

Global sales of *Aloe* species products in 2012 totalled US\$ 351 million, according to IMS Health MIDAS data. Most products were reported as derived from *Aloe vera* (90%). Substantial sales as a dietary supplement were reported in Brazil (US\$ 74 million), Indonesia (US\$ 50 million), India (US\$ 34 million), USA (US\$ 29 million), the Russian Federation (US\$ 19 million), Japan (US\$ 15 million), and Mexico (US\$ 12 million) ([IMS Health, 2012](#)).

1.4.3 Consumption

Consumers of products specified in Section 1.3 are exposed to *Aloe vera*. While the occasional short-term use of the latex as a laxative may allow exposure to be estimated for use in that context, it is unclear whether or not the gel products or liquid preparations are used over the short or long-term.

According to a representative survey conducted by the National Health and Nutrition Examination Survey from 1999 to 2010 ([NHANES, 2010](#)), the consumption of dietary supplements containing *Aloe vera* in the USA (prevalence of use in the past 30 days among adults in the USA) was 0.3% in 1999–2006 and 0.1% in 2007–2010 [figures calculated by the Working Group from publicly available data; due to the small use, the coefficient of variation is > 30%, so that the data for *Aloe vera* are less reliable than for other herbs]. In the context of complementary and alternative medicine, use

Table 1.4 Regulations for different *Aloe vera* products

Regulation	WHO Monograph on Selected Medicinal Plants (1999) ^a	Japanese Pharmacopoeia Sixteenth Edition (2011) ^b	European Pharmacopoeia 7.0 (2008) ^c	The International Aloe Science Council (2013) ^d
Regulated Aloe product	Dried juice	Dried juice	Concentrated and dried juice	Raw materials for use in products for oral consumption
Content	Min. 28% of hydroxyanthracene derivatives, expressed as aloin	Min. 4% aloin (dried material)	Min. 28% of hydroxyanthracene derivatives, expressed as aloin (dried drug)	Max. 10 ppm (aloin A + B)
Identity tests	Macroscopic and microscopic examinations, solvent solubility; TLC	Colour reactions with sodium tetraborate and nitric acid; TLC	TLC; fluorescence with disodium tetraborate; colour reaction with bromine water	Min. 5% acetylated mannan content by dry weight Organoleptic standards: Aloe solids in single strength juice (1% in leaf juice and 0.5% for inner leaf juice) Malic acid and glucose must be present at a minimum Whole leaf marker (isocitrate). Max. 5% for inner leaf by dry weight.
Moisture	Max. 12% for Curacao or Barbados Aloe	Contains 98.5% water		
Total ash	Max. 2%	Max. 2%	Max. 2%	< 40%
Loss on drying		Max. 12%	Max. 12%	
Foreign substances/contaminants	Limits for certain microorganisms, absence of adulterants such as black catechu, pieces of iron, and stones; limits for certain pesticides, heavy metals, and radioactive residues	Limits for certain microorganisms, pesticides, heavy metals, radioactive residues	Two different purity tests are specified	Microbiologicals (pathogens, lactic acid, mould, yeast), heavy metals, malto dextrin
Extract content	Min. 50% (water-soluble extract), max. 10% (alcohol-insoluble extract)	Min. 40% (water-soluble extract)		

^a WHO (1999)^b Eur.Ph (2008)^c JP XVI (2011)^d IASC (2013b)

max., maximum; min., minimum; TLC, thin-layer chromatography

of *Aloe vera* has been reported in 8.5–13.8% of people in predominantly Hispanic populations in the southern USA; according to surveys, it is also used frequently by 10.8%, 10.3%, and 7.6% of adults in Australia, Italy, and Jamaica, respectively ([Ngo et al., 2010](#)).

1.5 Occupational exposure

No specific studies on occupational exposure were identified. It can be assumed that workers in the production of *Aloe vera* may be exposed, as well as workers in pharmaceutical, cosmetic, and food industries that use *Aloe vera* as an ingredient.

1.6 Regulations and guidelines

Products made with various components of *Aloe vera* (aloin, aloe-emodin, and barbaloin) were at one time regulated by the FDA as oral over-the-counter (OTC) laxatives ([NCCAM, 2012](#)). In 2002, the FDA promulgated a regulation stating that the stimulant laxative ingredient *Aloe vera* in over the counter (OTC) drug products is not “generally recognized as safe and effective” or is misbranded ([FDA, 2002](#)). Because the companies that manufactured such products did not provide the necessary safety data, the FDA required that all OTC *Aloe vera* laxative products be removed from the USA market or reformulated ([NCCAM, 2012](#)). [The Working Group noted that currently no medicinal OTC *Aloe vera* products are available in the USA, unlike Europe where some medicinal *Aloe vera* products are still available.]

According to FDA regulations, *Aloe vera* may be safely used as a flavouring in foods as defined in 21CFR172.510. The Environmental Protection Agency (EPA) classified *Aloe vera* gel as a List 3 substance (inerts of unknown toxicity), and also listed *Aloe vera* gel as an inert ingredient of pesticide products ([SciFinder, 2013](#)).

A published tabulation of acceptable levels of natural flavourings by the Flavor and Extract Manufacturers’ Association indicates that an acceptable level of *Aloe vera* extract is 5–2000 ppm. No distinction is given for the part of the plant or type of plant extract used to produce the extract used as a flavouring additive ([Duke & Beckstrom-Sternberg, 1994](#)).

For cosmetic uses, many of the manufacturers of *Aloe vera* gel take care to supply an ingredient containing anthraquinones at no more than 50 ppm ([Committee of Experts on Cosmetic Products, 2008](#)). This maximum level was also demanded in a safety assessment of the cosmetic industry ([Cosmetic Ingredient Review Expert Panel, 2007](#)).

Aloe vera is specified in several official pharmacopoeias, and an industry quality standard of the International Aloe Science Council is also available ([Table 1.4](#)). An American Herbal Pharmacopoeia on “Aloe vera leaf, Aloe vera leaf juice, Aloe vera inner leaf juice” was provided ([AHP, 2012](#)).

2. Cancer in Humans

No data were available to the Working Group.

3. Cancer in Experimental Animals

3.1 Studies of carcinogenicity

Whole leaf extract of *Aloe barbadensis* Miller [*Aloe vera*] was tested for carcinogenicity by oral administration (drinking-water) in one study in mice and one study in rats.

3.1.1 Mouse

In a 2-year study of carcinogenicity, groups of 48 male and 48 female B6C3F₁ mice (age, 6–7 weeks) were given drinking-water containing 0 (controls), 1.0%, 2.0%, or 3.0% (wt/wt) whole leaf extract of *Aloe barbadensis* Miller [*Aloe vera*]

for 104 weeks. The average content of aloin A and aloe-emodin of the whole leaf test material was 6.40 and 0.071 mg/g respectively. The doses of whole leaf extract were equivalent to average daily doses of approximately 0, 2.9, 7.0, or 11.8 g/kg body weight (bw) in males; and 0, 2.2, 6.3, or 11.8 g/kg bw in females ([Boudreau et al., 2013a](#)). Survival of exposed groups was similar to that of controls. There was no significantly increased incidence of any tumour type in male or female mice. Whole leaf extract increased the incidence of goblet cell hyperplasia in the intestine of male and female mice ([Table 3.1](#)).

3.1.2 Rat

In a 2-year study of carcinogenicity, groups of 48 male and 48 female F344/N rats were given drinking-water containing whole leaf extract of *Aloe barbadensis* Miller [*Aloe vera*] at 0 (controls), 0.5%, 1.0%, or 1.5% (wt/wt) for 104 weeks. The average content of aloin A and aloe-emodin of the whole leaf test material was 6.40 and 0.071 mg/g, respectively. The doses of whole leaf extract were equivalent to average daily doses of approximately 0, 0.2, 0.6, or 1.1 g/kg bw in males and 0, 0.3, 0.7, or 1.3 g/kg bw in females ([Boudreau et al., 2013a](#)). Survival of exposed groups was similar to that of controls. Whole leaf extract caused increased incidences of adenoma and carcinoma of the large intestine (colon and caecum) in males and females. Other treatment-related lesions included hyperplasia and/or inflammation in the mesenteric lymph node, forestomach, small intestine, and large intestine in males and females ([Table 3.1](#)). [The Working Group noted that large intestine tumours are rare spontaneous neoplasms in F344/N rats.]

3.2 Photo-co-carcinogenicity studies

Mouse

There has been one study reported in which *Aloe barbadensis* Miller [*Aloe vera*] test articles were studied by dermal application in mice.

Groups of 36 male and 36 female Crl:SKH-1 (*hr/hr*) hairless mice (age, 8 weeks) received topical applications of control cream or creams containing: 3% or 6% (w/w) gel; 3% or 6% (w/w) whole leaf extract; 3% or 6% (w/w) decolorized whole leaf extract; or 7.46 or 74.6 µg/g of aloe-emodin to the dorsal skin region, for 5 days per week, for up to 40 weeks. After application of the cream in the morning, mice were exposed to filtered solar simulated light (SSL) at 0 (0.00 mJ.CIE/cm² per day) or 0.6 (13.70 mJ.CIE/cm² per day) minimal erythema doses of light ([NTP, 2010](#)). The minimal erythema dose is defined as the minimal amount of radiation that causes slight erythema within 24 hours after irradiation ([Table 3.2](#)). The mice were killed after a recovery/observation period of 12 weeks.

At 52 weeks, there was no significant increase in the incidence of skin neoplasms in any group receiving any of the four creams containing *Aloe* preparations without exposure to SSL. [The Working Group noted that the duration of the experiment, 1 year, was too short to consider this arm of the experiment as a full carcinogenicity study.]

There was no treatment-related increase in the incidence of skin neoplasms in any groups receiving any of the four creams containing *Aloe* preparations followed by SSL when compared with the groups receiving control cream followed by SSL. Almost all mice in groups exposed to SSL presented with skin neoplasms due to SSL exposure. [As a result, the primary experimental end-point was multiplicity of skin tumours.]

There was a significant enhancing effect of *Aloe* gel cream or of aloe-emodin cream on the photocarcinogenic activity of SSL in female mice, and there was a significant enhancing effect of the cream containing whole leaf extract, or cream containing decolorized whole leaf extract, on the photocarcinogenic activity of SSL in male and female mice, based on an increase in the multiplicity of squamous cell papilloma, carcinoma or carcinoma in situ (combined) ([NTP, 2010](#)).

Table 3.1 Studies of carcinogenicity in mice and rats given *Aloe vera* by oral administration

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, B6C3F ₁ (M, F) 104 wk Boudreau et al. (2013a)	Whole leaf extract of <i>Aloe barbadensis</i> Miller [<i>Aloe vera</i>]: 0 (control), 1.0%, 2.0%, or 3.0% (w/w) in drinking-water (estimated to be 0, 2.9, 7.0, or 11.8 g/kg bw (M); 0, 2.2, 6.3, or 11.8 g/kg bw (F)) 48 M and 48 F/group (age, 6–7 wk)	No significantly increased incidence of any tumour type		Aloin A content, 6.40 mg/g whole leaf test material Aloin-emodin content, 0.071 mg/g whole leaf.
Rat, F344/N (M, F) 104 wk Boudreau et al. (2013a)	Whole leaf extract of <i>Aloe barbadensis</i> Miller [<i>Aloe vera</i>]: 0 (control), 0.5%, 1.0%, or 1.5% (w/w) in drinking-water (estimated to be 0, 0.2, 0.6, or 1.1 g whole leaf/kg bw (M); 0, 0.3, 0.7, 1.3 g whole leaf/kg bw (F)) 48 M and 48 F/group (age, 6–7 wk)	All large intestine (colon and caecum) adenoma: M: 0/47 (0%) [#] , 0/48 (0%), 26/48 (54%)*, 23/48 (48%)* F: 0/48 (0%)*, 0/48 (0%), 6/48 (13%)*, 13/48 (27%)* All large intestine (colon and caecum) carcinoma: M: 0/47 (0%) [#] , 0/48 (0%), 10/48 (21%)*, 14/48 (29%)* F: 0/48 (0%) [#] , 0/48 (0%), 3/48 (6%), 4/48 (8%)* All large intestine (colon and caecum) adenoma or carcinoma (combined): M: 0/47 (0%) [#] , 0/48 (0%), 28/48 (58%)*, 31/48 (65%)* F: 0/48 (0%) [#] , 0/48 (0%), 8/48 (17%)*, 15/48 (31%)*	[#] $P \leq 0.001$ (trend) [#] $P \leq 0.01$ (trend) * $P \leq 0.001$ ** $P < 0.05$ *** $P \leq 0.01$	Aloin A content, 6.40 mg/g whole leaf Aloin-emodin content, 0.071 mg/g whole leaf

bw, body weight; F, female; M, male; wk, week; w, weight

Table 3.2 Co-carcinogenicity studies in SKH-1 mice given *Aloe vera* or aloë-emodin by skin application followed by exposure to simulated solar light

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Overall age-adjusted tumour multiplicity	Significance	Comments
Mouse, Crl:SKH-1 (<i>hr</i> / <i>hr</i>) hairless (M, F) 52 wk NTP (2010)	<i>Aloe vera</i> gel cream at 0%, 3%, or 6% (w/w) + SSL (13.70 mJ•CIE/cm ² per day). Cream applied in the morning; SSL in the afternoon. 5 d per wk for 40 wk, followed by 12-wk recovery/observation period 36 M and 36 F/group (age 8 wk)	Squamous cell papilloma, squamous cell carcinoma in situ, and/or squamous cell carcinoma of the skin: M: 5.8 (4.7–7.2), 6.8 (5.6–8.4), 7.1 (5.8–8.7) F: 6.4 (5.3–7.6)*, 9.2 (7.8–10.8)**, 8.1 (6.9–9.6)***	* $P < 0.05$ (trend) ** $P = 0.006$ *** $P < 0.05$	No significant increase in the incidence of skin neoplasms in any group receiving <i>Aloe vera</i> preparations without exposure to SSL
Mouse, Crl:SKH-1 (<i>hr</i> / <i>hr</i>) hairless (M, F) 52 wk NTP (2010)	Whole leaf <i>Aloe vera</i> cream at 0%, 3%, or 6% (w/w) + SSL (13.70 mJ•CIE/cm ² per day). Cream applied in the morning; SSL in the afternoon. 5 d per wk for 40 wk, followed by 12-wk recovery/observation period 36 M and 36 F/group (age 8 wk)	Squamous cell papilloma, squamous cell carcinoma in situ, and/or squamous cell carcinoma of the skin: M: 5.8* (4.7–7.2), 6.4 (5.2–7.9), 8.4** (6.8–10.3) F: 6.4* (5.3–7.6), 8.7** (7.4–10.3), 7.7 (6.5–9.1)	* $P < 0.05$ (trend) ** $P < 0.05$	
Mouse, Crl:SKH-1 (<i>hr</i> / <i>hr</i>) hairless (M, F) 52 wk NTP (2010)	Decolorized whole leaf <i>Aloe vera</i> cream at 0%, 3%, or 6% (w/w) + SSL (13.70 mJ•CIE/cm ² per day). Cream applied in the morning; SSL in the afternoon. 5 d per wk for 40 wk, followed by 12-wk recovery/observation period 36 M and 36 F/group (age 8 wk)	Squamous cell papilloma, squamous cell carcinoma in situ, and/or squamous cell carcinoma of the skin: M: 5.8 (4.6–7.3), 8.0* (6.5–9.9), 6.4 (5.2–8.0) F: 6.4** (5.2–7.7), 10.0*** (8.4–12.0), 9.3*** (7.8–11.1)	* $P < 0.05$ ** $P = 0.007$ (trend) *** $P = 0.002$ **** $P = 0.007$	
Mouse, Crl:SKH-1 (<i>hr</i> / <i>hr</i>) hairless (M, F) 52 wk NTP (2010)	Aloë-emodin cream at 0, 7.46, or 74.6 µg/g + SSL (13.70 mJ•CIE/cm ² per day). Cream applied in the morning; SSL in the afternoon. 5 d per wk for 40 wk, followed by 12 wk recovery/observation period 36 M and 36 F/group (age, 8 wk)	Squamous cell papilloma, squamous cell carcinoma in situ, and/or squamous cell carcinoma of the skin: M: 5.8 (4.7–7.2), 6.3 (5.1–7.8), 7.1 (5.8–8.7) F: 6.4* (5.3–7.7) 7.9 (6.6–9.4), 8.9** (7.5–10.6)	* $P < 0.05$ (trend) ** $P < 0.05$	

bw, body weight; CIE, Commission Internationale de l'Éclairage [International Commission on Illumination]; d, day; F, female; M, male; SSL, simulated solar light; wk, week

4. Mechanistic and Other Relevant Data

In reviewing studies relevant to the possible carcinogenicity of *Aloe vera*, the Working Group noted that attributing appropriate weight to individual studies was complicated by the consideration that, despite the terminology used, the material tested may not have been identical across various studies and/or may not have been identical to the material that was studied in experimental animals, as described in Section 3 of this *Monograph*.

4.1 Absorption, distribution, metabolism, and excretion

4.1.1 Humans

There were no reports of studies to determine the absorption, distribution, metabolism, or excretion of topically applied *Aloe vera* gel, whole leaf extract or decolorized whole leaf extract in experimental animals or humans.

Aloe vera whole leaf extract is composed of gel and latex. *Aloe vera* gel contains non-starch polysaccharides of high molecular weight (the major one being acemannan) that are composed of sugar moieties linked by β -1,4-glycosyl bonds (Fig. 1.3 in Section 1). *Aloe vera* latex contains the anthrone C-glycosides aloin A (barbaloin) and aloin B (isobarbaloin) that are linked by β -glycosyl bonds to D-glucopyranose. Other C-glycosides found in *Aloe vera* latex include aloesin (aloeresin B) and aloeresin A in which the glycosyl linkage is to the benzo ring of benzopyran-4-one (Boudreau & Beland, 2006). Aloenin, an O- β -glucoside, is also a component of *Aloe vera* latex (Hirata *et al.*, 1981; Matsuda *et al.*, 2008).

(a) Components of *Aloe vera* gel: metabolism *ex vivo*

Incubation of acemannan (aloemannan; molecular weight > 400 kDa) labelled with fluoresceinyl isothiocyanate (FITC) with a suspension of fresh human faeces for 5 days gave two metabolites, with molecular weights of 10 and 30 kDa, in 1% yield, meaning that aloemannan is catabolized by human intestinal bacteria (Yagi *et al.*, 1999).

(b) Components of *Aloe vera* latex

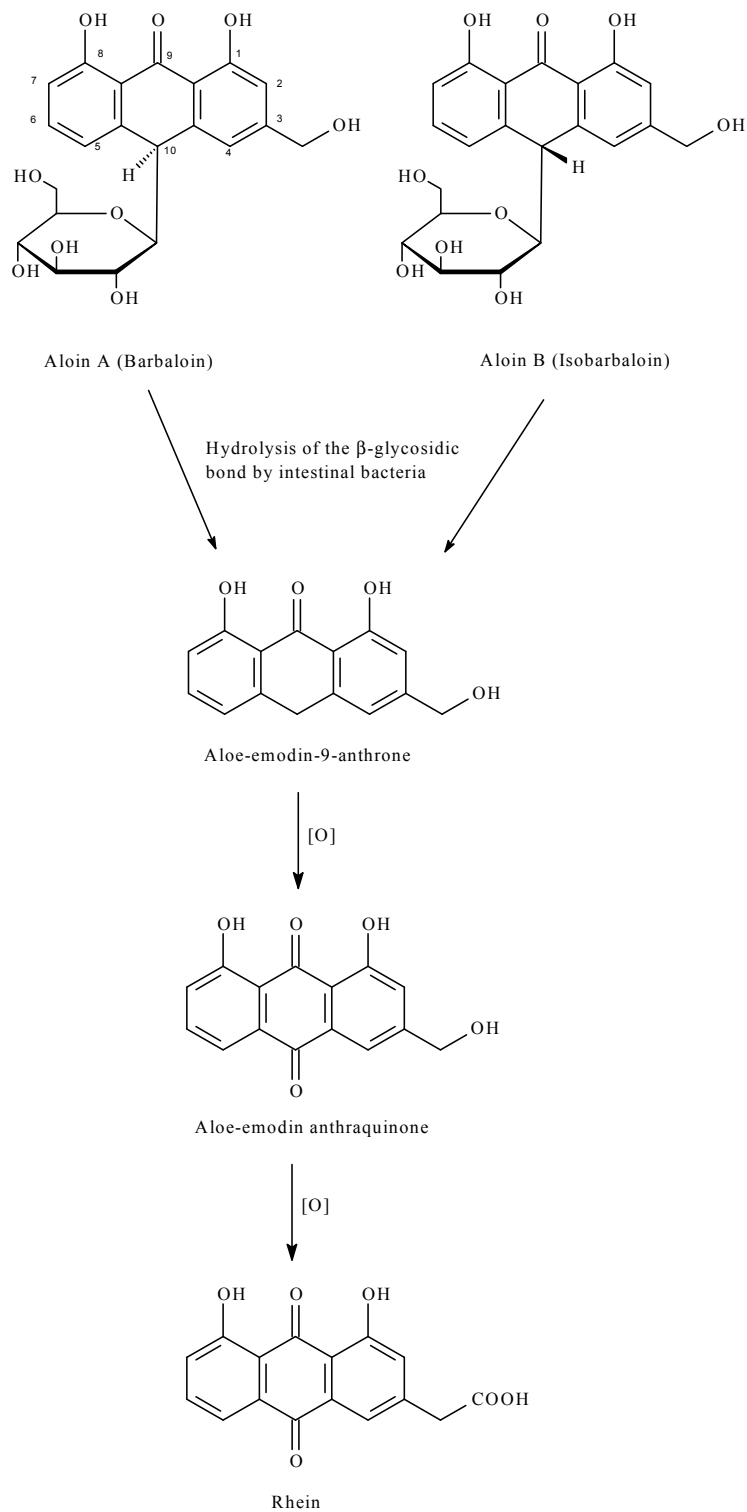
Orally ingested anthrone C-glycosides (*i.e.* aloin A and aloin B) pass intact through the upper portion of the gastrointestinal tract and upon reaching the lower gastrointestinal tract are cleaved to aloe-emodin-9-anthrone by human *Eubacterium* sp. BAR given to germ-free rats (Che *et al.*, 1991; Hattori *et al.*, 1993; Akao *et al.*, 1996). The free aglycone is then absorbed, undergoes oxidation, and is excreted in the urine as rhein, as was shown in three volunteers receiving *Aloe vera* or barbaloin (Vyth & Kamp, 1979; Fig. 4.1).

4.1.2 Experimental systems

(a) Components of *Aloe vera* gel

In beagle dogs, the oral administration of radiolabelled acemannan at a dose of 20 mg/kg body weight (bw) per day for 3 months resulted in peak blood concentrations at 4–6 hours and a half-life of > 48 hours (Fogleman *et al.*, 1992).

Male ddY mice were given FITC-labelled acemannan (aloemannan; molecular weight, 500 kDa) at a dose of 120 mg/kg bw by gavage, and urinary and faecal excretion was monitored for 48 hours. Of the administered dose, 95% was excreted in the faeces, with > 90% occurring within 24 hours. Only 0.3% of the material was found in the urine. In both urine and faeces, FITC-labelled acemannan was converted to substances of low molecular weight (< 9 kDa).

Fig. 4.1 Metabolites of aloin A and aloin B

Aloin A and B are constituents of *Aloe vera* whole leaf latex.
Compiled by the Working Group.

FITC-labelled acemannan was also administered to mice by intravenous injection at a dose of 120 mg/kg bw. Of the administered dose, 73% was excreted in the urine, with > 60% occurring within 24 hours; 13% of the material was found in the faeces. In both urine and faeces, FITC-labelled acemannan was converted to substances of low molecular weight (10–70 kDa in urine; 5 kDa in faeces) ([Yagi et al., 1999](#)).

(b) Components of *Aloe vera* latex

In male Wistar rats, oral administration of aloin A (barbaloin; 100 mg/kg bw) resulted in maximum serum concentrations of aloin A [340 ng/mL; ~0.8 μ M, based upon the molecular weight of aloin A of 404 Da] 1.5 hours after administration, followed by a decrease in concentration, with aloin A still detectable 6 hours after dosing ([Ishii et al., 1987](#)).

The ability to cleave anthrone C-glycosides varies among species; free anthrones are detected in faecal contents from humans and rats, but not mice or guinea-pigs ([Dreessen & Lemli, 1988](#); [Hattori et al., 1988](#)).

In male and female Brown-Norway rats, oral administration of [¹⁴C]aloe-emodin (4.5 mg/kg bw) resulted in maximum blood concentrations [~350 ng/mL; ~1.3 μ M, based upon the molecular weight of aloe-emodin of 270 Da] 2 hours after dosing, and a terminal half-life of elimination of approximately 50 hours. Seven metabolites were detected in the plasma. These were characterized as aloe-emodin, rhein, an unidentified aglycone, and conjugates of these aglycones. Approximately 20% of the radiolabel was eliminated in the urine, primarily as aloe-emodin, rhein, and their conjugates. More than 75% of the radiolabel was excreted in the faeces and nearly all of this was aloe-emodin. At early time-points (< 48 hours), a great majority of the radiolabel was associated with the gastrointestinal tract. At later time-points (i.e. 96 hours), the highest levels of radioactivity were found in the kidney and liver.

This material was characterized as aloe-emodin, rhein, and their conjugates ([Lang, 1993](#)).

Intracaecal administration of [¹⁴C]rhein to male Wistar rats resulted in 37% of the radioactivity being excreted in the urine and 53% in the faeces. The highest tissue concentrations were found in the kidney ([De Witte & Lemli, 1988](#)).

The oral administration of [¹⁴C]-labelled aloenin to rats resulted in the faecal and urinary excretion of the aglycone 4-methoxy-6-(2,4-dihydroxy-6-methylphenyl)-2-pyrone ([Hirata et al., 1981](#)).

4.1.3 Alterations in enzymes involved in metabolism

Incubation of the human colon carcinoma cell line LS180 with *Aloe vera* juice resulted in a significant increase in the expression of *CYP1A2*, *CYP3A4*, and multidrug resistance 1 genes ([Brandin et al., 2007](#)).

Commercial preparations of *Aloe vera* were tested for their ability to inhibit the activities of *CYP3A4* and *CYP2D6* in vitro. Inhibition was observed with half maximal inhibitory concentrations IC_{50} in the range 8–43 mg/mL, concentrations that were probably sufficiently high as to preclude any significant inhibition in vivo ([Djuv & Nilsen, 2012](#)). Rhein was shown to inhibit *CYP1A2*, *CYP2C9*, *CYP2D6*, *CYP2E1*, and *CYP3A* activities in rat liver microsomes, with K_i in the range of 10–74 μ M ([Tang et al., 2009](#)).

4.2 Genetic and related effects

4.2.1 Humans

No data were available to the Working Group.

4.2.2 Experimental systems

(a) DNA damage

An *Aloe vera* whole leaf extract induced single-strand breaks in pUC 9.1 plasmid DNA, and this was associated with decreased transformation efficiency of the plasmid ([Table 4.1](#); [Paes-Leme et al., 2005](#)).

Aloe-emodin and/or rhein induced DNA damage in NPC-039 and NPC-076 human nasopharyngeal carcinoma cells and SCC-4 human tongue cancer cells, as measured by comet assays ([Table 4.2](#); [Lin et al., 2007, 2010](#); [Chen et al., 2010](#)).

(b) End-points associated with DNA damage

In addition to inducing DNA damage (as indicated by comet assays), aloe-emodin significantly inhibited expression of genes associated with DNA damage and repair: ataxia telangiectasia mutated (*ATM*), ataxia telangiectasia and Rad3-related (*ATR*), 14-3-3 σ , breast cancer 1, early onset (*BRCA1*), and DNA-dependent serine/threonine protein kinase (*DNA-PK*) in SCC-4 human tongue squamous cancer cells ([Chen et al., 2010](#)). Aloe-emodin also induced the formation of reactive oxygen species (ROS) in SCC-4 cells, which was accompanied by S-phase cell-cycle arrest, apoptosis, and several molecular markers associated with apoptosis ([Chiu et al., 2009](#)). Rhein induced the formation of ROS in NPC-039 human nasopharyngeal carcinoma cells, SCC-4 human tongue squamous cancer cells, and A-549 human lung cancer cells, which was accompanied by apoptosis and several molecular markers associated with apoptosis ([Lin et al., 2007](#); [Hsia et al. 2009](#); [Lai et al., 2009](#)).

Aloe-emodin induced DNA damage in mouse lymphoma L5178 cells, as measured by comet assay ([Table 4.2](#); [Müller et al., 1996](#)).

(c) Gene mutation

Extracts in water, ethanol or methanol of *Aloe ferox* Mill., stabilized *Aloe vera* gel, *Aloe vera* whole leaf extract, *Aloe vera* decolorized whole

leaf extract, *Aloe vera* gel, acemannan, and aloin were tested in *Salmonella typhimurium* reverse mutation assays, *Bacillus subtilis* rec-assays, and/or SOS DNA damage-repair assays. With the exception of the *Bacillus subtilis* rec-assay with water extracts of *Aloe ferox* Mill., all gave negative results ([Table 4.1](#); [Table 4.2](#); [Brown & Dietrich, 1979](#); [Morimoto et al., 1982](#); [Boudreau et al., 2013a](#); [Sehgal et al., 2013a, b](#)).

Aloe-emodin was mutagenic in reversion assays with various strains of *Salmonella typhimurium*, at the *Tk*^{+/−} locus in mouse lymphoma L5178Y cells, and the *Gpt* locus in AS52 Chinese hamster cells ([Table 4.2](#); [Brown et al., 1977](#); [Brown & Dietrich, 1979](#); [Westendorf et al., 1990](#); [Heidemann et al., 1996](#); [Müller et al., 1996](#); [Müller & Stopper, 1999](#); [Nesslany et al., 2009](#)).

Mutation analysis of eight adenomas and four carcinomas from the large intestine of F344 rats given drinking-water containing an *Aloe vera* whole leaf extract ([Boudreau et al., 2013a, b](#)) indicated four point mutations in exons 1 and 2 of the *Kras* gene and four point mutations in exon 2 of the *Cttnb1* gene ([Table 4.1](#); [Pandiri et al., 2011](#)).

(d) Other genotoxicity end-points

Aloe vera inner leaf fillet Qmatrix® did not induce chromosomal aberration in Chinese hamster lung cells in vitro; micronuclei were not formed in bone-marrow cells of mice treated orally in vivo ([Williams et al., 2010](#); [Table 4.1](#)).

Aloe-emodin induced unscheduled DNA synthesis in primary hepatocytes from male Wistar rats, micronucleus formation in mouse lymphoma L5178Y cells and TK6 human lymphoblastoid cells, and chromosomal aberrations in Chinese hamster ovary cells. Aloe-emodin also inhibited topoisomerase II, gave positive results in comet assays in mouse lymphoma L5178Y cells, SCC-4 human tongue cancer cells, and NPC-039 human nasopharyngeal carcinoma cells, and transformed C3H/M2 mouse cells

Table 4.1 Genetic and related effects of *Aloe vera* preparations

Test system	Results		Dose (LED or HID)	<i>Aloe vera</i> preparation	Reference
	Without exogenous metabolic system	With exogenous metabolic system			
<i>In vitro</i> Single-strand breaks in pUC9.1 plasmid DNA	+	NT	3 µg/mL	Whole leaf extract	Paes-Leme et al. (2005)
<i>Bacillus subtilis</i> rec-assay	+	NT	6 mg/disk	<i>Aloe ferox</i> Mill. water extract	Morimoto et al. (1982)
<i>Bacillus subtilis</i> rec-assay	-	NT	6 mg/disk	<i>Aloe ferox</i> Mill. methanol extract	Morimoto et al. (1982)
<i>Salmonella typhimurium</i> , TA98, TA100, reverse mutation	-	-	10 mg/plate ^a	<i>Aloe ferox</i> Mill. water extract	Morimoto et al. (1982)
<i>Salmonella typhimurium</i> , TA98, TA100, reverse mutation	-	-	10 mg/plate ^b	<i>Aloe ferox</i> Mill. methanol extract	Morimoto et al. (1982)
<i>Salmonella typhimurium</i> , TA100, reverse mutation	-	-	NR	Stabilized gel; aloin A and aloin B, ≤ 10 ppm; in some instances, material was sterilized by filtration or autoclaving	Sehgal et al. (2013a)
<i>Salmonella typhimurium</i> , TA98, TA100, TA1535, TA1537, reverse mutation	-	-	10 mg/plate	Qmatrix [®] inner leaf fillet; aloin, < 10 ppm	Williams et al. (2010)
<i>Salmonella typhimurium</i> , TA98, TA100, reverse mutation	-	-	6 mg/plate	Whole leaf extract	Boudreau et al. (2013a)
<i>Salmonella typhimurium</i> , TA98, TA100, reverse mutation	-	-	6 mg/plate	Decolorized whole leaf extract	Boudreau et al. (2013a)
<i>Salmonella typhimurium</i> , TA97, TA98, TA100, TA1535, reverse mutation	-	-	10 mg/plate	Gel	Boudreau et al. (2013a)
<i>Salmonella typhimurium</i> , TA98, TA100, reverse mutation	-	-	21 × initial concentration	Decolorized whole leaf extract; aloin A & aloin B, ~1 ppm. Material sterilized by filtration.	Sehgal et al. (2013b)
<i>Escherichia coli</i> , WP2 <i>uvrA</i> /pKM101	-	-	6 mg/plate	Whole leaf extract	Boudreau et al. (2013a)
<i>Escherichia coli</i> , WP2 <i>uvrA</i> /pKM101	-	-	6 mg/plate	Decolorized whole leaf extract	Boudreau et al. (2013a)
<i>Escherichia coli</i> , WP2 <i>uvrA</i> /pKM101	-	-	3 mg/plate	Gel	Boudreau et al. (2013a)
<i>Escherichia coli</i> , SOS DNA damage repair assay	-	-	10 × initial concentration	Stabilized gel; aloin A and aloin B, ≤ 10 ppm	Sehgal et al. (2013a)

Table 4.1 (continued)

Test system	Results		Dose (LED or HID)	Aloe vera preparation	Reference
	Without exogenous metabolic system	With exogenous metabolic system			
<i>Escherichia coli</i> , SOS DNA damage repair assay	-	-	21 × initial concentration	Decolorized whole leaf extract; aloin A and aloin B, ~1 ppm. Material sterilized by filtration.	Sehgal et al. (2013b)
Chromosomal aberrations, Chinese hamster lung cells	-	-	10 mg/plate	Qmatrix inner leaf fillet; aloin, < 10 ppm	Williams et al. (2010)
<i>In vivo</i>					
Micronucleus formation, male ICR mice, bone-marrow cells	-	NT	5000 mg/kg bw, po	Qmatrix inner leaf fillet; aloin, < 10 ppm	Williams et al. (2010)
Gene mutations in exon 1 and 2 of <i>Kras</i> gene in large intestine adenomas and carcinomas, F344 rats	+	NT	1%	Whole leaf preparation	Pandiri et al. (2011)
Gene mutations in exon 2 of <i>Cttnb1</i> gene in large intestine adenomas and carcinomas, F344 rats	+	NT	1%	Whole leaf preparation	Pandiri et al. (2011)

+, positive; -, negative; LED, lowest effective dose; HID, highest ineffective dose; NR, not reported; NT, not tested; po, per oral

^a Toxic in TA98, without exogenous metabolic system, and in TA100, with or without exogenous metabolic system

^b Toxic in TA98, without exogenous metabolic system

Table 4.2 Genetic and related effects of constituents of *Aloe vera*

Constituent	Test system	Results		Dose (LED or HID)	Reference
		Without exogenous metabolic system	With exogenous metabolic system		
<i>Acemannan</i>					
<i>Salmonella typhimurium</i> reverse mutation <i>in vitro</i>		-	-	800 µL/plate	Fogleman et al. (1992)
<i>Aloin</i>					
<i>Salmonella typhimurium</i> , TA1535, TA100, TA1537, TA1538, TA98, TA100FR50, reverse mutation <i>in vitro</i>		-	-	250 µg/plate	Brown & Dietrich (1979)
<i>Aloe-emodin in vitro</i>					
<i>Salmonella typhimurium</i> , TA1537, reverse mutation		+	-	100 µg/plate	Brown et al. (1977) , Brown & Dietrich (1979)
<i>Salmonella typhimurium</i> , TA1535, TA100, TA1538, TA98, TA100FR50, reverse mutation		-	-	250 µg/plate	Brown et al. (1977) , Brown & Dietrich (1979)
<i>Salmonella typhimurium</i> , TA1537, TA102, TA1538, TA98, TA1978, reverse mutation		+ ^a	+ ^b	10 µg/plate	Westendorf et al. (1990)
<i>Salmonella typhimurium</i> , TA98, TA100, TA1535, TA1537, TA1538, reverse mutation		+ ^c	+ ^d	10 µg/plate	Heidemann et al. (1996)
<i>Salmonella typhimurium</i> , TA1537, TA98, TA100, reverse mutation		+	+	0.62 µg/plate	Nesslany et al. (2009)
Unscheduled DNA synthesis, male Wistar rat primary hepatocytes		+	NT	25 µg/mL	Westendorf et al. (1990)
Gene mutation, Chinese hamster lung V79 cells, 8-azaguanine resistance		(+)	NT	10 µg/mL	Westendorf et al. (1990)
Gene mutation, Chinese hamster lung V79 cells, <i>Hprt</i> locus, 6-thioguanine resistance		-	-	350 µg/mL	Heidemann et al. (1996)
Gene mutation, Chinese hamster lung V79 cells, <i>Hprt</i> locus, 6-thioguanine resistance		-	-	350 µg/mL	Brusick & Mengs (1997)
Gene mutation, mouse lymphoma L5178Y cells, <i>Tk</i> ^{+/+} locus, trifluorothymidine resistance		+	NT	37 µM	Müller et al. (1996)
Gene mutation, mouse lymphoma L5178Y cells, <i>Tk</i> ^{+/+} locus, trifluorothymidine resistance		+ ^e	NT	100 µM	Müller & Stopper (1999)
Gene mutation, AS52 Chinese hamster cells, <i>Gpt</i> locus		+	NT	28 µM	Müller et al. (1996)
Micronucleus formation, mouse lymphoma L5178Y cells		+	NT	37 µM	Müller et al. (1996)
Micronucleus formation, TK6 human lymphoblastoid cells		+	+	3.12 µg/mL	Nesslany et al. (2009)
Chromosomal aberrations, Chinese hamster ovary cells		+	+	18.75 µg/mL	Heidemann et al. (1996)
Topoisomerase II inhibition, decatenation of kDNA ^f		+	NT	1 mM	Müller et al. (1996)
Topoisomerase II inhibition, decatenation of kDNA ^f		+	NT	741 µM ^g	Müller & Stopper (1999)
DNA damage, comet assay, mouse lymphoma L5178Y cells		+	NT	55 µM	Müller et al. (1996)
DNA fragmentation, comet assay, SCC-4 human tongue cancer cells		+	NT	100 µM	Chen et al. (2010)

Table 4.2 (continued)

Constituent	Test system	Results		Dose (LED or HID)	Reference
		Without exogenous metabolic system	With exogenous metabolic system		
DNA fragmentation, comet assay, NPC-039 & NPC-076 human nasopharyngeal carcinoma cells		+	NT	60 µM	Lin et al. (2010)
Cell transformation, C3H/M2 mouse fibroblast cells		+	NT	3 µg/mL	Westendorf et al. (1990)
<i>Aloe-emodin in vivo</i>					
Chromosomal aberrations, Wistar rats, bone-marrow cells		-	NT	200 mg/kg bw, po	Heidemann et al. (1996)
Micronucleus formation, polychromatic erythrocytes, NMRI mice, bone-marrow cells		-	NT	1500 mg/kg bw, po	Heidemann et al. (1996)
Spot test in F1 offspring of NMRI female mice, X DBA male mice		-	NT	2000 mg/kg bw, po ^h	Heidemann et al. (1996)
Unscheduled DNA synthesis, hepatocytes of Wistar rats treated in vivo		-	NT	1000 mg/kg bw, po	Heidemann et al. (1996)
DNA damage, comet assay, male OF1 mice, kidney and colon, treated in vivo		+	NT	500 mg/kg bw, po	Nesslany et al. (2009)
<i>Rhein</i>					
<i>Salmonella typhimurium</i> , TA1537, TA102, TA1538, TA98, TA1978, reverse mutation		-	(+) ^j	NR	Westendorf et al. (1990)
Unscheduled DNA synthesis, male Wistar rat primary hepatocytes		-	NT	NR	Westendorf et al. (1990)
Gene mutation, Chinese hamster lung V79 cells, 8-azaguanine resistance		-	NT	NR	Westendorf et al. (1990)
DNA fragmentation, comet assay, NPC-039 human nasopharyngeal carcinoma cells		+	NT	180 µM	Lin et al. (2007)
DNA fragmentation, comet assay, SCC-4 human cancer tongue cells		+	NT	50 µM	Chen et al. (2010)
Cell transformation, C3H/M2 mouse cells		-	NT	NR	Westendorf et al. (1990)
Cell transformation, C3H/M2 mouse fibroblast cells		-	NT	10 µg/mL	Wölfle et al. (1990)

+, positive; (+), weakly positive; -, negative; bw, body weight; HID, highest ineffective dose; LED, lowest ineffective dose; NR, not reported; NT, not tested; po, oral

^a Not positive in TA102

^b Not positive in TA102 or TA1978

^c Positive only in TA98, TA1537, and TA1538

^d Positive only in TA1538

^e Mutations associated with loss of heterozygosity.

^f kDNA, kinetoplast DNA, a catenated network of mitochondrial DNA rings isolated from *Crithidia fasciculata*.

^g IC₅₀ = 741 ± 272 µM, represents the concentration at which the catalytic activity of the topoisomerase II was reduced to 50%.

^h The mother mice were treated on day 9 of the pregnancy.

ⁱ In TA1537 only.

(Table 4.2; [Heidemann et al., 1996](#); [Müller et al., 1996](#); [Müller & Stopper, 1999](#); [Lin et al., 2010](#)).

Rhein gave positive results in comet assays in SCC-4 human tongue cancer cells and NPC-039 human nasopharyngeal carcinoma cells ([Table 4.2](#); [Lin et al., 2007](#); [Chen et al., 2010](#)).

4.3 Toxic effects and other mechanistic data

[The Working Group noted that the following studies would have been strengthened by the inclusion of positive controls, and *Aloe vera* whole leaf was not included for comparison.]

Short-term studies were conducted in which technical-grade acemannan (acemannan, 78%) was fed to male and female Sprague-Dawley rats at doses up to 2000 mg/kg bw per day for 6 months, and to male and female beagle dogs at doses up to 1500 mg/kg bw per day for 90 days. There were no significant gross or microscopic lesions in either species that could be associated with the dietary administration of acemannan ([Fogleman et al., 1992](#)).

Short-term studies were conducted in which *Aloe vera* gel (designated “process A aloe”) or charcoal-treated *Aloe vera* gel (designated “process B aloe”) were fed to male F344 rats at dietary concentrations of 1% or 10% for up to 7 months [corresponding to doses of *Aloe vera* gel of ~0.33 and 3.3 g per kg bw per day]. Gross and microscopic histopathological analyses indicated that there were no significant differences between the control rats and rats fed either of the *Aloe vera* preparations ([Herlihy et al., 1998](#)).

Male F344 rats were given drinking-water containing *Aloe vera* gel at a concentration of 1% [~0.2 g/kg bw per day], or charcoal-treated *Aloe vera* gel at 1% [~0.2 g/kg bw per day], or charcoal-treated *Aloe vera* whole leaf at 0.02% [amount consumed could not be determined] for 30 months. None of the treatments caused any obvious histopathological changes ([Ikeno et al., 2002](#)).

Male and female Sprague-Dawley rats were treated by gavage with an *Aloe vera* preparation designated Qmatrix® at a dose of 0, 500, 1000, or 2000 mg/kg bw per day for 90 days. This material was prepared from *Aloe vera* inner leaf fillets and was further treated to reduce the aloin content to < 10 ppm. At necroscopy, there were no gross or histopathological alterations that could be ascribed to treatment with *Aloe vera* ([Williams et al., 2010](#)).

Short-term studies were conducted in which charcoal-treated *Aloe vera* gel (designated “Aloe juice”) was fed to male and female B6C3F₁ mice at a dose of 350–540 mg per day for 13 weeks. At necropsy, no significant differences were observed between mice fed Aloe juice and the control mice. Likewise, histopathological examination of the livers revealed no treatment-related lesions ([Sehgal et al., 2013a](#)).

Male and female Wistar Hannover rats fed whole leaf powder from *Aloe arborescens* Miller var. *natalensis* Berger at a dietary concentration of 0%, 0.16%, 0.8%, or 4% [corresponding to doses of whole leaf powder of 0, 99, 486, and 2447 mg per kg bw per day] for 1 or 2 years showed severe sinus dilatation and yellowish pigmentation of the ileocaecal lymph nodes, as well as yellow-brown pigmentation of the renal tubules. Rats from the 2-year study also showed pigmentation, epithelial thickening, and atypical hyperplasia of the large intestine ([Matsuda et al., 2008](#); [Yokohira et al., 2009](#)).

Male and female F344Du rats given drinking-water containing *Aloe vera* decolorized whole leaf juice at 0%, 0.5%, 1%, or 2% [corresponding to doses of decolorized whole leaf juice of 0, 565, 1201, and 2382 mg per kg bw per day] for 3 months. No alterations were detected upon histopathological examination of the caecum and colon ([Shao et al., 2013](#)).

Male and female B6C3F₁ mice were given an *Aloe vera* decolorized whole leaf extract to which had been added a high-molecular-weight *Aloe vera* polysaccharide designated Aloesorb,

by gavage, twice in 24 hours. The material was administered at 1% of the mouse body weight [the absolute amount of the decolorized whole leaf extract administered could not be determined] and the mice were monitored for up to 14 days after treatment. No adverse effects were detected. The same *Aloe* preparation was also mixed in the diet at a concentration of 100 g/kg and fed to male and female F344 rats for 3 months [total amount administered, 10 g of decolorized whole leaf extract per g bw]. Histopathological examination of the caecum, colon, and rectum indicated no significant alterations ([Sehgal et al., 2013b](#)).

Male and female F344/N rats exposed to drinking-water containing *Aloe vera* whole leaf extract at 1%, 2%, or 3% [corresponding to whole leaf extract at approximately 1.2, 2.4, and 3.6 g per kg bw per day] for 13 weeks, or *Aloe vera* whole leaf extract at 0.5%, 1.0%, or 1.5% [corresponding to whole leaf extract at 0.25, 0.65, and 1.2 g per kg bw per day] for 2 years, had dose-related increases in the incidence and severity of goblet cell and lymph node hyperplasia in the large intestine. Goblet cell hyperplasia also occurred in the large intestine of B6C3F₁ mice given drinking-water containing *Aloe vera* whole leaf extract at 1%, 2%, or 3% [corresponding to whole leaf extract at 2.55, 6.65, and 11.8 g per kg bw per day] for 13 weeks, but with lesser severity than that observed in rats ([Boudreau et al., 2013a, b](#)).

Aloe vera Liliaceae was extracted with 95% ethanol, the solvent was evaporated, and the residue was administered in the drinking-water at a dose of 100 mg/kg bw to male Swiss albino mice for 3 months. Of the treated mice, 30% (6/20) died compared with 10% (2/20) of the control mice, a difference that was not statistically significant. Mice treated with the *Aloe vera* preparation had an increased incidence ($P < 0.01$) of sperm abnormalities, including megacephaly, flat head, swollen acrosome, and rotated head ([Shah et al., 1989](#)). [The identity of the material being tested was not certain.]

4.4 Other mechanistic data

Gastrointestinal transit times were measured in B6C3F₁ mice and F344/N rats given drinking-water containing *Aloe vera* whole leaf extract (aloin A, 14.1–15.9 mg per g of extract), *Aloe vera* decolorized whole leaf extract (aloin A, 0.06–0.2 mg per g of extract), or *Aloe vera* gel (aloin A, 1.1–1.4 mg per g of gel) for 14 days. Without treatment, B6C3F₁ mice have shorter transit times than F344/N rats. *Aloe vera* whole leaf extract decreased transit times in the rats, but not in mice. A decrease in gastrointestinal transit times was also observed in a 13-week study in F344/N rats, but not B6C3F₁ mice, receiving *Aloe vera* whole leaf extract ([Boudreau et al., 2013a, b](#)).

Molecular pathways shown to be important in human colorectal carcinogenesis, including mitogen-activated protein kinases *MAPK*, *WNT*, and transforming growth factor *TGF-β* signaling pathways, were also altered in adenomas and carcinomas of the large intestine in F344 rats given drinking-water containing *Aloe vera* whole leaf preparations at 1% and 1.5% ([Pandiri et al., 2011](#)).

Aloe vera whole leaf preparations were incubated with pure and mixed human gut-bacteria cultures. The *Aloe vera* preparations possessed bacteriogenic activity and altered the production of acetic acid, butyric acid, and propionic acid ([Pogribna et al., 2008](#)).

4.5 Susceptibility

No data were available to the Working Group.

4.6 Mechanistic considerations

Upon oral ingestion, *Aloe vera* components pass through the upper portion of the gastrointestinal tract; upon reaching the lower gastrointestinal tract, the anthrone C-glycosides aloin A and aloin B are converted by the intestinal microflora to aloe-emodin-9-anthrone, which

undergoes sequential oxidation to aloe-emodin and rhein (Fig. 4.1). Likewise, intestinal microflora metabolize acemannan to smaller compounds by cleavage of the β -1 \rightarrow 4 linkages.

The oral administration of *Aloe vera* whole leaf preparation induces hyperplasia of the large intestine in mice and rats, and adenomas and carcinomas of the large intestine in rats. Rats dosed orally with acemannan for up to 6 months did not display any treatment-related pathological changes. Likewise, rats given *Aloe vera* gel orally, and mice and rats given charcoal-treated *Aloe vera* gel did not show any treatment-related non-neoplastic or neoplastic lesions.

Aloe vera preparations, acemannan, and aloin A do not display genotoxic activity in bacterial assays for mutagenesis and/or other assays for genotoxicity. In contrast, aloe-emodin is mutagenic in *Salmonella typhimurium* reversion assays, induces unscheduled DNA synthesis, gene mutations, micronucleus formation, and chromosomal aberrations, inhibits topoisomerase II, and gives positive results in comet assays. These data suggest that the neoplastic response observed with *Aloe vera* is a consequence of the conversion of the anthrone C-glycosides to aloe-emodin, which by itself or in combination with other *Aloe vera* components is responsible for the development of adenomas and carcinomas in the large intestine.

In the 2-year bioassays with *Aloe vera* whole leaf preparations, mice were exposed to nearly 10 times more test material (on a per kg bw basis) than rats. In spite of this higher exposure, the mice did not develop adenoma or carcinoma of the large intestine, which may be due to the fact that the intestinal bacteria in mice are less efficient than the intestinal bacteria of rats in converting aloin A and aloin B to aloe-emodin anthrone and subsequently aloe-emodin. In addition, mice have shorter gastrointestinal tracts and faster gastrointestinal transit times than rats, which could contribute to the lack of a tumour response in mice.

Although the carcinogenicity of *Aloe vera* appears to be dependent upon the presence of the anthraquinone fraction, in particular aloe-emodin, the mechanism by which this fraction causes intestinal tumours is presently unknown. The administration of *Aloe vera* whole leaf preparations to rats induced non-neoplastic lesions (i.e. goblet cell hyperplasia) that are not observed with other *Aloe vera* preparations (e.g. *Aloe vera* gel, decolorized gel, or decolorized whole leaf). These non-neoplastic changes may result in the formation of ROS that could promote neoplastic progression. Aloe-emodin has been shown to generate ROS after incubation with human cells in vitro, probably as a result of its anthraquinone structure. Aloe-emodin also contains a benzylic hydroxy moiety that has the potential to undergo esterification (e.g. sulfation) to a reactive electrophile that could bind to DNA. This pathway does not appear to have been investigated. The incubation of *Aloe vera* whole leaf preparations with human intestinal microflora results in an increased production of short-chain fatty acids. The impact of this increased production is presently not clear. Although the mechanism by which *Aloe vera* whole leaf preparations induce intestinal neoplasms in rats is not fully understood, it is clear that the molecular pathways observed in the intestinal neoplasms induced in rats by *Aloe vera* whole leaf preparations are also observed in human colorectal cancers.

5. Summary of Data Reported

5.1 Exposure data

Aloe vera, also known as *Aloe barbadensis*, is a perennial succulent plant with green fleshy leaves. The leaves contain two types of liquids: a yellow bitter latex under the skin, and a viscous gel in the inner section. Commercial products are made from processed leaves. Four major types of processed products were identified: whole leaf

extract; decolorized whole leaf extract; inner-leaf gel; and dried bitter latex. Decolorization removes pigments and anthraquinones from the whole leaf extract. The dried latex has medicinal uses as a laxative. The other forms are used in foods, dietary supplements, beverages, and cosmetic products. Exposure data, where they exist, do not identify the nature of products containing *Aloe vera* used by consumers.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

Whole leaf extract of *Aloe vera* was tested for carcinogenicity after oral administration in one 2-year study in mice, and one 2-year study in rats.

In male and female rats, drinking-water containing whole leaf extract of *Aloe vera* caused significantly increased incidences of adenoma of the large intestine (colon and caecum) and carcinoma of the large intestine (colon and caecum), tumours rarely developed spontaneously in rats.

In the 2-year study in mice, there was no significantly increased incidence of any type of tumours in males or females given drinking-water containing whole leaf extract of *Aloe vera*.

In a study of photo-co-carcinogenesis with simulated sunlight, four articles were studied by skin application in hairless mice: three test articles containing *Aloe vera* that included gel, whole leaf extract, and decolorized whole leaf extract; and an aloe-emodin preparation. Almost all mice exposed to simulated sunlight developed skin neoplasms. No increase in the incidence of skin neoplasms was observed in the groups receiving any of the four test articles applied as a cream followed by simulated sunlight when compared with the group receiving control cream followed by simulated sunlight. There was a significant

enhancing effect of *Aloe vera* gel cream or aloe-emodin cream on the photocarcinogenic activity of simulated sunlight in female mice based on an increase in the multiplicity of squamous cell papilloma, carcinoma or carcinoma in situ (combined). There was a significant enhancing effect of the whole leaf extract cream or decolorized whole leaf extract cream on the photocarcinogenic activity of simulated sunlight in both male and female mice, based on an increase in the multiplicity of squamous cell papilloma, carcinoma or carcinoma in situ (combined).

5.4 Mechanistic and other relevant data

The C-glycosides aloin A and aloin B, which are components of *Aloe vera* latex, are converted to aloe-emodin-9-anthrone by bacteria present in the gastrointestinal tract of rats and humans. Aloe-emodin-9-anthrone undergoes sequential oxidation to aloe-emodin and rhein. Preparations of *Aloe vera*, acemannan, and aloin A, do not display genotoxic activity in assays for mutagenesis in bacteria and/or other assays for genotoxicity. In contrast, aloe-emodin has genotoxic activity. These data suggest that the neoplastic response observed with *Aloe vera* is a consequence of the conversion of the anthrone C-glycosides to aloe-emodin, which by itself or in combination with other components of *Aloe vera* is responsible for the adenomas and carcinomas in the large intestine of rats.

6. Evaluation

6.1 Cancer in humans

There is inadequate evidence in humans for the carcinogenicity of *Aloe vera*.

6.2 Cancer in experimental animals

There is *sufficient evidence* in experimental animals for the carcinogenicity of whole leaf extract of *Aloe vera*.

6.3 Overall evaluation

Whole leaf extract of *Aloe vera* is *possibly carcinogenic to humans (Group 2B)*.

References

- Ahlawat KS & Khatkar BS (2011). Processing, food applications and safety of aloe vera products: a review. *J Food Sci Technol*, 48(5):525–33. doi:[10.1007/s13197-011-0229-z](https://doi.org/10.1007/s13197-011-0229-z) PMID:[23572784](https://pubmed.ncbi.nlm.nih.gov/23572784/)
- AHP; American Herbal Pharmacopoeia (2012). Aloe Vera Leaf, Aloe Vera Leaf Juice, Aloe Vera Inner Leaf Juice. Scotts Valley (CA): American Herbal Pharmacopoeia.
- Akao T, Che Q-M, Kobashi K, Hattori M, Namba T (1996). A purgative action of barbaloin is induced by Eubacterium sp. strain BAR, a human intestinal anaerobe, capable of transforming barbaloin to aloe-emodin anthrone. *Biol Pharm Bull*, 19(1):136–8. doi:[10.1248/bpb.19.136](https://doi.org/10.1248/bpb.19.136) PMID:[8820926](https://pubmed.ncbi.nlm.nih.gov/8820926/)
- Azaroual L, Liazid A, Barbero GF, Brigui J, Palma M, Barroso CG (2012). Improved chromatographic methods for determination of bioactive compounds from *Aloe vera* leaves. *ISRN Chromatography*, 2012:1–7. doi:[10.5402/2012/609095](https://doi.org/10.5402/2012/609095)
- Boudreau MD & Beland FA (2006). An evaluation of the biological and toxicological properties of Aloe barbadensis (miller), Aloe vera. *J Environ Sci Health C Environ Carcinog Ecotoxicol Rev*, 24(1):103–54. doi:[10.1080/10590500600614303](https://doi.org/10.1080/10590500600614303) PMID:[16690538](https://pubmed.ncbi.nlm.nih.gov/16690538/)
- Boudreau MD, Beland FA, Nichols JA, Pogribna M (2013a). Toxicology and carcinogenesis studies of a noncolorized whole leaf extract of Aloe barbadensis Miller (Aloe vera) in F344/N rats and B6C3F1 mice (drinking water study). *Natl Toxicol Program Tech Rep Ser*, 577(577):1–266. PMID:[24042237](https://pubmed.ncbi.nlm.nih.gov/24042237/)
- Boudreau MD, Mellick PW, Olson GR, Felton RP, Thorn BT, Beland FA (2013b). Clear evidence of carcinogenic activity by a whole-leaf extract of Aloe barbadensis miller (aloe vera) in F344/N rats. *Toxicol Sci*, 131(1):26–39. doi:[10.1093/toxsci/kfs275](https://doi.org/10.1093/toxsci/kfs275) PMID:[22968693](https://pubmed.ncbi.nlm.nih.gov/22968693/)
- Brandin H, Viitanen E, Myrberg O, Arvidsson A-K (2007). Effects of herbal medicinal products and food supplements on induction of CYP1A2, CYP3A4 and MDR1 in the human colon carcinoma cell line LS180. *Phytother Res*, 21(3):239–44. doi:[10.1002/ptr.2057](https://doi.org/10.1002/ptr.2057) PMID:[17163579](https://pubmed.ncbi.nlm.nih.gov/17163579/)
- Brown JP & Dietrich PS (1979). Mutagenicity of anthraquinone and benzanthrone derivatives in the Salmonella/microsome test: activation of anthraquinone glycosides by enzymic extracts of rat cecal bacteria. *Mutat Res*, 66(1):9–24. doi:[10.1016/0165-1218\(79\)90003-X](https://doi.org/10.1016/0165-1218(79)90003-X) PMID:[370585](https://pubmed.ncbi.nlm.nih.gov/370585/)
- Brown JP, Dietrich PS, Brown RJ (1977). Frameshift mutagenicity of certain naturally occurring phenolic compounds in the ‘Salmonella/microsome’ test: activation of anthraquinone and flavonol glycosides by gut bacterial enzymes [proceedings]. *Biochem Soc Trans*, 5(5):1489–92. PMID:[336434](https://pubmed.ncbi.nlm.nih.gov/336434/)
- Brusick D & Mengs U (1997). Assessment of the genotoxic risk from laxative senna products. *Environ Mol Mutagen*, 29(1):1–9. doi:[10.1002/\(SICI\)1098-2280\(1997\)29:1<1::AID-EM1>3.0.CO;2-J](https://doi.org/10.1002/(SICI)1098-2280(1997)29:1<1::AID-EM1>3.0.CO;2-J) PMID:[9020301](https://pubmed.ncbi.nlm.nih.gov/9020301/)
- Channe Gowda D, Neelisiddaiah B, Anjaneyalu YV (1979). Structural studies of polysaccharides from *Aloe vera*. *Carbohydr Res*, 72:201–5. doi:[10.1016/S0008-6215\(00\)83936-1](https://doi.org/10.1016/S0008-6215(00)83936-1)
- Che Q-M, Akao T, Hattori M, Kobashi K, Namba T (1991). Isolation of a human intestinal bacterium capable of transforming barbaloin to aloe-emodin anthrone. *Planta Med*, 57(1):15–9. doi:[10.1055/s-2006-960007](https://doi.org/10.1055/s-2006-960007) PMID:[2062951](https://pubmed.ncbi.nlm.nih.gov/2062951/)
- Chen Y-Y, Chiang S-Y, Lin J-G, Yang JS, Ma YS, Liao CL *et al.* (2010). Emodin, aloe-emodin and rhein induced DNA damage and inhibited DNA repair gene expression in SCC-4 human tongue cancer cells. *Anticancer Res*, 30(3):945–51. PMID:[20393018](https://pubmed.ncbi.nlm.nih.gov/20393018/)
- Chiu T-H, Lai W-W, Hsia T-C, Yang JS, Lai TY, Wu PP *et al.* (2009). Aloe-emodin induces cell death through S-phase arrest and caspase-dependent pathways in human tongue squamous cancer SCC-4 cells. *Anticancer Res*, 29(11):4503–11. PMID:[20032398](https://pubmed.ncbi.nlm.nih.gov/20032398/)
- Committee of Experts on Cosmetic Products (2008). Aloe extracts with anthraquinones. Active ingredients used in cosmetics: safety survey. Strasbourg, France: Council of Europe Publishing; pp. 9–27.
- Cosmetic Ingredient Review Expert Panel (2007). Final report on the safety assessment of AloeAndongensis Extract, Aloe Andongensis Leaf Juice, Aloe Arborescens Leaf Extract, Aloe Arborescens Leaf Juice, Aloe Arborescens Leaf Protoplasts, Aloe Barbadensis Flower Extract, Aloe Barbadensis Leaf, Aloe Barbadensis Leaf Extract, Aloe Barbadensis Leaf Juice, Aloe Barbadensis Leaf Polysaccharides, Aloe Barbadensis Leaf Water, Aloe Ferox Leaf Extract, Aloe Ferox Leaf Juice, and Aloe Ferox Leaf Juice Extract. *Int J Toxicol*, 26(1):Suppl 2: 1–50. doi:[10.1080/10915810701351186](https://doi.org/10.1080/10915810701351186) PMID:[17613130](https://pubmed.ncbi.nlm.nih.gov/17613130/)
- Dal’Belo SE, Gaspar LR, Maia Campos PM (2006). Moisturizing effect of cosmetic formulations containing Aloe vera extract in different concentrations assessed

- by skin bioengineering techniques. *Skin Res Technol*, 12(4):241–6. doi:[10.1111/j.0909-752X.2006.00155.x](https://doi.org/10.1111/j.0909-752X.2006.00155.x) PMID:[17026654](https://pubmed.ncbi.nlm.nih.gov/17026654/)
- Davis B & Goux WJ (2009). Single-laboratory validation of an NMR method for the determination of aloe vera polysaccharide in pharmaceutical formulations. *J AOAC Int*, 92(6):1607–16. PMID:[20166576](https://pubmed.ncbi.nlm.nih.gov/20166576/)
- De Witte P & Lemli J (1988). Excretion and distribution of [¹⁴C]rhein and [¹⁴C]rhein anthrone in rat. *J Pharm Pharmacol*, 40(9):652–5. doi:[10.1111/j.2042-7158.1988.tb05330.x](https://doi.org/10.1111/j.2042-7158.1988.tb05330.x) PMID:[2907037](https://pubmed.ncbi.nlm.nih.gov/2907037/)
- Dentali S (2013). “Nondecolorized” essential qualifier for NTP aloe vera study material. *Toxicol Sci*, 133(2):342 doi:[10.1093/toxsci/kft072](https://doi.org/10.1093/toxsci/kft072) PMID:[23492813](https://pubmed.ncbi.nlm.nih.gov/23492813/)
- Djuv A & Nilsen OG (2012). Aloe vera juice: IC₅₀ and dual mechanistic inhibition of CYP3A4 and CYP2D6. *Phytother Res*, 26(3):445–51. PMID:[21842479](https://pubmed.ncbi.nlm.nih.gov/21842479/)
- Dressen M & Lemli J (1988). Studies in the field of drugs containing anthraquinone derivatives. XXXVI. The metabolism of cascarosides by intestinal bacteria. *Pharm Acta Helv*, 63(9-10):287–9. PMID:[3237734](https://pubmed.ncbi.nlm.nih.gov/3237734/)
- Duke JA & Beckstrom-Sternberg SM (1994). “Acceptable” Levels of Flavoring Ingredients? *Developmental Food Science*, 34:741–757.
- Elsohly MA, Gul W, Avula B, Khan IA (2007). Determination of the anthraquinones aloe-emodin and aloin-A by liquid chromatography with mass spectrometric and diode array detection. *J AOAC Int*, 90(1):28–42. PMID:[17373434](https://pubmed.ncbi.nlm.nih.gov/17373434/)
- EMA (2006). Community herbal monograph on Aloe barbadensis MILLER and on Aloe (various species, mainly Aloe ferox MILLER and its hybrids). London, UK: European Medicines Agency.
- Eur Ph; European Pharmacopoeia (2008). European pharmacopoeia. 7.0. Strasbourg, France: European Directorate for the Quality of Medicines & HealthCare.
- FDA; Food and Drug Administration (2002). Status of certain additional over-the-counter drug category II and III active ingredients. *Fed Regist*, 67(90):31125–7. Available from: <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Over-the-CounterOTCDrugs/StatusofOTCRulemakings/ucm094018.pdf>. PMID:[12001972](https://pubmed.ncbi.nlm.nih.gov/12001972/)
- Femenia A, Sanchez E, Simal S, Rosselló C (1999). Compositional features of polysaccharides from *Aloe vera* (*Aloe barbadensis* Miller) plant tissues. *Carbohydr Polym*, 39(2):109–17. doi:[10.1016/S0144-8617\(98\)00163-5](https://doi.org/10.1016/S0144-8617(98)00163-5)
- Fogleman RW, Shellenberger TE, Balmer MF, Carpenter RH, McAnalley BH (1992). Subchronic oral administration of acemannan in the rat and dog. *Vet Hum Toxicol*, 34(2):144–7. PMID:[1509675](https://pubmed.ncbi.nlm.nih.gov/1509675/)
- Geisser J & Kratz E (2010). Determination of *Aloe vera* gel in cosmetics. *CBS Camag Bibliography Service*, 104:13–15.
- GRIN; Germplasm Resources Information Network (2013). National Germplasm Resources Laboratory, Beltsville (Md): USDA. Available from: <http://www.ars-grin.gov/cgi-bin/npgs/html/genform.pl>, accessed 5 June 2013
- Grindlay D & Reynolds T (1986). The Aloe vera phenomenon: a review of the properties and modern uses of the leaf parenchyma gel. *J Ethnopharmacol*, 16(2-3):117–51. doi:[10.1016/0378-8741\(86\)90085-1](https://doi.org/10.1016/0378-8741(86)90085-1) PMID:[3528673](https://pubmed.ncbi.nlm.nih.gov/3528673/)
- Groom QJ & Reynolds T (1987). Barbaloin in aloe species. *Planta Med*, 53(4):345–8. doi:[10.1055/s-2006-962735](https://doi.org/10.1055/s-2006-962735) PMID:[17269040](https://pubmed.ncbi.nlm.nih.gov/17269040/)
- Hamman JH (2008). Composition and applications of Aloe vera leaf gel. *Molecules*, 13(8):1599–616. doi:[10.3390/molecules13081599](https://doi.org/10.3390/molecules13081599) PMID:[18794775](https://pubmed.ncbi.nlm.nih.gov/18794775/)
- Hattori M, Akao T, Kobashi K, Namba T (1993). Cleavages of the O- and C-glucosyl bonds of anthrone and 10,10'-bianthrone derivatives by human intestinal bacteria. *Pharmacology*, 47:Suppl 1: 125–33. doi:[10.1159/000139851](https://doi.org/10.1159/000139851) PMID:[8234419](https://pubmed.ncbi.nlm.nih.gov/8234419/)
- Hattori M, Kanda T, Shu Y-Z, Akao T, Kobashi K, Namba T (1988). Metabolism of barbaloin by intestinal bacteria. *Chem Pharm Bull (Tokyo)*, 36(11):4462–6. doi:[10.1248/cpb.36.4462](https://doi.org/10.1248/cpb.36.4462) PMID:[3246014](https://pubmed.ncbi.nlm.nih.gov/3246014/)
- Heidemann A, Völkner W, Mengs U (1996). Genotoxicity of aloemodin in vitro and in vivo. *Mutat Res*, 367(3):123–33. doi:[10.1016/0165-1218\(95\)00084-4](https://doi.org/10.1016/0165-1218(95)00084-4) PMID:[8600368](https://pubmed.ncbi.nlm.nih.gov/8600368/)
- Herlihy JT, Bertrand HA, Kim JD, Ikeno Y, Yu BP (1998). Effects of *Aloe vera* ingestion in the rat I. Growth, food and fluid intake and serum chemistry. *Phytother Res*, 12(3):183–8. doi:[10.1002/\(SICI\)1099-1573\(199805\)12:3<183::AID-PTR219>3.0.CO;2-Q](https://doi.org/10.1002/(SICI)1099-1573(199805)12:3<183::AID-PTR219>3.0.CO;2-Q)
- Hirata T, Sakano S, Suga T (1981). Biotransformation of aloenin, a bitter glucoside constituent of *Aloe arborescens*, by rats. *Experientia*, 37(12):1252–3. doi:[10.1007/BF01948341](https://doi.org/10.1007/BF01948341) PMID:[7035211](https://pubmed.ncbi.nlm.nih.gov/7035211/)
- Hsia T-C, Yang J-S, Chen G-W, Chiu TH, Lu HF, Yang MD et al. (2009). The roles of endoplasmic reticulum stress and Ca²⁺ on rhein-induced apoptosis in A-549 human lung cancer cells. *Anticancer Res*, 29(1):309–18. PMID:[19331167](https://pubmed.ncbi.nlm.nih.gov/19331167/)
- IASC (2009). IASC Labeling Guidance. Silver Spring (MD): International Aloe Science Council. Available from: http://www.iasc.org/pdfs/10_0405_IASC_Labeling_Guidance_Definitions.pdf.
- IASC (2013a). The nomenclature of Aloe vera. Silver Spring (MD): International Aloe Science Council. Available from: http://www.iasc.org/Aloe_Taxonomy.pdf, accessed 3 June 2014.
- IASC (2013b). Aloe vera quality standard. Silver Spring (MD), USA: International Aloe Science Council. Available from: <http://iasc.org/pdfs/AloeVeraQualityStandard.pdf>, accessed 3 June 2014.
- Ikeno Y, Hubbard GB, Lee S, Yu BP, Herlihy JT (2002). The influence of long-term Aloe vera ingestion on

- age-related disease in male Fischer 344 rats. *Phytother Res*, 16(8):712–8. doi:[10.1002/ptr.1022](https://doi.org/10.1002/ptr.1022) PMID:[12458471](https://pubmed.ncbi.nlm.nih.gov/12458471/)
- IMS Health (2012). Multinational Integrated Data Analysis (MIDAS). Worldwide Sales of Selected Products. Plymouth Meeting, Pennsylvania: IMS Health
- Ishii Y, Tanizawa H, Takino Y (1987). Determination of barbaloin in rat serum. *Chem Pharm Bull (Tokyo)*, 35(11):4642–4. doi:[10.1248/cpb.35.4642](https://doi.org/10.1248/cpb.35.4642) PMID:[3442898](https://pubmed.ncbi.nlm.nih.gov/3442898/)
- Jiao P, Jia Q, Randel G, Diehl B, Weaver S, Milligan G (2010). Quantitative ¹H-NMR spectrometry method for quality control of Aloe vera products. *J AOAC Int*, 93(3):842–8. PMID:[20629385](https://pubmed.ncbi.nlm.nih.gov/20629385/)
- Joseph B & Raj SJ (2010). Pharmacognostic and phytochemical properties of Aloe vera Linn—an overview. *International Journal of Pharmaceutical Sciences Review and Research*, 4:106–110.
- JP XVI, The Japanese Pharmacopoeia (2011). The Japanese Pharmacopoeia. 16th ed. English Version, Tokyo, Japan: Ministry of Health, Labour and Welfare.
- Kim KH, Park JH (2006). Quality control and standardization of Aloe products. In: Park YI, Lee SK, editors. *New Perspectives on Aloe*. New York (NY), USA: Springer Science and Business Media; pp. 169–189
- Kratz E (2009). *Aloe vera*. Evidence of active content. *Cosmos*, 10:12–13.
- Kuzuya H, Shimpo K, Beppu H (2004). Aloe lectins and their activities. In: Reynolds T, editor. *Aloes: The genus Aloe*. 38th ed. Boca Raton (FL), USA: CRC Press; pp. 88–110
- Lachenmeier K, Kuepper U, Musshoff F *et al.* (2005). Quality control of Aloe vera beverages. *Electronic Journal of Environmental, Agricultural and Food Chemistry*, 4:1033–1042.
- Lai W-W, Yang J-S, Lai K-C, Kuo CL, Hsu CK, Wang CK *et al.* (2009). Rhein induced apoptosis through the endoplasmic reticulum stress, caspase- and mitochondria-dependent pathways in SCC-4 human tongue squamous cancer cells. *In Vivo*, 23(2):309–16. PMID:[19414420](https://pubmed.ncbi.nlm.nih.gov/19414420/)
- Lang W (1993). Pharmacokinetic-metabolic studies with ¹⁴C-aloe emodin after oral administration to male and female rats. *Pharmacology*, 47:Suppl 1: 110–9. doi:[10.1159/000139849](https://doi.org/10.1159/000139849) PMID:[8234417](https://pubmed.ncbi.nlm.nih.gov/8234417/)
- Lee S, Do SG, Kim SY, Kim J, Jin Y, Lee CH (2012). Mass spectrometry-based metabolite profiling and antioxidant activity of Aloe vera (Aloe barbadensis Miller) in different growth stages. *J Agric Food Chem*, 60(45):11222–8. doi:[10.1021/jf3026309](https://doi.org/10.1021/jf3026309) PMID:[23050594](https://pubmed.ncbi.nlm.nih.gov/23050594/)
- Leon L (2003). The medicinal plant Aloe. *Ganzheitliche Tiermedizin*, 17:138–143.
- Lin M-L, Chen S-S, Lu Y-C, Liang RY, Ho YT, Yang CY *et al.* (2007). Rhein induces apoptosis through induction of endoplasmic reticulum stress and Ca²⁺-dependent mitochondrial death pathway in human nasopharyngeal carcinoma cells. *Anticancer Res*, 27:5A: 3313–22. PMID:[17970076](https://pubmed.ncbi.nlm.nih.gov/17970076/)
- Lin M-L, Lu Y-C, Chung J-G, Li YC, Wang SG, NG SH *et al.* (2010). Aloe-emodin induces apoptosis of human nasopharyngeal carcinoma cells via caspase-8-mediated activation of the mitochondrial death pathway. *Cancer Lett*, 291(1):46–58. doi:[10.1016/j.canlet.2009.09.016](https://doi.org/10.1016/j.canlet.2009.09.016) PMID:[19942342](https://pubmed.ncbi.nlm.nih.gov/19942342/)
- Mandal G & Das A (1980). Structure of the D-galactan isolated from Aloe barbadensis Miller. *Carbohydr Res*, 86(2):247–57. doi:[10.1016/S0008-6215\(00\)85902-9](https://doi.org/10.1016/S0008-6215(00)85902-9)
- Mandrioli R, Mercolini L, Ferranti A, Fanali S, Raggi MA (2011). Determination of aloe emodin in Aloe vera extracts and commercial formulations by HPLC with tandem UV absorption and fluorescence detection. *Food Chem*, 126(1):387–93. doi:[10.1016/j.foodchem.2010.10.112](https://doi.org/10.1016/j.foodchem.2010.10.112)
- Matsuda Y, Yokohira M, Suzuki S, Hosokawa K, Yamakawa K, Zeng Y *et al.* (2008). One-year chronic toxicity study of Aloe arborescens Miller var. natalensis Berger in Wistar Hannover rats. A pilot study. *Food Chem Toxicol*, 46(2):733–9. doi:[10.1016/j.fct.2007.09.107](https://doi.org/10.1016/j.fct.2007.09.107) PMID:[17981383](https://pubmed.ncbi.nlm.nih.gov/17981383/)
- Morgan M, Bone K, Mills S *et al.* (2005). Aloe. Safety monograph. In: Mills S, Bone K, editors. *The essential guide to herbal safety*. St. Louis (MO), USA: Elsevier Churchill Livingstone; pp. 233–240
- Morimoto I, Watanabe F, Osawa T, Okitsu T, Kada T (1982). Mutagenicity screening of crude drugs with Bacillus subtilis rec-assay and Salmonella/microsome reversion assay. *Mutat Res*, 97(2):81–102. doi:[10.1016/0165-1161\(82\)90007-3](https://doi.org/10.1016/0165-1161(82)90007-3) PMID:[6804865](https://pubmed.ncbi.nlm.nih.gov/6804865/)
- Müller SO & Stopper H (1999). Characterization of the genotoxicity of anthraquinones in mammalian cells. *Biochim Biophys Acta*, 1428(2-3):406–14. doi:[10.1016/S0304-4165\(99\)00064-1](https://doi.org/10.1016/S0304-4165(99)00064-1) PMID:[10434060](https://pubmed.ncbi.nlm.nih.gov/10434060/)
- Müller SO, Eckert I, Lutz WK, Stopper H (1996). Genotoxicity of the laxative drug components emodin, aloe-emodin and danthron in mammalian cells: topoisomerase II mediated? *Mutat Res*, 371(3-4):165–73. doi:[10.1016/S0165-1218\(96\)90105-6](https://doi.org/10.1016/S0165-1218(96)90105-6) PMID:[9008718](https://pubmed.ncbi.nlm.nih.gov/9008718/)
- NCCAM (2012). Aloe vera. Bethesda (MD): National Center for Complementary and Alternative Medicine. Available from: <http://nccam.nih.gov/health/aloevera>, accessed 5 June 2014.
- Nesslany F, Simar-Meintières S, Ficheux H, Marzin D (2009). Aloe-emodin-induced DNA fragmentation in the mouse in vivo comet assay. *Mutat Res*, 678(1):13–9. doi:[10.1016/j.mrgentox.2009.06.004](https://doi.org/10.1016/j.mrgentox.2009.06.004) PMID:[19559101](https://pubmed.ncbi.nlm.nih.gov/19559101/)
- Newton LE (2004). Aloes in habitat. In: Reynolds T, editor. *Aloes: the genus Aloe*. Boca Raton (FL), USA: CRC Press; pp. 3–14
- Ngo MQ, Nguyen NN, Shah SA (2010). Oral aloe vera for treatment of diabetes mellitus and dyslipidemia. *Am J Health Syst Pharm*, 67(21):1804–11, 1806, 1808 passim. doi:[10.2146/ajhp100182](https://doi.org/10.2146/ajhp100182) PMID:[20966143](https://pubmed.ncbi.nlm.nih.gov/20966143/)
- NHANES (2010). National Health and Nutrition Examination Survey (1999–2010). Atlanta (GA):

- Centers for Disease Control and Prevention. Available from: <http://www.cdc.gov/nchs/nhanes.htm>; accessed 5 June 2014.
- Ni Y, Turner D, Yates KM, Tizard I (2004). Isolation and characterization of structural components of Aloe vera L. leaf pulp. *Int Immunopharmacol*, 4(14):1745–55. doi:[10.1016/j.intimp.2004.07.006](https://doi.org/10.1016/j.intimp.2004.07.006) PMID:[15531291](https://pubmed.ncbi.nlm.nih.gov/15531291/)
- NLM (2012). Products that contain active ingredient - Aloe vera. Dietary supplements labels database. United States National Library of Medicine. Available from: <http://www.dslid.nlm.nih.gov/dslid/>; accessed 5 June 2014.
- NTP; National Toxicology Program (2010). Photocarcinogenesis study of aloe vera [CAS NO. 481–72–1(Aloe-emodin)] in SKH-1 mice (simulated solar light and topical application study). *Natl Toxicol Program Tech Rep Ser*, 553(553):7–33, 35–97, 99–103 passim. PMID:[21031007](https://pubmed.ncbi.nlm.nih.gov/21031007/)
- Nutrition Business Journal (2010). NBJ's Supplement Business Report. An analysis of markets, trends, competition and strategy in the U.S. dietary supplement industry. New York (NY), USA: Penton Media, Inc.
- Nutrition Business Journal (2012). NBJ's Supplement Business Report. An analysis of markets, trends, competition and strategy in the U.S. dietary supplement industry. . New York (NY), USA: Penton Media, Inc. Available from: <http://newhope360.com/2012-supplement-business-report>; accessed 5 June 2014.
- O'Neil MJ, Heckelman PE, Koch CB *et al.* (2006). The Merck Index - An Encyclopedia of Chemicals, Drugs, and Biologicals. 14th Ed. Version 14.6. Whitehouse Station (NJ), USA: Merck & Co., Inc.
- Okamura N, Asai M, Hine N, Yagi A (1996). High-performance liquid chromatographic determination of phenolic compounds in *Aloe* species. *J Chromatogr A*, 746(2):225–31. doi:[10.1016/0021-9673\(96\)00342-1](https://doi.org/10.1016/0021-9673(96)00342-1)
- Paes-Leme AA, Motta ES, De Mattos JCP, Dantas FJ, Bezerra RJ, Caldeira-de-Araujo A (2005). Assessment of Aloe vera (L.) genotoxic potential on *Escherichia coli* and plasmid DNA. *J Ethnopharmacol*, 102(2):197–201. doi:[10.1016/j.jep.2005.06.013](https://doi.org/10.1016/j.jep.2005.06.013) PMID:[16054315](https://pubmed.ncbi.nlm.nih.gov/16054315/)
- Paez A, Michael Gebre G, Gonzalez ME, Tschaplinski TJ (2000). Growth, soluble carbohydrates, and aloin concentration of Aloe vera plants exposed to three irradiance levels. *Environ Exp Bot*, 44(2):133–9. doi:[10.1016/S0098-8472\(00\)00062-9](https://doi.org/10.1016/S0098-8472(00)00062-9) PMID:[10996366](https://pubmed.ncbi.nlm.nih.gov/10996366/)
- Pandiri AR, Sills RC, Hoenerhoff MJ, Peddada SD, Ton TV, Hong HH *et al.* (2011). Aloe vera non-decolorized whole leaf extract-induced large intestinal tumors in F344 rats share similar molecular pathways with human sporadic colorectal tumors. *Toxicol Pathol*, 39(7):1065–74. doi:[10.1177/0192623311422081](https://doi.org/10.1177/0192623311422081) PMID:[21937742](https://pubmed.ncbi.nlm.nih.gov/21937742/)
- Park MK, Park JH, Kim NY, Shin YG, Choi YS, Lee JG *et al.* (1998). Analysis of 13 phenolic compounds in *Aloe* species by high performance liquid chromatography. *Phytochem Anal*, 9(4):186–91. doi:[10.1002/\(SICI\)1099-1565\(199807/08\)9:4<186::AID-PCA406>3.0.CO;2-#](https://doi.org/10.1002/(SICI)1099-1565(199807/08)9:4<186::AID-PCA406>3.0.CO;2-#)
- Park YI, Jo TH (2006). Perspectives of industrial application of *Aloe vera*. In: Park YI, Lee SK, editors. *New Perspectives on Aloe*. New York (NY), USA: Springer Science+Business Media; pp. 191–200
- Pelley RP, Martini WJ, Liu DQ *et al.* (1998). Multiparameter analysis of commercial “*Aloe vera*” materials and comparison to *Aloe barbadensis* Miller extracts. *Subtropical Plant Science*, 50:1–14.
- Pellizzoni M, Molinari GP, Lucini L (2011). Stability of the main Aloe fractions and Aloe-based commercial products under different storage conditions *Agrochimica*, 5:288–296.
- Perkins SL & Livesey JF (1993). A rapid high-performance thin-layer chromatographic urine screen for laxative abuse. *Clin Biochem*, 26(3):179–81. doi:[10.1016/0009-9120\(93\)90023-Y](https://doi.org/10.1016/0009-9120(93)90023-Y) PMID:[8330386](https://pubmed.ncbi.nlm.nih.gov/8330386/)
- Pogribna M, Freeman JP, Paine D, Boudreau MD (2008). Effect of Aloe vera whole leaf extract on short chain fatty acids production by *Bacteroides fragilis*, *Bifidobacterium infantis* and *Eubacterium limosum*. *Lett Appl Microbiol*, 46(5):575–80. doi:[10.1111/j.1472-765X.2008.02346.x](https://doi.org/10.1111/j.1472-765X.2008.02346.x) PMID:[18363656](https://pubmed.ncbi.nlm.nih.gov/18363656/)
- Ramachandra CT & Rao PS (2008). Processing of *Aloe vera* leaf gel: a review. *Am J Agric Biol Sci*, 3(2):502–10. doi:[10.3844/ajabssp.2008.502.510](https://doi.org/10.3844/ajabssp.2008.502.510)
- Ramírez Durón R, Cenicerros Almaguer L, Cavazos Rocha NC, Silva Flores PG, De Torres NW (2008). Comparison of high-performance liquid chromatographic and thin-layer chromatographic methods for determination of aloin in herbal products containing Aloe vera. *J AOAC Int*, 91(6):1265–70. PMID:[19202785](https://pubmed.ncbi.nlm.nih.gov/19202785/)
- Reynolds T (2004). Aloe chemistry. In: Reynolds T, editor. *Aloes: The genus Aloe*. 38th Ed. Boca Raton (FL), USA: CRC Press; pp. 39–74
- Rodríguez ER, Martín JD, Romero CD (2010). Aloe vera as a functional ingredient in foods. *Crit Rev Food Sci Nutr*, 50(4):305–26. doi:[10.1080/10408390802544454](https://doi.org/10.1080/10408390802544454) PMID:[20301017](https://pubmed.ncbi.nlm.nih.gov/20301017/)
- Saccù D, Bogoni P, Procida G (2001). Aloe exudate: characterization by reversed phase HPLC and head-space GC-MS. *J Agric Food Chem*, 49(10):4526–30. doi:[10.1021/jf010179c](https://doi.org/10.1021/jf010179c) PMID:[11599983](https://pubmed.ncbi.nlm.nih.gov/11599983/)
- SciFinder (2013). CAS Registry Number 8001–97–6. Columbus (OH). USA: Chemical Abstracts Service, American Chemical Society. Accessed: 15 January 2013
- Sehgal I, Winters WD, Scott M, David A, Gillis G, Stoufflet T *et al.* (2013b). Toxicologic assessment of a commercial decolorized whole leaf aloe vera juice, lily of the desert filtered whole leaf juice with aloesorb. *J Toxicol*, Epub802453 doi:[10.1155/2013/802453](https://doi.org/10.1155/2013/802453) PMID:[23554812](https://pubmed.ncbi.nlm.nih.gov/23554812/)
- Sehgal I, Winters WD, Scott M, Kousoulas K (2013). An in vitro and in vivo toxicologic evaluation of a stabilized aloe vera gel supplement drink in mice. *Food*

- Chem Toxicol*, 55:363–70. doi:[10.1016/j.fct.2013.01.012](https://doi.org/10.1016/j.fct.2013.01.012) PMID:[23376510](https://pubmed.ncbi.nlm.nih.gov/23376510/)
- Sehgal I, Winters WD, Scott M, Kousoulas K (2013a). An in vitro and in vivo toxicologic evaluation of a stabilized aloe vera gel supplement drink in mice. *Food Chem Toxicol*, 55:363–70. doi:[10.1016/j.fct.2013.01.012](https://doi.org/10.1016/j.fct.2013.01.012) PMID:[23376510](https://pubmed.ncbi.nlm.nih.gov/23376510/)
- Shah AH, Qureshi S, Tariq M, Ageel M (1989). Toxicity studies on six plants used in the traditional Arab system of medicine. *Phytother Res*, 3(1):25–9. doi:[10.1002/ptr.2650030107](https://doi.org/10.1002/ptr.2650030107)
- Shao A, Broadmeadow A, Goddard G, Bejar E, Frankos V (2013). Safety of purified decolorized (low anthraquinone) whole leaf Aloe vera (L) Burm. f. juice in a 3-month drinking water toxicity study in F344 rats. *Food Chem Toxicol*, 57:21–31. doi:[10.1016/j.fct.2013.03.002](https://doi.org/10.1016/j.fct.2013.03.002) PMID:[23500775](https://pubmed.ncbi.nlm.nih.gov/23500775/)
- Spohn R (2013). Water colour of Aloe vera. Available from: <http://www.spohns.de/heilpflanzenillus/aloevera.html>; accessed 28 May 2014.
- Steenkamp V & Stewart MJ (2007). Medicinal applications and toxicological activities of Aloe products. *Pharmaceutical Biology*, 45(5):411–20. doi:[10.1080/13880200701215307](https://doi.org/10.1080/13880200701215307)
- Stolk LM & Hoogtanders K (1999). Detection of laxative abuse by urine analysis with HPLC and diode array detection. *Pharm World Sci*, 21(1):40–3. doi:[10.1023/A:1008647424809](https://doi.org/10.1023/A:1008647424809) PMID:[10214668](https://pubmed.ncbi.nlm.nih.gov/10214668/)
- Tang JC, Yang H, Song XY, Song XH, Yan SL, Shao JQ *et al.* (2009). Inhibition of cytochrome P450 enzymes by rhein in rat liver microsomes. *Phytother Res*, 23(2):159–64. doi:[10.1002/ptr.2572](https://doi.org/10.1002/ptr.2572) PMID:[18814214](https://pubmed.ncbi.nlm.nih.gov/18814214/)
- Turner CE, Williamson DA, Stroud PA, Talley DJ (2004). Evaluation and comparison of commercially available Aloe vera L. products using size exclusion chromatography with refractive index and multi-angle laser light scattering detection. *Int Immunopharmacol*, 4(14):1727–37. doi:[10.1016/j.intimp.2004.07.004](https://doi.org/10.1016/j.intimp.2004.07.004) PMID:[15531289](https://pubmed.ncbi.nlm.nih.gov/15531289/)
- Ulbricht C, Armstrong J, Basch E, Basch S, Bent S, Dacey C *et al.* (2007). An evidence-based systematic review of Aloe vera by the natural standard research collaboration. *J Herb Pharmacother*, 7(3-4):279–323. doi:[10.1080/15228940802153339](https://doi.org/10.1080/15228940802153339) PMID:[18928148](https://pubmed.ncbi.nlm.nih.gov/18928148/)
- Vogler BK & Ernst E (1999). Aloe vera: a systematic review of its clinical effectiveness. *Br J Gen Pract*, 49(447):823–8. PMID:[10885091](https://pubmed.ncbi.nlm.nih.gov/10885091/)
- Vyth A & Kamp PE (1979). Detection of anthraquinone laxatives in the urine. *Pharm Weekbl*, 1(1):456–9. doi:[10.1007/BF02293250](https://doi.org/10.1007/BF02293250)
- Waller TA, Pelley RP, Strickland FM (2004). Industrial processing and quality control of Aloe barbadensis (Aloe vera) gel. In: Reynolds T, editor. Aloes: The genus Aloe. 38th Ed. Boca Raton (FL), USA: CRC Press; pp. 139–205
- Westendorf J, Marquardt H, Poginsky B, Dominiak M, Schmidt J, Marquardt H (1990). Genotoxicity of naturally occurring hydroxyanthraquinones. *Mutat Res*, 240(1):1–12. doi:[10.1016/0165-1218\(90\)90002-J](https://doi.org/10.1016/0165-1218(90)90002-J) PMID:[2294411](https://pubmed.ncbi.nlm.nih.gov/2294411/)
- WHO (1999). Aloe and Aloe vera gel. WHO Monographs on selected medicinal plants. Vol. 1. Geneva, Switzerland: World Health Organization; pp. 33–49 (available from <http://apps.who.int/medicinedocs/en/d/Js2200e/5.html>)
- Williams LD, Burdock GA, Shin E, Kim S, Jo TH, Jones KN *et al.* (2010). Safety studies conducted on a proprietary high-purity aloe vera inner leaf fillet preparation, Qmatrix. *Regul Toxicol Pharmacol*, 57(1):90–8. doi:[10.1016/j.yrtph.2010.01.002](https://doi.org/10.1016/j.yrtph.2010.01.002) PMID:[20096744](https://pubmed.ncbi.nlm.nih.gov/20096744/)
- Wölfle D, Schmutte C, Westendorf J, Marquardt H (1990). Hydroxyanthraquinones as tumor promoters: enhancement of malignant transformation of C3H mouse fibroblasts and growth stimulation of primary rat hepatocytes. *Cancer Res*, 50(20):6540–4. PMID:[2208114](https://pubmed.ncbi.nlm.nih.gov/2208114/)
- Yagi A, Nakamori J, Yamada T, Iwase H, Tanaka T, Kaneo Y *et al.* (1999). In vivo metabolism of aloemannan. *Planta Med*, 65(5):417–20. doi:[10.1055/s-1999-14018](https://doi.org/10.1055/s-1999-14018) PMID:[10418327](https://pubmed.ncbi.nlm.nih.gov/10418327/)
- Yaron A (1993). Characterization of Aloe vera gel before and after autodegradation, and stabilization of the natural fresh gel. *Phytother Res*, 7(7):11 doi:[10.1002/ptr.2650070706](https://doi.org/10.1002/ptr.2650070706)
- Yokohira M, Matsuda Y, Suzuki S, Hosokawa K, Yamakawa K, Hashimoto N *et al.* (2009). Equivocal colonic carcinogenicity of Aloe arborescens Miller var. natalensis berger at high-dose level in a Wistar Hannover rat 2-y study. *J Food Sci*, 74(2):T24–30. doi:[10.1111/j.1750-3841.2009.01070.x](https://doi.org/10.1111/j.1750-3841.2009.01070.x) PMID:[19323775](https://pubmed.ncbi.nlm.nih.gov/19323775/)
- Zaffaroni M, Mucignat C, Pecere T, Zagotto G, Frapolli R, D'Incalci M *et al.* (2003). High-performance liquid chromatographic assay for the determination of Aloe Emodin in mouse plasma. *J Chromatogr B Analyt Technol Biomed Life Sci*, 796(1):113–9. doi:[10.1016/j.jchromb.2003.08.012](https://doi.org/10.1016/j.jchromb.2003.08.012) PMID:[14552822](https://pubmed.ncbi.nlm.nih.gov/14552822/)

