ORIGINAL ARTICLE

Effects of crude methanol extracts of *Banisteriopsis* spp. (Malpighiaceae) on *Allium cepa* root cells

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ABSTRACT

Brazil has a great number of species that present medicinal uses by the local population. Since the toxicity of medicinal plants is a serious public health problem, there is a need for studies on its phytotherapeutic actions. Plants of the genus *Banisteriopsis* are known both for their medicinal and psychotropic activities. The objective of the present study was to evaluate the cytotoxic and genotoxic effects of methanolic extracts of *Banisteriopsis malifolia* (Nees & Mart.) B.Gates and *Banisteriopsis variabilis* B.Gates, on concentrations of 9, 20, 33, and 50, on germination of onion (*Allium cepa* L.) seeds. Four replicates of 50 onion seeds, moistened with 10 ml of each extract and distilled water used as negative control, were done in a completely randomized design. In both treatments, at concentrations of 33% and 50%, we observed yellowish roots, thicker and less turgid in relation to the control. There was a reduction in cell divisions at the 33 and 50% concentrations and a positive correlation was observed with chromosomal aberrations at the same concentrations. These results suggest the cytotoxic and genotoxic activity of plants *B. malifolia* and *B. variabilis* directly proportional to the concentrations tested.
Keywords: Cytotoxicity, Genotoxicity, Medicinal plants, Micronucleus, C-metaphase

INTRODUCTION

The use of higher plants as a source of bioactive principles is still little explored. Only a small fraction of these vegetables was phytochemically analyzed. The assessment of the toxicologic potential is a complex process, as many factors (both plants-related and environmental) can contribute to the toxicity of medicinal herbal products. It is estimated that approximately 80% of the world's population uses herbal medicinal products for their therapeutic virtues. Even though herbal medicine products are usually perceived as low risk, their potential health risk should be carefully assessed (Jitareanu 2023). Bordoloi and Soren (2022) studied 42 plant families, and plants belonging to the family Fabaceae and Asteraceae have appeared to be in the highest level for genotoxicity. The reason of such high occurrence in genotoxicity phenomenon might be their constituents. However, little is known about the safe standards for the consumption of these products. To avoid any mutation in its users, genotoxicity assessment of therapeutic plants appears to be required (Bordoloi and Soren 2022).

Rich in biodiversity, over 45,000 species (20–22% of the total worldwide), the vast territory of Brazil contains many numbers of species already used as medicine by the native populations. However, the adverse effects of phytomedicine, including possible adulteration, toxicity, and synergistic effects are commonly observed. Approximately 74% of the main medicinal products derived from plant sources have been discovered based on results reported by popular medicine (Filho 2010). Nevertheless, research evaluating the use of medicinal plants and herbal medicines in Brazil is still lacking, as well as control of marketing by official bodies in street markets, public markets, or natural food stores. Dutra et al. (2016) describe the Brazilian large biodiversity and some attempts of Brazilian scientists to assess the pharmacological profile of most plant extracts

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or isolated active principles. Despite the substantial number of scientific publications on medicinal plants, only one phytomedicine is found in the top 20 market products (Dutra et al. 2016). Jitareanu et al. (2023) reviewed the current strategies and techniques used and recommended by regulatory authorities to investigate the authenticity and toxicity of medicinal herbal products.

In the search for new prototypes, plants of the genus *Banisteriopsis* have significate importance because their medicinal and psychotropic activities are known since the ancient times and can be used by the population therefore the health risk must be considered. *Banisteriopsis* is one of the largest and most widespread genera of the Malpighiaceae family, this neotropical genus is represented by ca 92 species and distributed mainly in Brazil, Bolivia, Colombia, Ecuador, and Peru (Frias et al. 2012).

Banisteriopsis malifolia (Ness & Mart.) B.Gates is a shrub that has many branches with subdivisions. It is native and endemic to Brazil. In phytochemical characterization, the plant *B. malifolia* has pharmacologically active compounds, such as alkaloids, flavonoids, tannins and has anticholinesterase activity (Frias et al. 2011). Martins et al. (2020) determined the seasonal chemical compositions of the *B. malifolia* leaves essential oils and subjected to antimicrobial activity tests. Terpenoids compounds (56.0%) and aliphatic alcohols (29.8%) were present in large amounts in rainy season essential oil compared to the dry season (20.93 % and 20.48 %, respectively). Phytol was the principal terpenoid compound present in both essential oils (52.70 %) stood out in the rainy essential oil versus 15.80 % in the dry essential oil). Both essential oils had no promising anti-*Candida* activity.

Banisteriopsis variabilis B.Gates is also a shrub endemic to Brazil. Queiroz et al. (2010) identified compounds considered to be chemomarkers of the genus *Banisteriopsis,* observing the presence of flavonoids such as: quercetin, rutin, [epi]catechin, apigenin, and [epi]catechin gallate in the ethanolic extract of leaves of *B.variabilis*. According to Simoni et al. (2007) the *B. virabilis* extract has antiviral activity for both BHV-1 and SHV-1, both viruses with DNA envelope, but it also has antiviral activity for the avian retrovirus.

The lack of more detailed information on the content of toxicity and genotoxicity of the active ingredients from *B. malifolia* and *B. variabilis,* make them attractive for studies. This study aimed to evaluate the genotoxic and cytotoxic potentials of methanol extracts of *B. malifolia* and *B. variabilis*, at different concentrations, on onion root cells (*Allium cepa* L.) in mitosis.

MATERIAL AND METHODS

Plant samples were collected in the Reserva Particular do Patrimônio Natural do Clube de Caça e Pesca Itororó Uberlândia, MG situated at I19°00’06” S 48°18’38” W. *B. malifolia*: Collector: Torezan-Silingardi HM; Exsicata HUFU#13413. *B. variabilis*: Collector: Torezan-Silingardi HM; Exsicata HUFU#62950. After collection, the leaves were dried, pulverized and crushed to obtain extracts by maceration using methanol as liquid extractor. Dilutions were made to obtain four different concentrations of the extracts (9, 20, 33, and 50%, v/v).

The *A. cepa* seeds (2n=16) of the cultivar Texas 502 PRR were used as a test-organism. Bioassays were performed in ventilated and illuminated environment, at room temperature, following the Rules for Seed Analysis (Brasil 1992). Onion seeds were germinated in gerboxes (11 x 11 cm) with germ test paper, moistened with 10 ml of each extract or distilled water as a negative control, maintained at room temperature for 6 days. There were four replicates of 50 seeds for each concentration of the tested extracts and control, in a completely randomized experimental design.

Physiological quality was evaluated for: germination test, obtaining the germination index (GI) on the sixth day; root growth, to obtain length, change in color, turgor, hardening of root tips and thickenings (tumors).

Onion roots were collected after 6 days of germination and fixed in Carnoy’s solution (Ethanol: Acetic Acid 3: 1-v/v) for 24 h at room temperature, and then, freezer stored in 70% alcohol. To determine the mitotic index, we used the crushing technique (Guerra and Souza 2002).

The slides analyze were carried out under light microscopy at 400x magnification. For cytogenetic analysis, we observed the presence or absence of chromosomal aberrations (CA). The following chromosome and nuclear aberrations were considered: chromosome adherence, C-metaphase, chromosome bridge, genetic material loss, micronuclei presence, apoptosis and necrosis. Mitotic index (the ratio of number of cell division over total cells analyzed) was also considered for analyses.

Data were analyzed by analysis of variance and regression analysis accepting the 0.05 probability to indicate a significant effect. Descriptive statistics was also used to present mean and standard deviation, and absolute and percentage frequencies.

RESULT AND DISCUSSION

For both *B. malifolia* and *B. variabilis* extracts, the results regarding the growth inhibition of *A. cepa* roots after 3 and 6 days of germination were directly proportional to increasing concentrations (Figures 1 and 2). At 9% concentration the reduction effect began to be observed and persisted at higher concentrations (20, 33, and 50%, v/v). The RC_{50} index translates the growth parameter, indicating the concentration that causes a 50% reduction in root growth compared to the control. In the present study, after substitutions, the concentration that would reduce onion root growth by 50% under the *B. malifolia* extract would be the concentration of 27% on the 3rd day of germination and 32% on the 6th day of germination. For *B. variabilis* of the tested concentrations, the one that would reduce root growth by 50% on the 3rd day of germination would be the concentration of 32% and 33% on the 6th day of germination. The values found are very close to the concentration of 33% (w/v) tested in the present work, which proves the intervention in the root growth parameter of *A. cepa* under the action of the extracts of *B. malifolia* and *B. variabilis.*

For both extracts tested, the control seedlings showed root with normal development and color, whereas in the treatments, seedlings showed damaged roots with dark color. At the two highest concentrations, 33% and 50%, it was observed roots with yellowish stiffened tips, and thickenings.

Kamal (2020) defined allelopathy as the inhibition or promotion of growth in one plant species by chemicals produced by another species. Allelochemicals can cause several direct or indirect effects on other plants. Several plant species have been reported to affect the growth of others. Peloso et al. (2022) showed the allelopathic ability of aqueous extracts *of Achyrocline satureioides* (Lam.) DC. on

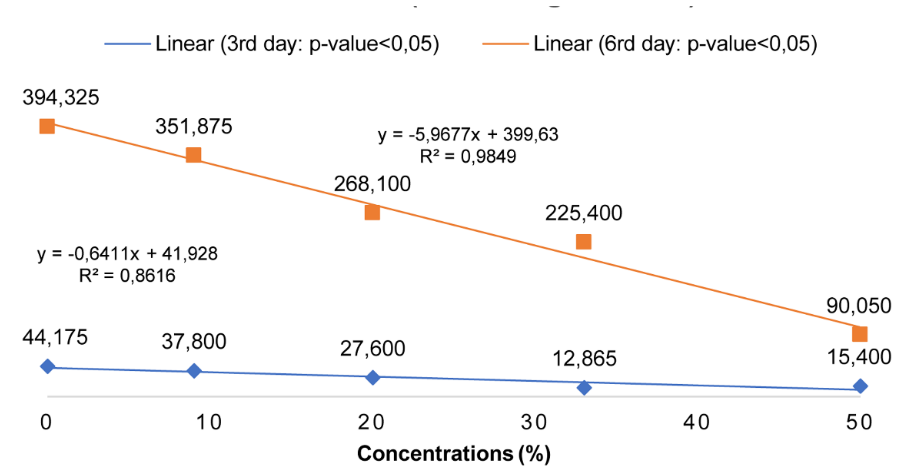

Figure 1. Mean root length of seedlings of *Allium cepa* at 3 and 6 days after germination according to different concentrations of the extract from *Banisteropsis malifolia*.

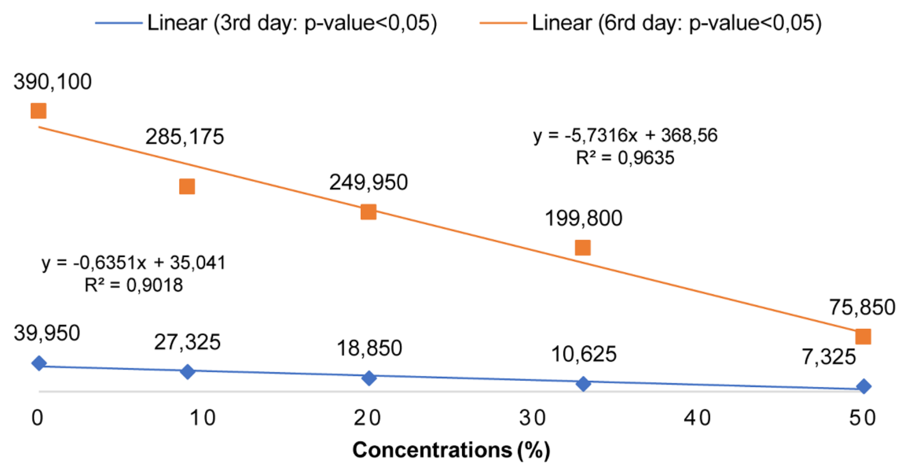

Figure 2. Mean root length of seedlings of *Allium cepa* at 3 and 6 days after germination according to different concentrations of the extract from *Banisteropsis variabilis*.

the germination of *Bidens pilosa* L. Phytochemical study on various species of *Banisteriopsis* reported high diversity of metabolic compounds (Frias et al. 2011; Martins et al. 2020). The chemical composition of *Banisteriopsis* extracts may have contributed to the effects observed in this study. The appearance of roots of *A. cepa* observed herein confirms the results obtained by Periotto et al. (2004), who noted that, at the end of the bioassay, the roots emerged from lettuce seeds showed necrosis, and some of them exhibited radicle protrusion, but the cap was completely oxidized and darkened, and over time, roots no longer grew, occurring softening and deterioration of tissues.

Banisteriopsis extracts at higher concentrations (33 and 50%) showed cytotoxic potential on *A. cepa* because they decrease the mitotic index and induced significantly chromosomal aberrations (CA) in relation to the control treatment.

There was a significant decrease in the number of dividing cells compared to the total (mitotic index). In turn, lower concentrations (9 and 20%) resulted in similar values and even an increase in the mitotic index compared to the negative control (Figure 3). The mitotic indices varied according to the concentration (C) of the extract, being 18.25% (control); 19.6% (C1); 21.71% (C2); 15.85% (C3), and 12.41% (C4) for *B. malifolia*. The mitotic indices were 19.92% (control); 20.65% (C1); 18.27% (C2); 17.9% (C3), and 17% (C4) for *B. variabilis*. A difference in behavior can be noticed between the two species of *Banisteriopsis* in relation to the concentrations. *B. malifolia* showed an increase in the average value of the MI at the concentration of 20%, while in *B. variabilis* there was a decrease. This discrepancy shows that the allelopathic effect can be on growth or inhibition promotion depending on the concentration and type of chemical constituent that each species presents. It is interesting to note that at 50% concentration the inhibitory effect is greater in *B. malifolia*.

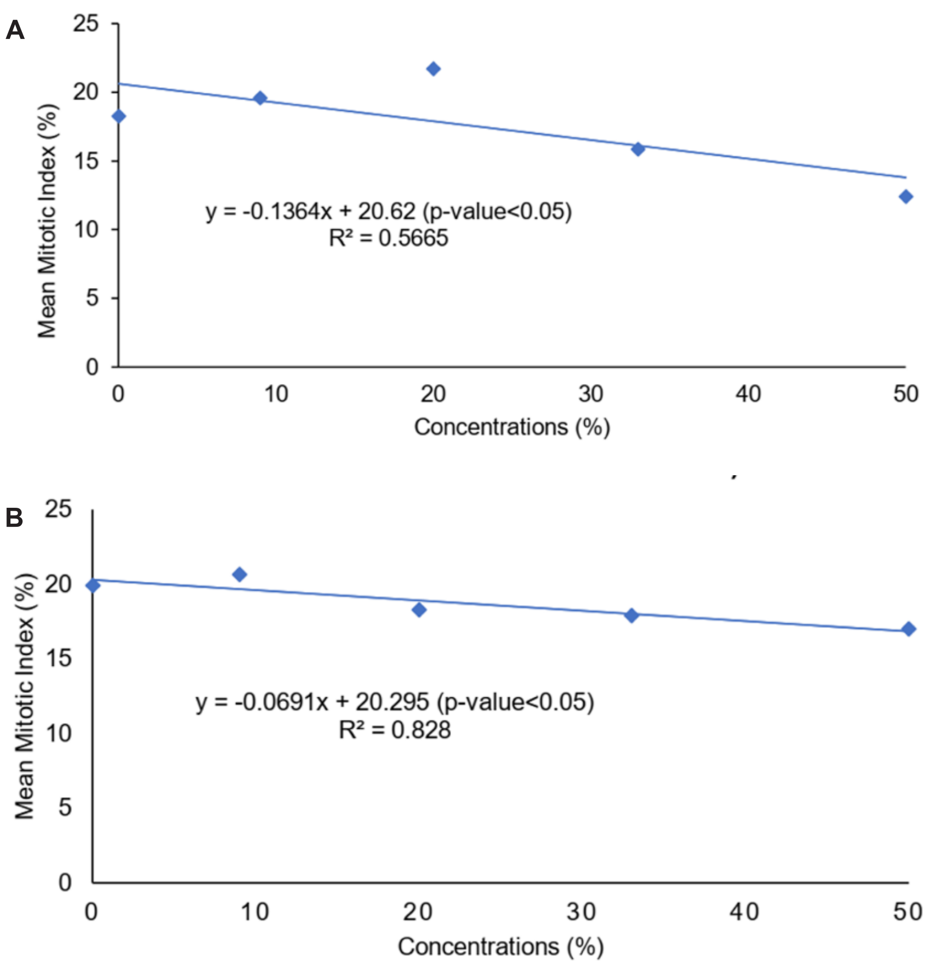

Figure 3. Mean values of the mitotic index of onion root cells according to different concentrations of extracts (0%, 9%, 20%, 33% and 50%) from (A) *Banisteriopsis malifolia*, and (B) *Banisteriopsis variabilis*.

The interaction of any toxic material may lead to the inhibition of cell division, and to numerous chromosomal aberrations which may be caused by the action of components in medicinal plants (Frescura et al. 2012). Chiavegatto et al. (2017) investigated the cytotoxic and genotoxic potential of methanol and hexane extracts of *Solanum lycocarpum* A.St.-Hil. on growth and cell cycle of *Lactuca sativa* L. and *A. cepa*. In both plant models there was a significantly decreased of the mitotic index as the concentrations of the extracts increased. Bibi et al. (2019) analyzed the mitotic effect of *Annona muricata* L. leaf extracts on *A. cepa* root tip cells showing that all studied concentrations of *A. muricata* methanol extract showed significant ($p \leq 0.05$) drop in the mean mitotic index when compared with control. These results are not in agreement with those of the present study because there was variation in the allelopathic effect depending on the concentration and plant species.

When there is a significant decrease of mitosis due to the action of toxic substances, there is a direct influence on growth and development of the organism exposed, because cytotoxic substances can block the G2 phase of the cell cycle, preventing the cell from entering into mitosis or inhibiting the DNA synthesis, leading to a decrease of the mitotic index in relation to control organisms (Leme and Marin-Morales 2009; Jairajpuri et al. 2016).

In an experiment to identify phytochemical groups in several species of the genus *Banisteriopsis* conducted by Frias et al. (2011), it was found in *B. malifolia* alkaloids in a higher number compared to other species. Flavonoids and tannins were identified in all tested species, including *B. malifolia* and *B. variabilis*, justifying the cytotoxic and mutagenic effects demonstrated in the present work. The decrease root growth observed with the higher concentrations of the *Banisteriopsis* extracts can be explained by the reduced dose-dependence of the mitotic index.

It was also observed the occurrence of chromosomal aberrations (CA) in seeds treated with higher concentrations of the extracts. The most frequent CA caused by extracts of both species analyzed were micronucleus (Figure 6A), C-metaphase (Figure 6B), stickiness (Figure 6C), and apoptosis, among others (Figures 4, 5, and 6).

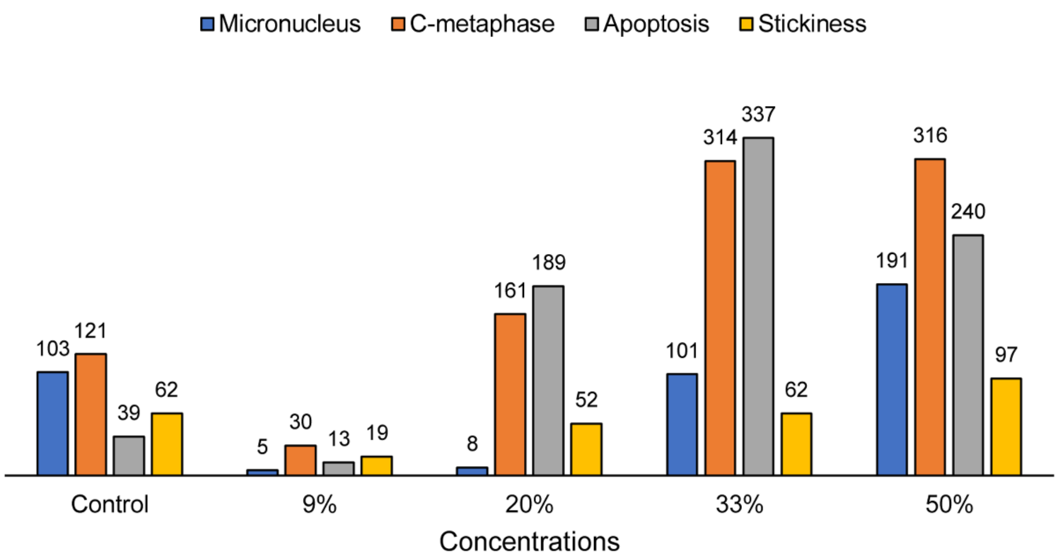

Figure 4. Number of chromosomal aberrations, obtained for different concentrations of the extract from *Banisteriopsis malifolia* in *Allium cepa* test system.

Figure 4 shows that C-metaphases and apoptosis were the most frequent aberrations found at a concentration of 33% for *B. malifolia*, whereas for *B. variabilis* (Figure 5) they were C-metaphases and micronuclei. There was a decrease in the frequency of CA at the 9% concentration, indicating an antimutagenic effect at that concentration, in both species.

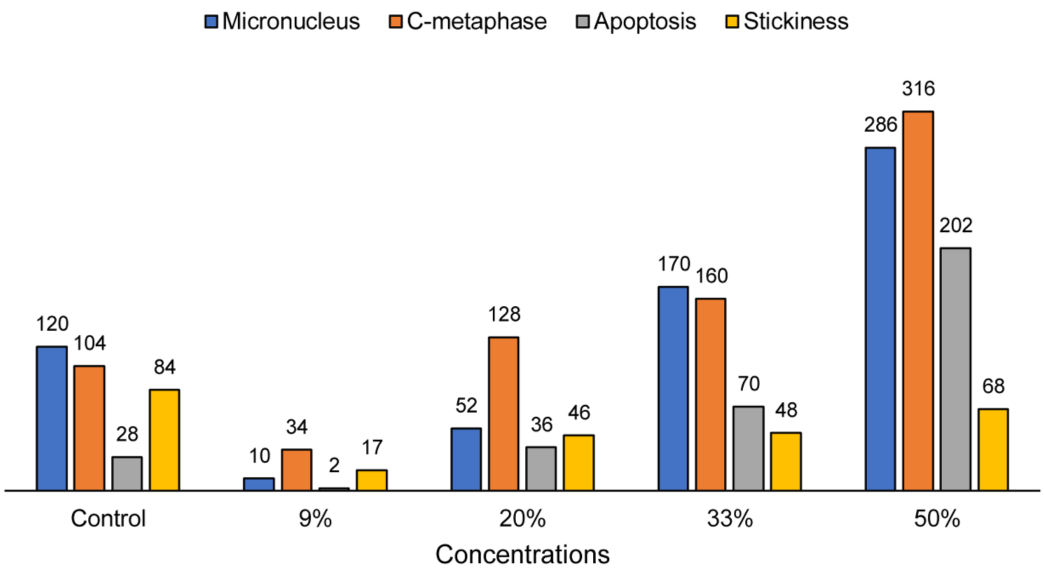

Figure 5. Number of chromosomal aberrations, obtained for different concentrations of the extract from *Banisteriopsis variabilis* in *Allium cepa* test system.

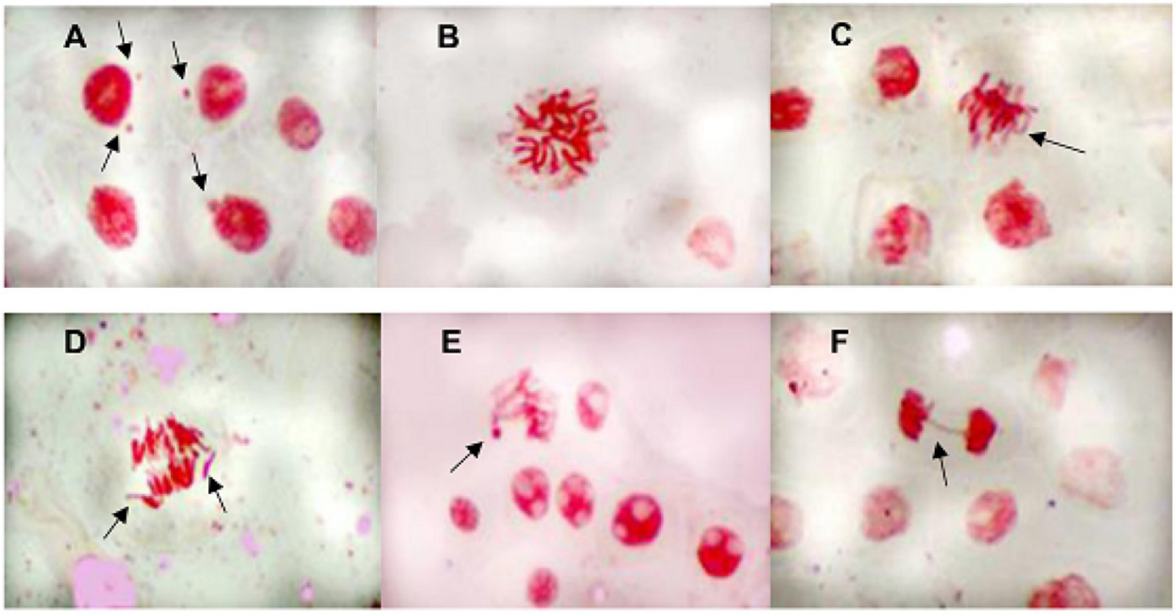

Figure 6. Chromosomal aberrations in root cells of *Allium cepa* treated with higher concentrations of *Banisteriopsis malifolia* and *Banisteriopsis variabilis* extracts. (A) Cells with micronuclei, (B) C-metaphase, (C) Chromosomal adherence, (D) Chromosomal fragment (arrow), (E) Adherence and micronucleus, (F) Chromosomal bridge (arrow). Bar = 10 µm for all figures.

The mechanism of action of substances or compounds on the genetic material can be classified into clastogenic*,* when involves chromosomal breakage, or aneugenic activities*,* when leads to chromosomal delays or affects the spindle. Our results are consistent with those observed by Pesnya et al. (2017) because, in addition to demonstrating a significant decrease in the mitotic index of *Heracleum sosnowskyi* Manden. juice, their most common anomalies were chromosomal delays, suggesting that *H. sosnowskyi* juice has clastogenic and aneugenic activities. Numerical and chromosome aberration evaluation has proved a sensitive analysis for making the investigation of test agent actions even more accurate in relation to their effects on the DNA of exposed organisms (Leme and Marin-Morales 2009).

The observation of stickiness metaphases reinforces the hypothesis of the toxic effect of extracts from *B. malifolia* and *B. variabilis*. The detection of this type of aberration reflects the toxic effect on chromatin, which generally leads irreversibly to cell death (Fiskesjo 1985; Andrade-Vieira et al. 2014; Pesnya et al. 2017). Stickiness has been attributed to the effect on physical and chemical properties of DNA, protein, or both, on the formation of complexes with phosphate groups in DNA, on DNA condensation or on formation of inter- and intra-chromatid cross-links (El-Ghamery et al. 2003). Non-orientation of chromosomes on the metaphase plate and consequent permanence, dispersed in the cytoplasm, characterizes abnormality known as C-metaphase (Teixeira et al. 2015). C-metaphase may result from the action of aneugenic agents on the cells whose compounds promote a complete inactivation of the mitotic spindle (Ventura-Camargo 2011). The presence of significantly number of C-metaphase on onion cells reinforces the aneugenic action of the *B. malifolia* extracts. As for *B. variabilis*, there was a significant increase in micronuclei along with C-metaphase.

Micronuclei are the result of the development of chromosomal aberration, such as chromosomal breaks and losses, which are not correctly repaired in the parental cells, being easily observed in the daughter cells as a structure similar to the main nucleus but in reduced size (Fernandes et al. 2007). As a result, they appear as an extranuclear mass of chromatin, reflecting both actions, clastogenic and aneugenic, of a substance or compound (Leme and Marin- Morales 2009). Fernandes et al. (2007) suggested that micronuclei elimination can be an indicator of maintenance of cell physiology, since any elimination activity of a given structure means that the cells present a physiological response. Nuclear changes, such as chromatin condensation, indicate that cells undergo programmed cell death (Andrade-Vieira et al. 2014). Apoptosis, a type of programmed cell death, is characterized primarily by reduction of the cell and then condensation of the nucleus, and the cell finally disintegrates into apoptotic bodies (Ventura et al. 2008). The present study showed significant frequencies of cells under death process (apoptosis and necrosis) in the *A. cepa* meristems exposed to *Banisteriopsis* extracts especially at 33% of *B. malifolia*. These results show that *Banisteriopsis* extract was cytotoxicity to the concentration mentioned. Plants and plant products that are potent apoptosis inducers are gaining interest in anticancer drug discovery since apoptosis forms the basis of the drugs targeting cancer cells (Ravindran and Thoppil 2019).

While some compounds in plants, such as flavonoids, have medicinal actions, many can be harmful to the organism, in other words, as any synthetic drug may be toxic, compounds present in medicinal plants may also cause toxicity at the systemic and cellular levels, depending on the time of use and the doses used (Silva et al. 2015). According to Teixeira et al. (2003), chemical compounds, such as tannins and flavonoids, inhibit enzymatic activity and may play cytotoxic activity, respectively. The activity enzymatic assigned to these compounds can be responsible for the inhibition of cell division in meristematic cells of *A. cepa*, as seen in the present study. In *B. malifolia* extract, it was identified alkaloids in a higher number compared to other species, as well as flavonoids and tannins in several species of the genus *Banisteriopsis*, including *B. malifolia* and *B. variabilis*, justifying the cytotoxic and mutagenic effects demonstrated in this study (Frias et al. 2012).

Our findings suggest inhibitory and genotoxic activity, as well as toxic effects directly proportional to doses tested, evidencing that the analyzed species contain bioactive ingredients with cytotoxicity and genotoxicity potential. Although, the positive results obtained in *Allium cepa* roots under the influence of methanol extracts from *B. malifolia* and from *B. variabilis* may be indicative of risk to human health cytotoxic effects on *A.cepa* root tips shows the apoptotic potential of the plant extracts and the present study enlightens a possible anticancer potential of the plant.

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AUTHORS' CONTRIBUTION

Conceptualization, L.B.X.C., M.C.MC.

and A.O.R; Data curation, L.B.X.C., M.C.MC. and A.O.R; Formal analysis, L.B.X.C. and M.C.MC.; Investigation, L.B.X.C., Methodology, L.B.X.C. and M.C.MC.; Project administration, M.C.MC.; Resources, M.C.MC.; Supervision, M.C.MC. and A.O.R.; Validation, L.B.X.C.; Visualization, L.B.X.C.; Writing – original draft, L.B.X.C.; Writing – review & editing, L.B.X.C., M.C.MC. and A.O.R. All authors read and approved the final manuscript.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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