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Original Research Article

Unveiling The Dual Anticancer Role of *Hilleria Latifolia* (Phytolaccaceae): Use of Preliminary Bench-Top Bioassays in A Resource-Challenging Environment

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ABSRTACT

Medicinal plants remain a vital source for modern drug discovery. Research into plants traditionally used for tumour-related disorders is essential, considering the rising incidence of various forms of cancer. *Hilleria latifolia* is among the plants documented in traditional medicine for treating tumour-related ailments, but with limited scientific evidence. This study aimed to investigate the growth-inhibitory (antiproliferative) and cytotoxic potentials of the methanol extract of the whole plant of *H. latifolia* and its fractions using simple bench-top assay methods. Antiproliferative activity was conducted using guinea corn (*Sorghum bicolor*) at 1–30 mg/mL over 24-96 hours, while cytotoxicity was evaluated using tadpoles (*Raniceps raninus*) after 24 hours at 10–400 µg/mL. The crude methanol extract remarkably suppressed seed radicle proliferation in a concentration- and time-dependent manner, achieving 95.24% inhibition at 30 mg/mL. The aqueous and chloroform fractions exhibited 99.42% and 80.38% inhibition, respectively, at similar concentrations. In the cytotoxicity assay, the chloroform fraction and the crude methanol extract demonstrated the highest cytotoxicity, achieving 100% mortality at 200-400 µg/mL. The aqueous fraction achieved 93.3% mortality at 400 µg/mL. LC_{50} values of 159.26, 215.10, and 99.55 µg/mL were calculated for the methanol extract, the aqueous, and the chloroform fractions, respectively. Phytochemical evaluation confirmed the presence of condensed tannins, flavonoids, glycosides, alkaloids, and steroids, which have been linked to anticancer properties. These findings provide evidence supporting the ethnomedicinal use of *H. latifolia* for managing tumour-related conditions and suggest its potential as a lead in anticancer drug discovery, pending confirmation studies with established cancer cell lines.

Keywords: Cancer cell lines, Cytotoxicity, Growth Inhibition, Medicinal plants, Phytochemicals.

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Introduction

Medicinal plants, also known as medicinal herbs, have been essential to traditional healthcare systems due to their therapeutic effects on humans since ancient times.[1,2] Interest in the medicinal properties of plants has increased due to their active pharmacological activities, affordability, minimal side effects, and cultural acceptance by users.[3,4] Modern medicines derived from plant extracts are developed based on the traditional uses of these plants.[5] For example, the antimalarial drug quinine was extracted from the bark of *Cinchona officinalis*.[6] and codeine was obtained from *Papaver somniferum*;[7] in contrast, vincristine and vinblastine, potent anticancer compounds, are extracted from *Catharanthus roseus*.[8] However, relatively few medicinal plants have been scientifically evaluated for their quality, efficacy, and toxicity, despite their significance in drug discovery.[9,10]
Cancer is a diverse group of disorders characterised by the unregulated proliferation and division of abnormal cells across different tissues in the body.[11]

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It remains a major global health burden and is currently ranked as the second leading cause of mortality globally, after cardiovascular diseases.[12,13] According to estimates from 2022, approximately 20 million new cases and 9.9 million cancer-related deaths were reported worldwide. Africa accounted for approximately 1.2 million of these new cases, with Nigeria contributing 11% of Africa's new cases and exhibiting a high fatality ratio.[13,14] It is projected that cancer mortality in low- and middle-income countries will nearly double by 2050.[12,15] Most of this increase is due to population growth, longer life expectancy, physical inactivity, and obesity.[13,16,17] Established causes and risk factors for cancer include poor diet, genetic predisposition, environmental exposures, and infections.[12,18,19] Furthermore, humans are affected by over 100 different types of cancer, with lung, breast, prostate, and colorectal cancers among the most prevalent worldwide.[12,13] Treatment options such as surgery, radiation, laser therapy, chemotherapy, or a combination thereof are employed in managing various cancer types.[20,21] These traditional treatments are often associated with harmful side effects on healthy cells, issues with availability, and high costs. Due to these limitations, there is an urgent need for alternative therapies, including the use of medicinal plants such as *Moringa oleifera*, *Rauwolfia caffra*, *Hymenocardia acida*, *Zingiber officinale*, and *Hilleria latifolia*, among others.[22-26]
Hilleria latifolia (*H. latifolia*), part of the *Phytolaccaceae* family, is also known by several local names, such as "Avegboma" (Ewe), "Anafranaku" (Asantes), "Aka ato" (Igbo), "Efehentok" (Ibibio), and "Ogo" (Yoruba).[27-30] This perennial herb reaches heights of about 1–2 m. It features ovate-elliptic leaves measuring 15 cm long and 6 cm broad, with obtuse or subacute bases and numerous short, hair-like structures on the underside. The plant exhibits hypostomatic characteristics with normocytic stomata and contains abundant

prismatic crystals throughout its parts.[31,32] Traditionally, *H. latifolia* is well known for its medicinal uses in West and Central Africa, treating conditions such as urethral discharge, food poisoning, gonorrhoea, haemoptysis, asthma, leprosy, and breast cancer, particularly in countries like Côte d'Ivoire, Congo, Nigeria, and Ghana.[29,33,34] Earlier phytochemical studies have indicated that the plant comprises alkaloids, saponins, flavonoids, carbohydrates, triterpenoids, tannins, and glycosides across various parts.[26,27,32,35] The pharmacological properties of *H. latifolia*, as documented in the literature, include anti-inflammatory, wound-healing effects, as well as antinociceptive, anti-arthritic, antiplasmodial, antioxidant, antidepressant, and antimicrobial activities.[27-29,36-38] This research aimed to investigate the cytotoxic and antiproliferative potentials of the methanol extract and fractions of *H. latifolia* (whole plant) using bench-top assay methods such as tadpoles (*Raniceps ranninus*) and guinea corn (*Sorghum bicolor*).

Materials and Methods

Chemicals and Equipment

All reagents and chemicals used were of the analytical grade (≥99.5%). They include Methanol, Chloroform, Dimethyl sulfoxide (DMSO), Ethanol, Distilled/deionized water, Ferric chloride solution, Dragendorff's reagent, Wagner's reagent, Mayer's reagent, Borntrager's reagent, Liebermann–Burchard reagent, Salkowski's reagent, Keller–Killiani reagent, and Lead acetate solution.

All reagents listed above were obtained from Sigma-Aldrich (Germany), while all chemicals used were obtained from BDH Chemicals (UK).

The equipment used includes an electric milling machine (Chris Norris, England), thermostat oven (Model DHG-9101-ISA, China), Soxhlet extractor (1 L glass apparatus, Quickfit & Quartz Ltd, UK), weighing balance (Ohaus®, USA), refrigerator (Haier Thermocool®, Nigeria), rotary evaporator (Rotavapor R-210, Büchi AG, Switzerland), thermo-regulated digital water bath (EM-19, England) Separatory funnel (1000 mL borosilicate glass, Pyrex UK), Petri dishes and beakers (borosilicate glassware, Pyrex UK), Filter paper (Whatman No. 1 Filter Paper, Whatman International Ltd, UK), Statistical software (Microsoft Excel 2023, Microsoft Corporation, USA).

Collection and Identification of Plant

H. latifolia (whole plant) used for this study was collected in June 2019, from a cocoa plantation in Agbegi Village, Ikire, Osun State, Nigeria (Latitude: 7°21′36.00″N; Longitude: 4°11′6.00″E). Identification and authentication were conducted by Dr Samuel Odewo, a taxonomist at the Forest Research Institute of Nigeria (FRIN), Ibadan. A voucher specimen number FHL113269 was subsequently lodged in the FRIN Herbarium.

Plant Preparation.

The collected plant was cut into pieces and rinsed twice with a large amount of de-ionized water to remove surface debris. The plant was initially air-dried for three weeks under laboratory conditions and subsequently oven-dried at 50 °C. to completely remove residual moisture. After drying, the plant was ground into a coarse powder using a laboratory grinder and stored in containers.

Extraction

Approximately 3 kg of powdered material was extracted exhaustively with absolute methanol using a Soxhlet extraction apparatus. The crude extract was concentrated using a rotary evaporator under reduced pressure to yield a crude methanol extract, which was weighed and kept in a refrigerator at 4 °C until needed.

Solvent Fractionation

Approximately 150 grams of the methanol extract was dissolved in water and partitioned exhaustively with about 800 mL of chloroform using a 1000 mL separating apparatus. The chloroform and aqueous fractions were collected, dried using a rotary evaporator, and their yields were recorded for subsequent use.

Preliminary Phytochemical Evaluation

Qualitative phytochemical screening was conducted using standard procedures to detect the presence of flavonoids, alkaloids, anthraquinones, steroids, glycosides, and condensed tannins.[39-41]

Guinea Corn (Sorghum bicolor)

S. bicolor seeds were purchased from Uselu Market, Benin City, Edo State, Nigeria. Their viability was tested by immersion in a 500 mL beaker containing distilled water. Those that sank and remained submerged were considered viable, while unhealthy seeds were discarded. The Viable seeds were surface-sterilized with ethanol, rinsed, and dried on filter paper at room temperature before use.[42]

Tadpole (Raniceps ranninus)

Viable tadpoles of small sizes were collected from stagnant water bodies along Eagle Furniture Street, off Uwasota, Ugbowo, Benin City, Edo State. They were taxonomically identified and authenticated by experts in the Animal and Environmental Biology Department, Faculty of Life Sciences, University of Benin, Nigeria.

Growth Inhibitory Assay Using Sorghum bicolor.

Approximately 10 mL of each sample at (1–30 mg/mL) containing 5% DMSO in distilled water was prepared. These solutions were transferred into Petri dishes lined with filter paper.

Twenty viable seeds were spread per dish and incubated at room temperature. The length of emerging radicles was measured (to the nearest millimeter) after 24, 48, 72, and 96 h. 5% DMSO in distilled water was used to treat the control seeds. All experiments were conducted in triplicate.[43,44] ([The % inhibition was calculated using equation1

$$\%\ \text{inhibition} = \left((\text{MRL of negative control} - \text{MRL of test agent}) \times 100\right) \div \text{MRL of negative control} \quad (equation\ 1)$$

MRL means the mean radicle length.

Cytotoxic Assay

Using a Pasteur pipette, ten similarly sized tadpoles were transferred into different well-labelled 100 mL beakers, each containing 30 mL of pond water. To each beaker, 19 mL of distilled water was added with 1 mL of each sample dissolved in 5% DMSO, at (1–20 mg/mL), resulting in a final volume of 50 mL. This gives subsequent extract concentrations equivalent to 20–400 µg/mL. Control experiments contained 30 mL of pond water, topped up to 50 mL with distilled water. All experiments were conducted in triplicate. Mortality was evaluated within 24 hours.[44,45] The total submergence of the tadpoles served as an indicator of mortality, and the LC_{50} was calculated using the regression equation 2.

$$Y = ax + b \quad (equation\ 2)$$

Statistical Analysis

Each experiment was performed in triplicate. Data were analyzed using Microsoft Excel and expressed as mean ± standard error of the mean (SEM). Statistical comparisons were determined using one-way analysis of variance (ANOVA), supported by the Kruskal–Wallis test with a significance threshold of $p < 0.05$.

Results and Discussion

Extract Yield and Phytochemical Evaluation

Three kilograms of the powdered whole plant of *H. latifolia*, extracted with absolute methanol, yielded 353.99 g of extract, corresponding to 11.80%. Partitioning of 150.0 g from the methanol crude extract gave 79.72 g (53.15%) aqueous fraction and 48.04 g (32.02%) chloroform fraction.

The medicinal properties of plant materials arise from a mixture of phytochemicals stored in specialized cells across various plant tissues. These phytochemicals are typically extracted using different methods, such as Soxhlet extraction. Ongoing research on medicinal plants continues to provide valuable resources in the quest for new drugs.[46,47]

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Qualitative phytochemical evaluation revealed various phytochemicals, including Glycosides, steroids, tannins, and flavonoids (Table 1). These classes of secondary metabolites have been reported to produce compounds that exhibited cytotoxic activity, hence preventing the development of cancer.[48-50] These findings support the previous data that *H. latifolia* possesses similar classes of compounds.[51]

Table 1: Phytochemical Evaluation of *H. latifolia* (whole plant)

Class of phytochemical	Result
Flavonoids	+
Anthraquinones	-
Glycosides	+
Steroids	+
Condensed tannins	+
Alkaloids	+

+ present - absent

Effect of Extract and Fractions on S. bicolor Radicle Growth

A significant suppression of *S. bicolor* radicle elongation was observed with the crude extract in a concentration-related manner ($p < 0.05$). The anti-proliferative action was sustained throughout the experiment period. At 24 h, an average radicle length of 7.03 ± 0.29 mm was attained by untreated seeds. However, shorter lengths of 6.30 ± 0.54, 4.73 ± 0.19, 3.50 ± 0.22, 1.62 ± 0.16, and 0.73 ± 0.02 mm were achieved by those treated with 1, 2, 5, 10, and 20 mg/mL of the extract, respectively. Compared with the control, a significant difference ($p < 0.05$) was observed in all reductions in length. At 30 mg/mL, complete growth inhibition was nearly achieved. After 96h, an average radicle length (55.23±1.57 mm) was achieved by the untreated seeds, while average lengths of 37.63±0.65, 25.60±0.79, 19.00±0.49, 7.13±0.18, 3.25±0.25, and 2.63±0.08 mm were attained at 1, 2, 5, 10, 20, and 30 mg/mL of the extract, respectively (Figure 2).

Figure 1: *Hilleria latifolia* collected from Ikire community (Osun state, Nigeria)

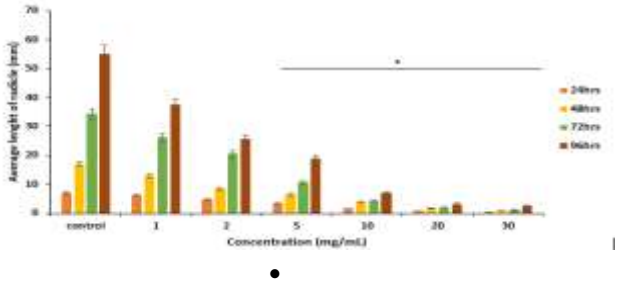

Figure 2: Growth inhibitory effect (using *S. bicolor*) of *H. latifolia* crude extract at concentrations ranging from 1–30 mg/mL. Values are mean ± S.E.M, n = 3. Samples with superscript * indicate a significant difference at $P<0.05$ relative to the negative control using one-way ANOVA (Kruskal–Wallis test).

This implied reductions of 87.09%, 94.12%, and 95.24% at concentrations of 10, 20, and 30 mg/mL (Figure 5). The aqueous fraction produced the strongest inhibitory effect. At 24 h, control seed radicles reached a radicle length (5.47±0.50 mm) in contrast with 4.52±0.12, 3.68±0.58, 1.17±0.33, and 0.10±0.10 mm, yielded by seeds treated with 1, 2, 5, and 10 mg/mL, respectively. At 20-30 mg/mL, complete inhibition of radicle growth was observed (Figure 3). After 96 hours, a similar trend was observed as the untreated seeds had an average radicle length (65.07±1.06 mm) as against 42.27±1.51, 34.80±0.33, 14.78±0.23, 7.17±0.23, 3.13±1.01, and 0.38±0.22 mm measured by groups treated with the 1, 2, 5, 10, 20, and 30 mg/mL, respectively (Figure 3).

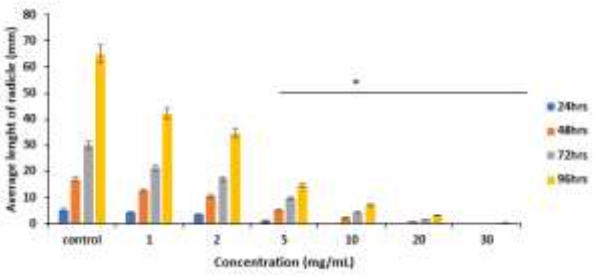

Figure 3: Growth inhibitory effect (using *S. bicolor*) of *H. latifolia* aqueous fraction at concentrations ranging from 1–30 mg/mL. Values are mean ± S.E.M, n = 3. Samples with superscript * indicate a significant difference at $P<0.05$ relative to the negative control using one-way ANOVA (Kruskal–Wallis test).

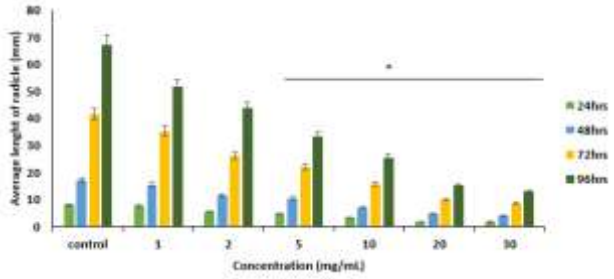

Figure 4: Growth inhibitory effect (using *S. bicolor*) of *H. latifolia* chloroform fraction at concentrations ranging from 1–30 mg/mL. Values are mean ± S.E.M, n = 3. Samples with superscript * indicate a significant difference at $P<0.05$ relative to the negative control using one-way ANOVA (Kruskal–Wallis test).

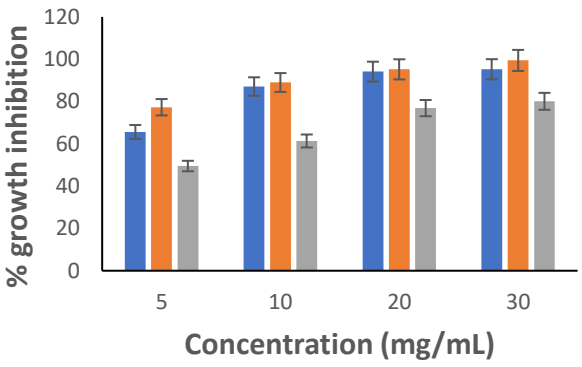

Figure 5: Percentage growth inhibitory effect of the methanol extract, aqueous, and chloroform fractions on *S. bicolor* radicle length in 96 hours.

This corresponded to percentage inhibitions of 88.98%, 95.19%, and 99.42% at 10, 20, and 30 mg/mL, respectively (Figure 5). Similarly, the chloroform fraction suppressed radicle elongation, though less effectively compared to the aqueous fraction. At 24 h, the control seeds achieved an average radicle length of 8.12±0.96 mm, whereas the test seeds measured 7.72±0.41 to 1.80±0.21 mm across the concentration range of 1–30 mg/mL. At 96 h, the control radicles attained an average radicle length of 67.27±1.54 mm, compared with 51.77±1.77 to 13.20±1.18 mm obtained for the treated groups (Figure 4). These variations in height were significant at $p<0.05$. The percentage inhibition at 10, 20, and 30 mg/mL was consequently found to be 61.34%, 76.87%, and 80.08%, respectively (Figure 5). Overall, the aqueous fraction produced the highest growth inhibition ($p < 0.05$), followed by the methanol extract and the chloroform fraction. The growth inhibitory effect correlated strongly and positively as the sample concentrations increased. Additionally, in many cases, the percentage growth inhibition increased with the duration of the experiments (Figure 5).

The bench-top assay, which includes the *Artemia salina* lethality test, *Raniceps ranninus* cytotoxicity assay, and mosquito larval toxicity assays, has been employed in various studies to assess the cytotoxic effects of plant extracts, particularly when cancer cell lines are not readily available.[45,52,53] These methods are straightforward, reproducible, and suitable for screening medicinal plants for their potential antitumor properties. The abnormal multiplication of cells is a characteristic of cancer cells. This behaviour resembles the active proliferation seen in the meristematic cells of guinea corn radicles under favourable conditions, which leads to radicle elongation. This similarity justifies the use of *S. bicolor* seeds in this research, as their meristematic tissues can proliferate under optimal conditions.[54] This study demonstrated that the methanol extract of *H. latifolia* (whole plant) and its fractions significantly inhibit *S. bicolor* radicles in a dose- and time-dependent manner. The untreated group exhibited the longest radicle length compared with those subjected to various extract concentrations after 24, 48, 72, and 96 h. Additionally, results showed that the length of guinea corn radicles decreased progressively as the concentration of the plant extract increased. Methanol extract fractionation into aqueous and chloroform fractions yielded improved inhibitory activity, with the aqueous fraction exhibiting the highest potency, achieving nearly 100% inhibition at a concentration of 30 mg/mL. These findings suggest that the active constituents responsible for growth inhibition are more concentrated in the aqueous fraction compared to other samples. Antiproliferative tests, evidenced by reduced radicle length, suggest the potential use of *H. latifolia* as an herbicide, allelopathic agent, or anticancer agent. This observed activity can be via interference with biochemical processes regulating cell proliferation, such as DNA replication; however, this claim requires further molecular studies and has not been scientifically validated.[45,47]

Cytotoxicity Activity of Methanol Extract and Fractions on Raniceps ranninus

Concentration- and time-dependent cytotoxic effects were exhibited by all the samples on the *Raniceps ranninus*. No mortality was recorded for the organisms treated with 5% DMSO (negative control group). The crude extract exhibited 90±5.78% and 100±0.00% mortality at 200 and 400 µg/mL, respectively. The aqueous fraction, however, resulted in 70±5.78% and 93.3±3.33 % mortality at 200 and 400 µg/mL, respectively. Conversely, the chloroform fraction exhibited the greatest potency, with 100.00±0.00 % mortality at concentrations of 200 and 400 µg/mL within one hour (Figure 6). LC_{50} values of 159.26, 215.10, and 99.55 µg/mL were calculated to show differences in cytotoxic activity for the methanol extract, aqueous fraction, and chloroform fraction, respectively.

Raniceps raninus were selected for the second bench-top cytotoxicity assay of this study due to their seasonal availability, especially during the rainy season. However, conducting such an assay during the dry season or in areas with limited water may present challenges. *R. raninus* is considered an appropriate model for cytotoxicity studies since its cells are eukaryotic, like human cancer cells. Thus, any plant extract or fraction that results in tadpole mortality is likely to inhibit the growth of tumour-producing cells.[55] The findings demonstrated that the samples produced a dose-dependent cytotoxic effect on *R. raninus*. The percentage mortality in *R. raninus* increased significantly with concentrations. The cytotoxic effects were indicated by the complete submersion of the organisms and their tendency to turn upside down in the water. While the methanol extract and aqueous fraction showed no lethality in *R. raninus* at concentrations of 20 and 40 µg/mL, the chloroform fraction caused a mortality rate of 30.00±3.33% at 40 µg/mL, which escalated to 100% at 200 µg/mL within 2 h of treatment. The chloroform fraction exhibited the most potent lethality effect on *R. raninus*, evidenced by its LC_{50} value of 99. 55 µg/mL compared to 215.10. 10 µg/mL for the aqueous fraction and 159.26. 26 µg/mL for the crude extract. This suggests that the active constituents responsible for cytotoxicity are more concentrated in the chloroform compared to the aqueous fraction and the crude extract. A comparable report described by Ogundare *et al*.,[51] *H. latifolia* was reported to have demonstrated an active cytotoxic effect using the Brine Shrimp lethality assay with an LC_{50} value of 63.19 µg/mL. A previous study by Dapaah *et al*.,[36] also indicated that *H. latifolia* demonstrated cytotoxicity against HaCaT-keratinocyte cells at elevated concentrations. Researchers have linked the cytotoxic properties of medicinal plants to phytochemicals like coumarins, flavonoids, and phenolic compounds.[51,56] These studies highlighted the increasing recognition of the anticancer potential found in African medicinal plants.

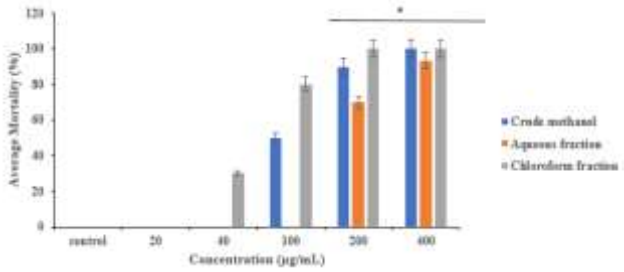

Figure 6: Effect of crude extract and fractions of *H. latifolia*, on *R. ranninus* % mortality at concentrations ranging from 20–400 µg/mL–an index of cytotoxic effect. A 5% DMSO solution was used as the negative control. Each bar represents the mean ± SEM of 10 (ten) independent experiments ($n = 10$). Samples with superscript * indicate a significant difference at $p<0.05$ relative to the negative control.

Conclusion

This study has demonstrated the growth-inhibitory and cytotoxic activities of *H. latifolia*, a plant commonly used in various aspects of African traditional medicine. The aqueous fraction has shown greater potential as a growth inhibitor, while the chloroform fraction displays stronger cytotoxic properties. Although validation with appropriate cancer cell lines is needed, the preliminary findings from the bench-top assay support the traditional medicinal use of this plant for treating tumor-related conditions. Future research should focus on bioassay-guided isolation and structural elucidation of the specific active compounds responsible for the observed antiproliferative and cytotoxic effects, using chromatographic and spectroscopic methods.

Conflict of interest

The authors declare no conflict of interest

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them

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