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Review Article

# Aloe Induced Toxicity: Phytochemistry and Pharmacodynamics, Toxicokinetics and Case Study

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ABSTRACT

Toxicity is defined as "the capacity of a substance to produce injury to a living organism and toxicology as the study of the adverse effects of chemicals on living organisms". Acute toxicity and chronic toxicity can lead to life-threatening conditions; therefore the concern for toxicology studies has increased. Many concerns have been raised regarding the safety of herbal products and unwanted side effects, particularly hepato-toxicity, genotoxicity, cardiotoxicity, nephro-toxicity, have been reported for many herbal products. Aloe Vera is widely used, as an OTC drug, as a supplement, and in cosmetics. Various cases caused due to *Aloe vera* is studied, liver damage associated with *Aloe vera* ingestion, in a 57-year old female patient; acute hepatitis associated with *Aloe Vera* ingestion, in a patient; case of acute hepatitis associated with *Aloe Vera* ingestion, in a patient; death of 4 patients after they were injected with Aloe Vera injection to treat cancer.



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## Introduction

Herbal remedies have nature as an origin and are considered to be the best choice as alternative medicine all around the world. People be sure of herbal drugs, owing synthetic drug has side effects and high prices, in both developed and developing countries. Among healthy individuals, the use and popularity of herbal medicines and remedies are increasing gradually. Many concerns have been raised regarding the safety of herbal products and unwanted side effects, particularly hepato-toxicity, genotoxicity, cardiotoxicity, nephro-toxicity, have been reported for many of herbal products (Ekor, 2014; Stickel *et al*., 2005). In the United States, around 18% of adults have adopted herbal remedies to treat illnesses, and the popularity of herbal remedies has begun to spread to other parts of the world in recent years (Barnes et al., 2008; Ye and He, 2010). In a survey by the U.S.

Centre for Disease Control and Prevention, 52 million Americans (4 in 10 adults) were reported to using herbal complementary and alternative medicine (Barnes et al., 2008). American consumers used dietary supplements to feel better, improve energy levels, and boost the immune system, which was reported in a survey of 2011 performed by the Harvard Opinion Research Program (Blendon *et al*., 2013). Aloe Vera is a perennial, succulent xerophytes grown in temperate and sub-tropical parts of the world, which was originated from Africa. Aloe Vera or *Aloe barbadensis* is of the Aloe genus and belongs to the Asphodelaceae family (Vogler and Ernst, 1999). Aloe Vera is considered to be the safe herbal remedies or as a folk medicine all over the world. The use of Aloe Vera has been recorded in the traditional system of medicines. In this paper, we present the case reports, in vitro, and in vivo studies of Aloe Vera induced toxicity. There have been 6 case reports registered in the past. The case reported shows the acute hepato-toxicity induced by Aloe Vera intake. 4 patients reported being dead on getting injected with *Aloe vera*. As Aloe Vera is widely used, as OTC drug, as a supplement, and in cosmetics, systematic examination of its toxicology has not been carried out. Cases of Aloe Vera related acute and chronic hepatitis, even in healthy individuals, are likely to be reported by clinicians.

**Literature Search**

To collect all cases of Aloe Vera induced toxicity, a selective literature search using publicly available electronic databases (especially the PubMed database, Scopus, and five Korean electronic databases) was performed. We used the search items including "Aloe Vera toxicity", "Aloe Vera safety pharmacology", "*Aloe barbadensis* side effects", and "Aloe Vera poising" alone and combined with the terms "herbal hepato-toxicity", or "herb induced liver injury". The search was primarily focused on English-language case reports, case series, and clinical reviews, published till May 2020. The literature with a language other than English was used by converting them into English. All citations in these publications were searched for other yet unidentified case reports.

**Toxicity**

Toxicology defines toxicity as the capacity of a substance to produce injury to a living organism and toxicology as the study of the adverse effects of chemicals on living organisms (Doull *et al*., 1980). In the context of human health safety assessment, the main types of animal-based toxicity tests are conducted for acute toxicity (skin and eye irritation/corrosion, acute systemic toxicity), allergenicity (skin and respiratory sensitization), repeated dose toxicity, genotoxicity and mutagenicity, carcinogenicity, reproductive and developmental toxicity, and biokinetics. Biokinetics is also referred to as toxicokinetics or pharmacokinetics (Worth, 2019). Toxicity occurring immediately (seconds/minutes/hours/days) after exposure is Acute Toxicity. Acute exposure includes Single does or a series of doses within 24 hours span. Cumulative damage of specific organ systems on exposure to drugs for many months or years is termed as chronic toxicity. Carcinogenicity leads to the development of cancer, by a complex multistage process which leads to abnormal cell growth and differentiation of cells. The adverse effect of developing an embryo or fetus refers to Developmental toxicity. Toxicokinetics deals with the kinetic patterns (metabolism and excretion pattern) of higher doses of chemicals/toxins/xenobiotics. Toxicokinetics studies are usually carried out in rodents, rabbits, dogs, nonhuman primates, and swine using many different routes of administration (Parasuraman, 2011).

**Phytochemistry and Pharmacodynamic**

Aloe leaf consists of two parts: Parenchymatous cells and outer pericyclic tubules.

**A. Parenchymatous cells**

Parenchymatous cells of fresh Aloe Vera leaf pulp gives gel by mechanical extrusion. A gel is a transparent mucilaginous jelly-like substance having a yield of roughly about 70% (Femenia *et al*., 1999). The gel consists of 99%-99.5% of water and the remaining 0.5%-1% constitutes for soluble solids (Hamman, 2008). A gel is acidic

chemically and has a pH in the range of 4.4-4.7 (Wang and Strong, 1995). Chemical composition of Aloe Vera gel consists of 35% dietary fibres (non-starch polysaccharides + lignin), 27% soluble sugars, 24% ash, and a minor fraction of lipids, proteins, enzymes, and mineral elements, calculated on the dried basis (Femenia *et al*., 1999; Grindlay and Reynolds, 1986)

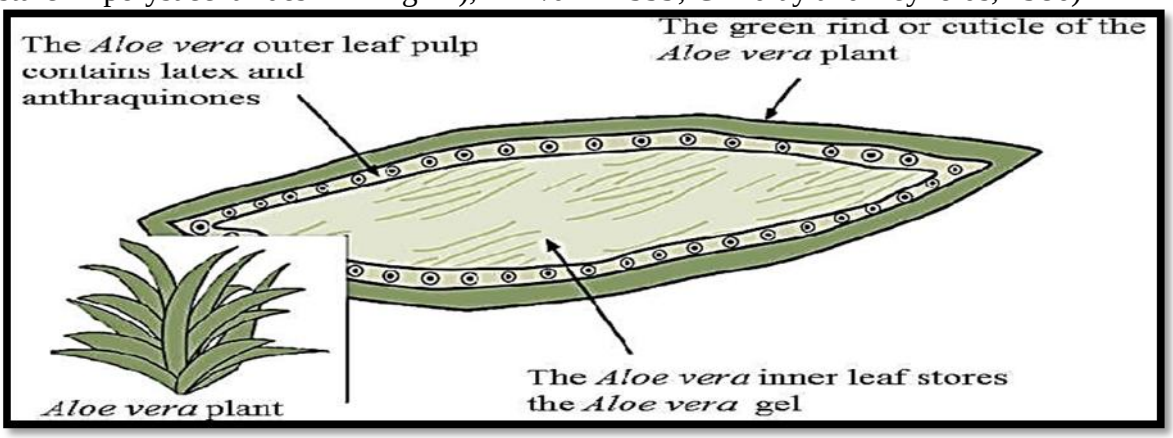


**Fig.1: Anatomy of Aloe Leaf**

**B. Outer pericyclic tubules**

Bitter yellow exudates are obtained from outer pericyclic tubules (present just beneath the outer green rind or cutinized epidermis of the leaves). Bitter yellow exudates consists of bitter reddish-yellow latex, which has a powerful laxative property (Wynn, 2005). Latex has a bitter taste. About 80 chemical constituents have been isolated by liquid chromatography in the latex. Latex mainly contains compounds that are phenolic chemically (anthraquinone C glycosides, anthrones, and free anthraquinones) (Park et al., 1998; Rebecca et al., 2003). Major constituent in the latex is Barbaloin, which is also known as Aloin A (Boudreau and Beland, 2006; Reynolds, 1985). Isobarbaloin (Aloin B), Aloesin (Aloeresin B), and Aloeresin A are other three main components isolated from latex (Saccu et al., 2001). The latex also contains several other anthraquinones/anthrones and chromones including Aloe-emodin, Aloeresin E, Aloenin, (Park et al., 1998) as well as some aromatic compounds, which includes aldehydes (butanal, pentanal, etc.) and ketones (2-butanone, 2-heptanone, etc.) (Saccu et al., 2001).

**Vitamins**

Vitamins A, C, F, B (thiamine), niacin, vitamin B2 (riboflavin), vitamin B12, choline, and folic acid are obtained from Aloe Vera gel. Vitamin A, C, and F are important antioxidants (Coats, 1979).

**Enzymes**

Amylase and lipase are biochemical catalysts, which help in digestion by breaking down fats and sugars. During the inflammatory process, bradykinin produces pain associated with vasodilation. Carboxypeptidase shows the analgesic effect and anti-inflammatory effect by inactivation of bradykinins (Obata *et al*., 1993; Shelton, 1991).

**Minerals**

Aloe plants mainly consist of sodium, potassium, calcium, magnesium, manganese, copper, zinc, chromium, and iron. Magnesium lactate inhibits the histidine decarboxylase enzyme. Formation of histamine from the histidine (amino acid) is prevented by inhibition of histidine decarboxylase enzyme. Intense itching and pain are caused by histamine (released in many allergic reactions). The prevention of histamine explains the antipruritic effect of Aloe Vera (Femenia *et al*., 1999; Mohamed, 2011; Nwaoguikpe *et al*., 2010; Samuelsson and Bohlin, 2004).

**Sugars**

Sugars are derived from the mucilage layer of the plant. The solid fraction of gel mainly comprises of both mono- and polysaccharides. The most important are the long-chain polysaccharides known as the glucomannans (glucose and mannose). The polysaccharides act as immunomodulators as they are absorbed complete and appear in the bloodstream unchanged (Green, 1996; Kahlon et al., 1991; Sheets *et al*., 1991).

**Anthraquinones**

Aloe Latex consists of free anthraquinones and their derivatives, Barbaloin, Aloe-emodin-9-anthrone, lsobarbaloin, Anthrone-C-glycosides, and chromones. These compounds in large concentration exert a powerful purgative effect, but they appear to aid absorption from the gut, potent antimicrobial agents and powerful analgesic effects when used in small concentration (Lorenzetti et al., 1964; Rezazadeh et al., 2016) formation of melanin and any tendency to hyper-pigmentation is also reduced by anthraquinones (Al-Snafi, 2015; Strickland et al., 1994).

**Lignin**

Lignin has the penetrative ability and thus carries other active ingredients deep into the skin along with it, thus lignin has dermis nourishing property (Coats, 1979).

**Salicylic acid**

Aspirin, Methyl Jasmonate, and ethephon compound possess anti-inflammatory (Lee *et al*., 2013) and antibacterial properties (Surjushe et al., 2008). It has a keratolytic effect which helps to debride a wound of necrotic tissue (Bhaskar et al., 2009).

**Amino Acid**

Around 20 amino acids are present in Aloe Vera gel among which seven are essential amino acids (Alanine, arginine, aspartic acid, cysteine, glutamic acid, glycine, histidine, hydroxyproline, isoleucine, leucine, lysine, methionine, phenylalanine, proline, threonine, serine, tyrosine, and valine) (Ahlawat and Khatkar, 2011).

**Other uses**

The use of Aloe Vera for healing and beauty purposes is known since ancient times. In India, since the Vedic period, the whole Aloe plant has been used as a purgative, stomachic, anthelmintic and emmenagogue, menstrual suppression, and the root for colic pain. Aloe has also been used for a large number of human illnesses like the development of the mammary glands, to correct kidney ailments, enhancement of sexual excitement, suppressing fever in children, relieve headaches, as a laxative, treating skin injuries, wound healing and anti-inflammatory effect. Aloe also has been found to be effective in arthritis, gastric ulcer, cancer, AIDS, and colitis. Clinical trials are now in improvement to afford convincing evidence for the treatment of some of these diseases (Mukherjee *et al*., 2014).

**Toxicokinetics**

Toxicokinetics study was performed on Human liver cells (L-02) obtained from Cell Bank. The dynamic alteration of emodin concentration was analyzed after different exposure times, in extracellular and intracellular extractions, to understand the cellular uptake of emodin in L-02 cells. the adherent cells, cell media, and floating cells were processed separately, at different intervals of incubation time, to provide the cell extract and supernatant extract for analysis. A highly sensitive and selective liquid chromatography-mass spectrometry (LC-MS) method was employed and validated to explain the toxicokinetic characteristics of emodin in cells and cell culture media. To explain cytotoxic manners of emodin on L-02 cells, extracellular and intracellular concentration variation of emodin was determined. During the first 12 h, the concentration of emodin in adherent cells increased rapidly, and approximately after 12 h reached near to saturation concentration. More and more cells were observed detaching from the surface and floating in the culture medium After 12 h of treatment with emodin. After 12 h there was a decreased number of adherent cells and emodin metabolism. These results indicated that emodin exerts its cytotoxicity after entering into the cytoplasm and accumulating in the L-02 cells (Li *et al*., 2012).

**Toxicity Case Report (Humans)**

**57-year old German female (Acute Hepatotoxicity)**

Here, we describe the first case of liver damage associated with Aloe Vera ingestion, in a 57-year old female patient. At the time of hospitalization, she had progressive jaundice, pruritus, acholic bowel movements, and right upper quadrant abdominal discomfort. No, any preexisting liver disease was reported in past medical history. She disclosed the use of Aloe Vera tablets, containing 500 mg of an extract of Aloe barbadensis miller (for about 4 weeks before admission), to delay

ageing. Clinical, Laboratory, and technical examination was performed.Laboratory abnormalities were reported, which included a bilirubin concentration of 8.9 mg/dL (normal: <1.1mg/dL), ALAT 1480 U/L (normal: <22 U/L), ASAT 711 U/L (normal: <15 U/L), LDH 506 U/L (normal<240 U/L), alkaline phosphatase 265 U/L (normal: <160 U/L), GGTP 244 U/L (normal: <18 U/L). Anti-HBc-IgG and anti-HBs-IgG were reported positive, while HBsAg and anti-HBc-IgM were reported negative in Serologic examinations. Severe acute hepatitis with portal and acinar infiltrates predominantly (consisting of lymphocytes, plasma cells, and eosinophilic granulocytes) along with bridging necrosis, and bilirubinostasis was revealed in liver biopsy. Amino-transferases, as well as the bilirubin concentration, gradually returned to normal levels, after all, medications were stopped for several months. ALAT concentration level of 226 U/L, 180 U/L, and 40 U/L, was reported two weeks after admission, 5 months after discharge, and 1 year after discharge respectively. After discontinuing this medication, the patient´s hepatitis resolved completely and never happened so on (Rabe *et al*., 2005).

**24-year old Turkish male (Acute Hepatotoxicity)**

Here, we describe the second case of acute hepatitis associated with Aloe Vera ingestion, in a patient. At the time of hospitalization, he had complaints of jaundice, pruritis, fatigue, and right upper abdominal discomfort, together with mild nausea and vomiting. No pre-existing liver disease, blood transfusion, or alcohol consumption was reported in past medical history. The patient disclosed that he had been taking Aloe Vera capsules (for a healthier living) containing 500 mg of the extract of *Aloe barbadensis* miller (1 capsule/day) for 3 weeks before he was admitted to hospital. He did not consume any other medication along with Aloe Vera. Physical examination was normal. Laboratory abnormalities were reported, which included total bilirubin 9 mg/dL (normal:<1.0 mg/dL), conjugated bilirubin 8.2 mg/dL (normal: <0.2 mg/dL), AST 2550 U/L (normal: & lt; 40 U/L), ALT 2400 U/L (normal: < 40 U/L), ALP 400 U/L (normal: < 155 U/L), GGTP 140 U/L (normal: < 49 U/L). Drug-induced hepatitis with marked, portal and acinar infiltrates predominantly (consisting of lymphocytes, monocytes, and eosinophils) along with bridging necrosis was revealed in liver biopsy. The patient symptoms resolved completely within 7 days, on discontinuation of Aloe Vera. Test performed after 6 weeks, after discontinuation of the drug, Laboratory abnormalities gradually returned to normal range (Kanat *et al*., 2006).

**73-year old American female (Acute Hepatitis)**

Here, we describe the case of acute hepatitis associated with Aloe Vera ingestion, in a patient. She was transferred from an outlying community hospital to a large community teaching hospital, for further evaluation and management of possible acute cholecystitis. She had symptoms like general malaise, poor appetite, nausea, right shoulder pain, and a weight loss of approximately 1.8 kg for several weeks. She developed jaundice. No pre-existing liver disease, cardiac, respiratory, genitourinary, or renal disease was reported in past medical history. She did not consume tobacco, alcohol, or illicit drug. When she was asked specifically if she had taken any herbal products, she revealed of taking Aloe Vera capsules (1 capsule every 2–3 days for the past 5 years) in order to treat constipation. It was found that each capsule contained 500 mg of Aloe Vera leaf powder. Physical examination was normal. Laboratory abnormalities were reported, which included TB 10.7 mg/dL, direct bilirubin 7.2 mg/dL, ALP 535 U/L, AST 1495 U/L, and ALT 1451 U/L. Jaundice was reported in clinical examination. Thickened gallbladder wall measuring 0.89 cm, a nondilated common bile duct, and some small stones within her gallbladder was reported. Active hepatitis was reported in liver biopsy. The patient was diagnosed with acute hepatitis, based on symptoms and results of the testing. Her liver function tests began to improve, after several days of observation and supportive care, on discontinuation of Aloe Vera capsule. The

patient was discharged home with instructions to avoid taking the oral Aloe Vera. Her liver function tests following 4 months after discharge from the hospital showed TB, ALP, AST, ALT level to be 0.5 mg/dL, 163 U/L, 77 U/L, 52 U/L respectively (Bottenberg et al., 2007).

**Death of 4 patients**

An article in the past presented the death of 4 patients after they were injected with Aloe Vera injection to treat cancer. Characteristics of Patients who died after getting Aloe Vera injection are given in Table 1. It was reported that the Aloe Vera mixture, Dr Donald L. MacNay used, has not been approved by the Food and Drug Administration for treating cancer. It was also reported that Dr MacNay was not authorized to conduct research trials and MacNay is an orthopaedic surgeon with no known training in cancer research. He had injected four cancer patients with Aloe Vera injection and all of them died. Douglas Crabbe paid a doctor USD 12,000 to MacNay for his oesophagal unorthodox cancer treatment. Crabbe was asked to take 21 injections of Aloe Vera. Crabbe's lower body swelled to four times its normal size, cracking the skin on his feet on taking Aloe Vera injection. He was dead in less than a month, after taking his first Aloe Vera injection. Dr MacNay was suspended. Although autopsies did not directly blame Aloe Vera in any of the deaths. MacNay said that the treatment is intended to help the immune system, and usually works best in healthier patients ("Doctor injected cancer patients with Aloe Vera; four have died | National | journaltimes.com," n.d.).

**Table 1: Characteristics of the Patient Died on Being Injected With Aloe Vera Injection**

| Patient number | Name | Age (years) | Sex | Type of cancer patient had | Approximate period of death after being injected |
|---|---|---|---|---|---|
| 1[#] | Douglas Crabbe | 48 | M | Oesophagul | Within one month |
| 2[#] | Waco | 83 | M | Unknown | Unknown |
| 3[#] | Alabama | 57 | M | Prostate and Kidney | Within hour |
| 4[#] | Unknown | 41 | M | Renal Cell | After an hour |

[#]("Doctor injected cancer patients with Aloe Vera; four have died | National | ournaltimes.com," n.d.)

**Discussion**

The study of Aloe induced case reports, showed acute hepatitis on the consumption of formulation containing Aloe Vera Extract. Out of 11, 4 patients died on being injected with Aloe Vera injection. Remaining 7 cases who were admitted to the hospital had no physical abnormalities; laboratory findings reported an increase in TB, AST, ASP, ALT level significantly. The highest does consume had 500 mg of Aloe Vera extract for around 3-260 weeks. Liver biopsy showed portal and acinar infiltrates. Their clinical manifestation, liver biopsy, and laboratory findings supported the diagnosis of toxic hepatitis. All seven patients showed improved conditions after discontinuing of Aloe Vera. The examination post stopping consumption was found to be normal. As the effect seen can lead to life- threatening conditions, the patients were not rechallenged. Although 62-year-old female (case given in table 2) started taking the same Aloe extract again 1 month after her discharge from the hospital and on follow-up liver function test AST, ALT and AP increased again. As hepato-toxicity reoccurred after re-challenging with Aloe Extract, proves Aloe-induces hepato-toxicity. LD 50 in Swiss albino mice reported, indicates toxicity of Aloe Vera. Maximum tolerated dose and LOAEL of Aloe Vera extract were found to be 100 mg/kg BW and 2 g/kg BW respectively. Trials on animals showed reproductive toxicity.

**Conclusion**

This paper emphasizes the importance of considering Aloe Vera Product (OTC drugs) as causative agents in hepatotoxicity. However, as a result of our experience and a literature review, we recommend detail controlled toxicological studies and pharmacovigilance should be carried out before marketing and consumption for all

Aloe Vera products like any other synthetic drugs.

**References**

1. Ahlawat, K.S., Khatkar, B.S. (2011). Processing, food applications and safety of Aloe Vera products: A review. J. Food Sci. Technol. 48, 525–533. https://doi.org/10.1007/s13197-011-0229-z
2. Al-Snafi, A.E. (2015). The Pharmacological Importance of Aloe Vera- A Review. Int. J. Phytopharm. Res. 6, 28–33.
3. Barnes, P.M., Bloom, B., Nahin, R.L. (2008). Complementary and Alternative Medicine Use Among Adults and Children : United States , 2007. Natl. Health Stat. Report. 1–23. https://doi.org/10.1037/e623942009-001
4. Bhaskar, G., Arshia, S., Priyadarshini, S.R.. (2009). Formulation and evaluation of topical polyherbal antiacne gels containing Garcinia mangostana and Aloe Vera. Pharmacogn. Mag. 5, 93–99.
5. Blendon, R.J., Benson, J.M., Botta, M.D., Weldon, K.J. (2013). Users' views of dietary supplements. JAMA Intern. Med. 173, 74–76. https://doi.org/10.1001/2013.jamainternmed.311
6. Bottenberg, M.M., Wall, G.C., Harvey, R.L., Habib, S. (2007). Oral Aloe Vera-Induced Hepatitis. Ann. Pharmacother. 41, 1740–1743. https://doi.org/10.1345/aph.1K13
7. Doull, J., Klaassen, C., Amdur, M. (1980). Casarett and Doull's toxicology: the basic science poisons, 2nd ed. Macmillan, New York
8. Ekor, M. (2014). The growing use of herbal medicines: Issues relating to adverse reactions and challenges in monitoring safety. Front. Pharmacol. 4 JAN, 177. https://doi.org/10.3389/fphar.2013.00177
9. Femenia, A., Sanchez, E.S., Simal, S., Rossello, C. (1999). Compositional features of polysaccharides from Aloe Vera (Aloe barbadensis Miller) plant tissues. Carbohydr. Polym. 39, 109–117. https://doi.org/10.1016/S0144-8617(98)00163-5
10. 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, 117–151. https://doi.org/10.1016/0378-8741(86)90085-1
11. Green, P., 1996. Aloe Vera extracts in equine clinical practice. Vet. Times 26
12. Hamman, J.H. (2008). Composition and Applications of Aloe Vera Leaf Gel. Molecules 13, 1599–1616. https://doi.org/10.3390/molecules13081599
13. Kanat, O., Ozet, A., Ataergin, S. (2006). Aloe Vera-induced acute toxic hepatitis in a healthy young man. Eur. J. Intern. Med. 17, 589. https://doi.org/10.1016/j.ejim.2006.04.017
14. Lee, Y.S., Ju, H.K., Kim, Y.J., Lim, T.-G., Uddin, M.R., Kim, Y.B., Baek, J.H., Kwon, S.W., Lee, K.W., Seo, H.S., Park, S.U., Yang, T.-J. (2013). Enhancement of Anti-Inflammatory Activity of *Aloe Vera* Adventitious Root Extracts through the Alteration of Primary and Secondary Metabolites via Salicylic Acid Elicitation. PLoS One 8. https://doi.org/10.1371/JOURNAL.PONE.0082479
15. Park, M.K., Park, J.H., Kim, N.Y., Shin, Y.G., Choi, Y.S., Lee, J.G., Kim, K.H., Lee, S.K. (1998). Analysis of 13 phenolic compounds in Aloe species by high performance liquid chromatography . Phytochem. Anal. 9, 186–191.
16. Rabe, C., Musch, A., Schirmacher, P., Kruis, W., Hoffman, R. (2005). Acute hepatitis induced by an Aloe Vera preparation: A case report. World J. Gastroenterol. 11, 303–304. https://doi.org/10.3748/wjg.v11.i2.303
17. Wang, Y.T., Strong, K.J., 1995. A two-year study monitoring several physical and chemical properties of field-grown Aloe barbadensis Miller leaves. Subtrop. Plant Sci. 47, 34–38.
18. Worth, A.P. (2019). Types of Toxicity and Applications of Toxicity Testing, in: Balls, M., Combes, R., Worth, A. (Eds.), The History of Alternative Test Methods in Toxicology. Elsevier, London (UK), pp. 8–8. https://doi.org/10.1016/B978-0-12-813697-3.00002-0.