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Review Article

Economical Medical Compounds of Aloe Vera

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Abstract

Aloe vera is a traditional remedy for diabetes mellitus (DM) in many parts of the world, including Latin America and the Arabian Peninsula. Some evidence in humans and animals suggests that Aloe vera is able to alleviate the chronic hyperglycemia and perturbed lipid profile that are characteristic of DM, which are major risk factors for cardiovascular complications in the disease. Aloe vera gel to streptozotocin (STZ)-induced diabetic rats resulted in significant reductions in fasting blood glucose. Conversely, Aloe vera gel was reported to increase plasma glucose levels in alloxan-induced diabetic rats. More recently, the antidiabetic effects of processed Aloe vera gel were investigated in mice exhibiting diet-induced obesity (DIO), an animal model that has been shown to demonstrate metabolic abnormalities that closely resemble those found in human noninsulin-dependent DM, including hyperglycemia, obesity, and insulin resistance. Oral administration of the gel reduced circulating blood glucose concentrations to a normal level, significantly decreased plasma insulin, and lowered triglyceride levels in the liver and plasma of the DIO mice. Similarly, Aloe vera gel extract has been shown to normalize the fasting blood glucose and plasma insulin levels and reduce the concentrations of cholesterol, triglycerides, and free fatty acids in the plasma, liver, and kidney of STZ-induced diabetic rats. Aloe-emodin has been suggested to have antiangiogenic properties; it has been demonstrated to be a potent inhibitor of urokinase secretion and tubule formation of endothelial cells, both key events in angiogenesis.

Phytosterols have been shown to lower plasma cholesterol concentrations, including the atherogenic LDL fraction action by which Aloe vera modulates blood glucose are unknown, but it has been suggested that it may interact with insulin. It has been hypothesized that Aloe stimulates insulin synthesis or its release from pancreatic β cells. Processed Aloe vera gel was found to suppress the expression of the adipogenic genes SREBP-1a, FAS, and GPAT, suggesting that the gel improves insulin resistance by the reducing toxic effects of lipids in the liver.The Natural Standard Research Collaboration further concluded that the oral use of Aloe vera gel for its potential hypoglycemic effects and the short-term use of oral Aloe latex as a laxative are possibly safe; however, prolonged use of the latex is likely to be unsafe due to a theoretical risk of dehydration and electrolyte imbalance. Tumor-promoting and antimutagenic activities have been ascribed to the latex of Aloe vera. Phototoxicity of aloe-emodin has been demonstrated in animal studies; however, phototoxicity was not observed in several clinical studies in humans using amounts of aloe-emodin that are commonly found in commercially available Aloe vera preparations.

Aloe vera gel has been shown to enhance vitamin C and E's bioavailability in a double-blind, randomized, controlled trial. Aloe vera gel has been shown to significantly increase the transport of insulin in a cell model, and limited information suggests that if co-administered, it may also enhance the intestinal absorption of other poorly absorbed drugs.

Kew Words: phytosterols; dabetes mellitus (dm); alloxan-induced; aoe-emodin and tumor-promoting

Introduction

Aloe vera has a long history of popular and traditional use. It is used in traditional Indian medicine for constipation, colic, skin diseases, worm infestation, and infections (Heber 2007). It is also used in Trinidad and Tobago for hypertension (Lans, 2006) and among Mexican Americans for the treatment of type 2 diabetes mellitus (DM; Coronado *et al.*, 2004). In Chinese medicine, it is often recommended in the treatment of fungal diseases (Heber, 2007). *Aloe vera* is one of approximately 420 species of the genus *Aloe* (Dagne et al.,2000), which is variously classified as belonging to the Asphodelus, Liliaceae, or Alliaceae families. *Aloe vera* was officially listed as a purgative and skin protectant by the U.S. pharmacopoeia in 1820 (Park and Lee 2006) and was clinically used in the 1930s for the treatment of radiotherapy burns to the skin and mucous membranes. *Aloe vera* is one

of the few herbal medicines widely used in Western society, with the manufacturing of *Aloe vera* extracts being one of the largest botanical industries worldwide (Eshun and He, 2004). In 2004, the value of the *Aloe* industry was estimated to be US$125 million for the cost of the raw *Aloe* material and US$110 billion for finished *Aloe*-containing products (International Aloe Science Council, 2004). *Aloe vera* is used in the cosmetic, food, and pharmaceutical industries. In the cosmetic and toilet industry, it is used as a base material for skin moisturizers, soaps, shampoos, sun lotions, makeup creams, perfumes, shaving creams, bath aids, and many other products (Eshun and He, 2004; Boudreau and Beland, 2006). The food industry uses *Aloe* in the manufacture of functional foods, especially health drinks, and as a bitter agent (Sacco). Pharmaceutical products are available for topical applications (gels and ointments) and oral use (Hamman, 2008). The leaf is protected by a thick, green epidermis layer (skin or rind), which surrounds the mesophyll. Immediately beneath the rind are located the vascular bundles, which are composed of three types of tubular structures: the xylem (transports water and minerals from roots to leaves), the phloem (transports starch and other synthesized products to the roots), and the large pericyclic tubules (contains the yellow leaf exudate commonly referred to as "aloes, "sap," or "latex"; Boudreau and Beland 2006). The pericyclic portion of the vascular bundle is adherent to the rind, whereas the remainder of the vascular bundle protrudes into the mesophyll layer. The mesophyll can be differentiated into chlorenchyma cells and thinner-walled parenchyma cells. The parenchyma (filet or pulp), which is the major part of the leaf by volume, contains a clear mucilaginous gel (Famennian).

Aloe vera is considered to be the most biologically active of the *Aloe* species. More than 75 potentially active constituents have been identified in the plant including vitamins, minerals, saccharides, amino acids, anthraquinones, enzymes, lignin, saponins, and salicylic acids. The leaf exudate contains anthraquinones, particularly barbaloin, which appear to be responsible for its bitter taste and cathartic effect (Dagne *et al.,* 2000). Barbaloin and other products of the phenylpropanoid pathway are commonly referred to as polyphenolic compounds. These are derived from the precursor phenolic acids, and they may act as antioxidants to inhibit free radical–mediated cytotoxicity and lipid peroxidation. *Aloe vera* also contains products of the isoprenoid pathway, including carotenoids, steroids, terpenes, and phytosterols. Isoprenoids can be regarded as sensory molecules because they contribute to the color and fragrance of the products in which they exist (Boudreau and Beland, 2006). It is possible that the biological activities of *Aloe vera* result from the synergistic action of a variety of compounds, rather than from a single defined component (Dagne *et al.*, 2000; Hamman, 2008). Equally, the potential for constituents to exhibit antagonistic and competitive activities also influences the overall biological activity of particular *Aloe vera* preparations (Hamman, 2008). The composition of *Aloe vera* extracts differs according to the plant variety, climatic and seasonal variations, and the age of the plant (Eshun and He, 2004). However, the processing method has the largest effect on the number and amount of active ingredients in a product. The commercial production process of *Aloe vera* products typically involves crushing, grinding, or pressing of the whole *Aloe vera* leaf to produce juice, followed by various steps of filtration and stabilization to achieve the desired extract (Eshun and He, 2004). This method provides ease of processing and higher efficiency in the recovery of the solids, but it can result in a product that contains little or no active ingredients (Eshun and He, 2004). In an analysis of 18 commercial *Aloe vera* products, only 9 exhibited quantifiable amounts of mucilaginous polysaccharide. Only three of the nine commercial *Aloe vera* gel powders sourced from leading international suppliers demonstrated satisfactory amounts of the polysaccharide Ace Mannan (Bozzi *et al.,* 2007). Variable polysaccharide content in *Aloe vera* has been attributed particularly to heating the plant extract to >60°C, which results in significant changes in molecular weight (Turner et al. 2004). A further issue with the commercial production process is that during the commercial extraction of *Aloe vera* gel, it is virtually impossible to prevent the contamination by leaf exudates (Eshun and He 2004). Finally, the adulteration of *Aloe vera* products using fillers such as maltodextrin, glucose, glycerin, and malic acid represents a major concern for the *Aloe vera* market (Bozzi *et al.,* 2007). As a counter to such misrepresentations in the industry, the International Aloe Science Council developed a certification program that validates the quality and quantity of *Aloe vera* in approved commercial products. The *Aloe vera* or placebo gel was applied twice daily for 4 weeks to symmetrical test lesions using an intraindividual right/left comparison study design. The sum score of erythema, infiltration, and desquamation significantly favored the placebo treatment (Paulsen, Korsholm, and Brandrup 2005).

Aloe vera did not significantly protect against radiation-induced skin changes (Olsen et al. 2001). In a study involving 225 patients undergoing radiation therapy, the topical application of *Aloe vera* gel thrice a day throughout the treatment and for an additional 2 weeks after the completion of radiation therapy was significantly less efficacious in reducing the treatment-related side effects than aqueous cream (Heggie *et al.,* 2002). In the pediatric setting, 45 patients undergoing radiation therapy for various diagnoses were treated with either an *Aloe* vera–based gel or a anionic polar phospholipid (APP)-based cream applied symmetrically within the irradiated field after each session. The authors reported statistically significant results favoring the APP-based cream on a number of skin assessment variables, including dryness, comfort, erythema, and peeling. The study was limited by a lack of description of randomization and blinding and the inclusion of patients with varied diagnoses, radiotherapy sites, and cancer treatment regimes (Merchant *et al.,* 2007). A 20 mL "swish and swallow" of *Aloe vera* solution (94.5% aloe juice) four times daily in addition to conventional treatment (baking soda mouth rinse, Benadryl and nystatin combination mouth-washes, and viscous lidocaine, as needed) did not improve radiation-related mucositis in patients with head-and-neck neoplasms. Study limitations included a small sample size, patient heterogeneity, a large distribution of primary cancer sites, and an inability to monitor compliance (Su *et al.,* 2004).

In 1959, the U.S. Food and Drug Administration approved the use of *Aloe vera* ointment as an over-the-counter medication for healing burns on the skin (Park and Lee, 2006). Using the duration of wound healing as an outcome measure, the meta-analysis of the efficacy of *Aloe vera* in burn wound healing concluded that *Aloe vera* treatments reduced healing time by approximately 9 days compared to conventional treatment groups (p = .006; Maintaining et al. 2007). The outcomes measured were wound healing time, described as time to complete epithelization or not defined; the success rate of wound healing; and epithelization rate. Maintaining et al. (2007) note that, due to differences in *Aloe vera* products and outcome measures used, it is difficult to draw a specific conclusion regarding the effect of *Aloe vera* on burn healing. *Aloe vera* latex is commonly used in the treatment of constipation; the laxative effect of the anthraquinone glycosides found in *Aloe vera* latex is well established (Ulbricht et al. 2008). *Aloe vera* is a traditional remedy for diabetes mellitus (DM) in many parts of the world, including Latin America (Coronado et al. 2004) and the Arabian Peninsula (Yeh et al. 2003). Some evidence in humans and animals suggests that *Aloe vera* is able to alleviate the chronic hyperglycemia and perturbed lipid profile that are characteristic of DM, which are major risk factors for cardiovascular complications in the disease. *Aloe vera* gel to streptozotocin (STZ)-induced diabetic rats (Rajasekaran *et al.,* 2004) resulted in significant reductions in fasting blood glucose. Conversely, *Aloe vera* gel was reported to increase plasma glucose levels in alloxan-induced diabetic rats. More recently, the antidiabetic effects of processed *Aloe vera* gel were investigated in mice exhibiting diet-induced obesity (DIO), an animal model that has been shown to demonstrate metabolic abnormalities that closely resemble those found in

human noninsulin-dependent DM, including hyperglycemia, obesity, and insulin resistance (Kim *et al.,* 2009). Oral administration of the gel reduced circulating blood glucose concentrations to a normal level, significantly decreased plasma insulin, and lowered triglyceride levels in the liver and plasma of the DIO mice. Similarly, *Aloe vera* gel extract has been shown to normalize the fasting blood glucose and plasma insulin levels and reduce the concentrations of cholesterol, triglycerides, and free fatty acids in the plasma, liver, and kidney of STZ-induced diabetic rats (Rajasekaran *et al.,* 2006). No adverse effects were observed during the trial, and the authors note that a higher dose may have been more efficacious and suggest the need for further, larger controlled trials of *Aloe vera* gel in active ulcerative colitis and in the maintenance of remission (Langmead *et al.,* 2004).

In vitro and in vivo studies in rats demonstrated that aloe-emodin-9-anthrones reduce the absorption of water from the intestinal lumen by inhibiting the activity of Na^+, K^+-adenosine triphosphatase (ATPase) and stimulate water secretion by increasing the paracellular permeability across the colonic mucosa. Secretion of water into the lumen by a prostaglandin-dependent mechanism has also been reported. The net result is a reduction in water absorption and the formation of softer stools (Boudreau and Beland, 2006). Aloe-emodin has been suggested to have antiangiogenic properties; it has been demonstrated to be a potent inhibitor of urokinase secretion and tubule formation of endothelial cells, both key events in angiogenesis (Cárdenas, Quesada, and Medina, 2006). Among the no polysaccharide gel constituents, salicylic acid and other ant prostaglandin compounds may contribute to the local anti-inflammatory activity of *Aloe vera* via the inhibition of cyclooxygenase (Ulbricht *et al.,* 2008). Potent antioxidant effects, including the ability to scavenge superoxide anions, have been attributed to the caffeoyl group of isorabaichromone, a derivative of aloesin (C-glycosylated 5-methylchromone). Five phytosterols have been isolated from *Aloe vera* gel based on their ability to decrease the HbA1c level in a mouse model (*db/db*) of type 2 DM. Each of the phytosterols, namely lophenol, 24-methyl-lophenol, 24-ethyl-lophenol, cycloartenol, and 24-methylene-cycloartanol, was shown to significantly decrease fasting blood glucose levels in the *db/db* mice compared to controls at a dose of 1μg/day (Tanaka et al. 2006). Phytosterols are not extensively absorbed from the intestine but can bind cholesterol and prevent it from being absorbed (Ralph and Provan, 2000). Phytosterols have been shown to lower plasma cholesterol concentrations, including the atherogenic LDL fraction action by which *Aloe vera* modulates blood glucose are unknown, but it has been suggested that it may interact with insulin. It has been hypothesized that *Aloe* stimulates insulin synthesis or its release from pancreatic β cells. Processed *Aloe vera* gel was found to suppress the expression of the adaptogenic genes *SREBP-1a, FAS*, and *GPAT*, suggesting that the gel improves insulin resistance by the reducing toxic effects of lipids in the liver (Kim *et al.,* 2009). Despite these challenges, a recent systematic review of *Aloe vera* by the Natural Standard Research Collaboration concluded that topical application of *Aloe vera* gel or extract is safe for the treatment of mild to moderate skin conditions, burns, wounds, and inflammation (Ulbricht *et al.,* 2008). The Natural Standard Research Collaboration further concluded that the oral use of *Aloe vera* gel for its potential hypoglycemic effects and the short-term use of oral *Aloe* latex as a laxative are possibly safe; however, prolonged use of the latex is likely to be unsafe due to a theoretical risk of dehydration and electrolyte imbalance (*Ulbricht et al.,* 2008).

Until now there are no published controlled in vivo toxicology studies of *Aloe vera* in humans (Steenkamp and Stewart, 2007). In animal studies, *Aloe vera*-derived ingredients were not found to be toxic in acute oral studies using mice and rats. In mice, the LD_{50} was >200 mg/kg and >80 mg/kg in parenteral and intravenous studies, respectively, whereas in rates the corresponding LD_{50} values were >50 mg/kg and >15 mg/kg, respectively. No significant toxicity was seen with acemannan given intravenously or intraperitoneally at 4-day intervals over 30 days at maximum dose levels of 200 mg/kg in mice and 50 mg/kg in rats (Cosmetic Ingredient Review Expert Panel 2007). The no observed adverse effect level (NOAEL) for whole-leaf *Aloe vera* powder was 87.7 and 109.7 mg/kg/day in male and female rats, respectively (Matsuda *et al.,* 2007). Life-long *Aloe vera* gel ingestion (contributing 1% of total diet) in rats was demonstrated to produce no harmful effects or deleterious changes (Ikeno *et al.,* 2002). In contrast, chronic ingestion of 100 mg/kg *Aloe vera* (extracted in ethanol) given orally in rats produced reproductive toxicity, significant sperm damage, inflammation, and mortality compared to control animals (Shah et al. 1989). In a recent safety assessment of *Aloe*, the Cosmetic Ingredient Review Expert Panel (2007) concluded that *Aloe* latex, but not the polysaccharide material derived from the inner gel, is cytotoxic. Tumor-promoting and antimutagenic activities have been ascribed to the latex of *Aloe vera* (Boudreau and Beland, 2006). Multiple in vitro studies have demonstrated the potential genotoxicity of anthraquinones; however, anthraquinones in *Aloe vera* do not appear to be well absorbed, and four in vivo studies resulted in no genotoxicity from aloe-emodin and emodin. Anthropoid-containing laxatives such as aloe-emodin have been suggested to cause colorectal cancer; however, recent research has not shown any correlation. A 2-year carcinogenicity study in rats reported that whole-leaf *Aloe* powder was not carcinogenic at nontoxic dose levels in the colon (Yokohama). In many large epidemiological studies in humans, long-term laxative abuse has not been associated with colorectal cancer (Noskov; Park *et al.,* 2009).

Phototoxicity of aloe-emodin has been demonstrated in animal studies; however, phototoxicity was not observed in several clinical studies in humans using amounts of aloe-emodin that are commonly found in commercially available *Aloe vera* preparations (Cosmetic Ingredient Review Expert Panel, 2007). In case reports, hypersensitivity and allergic responses to *Aloe vera* are the most commonly described adverse effects of *Aloe vera* use. The topical application of *Aloe vera* gel has resulted in contact dermatitis, and oral use may cause diarrhea or vomiting (Ernst 2000; Wang *et al.,* 2003; Chinnamal *et al.,* 2009).

In rare cases, severe adverse effects have been associated with the oral application of *Aloe vera*. Induced acute toxic hepatitis has been observed in four instances of *Aloe vera* ingestion (Luyckx *et al.,* 2002; Rabe *et al.,* 2005; Kanat, Zoet, and Ataergin, 2006). In one case, a 47-year-old man presented with acute oliguric renal failure and liver dysfunction after consuming high oral doses of *Aloe vera* (*Luyckx et al.,* 2002). *Aloe vera* was also believed to be the cause of hypothyroidism in one female patient (Pigatto and Guzzi, 2005) and Henoch–Schonlein purpura in another after an *Aloe vera* remedy juice was taken for back pain (Evangelos, Spyros, and Spyros, 2005). Use of *Aloe vera* preparations should be avoided in individuals with a known allergy to plants of the Liliaceae family (garlic, onions, and tulips; Ulbricht *et al.,* 2008). Use of *Aloe vera* as a laxative during pregnancy may pose potential teratogenic and toxicological effects on the embryo and fetus (Ulbricht *et al.,* 2008).

Prolonged use of *Aloe vera* latex has been associated with watery diarrhea resulting in electrolyte imbalance (Boudreau and Beland, 2006), and anecdotal reports suggest that the increasing loss of potassium may lead to hypokalemia. Therefore, the *Aloe vera* latex is contraindicated in patients with a history of renal or cardiac disorders. Potential interactions have been suggested for *Aloe vera* and drugs that may alter electrolyte balance, such as thiazide diuretics and corticosteroids. Possible hypokalemia-related arrhythmia suggests a potential herb–drug interaction with cardiac glycosides. Caution is warranted in patients taking hypoglycemic agents as interactions with *Aloe vera* gel have been reported (Boudreau and Beland ,2006). There exists a case report of a 35-year-old woman who lost 5 L of blood during surgery as a result of a possible herb-drug interaction between *Aloe vera* and sevoflurane, an inhibitor of thromboxane A_2 (Lee *et al.,* 2004). *Aloe vera* gel has been shown to enhance vitamin C and E's

bioavailability in a double-blind, randomized, controlled trial (Vinson, Al Kharrat, and Andriole 2005). The authors suggest that *Aloe vera* gel protects against the degradation of vitamins in the intestinal tract and the gel polysaccharides may bind to vitamins and thereby slow down their absorption rate. *Aloe vera* gel has been shown to significantly increase the transport of insulin in a cell model, and limited information suggests that if co-administered, it may also enhance the intestinal absorption of other poorly absorbed drugs (Hamman).

In the study of Win tola et al. (2010), the efficacy of an aqueous total leaf extract of Aloe ferox Mill. the dried leaves were grinded into powder and 100 g of the material was extracted by shaking for 24 h in 1000 ml of distilled water, filtered freeze dried and reconstituted in water (ratio not defined) was studied against loperamide-induced constipation in Wistar rats. Constipation was induced by oral administration of loperamide (3 mg/kg body weight) while the control rats received normal saline. The constipated rats were treated with 50, 100 and 200 mg/kg body weight/day of the extract for 7 days during which the feeding characteristics, body weight, faecal properties and gastrointestinal transit ratio were monitored. The extract improved intestinal motility, increased faucal volume and normalized body weight in the constipated rats. The study of Ashafa et al. (2011) evaluated the effect of an ethanolic total leaf extract of Aloe vera against loperamide-induced constipation in rats. Treatment of constipated rats with the extract at 50, 100, and 200 mg/kg body weight for 7 days improved intestinal motility, increased faecal volume, and normalized body weight in the constipated rats. The absorption rate of test compounds except aloesin was similar in two models; more aloes in was absorbed in the everted gut sac than in the Caco-2 monolayer. These results provide information to establish adequate intake level of aloe to maintain effective plasma level (Park *et al.*, 2009). Chen et al. (2004) evaluated the chemo preventive role of aloe-emodin in human promyelocytic leukemia HL-60 cells in vitro by studying the regulation of proliferation, cell cycle and apoptosis. The authors concluded that aloe-emodin appears to exert its anti-carcinogenesis properties by inhibiting proliferation and inducing cell cycle arrest, and apoptosis underwent activation of caspase-3 in human leukemia HL-60 cells. Lee et al. (2005) demonstrated that aloe-emodin induced a significant change in the expression of lung cancer cell apoptosis-related proteins compared to those of control cells.

Win tola et al. evaluated in 2011 the toxicological effect of aqueous leaf extract of the herb at 50, 100 and 200 mg/kg body weight for 7 days on the hematological parameters as well as liver and kidney function indices in loperamide-induced constipated rats. The extract did not cause any significant ($p > 0.05$) effect on the kidney and liver-body weight ratio as well as the kidney function indices including serum levels of creatinine, uric acid, urea, calcium and potassium ions at all the dosages investigated. Whereas the serum levels of total protein, albumin, bilirubin and gamma glutamyl transferase (GGT) were not affected, the elevated activities of alkaline phosphatase (ALP), alanine transaminase (ALT) and aspartate transaminase (AST) in the untreated constipated animals were normalized following treatment with extract. Chronic use or abuse of aloe dried juice preparations may lead to hypokalemia. This hypokalemia and the increased loss of potassium may increase the activity of cardiac glycosides and interfere with the action of antiarrhythmic agents (interaction with antiarrhythmic medicinal products, which induce reversion to sinus rhythm, e.g. quinidine) and medicinal products inducing QT-prolongation (Haverkamp, 2002). The % absorption of aloin, aloe-emodin, and aloesin ranged from 5.51% to 6.60%, 6.60% to 11.32%, and 7.61% to 13.64%, respectively. Up to 18.15%, 18.18%, and 38.86% of aloin, aloe-emodin, and aloesin, respectively, was absorbed as glucuronidase or sulfated form. These results suggest that a significant amount is transformed during absorption. These results provide information to establish an adequate intake level of aloe to maintain an effective plasma level (Park *et al.*, 2009).

Longo (2002) referred in his monograph "Aloe today" (part four) to recent investigations that produced a better explanation of the mechanism of the action of stimulus on the colon. The inhibition of Na^+/K^+-ATPase and the release of NO are relevant to stimulate the secretion ofelectrolytes and the relaxation of smooth intestinal muscles. Furthermore, investigations outlined that NO plays a new physiopathological role regarding PAF, which causes the contraction of the smooth musculature. The authors summarized that biological factors such as PAF and NO may play a role on the action of the stimulus on the colon, but it should be considered that the investigations were only experimental ones. The effects of aloe extracts were also dose-dependent. Addition of diethyl maleate (1 mM), a cellular glutathione-depleting agent, to hepatocytes treated with both 1, 4-naphthoquinone and aloe extract, induced depletion of GSH, but did not affect protein-SH or lactate dehydrogenase. These results suggest that the 1,4-naphthoquinone-induced toxicity in rat hepatocytes was inhibited by aloe extract, and that this protective effect was due to the maintenance of cellular thiols, especially protein-SH (Norikura *et al.*, 2002). Relative kidney weight showed increase in the female 4.0% group and relative heart and brain weights were decreased in the female 4.0% and 0.8% groups. Histopathologically, both sexes receiving 4.0% showed severe sinus dilatation of ileocecal lymph nodes, and yellowish pigmentation of ileocecal lymph nodes and renal tubules. The no observed adverse effect level (NOAEL) for ALOE was the 0.16% in diet, which is equivalent to 87.7 and 109.7 mg/kg/day in males and females, respectively (Matsuda *et al.*, 2008).

Genetic toxicology studies were conducted with emodin (at least 94% pure) in Salmonella typhimurium and cultured Chinese hamster ovary cells (NTP, 2001). Emodin was mutagenic in Salmonella typhimurium strain TA100 in the presence of S9 activation; no mutagenicity was detected in strain TA98, with or without S9. Boudreau et al. (2013).concluded that nondecolorized Aloe vera caused cancers of the large intestine in male and female rats and also caused hyperplasia of the large intestine, small intestine, stomach, and lymph nodes in male and female rats. Aloe vera extract also caused hyperplasia of the large intestine in male and female mice and hyperplasia of the mesenteric lymph node in male mice and hyperplasia of the stomach in female mice. Prolonged use of aloe containing preparations is associated with watery diarrhoea leading to electrolyte imbalance and the increased loss of potassium can lead to hypokalaemia. The increased loss of potassium is largely the result of compensatory reaction to the excessive loss of sodium, which induces a compensatory production of aldosterone that can exacerbate the hypokalemic condition and increase renin production (Mascolo *et al.*, 2004).

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