



# Antimutagenicity and antigenotoxicity of *Aloe arborescens* Miller and *Aloe barbadensis* Miller in *Aspergillus nidulans* and Wistar rats

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**ABSTRACT.** Medicinal plants such as *Aloe arborescens* Miller and *Aloe barbadensis* Miller are used by the general population to treat various diseases. Therefore, the aim of this study was to evaluate the antimutagenicity of these two species using a *methG1* system in *Aspergillus nidulans* and the comet assay in rats. The animals were treated with the plants at concentrations of 360 and 720 mg/kg body weight (1 and 2, respectively) by gavage for 14 days, followed by the administration of etoposide on treatment day 8. Blood samples were prepared for analysis of DNA damage. For the test in *A. nidulans*, the *biA1methG1* lineage conidia were treated for 4 h with both plant species at concentrations of 4 and 8% (w/v). Then, they were washed

and plated on a selective medium for frequency analysis of survival and mutation. The results of the comet assay showed that both plants were antigenotoxic compared to etoposide, which was not a typical response of *methG1* systems, where only the highest concentration of plant extracts usually exhibit beneficial effects. This study demonstrates the potential antigenotoxicity and antimutagenicity of the *Aloe* plants tested and, therefore, supports their use as a form of preventive therapy and for health maintenance by the population.

**Key words:** Medicinal plants; *Aloe*; Etoposide; Comet assay; *methG1* system

## INTRODUCTION

The interactions between genetic and environmental factors such as diet and lifestyle, especially in relation to nutrition and physical inactivity, can promote the progression of diseases such as obesity, diabetes, and cancer, which is currently dramatically increasing in prevalence in epidemic proportions (Phillips, 2013). This can be attributed to the constant exposure of the cells of all living organisms to exogenous and endogenous agents, which damages the genetic information because DNA molecules are not static, and their bases are constantly susceptible to change (Erdtmann, 2003).

Carcinogenesis is initiated by an irreversible alteration of DNA replication and cell proliferation that is activated to repair the initial mutation, which indicates a direct relationship clearly exists between mutagenicity and carcinogenicity (Loureiro et al., 2002). Therefore, cancer is a consequence of the progressive accumulation of random mutations in individuals who are prone to the development of this disease. Therefore, the use of antimutagenic substances in the prevention of cancer by decreasing the rate of mutation has been investigated (Liviero and von Borstel, 1996).

Etoposide is one of the most widely used chemotherapeutic agents for the treatment of numerous cancers. It acts by inducing lesions in the genome such as breakage of one or both strands of the DNA, causing cytotoxicity to sick cells; however, it also affects healthy cells (David et al., 2001). Chemotherapy shocks the immune system and drastically weakens the organism and, therefore, an appropriate diet is necessary to improve the immunity of the patient.

*Aloe arborescens* Miller and *Aloe barbadensis* Miller are *Aloe* species that possess great medicinal value (Singh et al., 2000), and are widely used by the general Brazilian population. These plants have several activities that are beneficial to the body, and in particular, their antioxidant (Ojha et al., 2011), antitumoral (Tomasin and Gomes-Marcondes, 2011), antidiabetic (Misawa et al., 2008; Abo-Youssef and Messiha, 2013), and immune system stimulating (Lissoni et al., 2009; Picchiatti et al., 2013) functions stand out.

The present study aimed to evaluate the possible antimutagenic actions of *A. arborescens* and *A. barbadensis* in *methG1* system *Aspergillus nidulans* and the antigenotoxicity by using the comet assay in rats.

## MATERIAL AND METHODS

### Reagents

The chemotherapeutic agent, etoposide (ETO), was purchased as the branded product,

Posidon® (100 mg) from Darrow Laboratory. For the comet assay, low melting point (LMP) and normal melting point agarose were obtained from Invitrogen while all other reagents were from Merck.

## Treatments

The mucilage was obtained from the fresh leaves of *A. arborescens* and *A. barbadensis*, after the removal of the shell and gel extraction (parenchyma). The mucilage of the leaves of each species was processed in a blender and then filtered through a 20-mm pore size filter paper (Millipore, for the antimutagenicity experiments). The gels were diluted in water to obtain the required dose and immediately used for the treatments and was not stored.

## Comet assay in rats

### *Animals*

Each experimental group consisted of five male Wistar rats (*Rattus norvegicus*) obtained from the Central Biotery of Universidade Estadual de Maringá (UEM). In the vivarium, the rats were housed under controlled conditions of 25°C temperature, 50% humidity, and a 12-h light/dark photoperiod, while water and ration feed were provided *ad libitum*. The animal experiments were initiated only after a 1-week acclimatization. In addition, all the ethical principles, protocols, and regulations of the animal experimentation laboratory were in strict accordance with the international standards established. Furthermore, the project was approved by the Institutional Ethics Committee of UEM and the Ethics Committee on Animal Use in Research/UEM and followed the Ethical Principles in Animal Experimentation established by the Brazilian College of Animal Experimentation. Moreover, specific treatment protocols were used for the sample collection and comet assay.

### *Treatments*

Each group consisted of five randomly assigned male rats, weighing approximately 100 g body weight (bw). The negative controls (CO) received 0.1 mL/100 g (bw) mineral water, and the positive controls were treated with ETO, while the four test groups received the *A. arborescens* and *A. barbadensis* mucilage at two different doses, 360 and 720 mg/kg bw (1 and 2, respectively) via gavage for 14 days. In addition, another four groups received the same treatment with both plant species but were administered ETO (50 mg/kg bw), intraperitoneally on day 8. The CO and four test substance control groups (A1, A2, B1, B2) received 0.1 mL/100 g bw 0.9% saline solution. The blood was collected from all groups before, 1, 24 h, and 7 days after administration of ETO and saline. In summary, the groups were treated for 14 days according to the experimental protocol shown in Table 1.

### *Comet assay*

The comet assay was performed in accordance with the methods of Singh et al. (1988) and Tice et al. (2000). Briefly, a 5- $\mu$ L blood sample was withdrawn from the tail of each animal, added to 120  $\mu$ L LMP agarose [0.5% phosphate-buffered saline (PBS)], the mixture

was pre-applied onto two slides covered with normal agarose (1.5% PBS), and then cooled to 4°C for 5 min. Then, the slides were immersed in the lysis solution at 4°C [4.5 M sodium chloride, NaCl; 100 mM ethylene diaminetetra acetic acid (EDTA); 10 mM Tris, pH 10.0; 1% Triton-X; and 10% dimethyl sulfoxide] for 24 h. Then, the slides were incubated in the electrophoresis buffer (300 mM sodium hydroxide, NaOH and 200 mM EDTA, pH > 13) at 4°C for 25 min, and the electrophoresis (300 mA, 0.7 V/cm) was subsequently performed for 25 min. Then, the slides were neutralized thrice (5 min each) in a neutralization solution (0.4 M Tris-hydrochloride, HCl, pH 7.5), fixed with absolute ethanol for 5 min, dried at temperature 25°C temperature, and then held at 4°C before the analysis. The slides were stained with 20 µL ethidium bromide (20 mg/mL), coverslipped, and then analyzed by using a fluorescence microscope.

**Table 1.** Grouping of Wistar rats treated with *Aloe arborescens* and *Aloe barbadensis* in comet assay.

Group	Treatment
CO	Water, on the 8th day, saline injection
ETO	Water, on the 8th day, etoposide injection
A1	[1] <i>A. arborescens</i> , on the 8th day, saline injection
A2	[2] <i>A. arborescens</i> , on the 8th day, saline injection
B1	[1] <i>A. barbadensis</i> , on the 8th day, saline injection
B2	[2] <i>A. barbadensis</i> on the 8th day, saline injection
A1 + ETO	[1] <i>A. arborescens</i> , on the 8th day, etoposide injection
A2 + ETO	[2] <i>A. arborescens</i> , on the 8th day, etoposide injection
B1 + ETO	[1] <i>A. barbadensis</i> , on the 8th day, etoposide injection
B2 + ETO	[2] <i>A. barbadensis</i> , on the 8th day, etoposide injection

Fifty cells on each slide, totaling 100 cells per animal were analyzed in a blind fashion to determine the percentage of damaged cells per animal and the frequency of damage (FD). Each damaged cell was graded on a scale of 0 to 4 according to the size of the comet tail to determine the index of damage (ID), which was calculated by multiplying the number of cells in each level to obtain the final value. Thus, the values ranged from 0 (no damaged cells, 0 x 100) to 400 (all cells were maximally damaged, 4 x 100).

### ***methG1* system in *A. nidulans***

#### ***Lineage***

The *biA1methG1* lineage used in this experiment originated from Glasgow (Scotland). The strain was deficient in biotin (chromosome I) and methionine (chromosome IV).

#### ***Culture media***

The culture media were prepared according to the method of Pontecorvo et al. (1953) and Clutterbuck (1974). Complete medium (CM) was used to cultivate the *biA1methG1* strain while the selective medium (SM) used for the analysis of the mutants consisted of minimal medium supplemented with biotin (0.02 mg/mL). The medium used to evaluate the survival was prepared, and it contained the same composition as the SM and was supplemented with 50 mg/mL methionine (SMM).

### ***Treatments***

The dormant conidia of the *biA1methG1* strain were treated as follows: Control, distilled water; *A. arborescens* (4% w/v); *A. arborescens* (8% w/v); *A. barbadensis* (4% w/v); *A. barbadensis* (8% w/v).

### ***Concentration determination***

The effects of different concentrations of the mucilage from the leaves of the two *Aloe* species were tested on the germination of the fungus. These results were used to determine suitable concentrations for treating the conidia, and 4 and 8% (w/v) were selected for each plant species.

### ***Mutagenicity test***

The conidia of the colonies grown for 5 days at 37°C in CM were collected, agitated, filtered through glass wool, and then subjected to different treatments. The treatment time was set at 4 h depending on the nutritional value of the gels because the conidia tend to germinate when they are left for periods longer than 4 h, and the method requires dormant conidia. After the treatment, the conidia were washed and centrifuged thrice with distilled water. For the survival estimation, appropriate dilutions were prepared, and 0.1 mL of each was added to 10 plates containing SMM for each treatment, and this was incubated for 3 days at 37°C. For the analysis of the mutation, 0.1 mL was inoculated into the suspension without the dilution on 10 plates containing SM for each treatment, and the plates were incubated for 5 days at 37°C. The entire procedure was repeated in triplicate.

### **Statistical analysis**

The statistical analysis of the results of the *methG1* system experiments was performed according to the method of Munson and Goodhead (1977), which was adapted to the *methG1* system by Scott et al. (1982). The results of the comet assay were analyzed using the Tukey test ( $P < 0.001$ ).

## **RESULTS**

Table 2 shows that the groups of animals treated with the plant substances exhibited no genotoxicity because the IDs of their treatments were not statistically different from those of the negative control animals. The results of the ID determination of the samples collected after 7 days (14 days of gel treatment) show that both concentrations of *A. arborescens* reduced the basal damage observed in the negative control animals. The effects in the animals that received the chemotherapy and plant treatments were statistically different from the group that received only ETO for the two blood samples evaluated (1 and 24 h later). The samples were not collected after 7 days and, therefore, could not be analyzed because the vast majority of the chemotherapy-treated animals died before then.

**Table 2.** Index of damage and standard deviation of Wistar rat groups treated with *Aloe arborescens* and *Aloe barbadensis* in comet assay.

Treatment	1 h	24 h	7 days
CO	6.40 ± 2.97*	1.40 ± 1.52*	11.20 ± 4.76
A1	8.00 ± 6.590	3.80 ± 5.49	3.80 ± 2.49
A2	6.80 ± 4.60	4.60 ± 3.91	2.80 ± 2.95
B1	1.00 ± 0.70	8.40 ± 3.51	5.20 ± 4.08
B2	2.60 ± 1.50	3.00 ± 5.10	4.80 ± 4.08
ETO	170.4 ± 57.50	104.00 ± 41.20	-
A1 + ETO	38.00 ± 27.59*	45.8 ± 20.62*	-
A2 + ETO	34.40 ± 4.16*	22.20 ± 8.23*	-
B1 + ETO	16.60 ± 9.37*	29.40 ± 15.09*	-
B2 + ETO	29.80 ± 16.65*	38.80 ± 4.76*	-

Treatments for 14 days: CO: water, on 8th day, saline injection; ETO: water, on 8th day, etoposide injection; A1: [1] *A. arborescens*, on 8th day, saline injection; A2: [2] *A. arborescens*, on the 8th day, injection of saline; B1: [1] *A. barbadensis*, on 8th day, saline injection; B2: [2] *A. barbadensis* on 8th day, saline injection; A1 + ETO: [1] *A. arborescens*, on 8th day, etoposide injection; A2 + ETO: [2] *A. arborescens*, on 8th day, etoposide injection; B1 + ETO: [1] *A. barbadensis*, on 8th day, etoposide injection; B2 + ETO: [2] *A. barbadensis*, on 8th day, etoposide injection. \*Statistically significant compared to ETO.

The mean FD (Table 3) and the observed ID showed that treatment with the two gels was not genotoxic. The groups that were administered each plant substance (babosa) and the chemotherapy showed lower values than the ETO-treated group did for the analysis of the 1- and 24-h samples, which was indicative of antigenotoxicity. The samples collected after 7 days revealed that the groups treated with the gels did not show any statistically significant difference, although the values were lower than that of the control.

**Table 3.** Average frequency of damage and standard deviation of Wistar rat groups treated with *Aloe arborescens* and *Aloe barbadensis* in comet assay.

Treatment	1 h	24 h	7 days
CO	3.80 ± 1.30*	0.80 ± 0.45*	5.80 ± 2.77
ETO	79.20 ± 19.84	54.40 ± 17.82	-
A1	5.00 ± 4.00	2.80 ± 4.08	1.80 ± 1.09
A2	5.20 ± 3.70	3.40 ± 2.79	1.80 ± 1.64
B1	1.00 ± 0.70	5.80 ± 2.28	3.00 ± 2.00
B2	2.00 ± 1.00	2.00 ± 2.91	3.40 ± 3.36
A1 + ETO	22.20 ± 14.60*	25.40 ± 9.53*	-
A2 + ETO	19.40 ± 2.19*	14.00 ± 4.53*	-
B1 + ETO	9.20 ± 5.49*	17.40 ± 7.99*	-
B2 + ETO	19.00 ± 9.40*	18.00 ± 2.83*	-

Treatments for 14 days: CO: water, on 8th day, saline injection; ETO: water, on 8th day, etoposide injection; A1: [1] *A. arborescens*, on 8th day, saline injection; A2: [2] *A. arborescens*, on 8th day, saline injection; B1: [1] *A. barbadensis*, on 8th day, saline injection; B2: [2] *A. barbadensis* on 8th day, saline injection; A1 + ETO: [1] *A. arborescens*, on 8th day, etoposide injection; A2 + ETO: [2] *A. arborescens*, on 8th day, etoposide injection; B1 + ETO: [1] *A. barbadensis*, on 8th day, etoposide injection; B2 + ETO: [2] *A. barbadensis*, on 8th day, etoposide injection. \*Statistically significant compared to ETO.

We observed that from the second day after the intraperitoneal injection, all the ETO-treated animals presented with symptoms of weakness, loss of hair, diarrhea, and weight loss. Furthermore, most of these animals did not survive up to day 7 when the last blood sample analysis was to be performed based on the experimental design of the comet assay. Animal deaths were observed from day 3 after the administration of the chemotherapy while all the animals treated with only ETO died. However, some of the animals in the groups treated with the two *Aloe* species survived: groups A1, A2, B1, and B2 had one, two, four, and two surviving rats, respectively.

Table 4 presents the results of the mutagenicity evaluation in the *methG1* system. At a concentration of 4%, both gels decreased the frequency of mutation but did not increase the viability, which is why the statistical analysis showed no significance. However, at a concentration of 8%, the gels increased the survival and decreased the frequency of mutation, and the results were significant.

**Table 4.** Average values of three repetitions, feasibility, mutant frequency, and mutation of Control (C) and gel treated groups in *methG1* system.

Experiment	Treatment	No. of viable conidia x 10 <sup>5</sup> /mL	No. mutant/mL	Mutant frequency
1	C	70.13	52.66	12.30
	A4	40.23	71.66	18.30
	B4	44.87	83.66	19.07
2	C	98.04	45.66	4.60
	A8	146.19	38.33	3.09
3	C	50.21	35	7.02
	B8	55.11	33.66	6.36

A4: *Aloe arborescens* (4%), A8: *A. arborescens* (8%), B4: *Aloe barbadensis* (4%), B8: *A. barbadensis* (8%). Statistical analysis of treatment results using method of Munson and Goodhead (1977) produced the following straight slope: A4:  $m' = 9.15$ ,  $m'' = 18.30$ ,  $mc = 10.81$ ; A8:  $m' = 1.54$ ,  $m'' = 3.09$ ,  $mc = 3.87$ ; B4:  $m' = 9.53$ ,  $m'' = 19.07$ ,  $mc = 15.04$ ; B8:  $m' = 3.18$ ,  $m'' = 6.36$ ,  $mc = 7.09$ .

## DISCUSSION

The leaves of the plants surveyed in this study were not genotoxic when tested in isolation since they induced a similar degree of genetic lesions to the spontaneously induced lesions in the control group. This result provides evidence supporting the potential safety of the therapeutic use of these plants, which is in agreement with the results obtained by Munhoz et al. (2012), who evaluated three concentrations of a commercial *A. barbadensis* juice in mice using the comet assay. In addition, Ruiz et al. (1996) and Sturbelle et al. (2010) performed *in vitro* assays using *A. nidulans* and *in vivo* micronucleus tests in rats.

The statistical differences in both the median ID and FD between the group of animals treated with ETO and the Control, confirmed the genotoxicity of the chemotherapy, justifying its use as a positive control. Furthermore, the analysis of the group treated with ETO alone and all the groups that received the ETO in combination with the plant gel treatments demonstrated the antigenotoxic activity of the *Aloe* species at all the concentrations. This result indicated the protective action of the leaves of the *Aloe* species tested.

The animals in the ETO group showed a complete mortality after the chemotherapy, in contrast with the groups that received the chemotherapy in combination with the *Aloe* plant species, which had survivors. These results corroborate those of Lissoni et al. (2009) who studied the effects of several chemotherapies including ETO that was used in this study, in patients with cancer. Their results confirmed the multiple benefits experienced by patients who were administered chemotherapy in combination with the *A. arborescens* compared with the group that only received chemotherapy. The average number of lymphocytes observed after the chemotherapy was significantly higher in the patients who were also treated with the plant and the incidences of symptoms such as weakness and fatigue were lower, which correlated with the increase in the length of survival of these patients as well as the improvement in their quality of life.

The effects of the *Aloe* mucilage in this study corroborated those reported by Von Borstel et al. (1996), who found that numerous compounds derived from plants that were

administered in combination with chemotherapy prevented the damage these antineoplastic agents caused to healthy cells. Furthermore, Singh et al. (2000) reported that the extract of *Aloe vera* L. (synonymous with *A. barbadensis*) showed antioxidant activity and positively influenced the enzymes associated with the metabolism of carcinogens. This finding was based on a survey conducted *in vivo*, which confirmed the ability of the modular to reduce and even eliminate the toxicity of other biological agents (Davis, 1997).

Düsman (2007) demonstrated the antimutagenic activity of *A. barbadensis* by analyzing the chromosomal aberrations in Wistar rats, in relation to cyclophosphamide, another chemotherapeutic agent that is widely used to treat various cancers. However, according to Sturbelle et al. (2010), the same plant species exhibit antimutagenicity when combined with the mutagenic paracetamol. This effect was demonstrated in a micronucleus test using human lymphocytes and by antigenotoxicity evaluation of its commercial form in mice using the comet assay in relation to the agent methyl methanesulfonate in a post-treatment assessment by Munhoz et al. (2012).

Furthermore, the protective effects of the *A. barbadensis* gel were confirmed by Gbadegehin et al. (2009) in a study with mice exposed to petroleum products (diesel, kerosene, and hydraulic oil) in tests that investigated the factors associated with both hepatotoxicity and mutagenicity. Therefore, the antigenotoxic activity of the *A. arborescens* and *A. barbadensis* gels were compared with the effects of ETO in Wistar rats, and the results corroborated the information reported in most of the previously reported scientific studies described here.

The protective activity of *A. arborescens* and *A. barbadensis* observed in our present study suggest the involvement of multiple mechanisms such as the inhibition of genotoxic effects, antioxidant activity, inhibition of cell proliferation, and modulation of signal transduction. Many of these mechanisms are interconnected or partially overlap with various stages of the DNA repair process (Kojima et al., 1992; Kuroda et al., 1992).

The powerful effect of the substances contained in the *Aloe* plants was demonstrated by their ability to increase the exercising activity, as well as their antidiabetic and antioxidant effects (Abo-Youssef and Messiha, 2013). Furthermore, the *Aloe* plants blocked the replication of the human immunodeficiency virus, which was mediated by their immunomodulatory properties, as was demonstrated by the method described by Yu et al. (2009) and Toliopoulos et al. (2012).

In view of the strong association between the antimutagenic and anticarcinogenic potential, it is worth highlighting the study performed by Tomasin and Gomes-Marcondes (2011), who detected the antitumoral activity of *A. vera* L. and honey in Wistar rats, which controlled tumor growth, decreased cellular proliferation, and increased the apoptosis of cancer cells. The phytochemical composition of *A. barbadensis* mainly consists of anthraquinones, mucilage, polysaccharides, fatty acids, sterols, glycoproteins, enzymes, amino acids, minerals, and vitamins, which are responsible for the numerous therapeutic and nutritional benefits that are attributed to this plant (Choi and Chung, 2003). Aloctin A is an active substance extracted from *A. arborescens*, which has several biological and proven pharmacological activities such as antitumoral and anti-inflammatory. In addition, aloctin A is a promising candidate immunomodulatory agent (Imanishi, 1993).

Only the highest concentration (8%) of the two species tested in the *A. nidulans methG1* system showed antimutagenic activity that was statistically significant, suggesting a dose-response effect. However, the 4% concentration reduced the frequency of spontaneous mutations compared to the Control, which suggests the mucilage of the leaves may possess

antioxidant effects. This system-test is efficient and has been used in other investigations of phytotherapeutic products such as the study by Rodrigues et al. (2003) on the mushroom of the Sun (*Agaricus blazei*) and Souza-Paccola et al. (2004) who investigated the *Lentinula edodes* and *A. blazei* mushrooms.

It is also worth noting that according to Berti et al. (2015), both species surveyed in this study positively interfered in the development of several cell lines (normal and mutant) of *A. nidulans*. These effects included the stimulation of germination and a significant reduction in the dead or malformed conidia or both, which proved the potential benefit of these plants based on their ability to contribute to the homeostasis of organisms and their antioxidant activities, as well as the stimulation of self-protection and self-preservative activities.

The results of the present study apparently contradict those obtained by Kayraldiz et al. (2010) in a survey of the antigenotoxicity extract of *A. vera* L. investigated in chromosomal aberration, micronuclei, sister chromatid exchange, and Ames tests. The extract was genotoxic at all concentrations used in the test for chromosomal aberrations and cytotoxicity in human lymphocytes. We also observed that this plant did not increase the sister chromatid exchange, which is indicative of its beneficial effects. However, Sirdarta and Cock (2010) reported that the juice of *A. barbadensis* showed toxic effects by inducing oxidative stress, similarly to what was described by Tian and Hua (2005), who demonstrated that the components of this plant such as *Aloe*-emodina and Aloin can act as pro-oxidants or as antioxidants, depending on their concentration.

Mehrabian et al. (2012) evaluated the antimutagenic effect of the ethanol and aqueous extract of *A. barbadensis* from two different cities in Iran using the Ames test. Both samples reduced the rate of mutation; however, the plant that originated from one of cities showed a maximum reduction of mutations, indicating that environmental factors have an impact on the antioxidant components of plants.

The therapeutic effects of medicinal plants or other natural products are not usually associated with the active substance, which, despite being the main component for a specific activity, may not be as effective when isolated. This phenomenon is due to the synergism between the substances, which occurs as a means of mutual assistance between the plant components (Davis, 1993). The constituents of *A. arborescens* and *A. barbadensis* include the polysaccharides acemanan and glicomanan, which act as immunomodulators, and the anthraquinone, *Aloe*-emodina that has antitumor activities (Pecere et al., 2000; Lissoni et al., 2009).

The results of the present study largely support previously published reports of the beneficial properties of *A. arborescens* and *A. barbadensis*, suggesting that its consumption is potentially beneficial as a preventive therapy and for health maintenance, especially in individuals exposed to chemotherapy. These results also support the need for additional studies on the effects of the continuous internal use of these plants.

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