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Evaluation of *In Vitro* Cytotoxicity Potentials of *Synclisia scabrida* (Miers) ex Oliv and *Petiveria alliacea* L leaves on Colon, Breast, Pancreatic and Prostate Cancers

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Abstract

Despite tremendous advances in science and technology, patients and doctors still face many obstacles because the current medications have not been able to completely cure the disease due to resistance, side effects, and the high financial costs incurred by patients. There is an anecdotal report by the herbal practitioners in the Ugbine community that *S. scabrida* (SS) and *P. alliacea* (PA) are useful in cancer treatment. However, there is no known scientific evidence to support this. This study, therefore, sought to validate this. SS (1.5 kg) was sequentially extracted by maceration at room temperature using a solid–solvent ratio of 1:2 of hexane (HX), dichloromethane (DCM), ethyl acetate (EA), and methanol (MeOH) for 72 h. Thereafter, it was concentrated using a rotavapour and further dried for 3 days in an oven at 40^0C. *P. alliacea* (45 g) was similarly extracted using a solid–solvent ratio of 1:2 each of DCM, MeOH, and DCM: MeOH. In vitro cytotoxicity activities of the plants were assessed using the tetrazolium-based 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. SS leaf extract showed good activity against colon, breast, and pancreatic cancers. The lowest IC_{50} was 90 ± 17.3 against both breast and pancreatic cancer cells. On the other hand, *Petiveria alliacea* leaf extract showed promising activity on colon cancer cells (IC_{50} = 40 ± 10.4 µg/mL) and prostate cancer (IC_{50} = 60 ± 5.0 µg/mL). *S. scabrida* and *Petiveria alliacea* leaves demonstrated promising cytotoxicity potentials. Further studies to evaluate their mechanisms of action are warranted.

Keywords: *Synclisia scabrida*, *Petiveria alliacea*, colon, breast, pancreas, prostate cancers

Introduction

Cancer continues to be the second biggest cause of death globally, making it a significant global health concern. Despite tremendous advances in science and technology, patients and doctors still face many obstacles because the current medications have not been able to completely cure the disease due to resistance, side effects, and the high financial costs incurred by patients. Additionally, herbal practitioners in the Ugbine community in Benin City, Edo State of Nigeria, verbally reported using *Synclisia scabrida* (SS) and *P. alliacea* (PA) to cure cancer. Nevertheless, the usage of PA and SS for cancer treatment has not been scientifically validated or reported.

About 20 million new cases of cancer, with 9,743,832 mortalities, were expected to occur worldwide in 2022 (Bray *et al*., 2024). According to Bizuayehu *et al.* (2024), by 2050, the new cases are expected to increase to over 35 million. Global health is seriously threatened by cancer, which affects both wealthy and poor nations. Siegel *et al*., 2024 projected that 2,041,910 new cancer cases and 618,120 cancer deaths will occur in the United States of America in 2025.

Plants contain novel chemical constituents and are therefore a promising source for cancer drugs. Human and animal diseases have been prevented and treated with plants since time immemorial. Indeed, plant research has yielded about 60% of the anticancer drugs used in chemotherapy (Hashim *et al*., 2025).

The tropical African shrub *Synclisia scabrida* (Miers) ex Oliv (Menispermaceae) grows in South South Nigeria, Cameroon, Gabon, the Democratic Republic of the Congo, and Angola (Hutchinson & Dalziel, 1954). In the Ugbine community, Edo State, Nigeria, *S. scabrida* and *P. alliacea* grow commonly on farmland, a factor that influenced their choice for this study, as sources of alternatives, less expensive cancer therapies. In Nigeria and Cameroon, the leaves of *S. scabrida* are taken orally in the form of an alcoholic decoction for the treatment of gastric ulcers (Anowi *et al*., 2013).

A perennial shrub belonging to the Phytolaccaceae family, *Petiveria alliacea* L. thrives in the Amazonian Rainforest, tropical and Central America, as well as the Caribbean, and the Southeast United States. PA is a delicate, erect, and long-branched plant that ascends to about 1 m high. In natural medicine, *P. alliacea* leaf infusion has been used to treat muscle spasm, rheumatoid arthritis, and inflammation (Lopes-Martins *et al*., 2002). In addition, it has antinociceptive (Di Stasi *et al*., 1988), hypoglycaemic and abortifacient (de Lima *et al*., 1991) effects.

We hypothesised that leaf extracts of *S. scabrida* and *P. alliacea* exert anticancer activities against cancer cells. This study therefore, sought to validate this, thereby providing scientific evidence for the folklore use of these plants by Ugbine dwellers for cancer treatment.

Materials and Methods

Every chemical, reagent, and solvent utilised in this investigation was of analytical quality and laboratory grade and were purchased from Fisher Scientific, R & M Chemicals, or Friedemann Schmidt Chemical, Malaysia; Silica gel was purchased from Merck, Germany. RPMI 1640 and DMEM, penicillin-streptomycin, and trypsin EDTA (1X), were acquire from Gibco (Invitrogen Corporation, Carlsbad, CA, USA). Sigma Chemical Co. provided the fetal bovine serum and phosphate-buffered saline (St. Louis, MO, USA). TPP (Switzerland) supplied the cell culture flask and plates, while Nacalai Tesque (Japan) provided the 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2-tetrazolium bromide (MTT), Sigma-Aldrich (USA) supplied the dimethyl sulfoxide (DMSO), and other chemical reagents.

Gemcitabine was bought from Santa Cruz Biotechnology, Inc. Texas, USA.

Plant collection, identification, and authentication

Plant specimens were collected by Mr Samuel Oyebanji from a farm in the Ugbine community, Edo State, Nigeria. The plants were dried and sent to the Forestry Research Institute of Nigeria (FRIN) for identification and authentication. They were identified and authenticated by Mr S.A. Odewo of FRIN. Herbarium specimens with voucher numbers FHI – 111106 (for S*ynclisia scabrida* (Miers) ex Oliv) and FHI – 111105 (for *Petiveria alliacea* Linnaeus) were deposited at FRIN.

Preparation of Crude Extracts

After collection with documentation, samples of the herbs were prepared: dried under shade, crushed into a coarse powder, and then ground into a fine powder. The ground leaves of SS and PA were brought from Nigeria. Sequential extraction of SS leaves (1.5 kg) was performed using a solid–solvent ratio of 1:2 of hexane (HX), dichloromethane (DCM), ethyl acetate (EA), and methanol (MeOH), by cold maceration for 72 h followed by another cold maceration for 24 h. This was for exhaustive extraction of the marc, since at the end of 72 hours, the constituents were still remaining. Using Whatman no. 1 filter paper, the extract was filtered. Crude extracts were obtained by further drying the filtrate in an oven set at 40°C for three days after it had been concentrated under decreased pressure at 40°C using a rotavapour (Kaur *et al*., 2016). The same procedure was repeated using each of the solvents. In addition, the air-dried and ground leaves (45 g) of *P. alliacea* were subjected to extraction using a solid–solvent ratio of 1:2 each of DCM, MeOH, and DCM: MeOH (1:1) by cold maceration for 72 h followed by another cold maceration for 24 h. The solvent extracts were filtered and concentrated using a rotavapour and afterwards dried in an oven at 40°C for 3 days. The dried HX, DCM, EA, MeOH or DCM: MeOH (1:1) extracts from both plants were stored in amber-coloured bottles at -20°C until use. The percentage yield (% w/w) of each extract was calculated (Table 1).

MTT Assay of *S. scabrida* Crude Leaf Extracts

The MTT cell viability assay (Zhou *et al.*, 2001*)* was employed to assess the cytotoxic efficacy of the selected plant extracts. The MTT test is a colourimetric investigation that measures viable cells based on the formazan formed in metabolically active cells after digesting MTT with the help of NADPH oxidoreductase enzymes. Using this concept, the MTT assay quantifies the cell viability. The dose-response parameter determined was the half maximal inhibitory concentration (IC_{50}; concentration that inhibits cell viability by 50%; Body & Paull, 1995). The MTT assay was carried out as stated by Zulkipli *et al.* (2024*)*. All treatments were performed in triplicate. Briefly, sub-confluent colon (HCT-116), breast (MCF-7), pancreatic (PANC-1), and prostate (PC-3) cancer cell lines were detached from the culture flask using trypsin. Following that, they were triturated into a single-cell suspension and plated in 96-well plates (2×10^3 cells in 180 µL culture media). To enable adhesion to the wells, cells were cultured for 16–24 h at 37°C (5% CO2 and 95% air). SS leaf crude extracts were diluted serially (in culture medium) from 0.01 to 100 µg/mL, and the appropriate wells received 20 µL of each concentration (four replicates per concentration). Controls included untreated, gemcitabine (positive control, 0.01–10 µM), and 0.1% dimethyl sulfoxide (DMSO)-treated cells. Following 96 h of culturing at 37°C with 5% CO2 and 95% air, 50 µL of a solution of MTT (2 mg/mL in PBS) was applied to each well. The plates were incubated a second time for 4 h for metabolism of MTT by cellular

mitochondrial dehydrogenases, after which the supernatant was suctioned. DMSO (100 µL) was added to dissolve the formazan crystals that had formed. Using a VersaMax microplate reader (Molecular Devices, San Jose, CA, United States), the absorbance of formazan was measured at 550 nm. The quantity of living cells is reflected in the purple formazan's absorbance at 550 nm. Using the following formula, the percentage of cell viability was determined:

$$\% \text{ of cell viability} = \frac{\text{absorbance of treated cells}}{\text{absorbance of control cells}} \times 100$$

The IC_{50} was interpolated from the semi-log dosage-responses curve (percent cell viability vs concentration) that was created using 96-h MTT absorbance data (Rezk *et al*., 2015).

MTT Assay of *P. alliacea* Crude Leaf Extracts

The procedure described above for *S. scabrida* was repeated, but the cells were treated with *P. alliacea* crude leaf extracts diluted serially (in culture medium) from 0.01 to 100 µg/mL. According to Rezk *et al*. (2015), the IC_{50} was interpolated from semi-log dose-response curves (percent cell viability vs concentration) that were created using 96-h MTT absorbance data.

Statistical Analysis

The data are shown as the mean ± standard deviation. For data analysis, SPSS version 22 (IBM Corp., Armonk, NY, United States) was utilised. Tukey post hoc tests were employed after one-way analysis of variance (ANOVA) to compare the cells and treatment groups statistically. $p < 0.05$ was considered statistically significant.

Results

The yields of the SS leaf (SSL) and PA leaf (PAL) extracts obtained are shown in

Table . The MeOH extract of PAL yielded the highest (7.20%).

Table 1. Percentage yield of crude extracts of SS and PA leaves

Extract type	% Yield (w/w)	
	SSL	**PAL**
HX	1.24	nt
DCM	0.53	6.73
EA	0.45	Nt
MeOH	2.58	7.20
DCM: MeOH (1:1)	nt	5.26

Note: SSL = *Synclisia scabrida* leaf; PAL = *Petiveria alliacea* leaf; nt – not tested

Cytotoxic Activity of crude leaf extract of SS Against Cancer Cells

The IC_{50} of *Synclisia scabrida* leaf crude extracts are as shown in Table 2. The *Synclisia scabrida* leaf extract showed promising activity against any of the screened cells at the tested concentration. The lowest IC_{50} was 90 ± 17.3 against both MCF-7 and PANC-1 cells.

The IC_{50} values for the SS crude leaf extract against tumour cells are presented in Table 2. The hexane extract is active against colon (96.67 ± 5.8 µg/mL) and breast (90.00 ± 17.3 µg/mL) cancers, and similarly, the methanol extract (90.00 ± 17.3 µg/mL).

Table 2. Half maximal inhibitory concentration (IC_{50}) of crude leaf extract of SS on cancer cells

Extract (% yield)	IC_{50} (µg/mL)		
	HCT-116	MCF-7	PANC-1
HX (1.24)	96.67 ± 5.8	90.00 ± 17.3	> 100
DCM (0.53)	> 100	> 100	> 100
EA (0.45)	> 100	> 100	> 100
MeOH (2.58)	> 100	> 100	90.00 ± 17.3
Gemcitabine*	0.50±0.0	0.03 ±0.01	9.00±4.4

Note: Cells were treated with SS leaf extracts (0.01–100 µg/mL) for 96 h, and cell viability was evaluated with the MTT test. *The gemcitabine IC_{50} values are presented in µM. The IC_{50} is the concentration that inhibits cell viability by 50%. The data are shown as the mean ± standard deviation of three independent experiments. HCT-116: colon, MCF-7 breast, PANC-1: pancreatic, PC-3: prostate cancers.

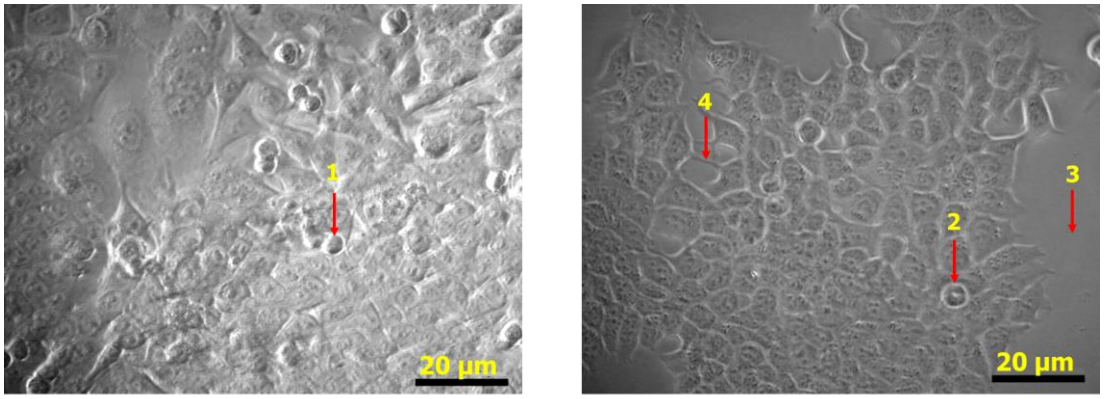

Figure 1. Plates representing the effects of 0.1% DMSO (a) and 0.01 µg/mL SS hexane leaf extract (b) on MCF-7 cells after 96 h treatment (magnification = 400 x). Arrows indicate [1] control cell, [2] membrane blebbing, [3] empty plate due to cell death, [4] echinoid spikes.

Cytotoxic Activity of Crude Leaf Extract of PA Against Cancer Cells

The IC_{50} values for the *Petiveria alliacea* crude leaf extract against tumour cells are presented in Table 3. The DCM: MeOH extract was the most active against HCT-116 cells (IC_{50} = 40 ± 10.4 µg/mL) while DCM (IC_{50} = 60 ± 5.0 µg/mL) and DCM:MeOH (IC_{50} = 75 ± 5.0 µg/mL) extracts were active against PC-3 cells. PANC- 1 cells were non-responsive to all extracts. The dose-response curves of the activities of PA leaf extracts on MCF-7, PANC-1, and PC-3 cells are shown in Figures 1 – 3, respectively.

Table 3. Half maximal inhibitory concentration (IC_{50}) of crude leaf extract of PA on tumour cells

Extracts	IC_{50} (µg/mL)			
	HCT-116	MCF-7	PANC-1	PC-3
DCM	>100	>100	>100	60 ± 5.0
MeOH	Nt	>100	>100	>100
DCM: MeOH (1:1)	40 ± 10.4	>100	>100	75 ± 5.0
Gemcitabine*	0.5 ± 0.0	0.03 ± 0.01	9.0 ± 4.4	nt

Note: Cells were treated with PA leaf extract (0.01–100 µg/mL) for 96 h and cell viability was assessed. The values show the mean ± standard deviation of three independent assays. *The gemcitabine IC_{50} values are presented in µM. nt: not tested. HCT-116: colon, MCF-7 breast, PANC-1: pancreatic, PC-3: prostate cancers.

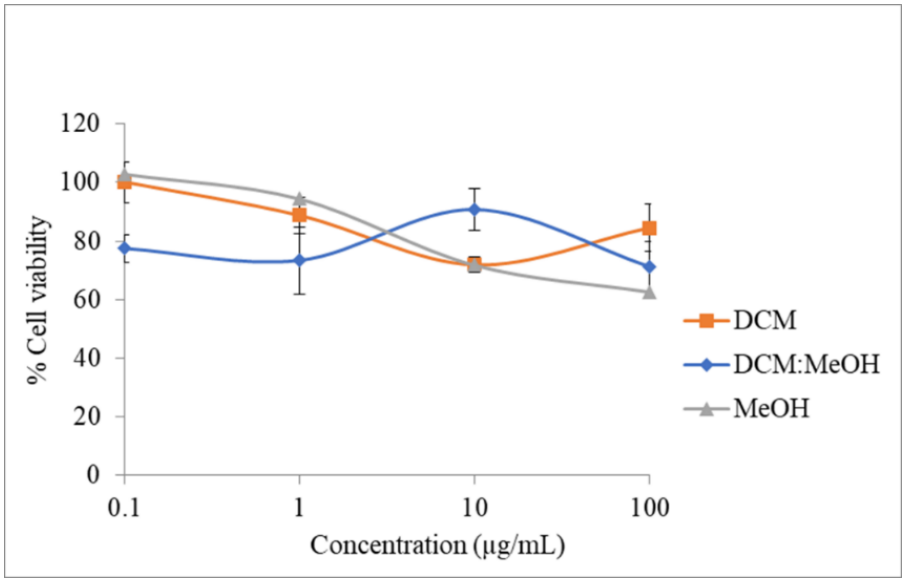

Figure 1. Dose-response curves presenting the activities of PA leaf DCM, DCM: MeOH, and MeOH extracts on % cell viability on MCF-7 cells after 96 h treatment**.** Values presented as mean ± SD of 4 values. DCM: dichloromethane, DCM: MeOH: dichloromethane: methanol (1:1), MeOH: methanol.

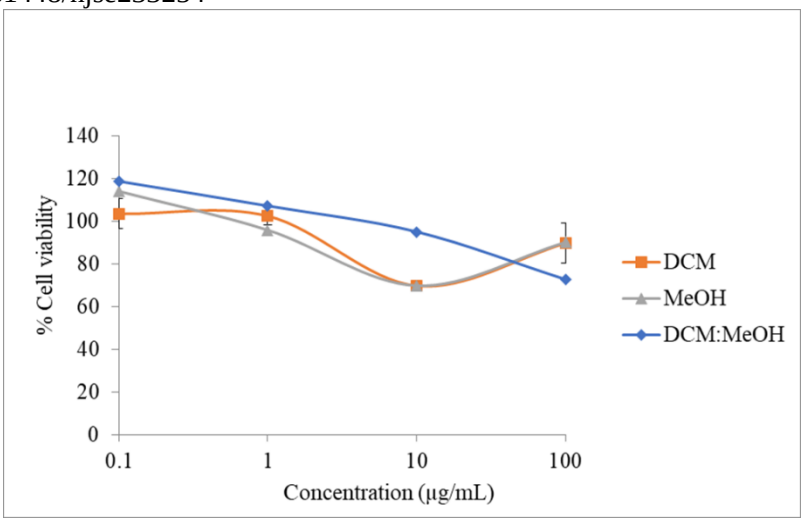

Figure 2. Dose-response curves presenting the activities of PA leaf DCM, DCM: MeOH and MeOH extracts on % cell viability of PANC-1 cells after 96 h treatment**.** Values presented as mean ± SD of 4 values. DCM: dichloromethane, DCM: MeOH: dichloromethane: methanol (1:1), MeOH: methanol

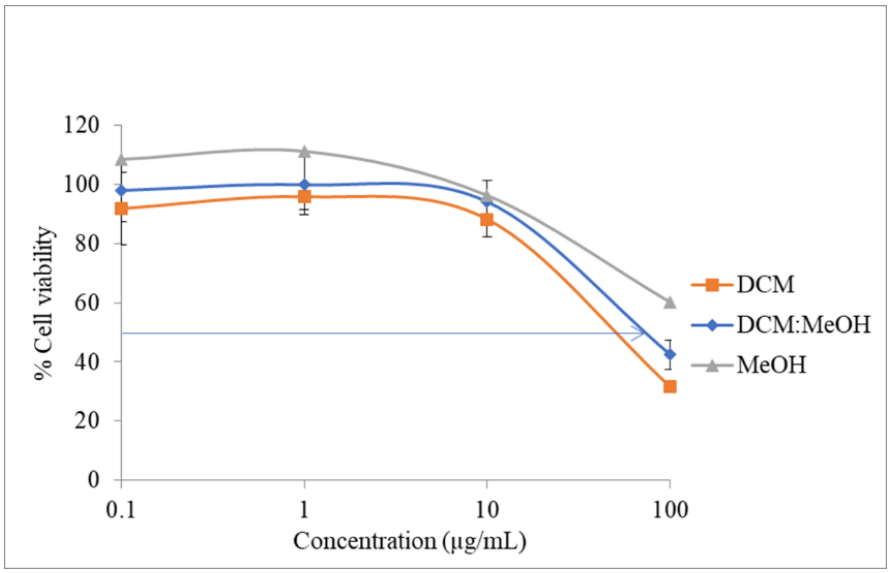

Figure 3. Dose-response curves presenting the activities of PA leaf DCM, DCM: MeOH and MeOH extracts on % cell viability on PC-3 cells after 96 h treatment**.** Values presented as mean ± SD of 4 values. DCM: dichloromethane, DCM: MeOH: dichloromethane: methanol (1:1), MeOH: methanol

Discussion

The MTT test was used to assess the cytotoxicity of *Synclisia scabrida* leaf extract on the tested cancer cells. The MTT assay quantifies the amount of yellow-coloured MTT that is reduced by mitochondrial succinate dehydrogenase. In this study, the phytoconstituents found in the leaf extracts of SS converted MTT to an insoluble, dark purple formazan. Since only metabolically active cells can reduce MTT, the activity level was thought to be an indicator of cell viability (Warake *et al*., 2021). Plant extracts

are regarded as active when the IC_{50} is between 10 µg/mL and 100 µg/mL (Njagi *et al*., 2016), and when significantly inhibited proliferation of a particular cell within the test concentration of less than 200 µg/mL is thought to be a sign of even more powerful effects in the refined state (Saudat *et al*., 2013). The IC_{50} of the leaf extract of *S. scabrida* leaf crude extract, in this study, showed promising anticancer activity against HCT-116, MCF-7, and PANC-1. This agrees with Warake *et al*. (2021) and colleagues who discovered that the IC_{50} of *C. zeylanica* ethanolic leaf extract against MCF-7 cells was 199.0 µg/mL, indicating a possible anticancer potential against MCF-7 cells. SS belongs to the Menispermaceae family, which is known to contain numerous alkaloids with anticancer properties. For example, bisbenzylisoquinoline alkaloids like cycleanine cause apoptosis by stimulating caspase-3 and caspase-7 and cleaving *poly-(ADP-ribose) polymerase* (PARP) to form PARP1 in Ovcar-8 and A2780 ovarian cancer cells (Uche *et al*., 2016). Neferine, another bisbenzylisoquinoline alkaloid, induces apoptosis in A549 cells; this activity is associated with the activation of mitogen-activated protein kinases (MAPKs) and loss of mitochondrial membrane potential. It arrests cells in the G1 phase, with overexpression of p53 and p21, together with downregulation of cyclin D1 (Poornima *et al*., 2014).

The cytotoxic potential of *Petiveria alliacea* against cancer cells was also examined. HCT-116 was the most sensitive cell. The plant exhibited promising cytotoxicity potentials against HCT-116, PANC-1, and PC-3. In addition, PA extract has been reported to cause apoptosis and reduced colony growth in murine 4T1 cells (Urueña *et al*., 2008). Furthermore, a phytochemical study on PA revealed that each gram of dry PA leaves has abundant phytochemicals like alkaloids (19.35 ± 0.10 mg), flavonoids (15.31 ± 0.19 mg/g), saponins (9.55 ± 0.13 mg), terpenoids (8.60 ± 0.10 mg), and phenolic compounds (47.40 ± 0.20 gallic acid equivalents [GAE]/g), along with notable antioxidant capacity (relative scavenging capacity = 59.23% ± 0.16%), which supports the basis for their medicinal use in folk medicine, like treatment of rheumatoid arthritis, and inflammation and as anti-helminthic, emmenagogue, and anaesthetic agent (Ayodele *et al*., 2015; Lopes-Martins *et al*., 2002). Hernández *et al*. (2017) reported that a PA dry extract is cytotoxic in a dose-dependent manner to human breast (HS578T) and colon (HCT-116) tumour cells, with IC_{50} values of 30 and 88 µg/mL, respectively. Thus, the ethnobotanical data for PA have already established and correlated this cytotoxicity assay result; however, further biological activity testing is warranted.

Conclusion

It is concluded that *S. scabrida* and *Petiveria alliacea* leaves demonstrated promising cytotoxicity potentials, indicating they could act as leads for the development of new anticancer therapies for colon, breast, pancreatic, and prostate cancers. Further studies to evaluate their mechanisms of action are warranted.

Conflict of Interest

The authors declare no conflicts of interest.

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